

Potential Resuscitation Strategies for Treatment of Hemorrhagic Shock¹

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ABSTRACT

Exsanguination is the major cause of death on the battlefield. Of those who die on the battlefield, it is estimated that 20% could be salvaged before exsanguination if provided with immediate care. Upon arrival at the scene, a First Responder must immediately control bleeding. If the injury is on the body surface or extremity and compressible, direct pressure or a tourniquet is current standard treatment for attempting adequate hemostasis. Ideally, a hemostatic dressing would circumvent the tourniquet by staunching severe bleeding, and require no further attention by the medic. For suspected non-compressible bleeding, for which there is currently no adequate treatment, the ideal would be an intravenous resuscitation solution containing a substance that enhances clotting or clot stability only at the bleeding sites. Once bleeding is controlled, the next step is to resuscitate the patient. In the battlefield, if hemostasis is not assured, aggressive resuscitation may dislodge the clot and exacerbate bleeding; aggressive resuscitation also requires large volumes of fluid, presenting a logistical difficulty. An improved strategy would resuscitate only to the point at which survival was assured and would not cause further bleeding even during the predicted prolonged evacuations that may occur in an urban warfare environment. This article gives an overview of recent work using a severe hemorrhagic shock animal model with an arterial injury on 1) the point at which blood pressure dislodges the thrombus (the “pop-clot” pressure); 2) an injectable clot stabilizer (“fix-a-leak”) that is a naturally occurring factor in the clotting cascade (human recombinant Factor VIIa); and 3) the maximum time up to 24 hours for hypotensive resuscitation below the “pop-the-clot” pressure (“how low for how long”).

1.0 INTRODUCTION

The concept that early, aggressive high volume resuscitation is critical to the optimal treatment of hemorrhagic shock was widely accepted and practiced during the Vietnam War [1]. Subsequently, the practice of large volume crystalloid resuscitation became the standard of care for civilian trauma patients [2]. The foundation of this practice rests on the controlled hemorrhage studies conducted in the late 1960s and 1970s by Shires et al [3,4]. The metabolic benefit of fluid resuscitation was definitively demonstrated in controlled hemorrhage animal models and then implemented in patients suffering uncontrolled hemorrhagic shock [3].

¹ The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

However, numerous animal studies of uncontrolled hemorrhage have shown that there is increased blood loss following resuscitation induced by injury to blood vessels or organs [5-18]. Recent randomized clinical studies [19-21] and a review of data collected during WWI [22] and WWII [23] similarly question the prudence of aggressive resuscitation in patients prior to hemorrhage control. While the metabolic benefits of fluid resuscitation have long been recognized [24-26], these benefits must be balanced against the deleterious effects of rebleeding. It is therefore essential to determine if there is a reproducible point at which rebleeding occurs. The optimal endpoint of resuscitation in patients with truncal injury without definitive hemorrhage control might then be just below this rebleeding point.

Our laboratory has developed an animal uncontrolled hemorrhage model that uses an injury in the aorta that closely approximates a severe arterial hemorrhage potentially encountered in the military setting. A round hole is made in the aorta with a skin biopsy punch that creates a wound profile of a ballistic or shrapnel fragment injury with actual loss of a piece of arterial wall. Using small punches, we can create an injury that spontaneously clots but, if rebleeding occurs, the additional hemorrhage will likely be fatal. Using large punches, we can create an injury that causes the animal to exsanguinate unless the hemostatic agent that we are testing is effective. In another paper in this issue, Kheirabadi et al. describe how this model has been modified to test dressings that would be effective with accessible compressible injuries. For this paper, we will focus on reducing bleeding in non-compressible injuries.

2.0 POP THE CLOT PRESSURE

The first study explored the possibility of a reproducible point of rebleeding, or a “pop-the-clot” pressure. In catheterized 40 kg anesthetized pigs in the supine position, through a midline incision in the abdomen, an initial aortotomy made with a 2 mm skin biopsy punch (Fig. 1), simulated an injury to the aorta, and was allowed to clot. The unique feature of this experimental design is that all bleeding can be quantified because we have suction tubes in the abdomen. The aorta bleeds as it would in a real injury with the intestines over the aorta and injury. When the blood drains to the sides, the suction tubes take the blood into canisters that are on a balance and the weight of blood in the canister is recorded on a computer instantaneously. Figure 2 shows the blood pressure tracing in a representative experiment for the two-hour experimental period with simultaneous measurement of resuscitation volume and hemorrhage volume.

