# Permissive Hypotension Strategies for the Far-Forward Fluid Resuscitation of Significant Hemorrhage[1]

**Michael A. Dubick, Ph.D and COL James L. Atkins, MD, Ph.D.[2]**
U.S. Army Institute of Surgical Research, San Antonio, TX 78234
[2]Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA

Email: Michael.Dubick@amedd.army.mil

## *ABSTRACT*

*Acute hemorrhage accounts for about 50% of the deaths on the battlefield in conventional warfare. In addition, hemorrhage is the primary cause of death in 30% of injured soldiers who die from wounds. With future combat strategies focused around the Objective Force Warrior, greater dispersal of troops and fighting in urban settings and on non-linear battlefields, the likelihood of longer evacuation times for combat casualties is suggested. As a consequence of these conditions and the logistic limitations of weight and cube, fluid resuscitation research within the Army's Combat Casualty Care Research Program is focused to investigate limited- or small-volume fluid resuscitation strategies, including permissive hypotension, in far-forward areas for the treatment of severe hemorrhage. The goals are to improve battlefield survival and to reduce or prevent early and late deleterious sequelae. Utilizing both anesthetized and conscious large (swine) and small (rodent) animal models, current efforts are focused on evaluating available crystalloid and colloid fluids such as lactated Ringer's, Hespan and Hextend. In addition, other studies are evaluating hemoglobin therapeutics as well as hypertonic/hyperoncotic fluids. Preliminary data suggest that colloid containing fluids offer volume sparing effects over standard isotonic crystalloids, but under these animal model conditions, no obvious advantage of an oxygen-carrying fluid has been observed. Studies to evaluate limitations of hypertonic fluids under these conditions are currently in progress. As there are little data available on the consequences of permissive hypotension coupled with longer evacuation times for the military, these studies have important implications towards the development of optimal fluid resuscitation strategies for stabilization of the combat casualty.*

## 1.0 INTRODUCTION

Acute hemorrhage accounts for about 50% of battlefield deaths in conventional warfare, and for 30% of casualties who die from wounds [1]. Overall these data estimate that 65% to 80% of casualties may require some amount of fluid. In addition, lessons learned by the British in the Falkland Islands War, the Israelis in their past conflicts and the Indians in their Northern India military skirmishes, confirmed that prompt resuscitation improves survival [2,3]. In a recent consensus conference, Butler et al. [4] recommended fluid resuscitation for anyone who was unconscious (suggesting a systolic blood pressure less than 50 mmHg) or for any casualty with a change in mental status.

[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.

*Paper presented at the RTO HFM Symposium on "Combat Casualty Care in Ground Based Tactical Situations: Trauma Technology and Emergency Medical Procedures", held in St. Pete Beach, USA, 16-18 August 2004, and published in RTO-MP-HFM-109.*

# Report Documentation Page

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| **01 SEP 2004** | **N/A** | **-** |

| 4. TITLE AND SUBTITLE | 5a. CONTRACT NUMBER |
|---|---|
| **Permissive Hypotension Strategies for the Far-Forward Fluid Resuscitation of Significant Hemorrhage1** | 5b. GRANT NUMBER |
| | 5c. PROGRAM ELEMENT NUMBER |
| 6. AUTHOR(S) | 5d. PROJECT NUMBER |
| | 5e. TASK NUMBER |
| | 5f. WORK UNIT NUMBER |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br>**U.S. Army Institute of Surgical Research, San Antonio, TX 78234**<br>**2Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA** | 8. PERFORMING ORGANIZATION REPORT NUMBER |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | 10. SPONSOR/MONITOR'S ACRONYM(S) |
| | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) |

12. DISTRIBUTION/AVAILABILITY STATEMENT
**Approved for public release, distribution unlimited**

13. SUPPLEMENTARY NOTES
**See also ADM001795, Combat Casualty Care in Ground-Based Tactical Situations: Trauma Technology and Emergency Medical Procedures (Soins aux blessés au combat dans des situations tactiques : technologies des traumas et procédures médicales durgence)., The original document contains color images.**

14. ABSTRACT

15. SUBJECT TERMS

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | |
| **unclassified** | **unclassified** | **unclassified** | **UU** | **10** | |

**Standard Form 298 (Rev. 8-98)**
Prescribed by ANSI Std Z39-18

It is well recognized that limitations exist in providing fluid resuscitation to the injured in far-forward combat environments. Weight and cube limitations restrict the availability of large volumes of crystalloid resuscitation fluids for far-forward use, and there can be significant time delays and failure rates in obtaining intravenous access of peripheral veins. All the above are coupled to the noise and confusion of battle. To compound the problem, evidence from experimental animals suggests that interventions to re-establish homeostasis may need to be initiated within 30 minutes after injury to assure survival, [5] offering additional challenges to attempts to improve survival on the battlefield.

Future combat scenarios under the objective (future) force where the troops are more dispersed, imply that evacuation times of casualties will be prolonged. Evacuation times that exceed 24 hr may be common, particularly if from urban environments, as was learned in Somalia [6]. It has even been suggested that the time until air evacuation from battlefields of the future could approach 96 hours. Special operations forces currently operate under the assumption that evacuation of casualties may not be possible for up to 72 hours. Taken together, the implication is that at a minimum, several hours may pass before any surgical intervention is possible to treat the injured soldier. As indicated by Bellamy, [1] mortality increased from 20% to 32% when evacuation times of casualties was increased from immediately to 24 hours. Although his data did not extend beyond 24 hours, the mortality rate would be expected to continue to rise beyond this point, but whether this rise would be linear or exponential, is unknown.