To simulate varying times of arrival at the scene, we delayed aggressive resuscitation to 5, 15, or 30 minutes after the initial bleeding. We used two rates of resuscitation, 100 and 300 ml/min, with warmed lactated Ringer’s solution (6 or 7 animals per group). The 300 ml/min rate is approximately that which can be delivered on the battlefield through a large-bore (≤ 16 ga) catheter using a manually inflated pressure bag. The resuscitation was continued until the clot was dislodged and the aortotomy rebled. The blood pressure at the point when blood appeared in the suction canister is designated as the rebleed pressure. We thought that, if the clot gained strength as it matured, we would find that the rebleed pressure would increase with time, or that the higher rate of resuscitation would cause rebleeding sooner. Instead, as can be seen in Table 1, there were no systematic significant changes, regardless of delay or rate of infusion. The rebleed blood pressure, averaged over all the groups, proved to be a reproducible mean arterial pressure (MAP) of 64 ± 2 , a systolic pressure of 94 ± 3 , and a diastolic pressure of 45 ± 2 mmHg [27].

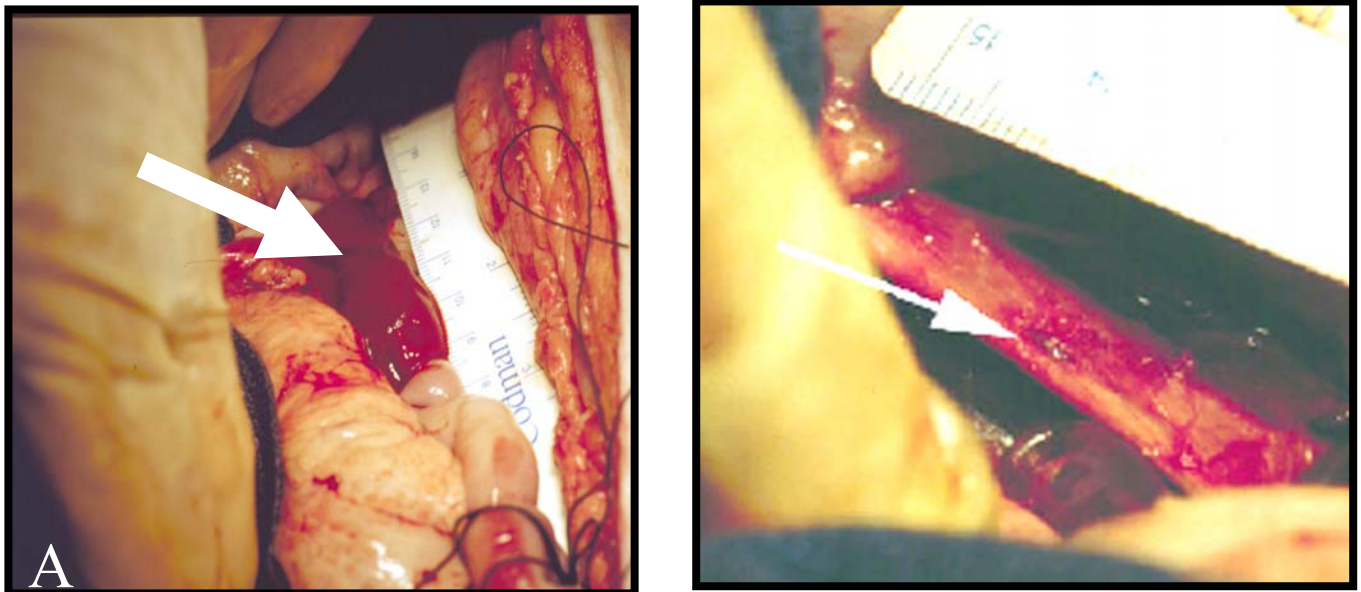


Figure 1: Abdominal aortotomy. A large central clot (white arrow) forms over the aorta to stop the initial bleeding. The majority of the blood has been suctioned into canisters and is not important in the initial hemostasis at the site of the clot (A). Postmortem, aortotomy size (arrow) is verified by exposing the site by clot removal (B). Interestingly, the gel clot (A) appeared to be the same even after rebleeding, so apparently, the clot was loosened with resuscitation, but not lost.

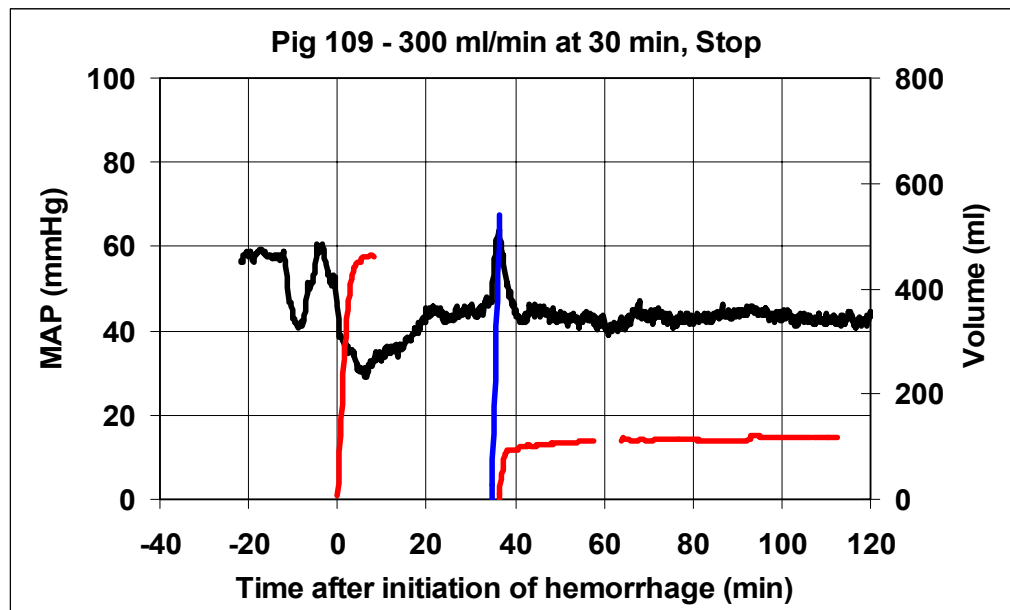


Figure 2. Blood pressure tracing over two-hours measuring resuscitation volume and hemorrhage volume. Resuscitation was discontinued at rebleed. Baseline MAP was taken. Intestines were retracted and aorta exposed. This caused variable changes in the MAP reflected by a transient drop and recovery of the MAP prior to the aortotomy at time 0. The first red line denotes the aortotomy hemorrhage volume and spontaneous clotting at 5 minutes. Blood pressure spontaneously recovered to near stable value below baseline. Resuscitation at 30 minutes, resuscitation began with warmed LR (blue line). Rebleed MAP was determined by appearance of blood in canister after resuscitation (second red line). Mean arterial pressure=MAP; lactated Ringer's solution = LR. Red line=instantaneous hemorrhage volume; blue line=resuscitation volume; black line=MAP

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Table 1: Mean arterial pressure at which rebleeding occurred in response to resuscitation with warmed lactated Ringer's solution at a rate of either 100 or 300 ml/min. The resuscitation was delayed 5, 15, or 30 minutes from the end of the initial hemorrhage.

Delay (minutes)	Rebleed Mean Arterial Pressure (mmHg)	
	Rate (ml/min)	
	100	300
5	70 ± 5	67 ± 5
15	57 ± 6	55 ± 5
30	63 ± 6	72 ± 4

3.0 CONTINUE OR STOP RESUSCITATION AFTER REBLEED POINT

Although the primary question in the rebleed study was to determine whether there is a reproducible rebleed pressure, another question that could be asked is what happens if resuscitation is either continued to return blood pressure to baseline levels, or if the resuscitation is stopped to minimize rebleeding. The animals were re-randomized into “continue” or “stop” resuscitation groups once they rebled. At that point, resuscitation (either at 100 or 300 ml/min rate) was either continued until the MAP returned to pre-hemorrhage baseline levels or was discontinued. In the continue group, the resuscitation pump was turned off when the pressure was at baseline, or was turned back on until baseline pressure was obtained. In the stop group, no further resuscitation was given once rebleeding occurred and the animals were observed until death or 2 for hours. There was also a group of animals that received the aortotomy, but no resuscitation (negative control group).

As can be seen in Table 2, all three groups bled a similar volume from the initial aortotomy. In the continue resuscitation group, the hemorrhage continued and the rebleed hemorrhage volume was four times higher than the rebleed hemorrhage volume in animals in which blood pressure was not returned to baseline levels after rebleeding occurred. In addition, 5 times the volume of lactated Ringer's was used in the continue group compared with the stop group. Despite the large amount of additional fluid received by the continue group, survival time was not significantly affected (Table 2).

Table 2: Initial hemorrhage volume, rebleed hemorrhage volume, volume of lactated Ringer's (LR) administered, and survival times in the No resuscitation, continue and stop resuscitation groups. ** different from all other groups. *different from No resuscitation.

Variable	Treatment		
	No Resuscitation (n=10)	Continue Resuscitation (n=16)	Stop Resuscitation (n=22)
Initial hemorrhage volume (ml/kg)	18 ± 2	16 ± 1	17 ± 1
Rebleed Hemorrhage Volume (ml/kg)	0 ± 0	29 ± 4**	7 ± 1*
Volume of LR administered (ml/kg)	0 ± 0	107 ± 15**	19 ± 3*
Survival time (minutes)	95 ± 13	85 ± 9	89 ± 8

Figure 3 shows the pattern of bleeding in representative experiments in the continue group. In some animals, although not all of them, rebleeding continued as long as resuscitation was continued. Contrast this with Figure 2 in which rebleeding stopped as soon as the resuscitation was discontinued. However, the blood pressure remained well below baseline values. Despite the fact that the continue group received far more fluid than the stop group, survival was not improved (Table 2). Part of the reduced survival was a result of the design of the study in which aggressive resuscitation was used throughout and resulted in a very low hematocrit that in and of itself resulted in death. To prevent this blood products are given as soon as possible in the emergency department. Only crystalloids and colloids are currently available on the battlefield, however, so we limited the choice of fluids to make the study relevant to the far-forward scenario.

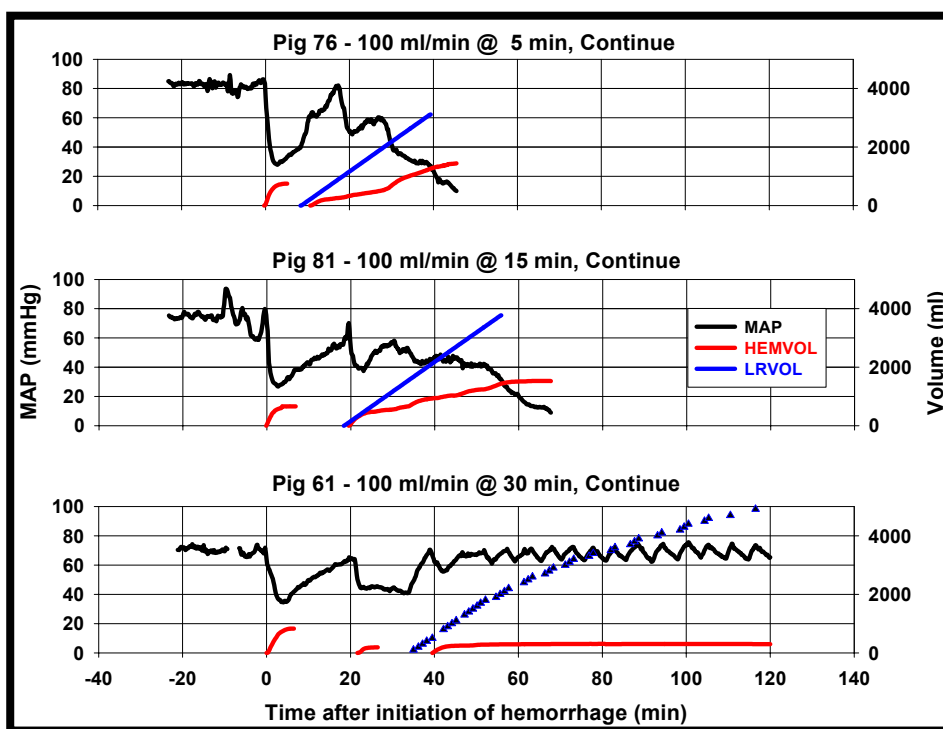


Figure 3. Three representative experiments of continued resuscitation after rebleed point. All three animals spontaneously recovered blood pressure following initial hemorrhage. After rebleeding, blood pressure fell and resuscitation continued for as long as blood pressure remained below baseline. Rebleeding continued as resuscitation continued if blood pressure did not be return to baseline (top 2 panels). This amount of resuscitation caused hematocrit to fall, and all resuscitation was stopped when the hematocrit reached 10 percent. Animal #61 spontaneously recovered to point of spontaneous rebleeding (bottom panel). Resuscitation was begun and the baseline blood pressure obtained. Resuscitation caused a third incidence of rebleeding, that did not continue despite continued resuscitation. The animal survived the entire 2 hours, hematocrit > 10 percent. Mean arterial pressure=MAP; lactated Ringer's solution = LR. Red line=instantaneous hemorrhage volume; blue line=resuscitation volume; black line=MAP

The interesting result was that there was no worse or even slightly improved survival in the animals that received no resuscitation at all – and that had no additional loss of blood. This suggests that even a small amount of rebleeding was associated with decreased survival. However, the lack of any resuscitation also resulted in less than a two-hour survival for the majority of the animals. These results agree with those from

studies that investigated an arbitrary partial resuscitation with either a given volume [7] or to an arbitrary blood pressure [12]; these demonstrated improved survival with limited resuscitation.

The finding of a reproducible rebleeding point suggests two strategies. One is to administer something that will stabilize the clot so that resuscitation to the baseline can be achieved while preventing further rebleeding. The other is to resuscitate to blood pressures below the rebleeding point. In the modern battlefield scenario, prolonged evacuation may occur due to wide dispersal of troops. Since others have demonstrated short term (up to 4 hours) benefits of hypotensive resuscitation, the remaining question is whether hypotensive resuscitation with fluids currently used by the combat medic can sustain a subject for as long as 24h at a blood pressure less than the rebleeding point. If hypotensive resuscitation is not beneficial for as long as 24h, then it becomes even more important to: 1) stabilize the clot so that a higher pressure can be obtained safely, or, 2) develop better resuscitation solutions that will increase survival in a prolonged hypotensive state.

4.0 STABILIZATION OF THE CLOT

Recombinant activated Factor VII (rFVIIa) is an FDA approved drug commonly utilized for the treatment of patients with hemophilia [28,29]. Attention has turned to its potential effectiveness in reducing bleeding in traumatic hemorrhage. Recent trauma studies have demonstrated its effectiveness in decreasing blood loss in models of hypothermic coagulopathic swine with Grade V liver injuries [30,31]. A growing body of literature documents its successful use in surgical and trauma patients with the acquired coagulopathy of trauma [32-34]. The purpose of this study was therefore to determine whether administration of rFVIIa to a pig—with normal coagulation and an uncontrolled hemorrhage—would enhance clot stability and increase rebleeding MAP in response to resuscitation.

In these experiments, the animal was prepared in a similar manner to the “pop-the-clot” study described above [27]. Five minutes before the aortotomy was made, an intravenous injection of either vehicle control, low dose (180 µg/kg) or high dose (720 µg/kg) rFVIIa was given. Five minutes after the injection was completed, the intestines were retracted and a 2.0-mm hole was made in the infra-renal aorta with a disposable skin biopsy punch. Ten minutes after the hole was made, resuscitation at 100 ml/min with lactated Ringer’s solution (LR) at 37°C was begun. Rebleed pressure was determined by noting the blood pressure at the time blood appeared in the suction canister. If the MAP reached a plateau after 4 L of fluid were given without causing rebleeding, the LR pump was stopped and an infusion of epinephrine at 1.0 µg/kg/min, as needed, was given to raise MAP to as high as 200 mmHg. If no rebleeding occurred with this treatment, the animal was recorded as a non-rebleeder. The total volume of LR administered and the rebleed hemorrhage volume were recorded. Survival time up to two hours post aortotomy was recorded.

Pre-treatment with rFVIIa significantly increased the MAP at which rebleeding occurred during resuscitation of an uncontrolled hemorrhage from 53 ± 7 mmHg in the control group, to 71 ± 6 mmHg in the low dose group, and to 88 ± 17 mmHg in the high dose ($p=0.05$ between high dose and control). More resuscitation fluid volume (55 ± 12 ml/kg at the high dose) was given compared with the control (20 ± 9 ml/kg, $p \leq 0.005$) before rebleeding occurred. Resuscitation was given for a longer time (21 ± 5 min at the high dose) before rebleeding was induced compared with the control (8 ± 4 minutes, $p \leq 0.005$). There was a trend toward a reduced rebleed hemorrhage volume with rFVIIa, from 39 ± 9 ml/kg in control to 21 ± 7 ml/kg at the high dose, but it did not reach statistical significance ($p=0.055$). There was no reduction in the initial hemorrhage volume among the groups (22 ± 2 , 20 ± 3 , and 19 ± 2 ml/kg in the control, low, and high dose groups, respectively), despite high levels of circulating rFVIIa.

Although the reduction of rebleed hemorrhage volume with rFVIIa treatment did not reach statistical significance, there was a significant metabolic consequence from the increased blood loss in the control group leading to an elevated plasma lactate concentration compared with the 180 and 720 $\mu\text{g}/\text{kg}$ groups and a trend toward a more negative base excess in the control group compared with the 180 and 720 $\mu\text{g}/\text{kg}$ groups. The change in the arterial base excess was not due to changes in the ventilation since the animals were on a ventilator. Although not significant, the control group showed a trend toward a shorter survival time than the low and high dose FVII groups (73 ± 11 , 87 ± 11 , and 95 ± 11 min, respectively, $p=0.238$).

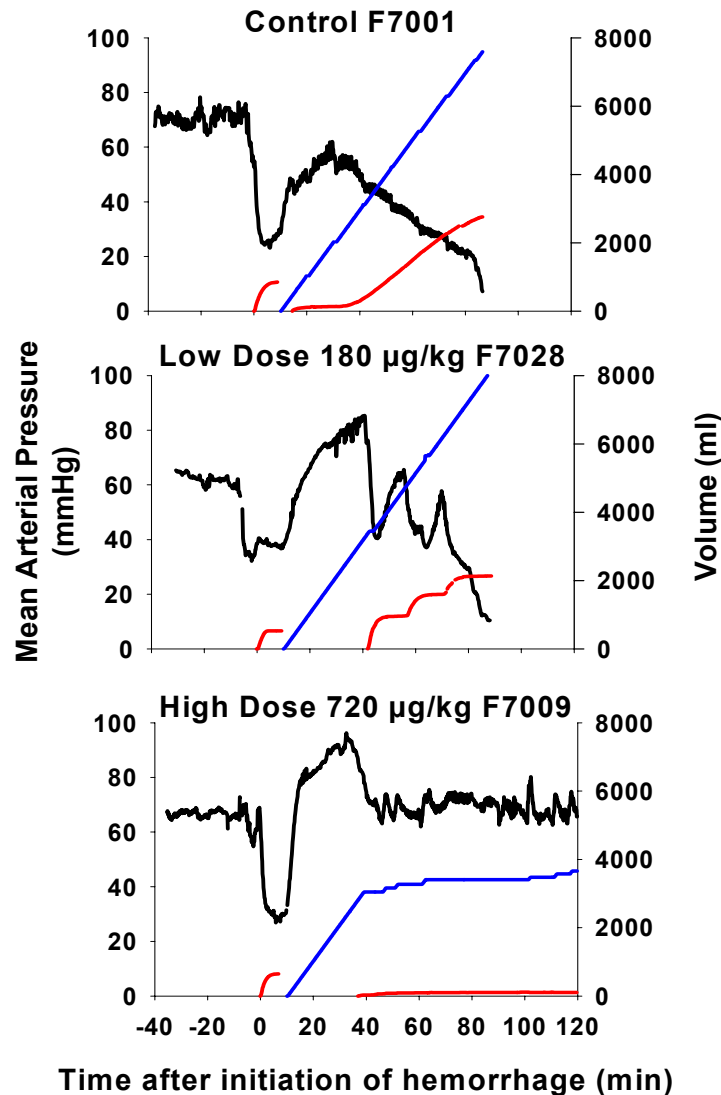


Figure 4. Control, low and high dose rFVIIa experiments: intermittent rebleeding with rFVIIa despite continuing resuscitation. Mean arterial pressure=MAP; lactated Ringer's solution = LR. Red line=instantaneous hemorrhage volume; blue line=resuscitation volume; black line=MAP

A very interesting pattern emerged among the groups and this pattern is depicted in the representative experiments shown in Figure 4 above. In this model, the usual finding was that, once the thrombus has been disrupted, bleeding continued for as long as resuscitation was administered, as occurred in 70% of the animals

in the control group (Top panel, Fig. 4 and in the pop-the-clot animals, Fig. 3). Although there was rebleeding in the groups that received rFVIIa, this bleeding stopped, at least for a short time, in 100% and 88% of the low and high dose animals, respectively, despite continued resuscitation (middle and bottom panels, Fig. 4).

Interestingly, rFVIIa pretreatment in the current study provided no hemostatic benefit in reducing the initial hemorrhage volume. This may indicate that the presence of rFVIIa has no measurable effect when the blood flows are high as they are in the pigs at baseline. Similar results were obtained by Schreiber et al, who treated pigs with rFVIIa 30 seconds after the induction of the liver injury [31] and began resuscitation 15 minutes after the injury. At high blood flows in the normotensive subject, the shear forces may therefore prevent platelets and other factors from concentrating at the site of injury. During the hypotension following hemorrhage, platelets may be able to collect at the injured site and a rapid, full thrombin burst may help to form a more stable clot with a firm fibrin structure that can better resist dislodging when normal rates of flow are reestablished following resuscitation.

Promising preliminary results from a group in England suggest that rFVIIa has a significant effect on survival time and hemorrhage volume in their model of combined controlled-uncontrolled hemorrhage. The rFVIIa was given just before an aortotomy was made and resuscitation begun, during a short period between the end of the controlled hemorrhage and the start of the uncontrolled phase. The animals were then given either full resuscitation to Advanced Trauma Life Support (ATLS) standards or hypotensive resuscitation to a systolic pressure of 80 mmHg. The different resuscitation methods (complete vs. hypotensive) showed a tendency towards a beneficial effect for hypotensive resuscitation that was most pronounced when the rFVIIa was combined with hypotensive resuscitation (Wayne Sapsford, Defense Science and Technical Laboratories, Porton Down, UK, personal communication).

5.0 HYPOTENSIVE RESUSCITATION

As mentioned previously, hypotensive resuscitation to arbitrary endpoints has been shown to reduce bleeding in uncontrolled hemorrhage models, at least in the short-term. We are currently conducting experiments to determine if resuscitation to a systolic blood pressure of 80 mmHg can be sustained for 24 hours. We chose a systolic pressure of 80 mmHg because it is below the “pop-the-clot” systolic pressure of 94 mmHg; additionally, it is the pressure at which a radial pulse can be detected and is therefore an appropriate target achievable on the battlefield. We are comparing various fluids that are either FDA- approved, or are undergoing application to the FDA for approval, for their efficacy under conditions of this hypotensive resuscitation. The fluids are lactated Ringer’s solution, 6% hetastarch in a lactated Ringer’s base (Hextend™), and a hemoglobin-based oxygen carrier (Polyheme™). The questions we are asking are 1) whether there is rebleeding during the hypotensive period; 2) whether the animals can tolerate prolonged hypotension; and 3) and which fluid provides the best metabolic support with the least volume. It is possible that the prolonged hypotension might cause some tissues to be relatively ischemic, so we are also taking samples to assess tissue function, oxidative, and nitrative states, and coagulation status. To see if there are changes in the synthesis of heretofore unknown metabolites, we are also performing genetic microarray analysis of the white blood cell response over the 24 h experimental course as is described in other papers found in this issue (Dubick and Bowman). At the end of the 24 h, we repair the aortotomy and then let the animal recover for an additional 2 days to ensure that multiple organ dysfunction does not develop. Based on acute studies and short-term clinical trials [19,20,35], the recommendations for hypotensive resuscitation has been promulgated for the special operations medics [36].

6.0 SUMMARY

The large animal, severe hemorrhagic shock models that we have been studying also allow us to investigate endpoints of resuscitation that are more sensitive than blood pressure. For example, in a series of non-resuscitated animals that bled different volumes in response to injury, three survival patterns emerged: those who survived for less than one hour, those who survived between 1 and 2 hours, and those who lived for the entire 2 hours (unpublished observations). Noninvasive and metabolic data from these experiments may yield new endpoints of resuscitation that may be early warning signs of impending circulatory collapse.

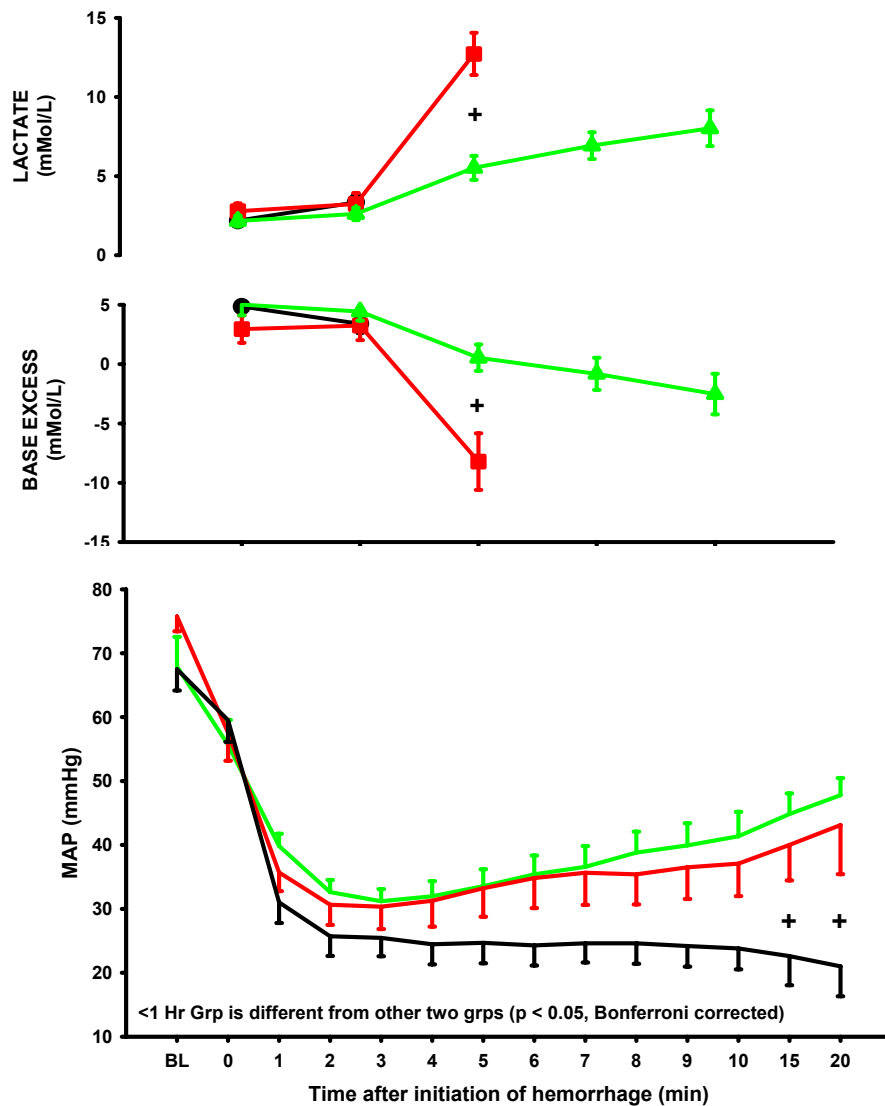


Figure 5. MAP in three groups of non-resuscitated pigs. Death \leq 1 hour = black line; Death at 1-2 hours = red line; Survival $>$ 2 hours = green line. Early changes in arterial lactate and base excess may differentiate between survivors and non-survivors although blood pressures are similar.

The normal response to severe hemorrhage when bleeding stops is for the blood pressure to spontaneously increase as the animal's intrinsic compensatory mechanisms start to operate. As can be seen in Figure 5 above, those animals that did not start to increase their blood pressure within 10 minutes did not survive a full hour. The other two groups did compensate with similar increases in blood pressure, yet one group succumbed earlier than the other. By looking at other endpoints, we found that large changes in lactate and arterial base excess as early as 15 minutes after injury distinguish between those who die early and those who survive. Because of studies and results like these, we feel that strategies to develop rugged instruments and realistic decision assist algorithms can be developed to better help the medic perform triage in the far-forward environment.

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