## 2.0 PERMISSIVE HYPOTENSION

Based on this information, one of the goals of the US Army's Combat Casualty Care program is to develop a strategy to improve field fluid resuscitation for the treatment of significant hemorrhage in combat casualties expecting longer evacuation times and limited availability of resources. The concept of permissive hypotension, or fluid resuscitation to a blood pressure lower than normal, as a far-forward treatment strategy for special operations forces grew out of a workshop held at the 1998 Special Operations Medical Association meeting[4] but, permissive hypotension was recognized as a reasonable approach in the care of combat casualties in both World Wars I and II [7,8]. Thus, permissive hypotension remains a logical choice for far-forward resuscitation of casualties.

Until very recently, the standard practice for trauma resuscitation in civilian urban setting s involved the infusions of large volumes of fluids to try to normalize blood pressure. Today, this practice is being challenged, especially for treating hemorrhagic-shock victims with penetrating injuries [9,10]. Even for blunt trauma patients, the wisdom of rapid volume infusion is being questioned [11]. It has been argued that resuscitation to baseline or normal blood pressure can increase bleeding and worsen outcome because of severe hemodilution and disruption of newly forming blood clots. Thus, it is hoped that permissive hypotensive resuscitation can improve outcome, yet avoid these adverse hemostatic effects [9,10,12,13]. For example, studies in experimental animals have shown that in the treatment of uncontrolled hemorrhage from a vascular injury, restoring blood pressure to 40 or 60 mmHg resulted in longer survival compared to animals resuscitated to the baseline mean arterial pressure of 80 mmHg or animals that received no fluid [14,15]. Providing some fluid even before surgical repair of the injury, also appeared to produce better outcomes than delaying all fluid until after surgery [14]. Recently, a study in our laboratory showed that fluid resuscitation with lactated Ringer's (LR) to a mean arterial pressure (MAP) of 70 mmHg in rats improved hemorrhage-induced vascular hyporeactivity to norepinephrine better than LR resuscitation to baseline MAP during the 4-hr study period [16]. Rats were anesthetized and hemorrhage to a MAP of 50 mmHg for 60 min. This degree of hemorrhaged corresponded to about 19 + 2 ml/kg body weight. The rats were then resuscitated with different fluids (Table 1) to achieve and maintain a MAP of 70 mmHg and monitored for up to 4 hr or until

death. An additional group received LR infusion to return MAP to pre-hemorrhage levels. Resuscitation to baseline MAP with LR resulted in severe hemodilution and deterioration of vascular responsiveness to norepinephrine.

**Table 1: Infusion volume of each fluid to maintain MAP of 70 mm Hg after hemorrhage in rats[1]**

| | LR[2] | HS-LR[3] | Hespan | Hextend | LR-BL[4] |
|---|---|---|---|---|---|
| Volume infused (ml/kg) | 156±23 | 100±14* | 17±2* | 24±5* | 399±30* |

[1]Data expressed as mean ± SEM of n=7/group
[2] Lactated Ringer's group
[3] 5% Hypertonic saline during first hr and LR thereafter
[4] LR resuscitation to baseline MAP

*P<0.05 as compared to the LR group

Nevertheless, the adequacy of hypotensive fluid resuscitation has recently been questioned. For example, studies have suggested that hypotensive crystalloid resuscitation to a MAP of 60 to 70 may be inadequate to prevent metabolic derangements associated with hemorrhagic shock [17,18]. It should be noted that over the last decade of research into hypotensive resuscitation, the majority of these studies have only followed animals for a few hours and LR or normal saline has been the primary fluid evaluated [19,20]. However, a study in rats, [14] pigs, [15] and dogs [21] have now included an observation time of 72 hours or longer after a hypotensive period. Since not all animals in the hypotensive resuscitation groups survived in some of these studies, further investigation warrants use of different fluids, resuscitation to a higher blood pressure, or resuscitation to better physiologic endpoints in an attempt to improve outcome. The limits of permissive hypotension as a fluid resuscitation strategy remain unknown.

## 3.0 SMALL VOLUME RESUSCITATION

To compensate for the logistic problems of providing enough crystalloid fluids on the battlefield to resuscitate the injured soldier adequately, the U.S. Army initiated studies to investigate the potential efficacy of resuscitation fluids that could be effective in small volumes. This led to an extensive effort to evaluate 7.5% NaCl/6% Dextran-70 (HSD). Results from pre-clinical and clinical studies have shown that HSD could be at least as effective as LR for the treatment of significant hemorrhage [22-27] In experimental animals resuscitated from a controlled hemorrhage with a bolus dose of HSD, the volumes required were only 1/10-1/12 the volume of LR to achieve similar hemodynamic effects [22-24]. The differences in volume requirements of various fluids are illustrated in Figure 1. The premise here is that for treating a 1L blood loss, 3L of LR would be the standard fluid resuscitation strategy. In contrast, only 1L of a colloid solution such as Hextend (illustrated) or Hespan would be required. Combining a colloid with a hypertonic crystalloid further reduces the fluid requirement such that only a 250 ml bag of HSD (illustrated) would provide similar resuscitation as the 3L bag of LR. The implication of this research strategy on reducing the logistic burden on the battlefield is obvious and potentially offers a wider range from hypotensive resuscitation to full restoration of baseline blood pressure, but with much smaller volumes.

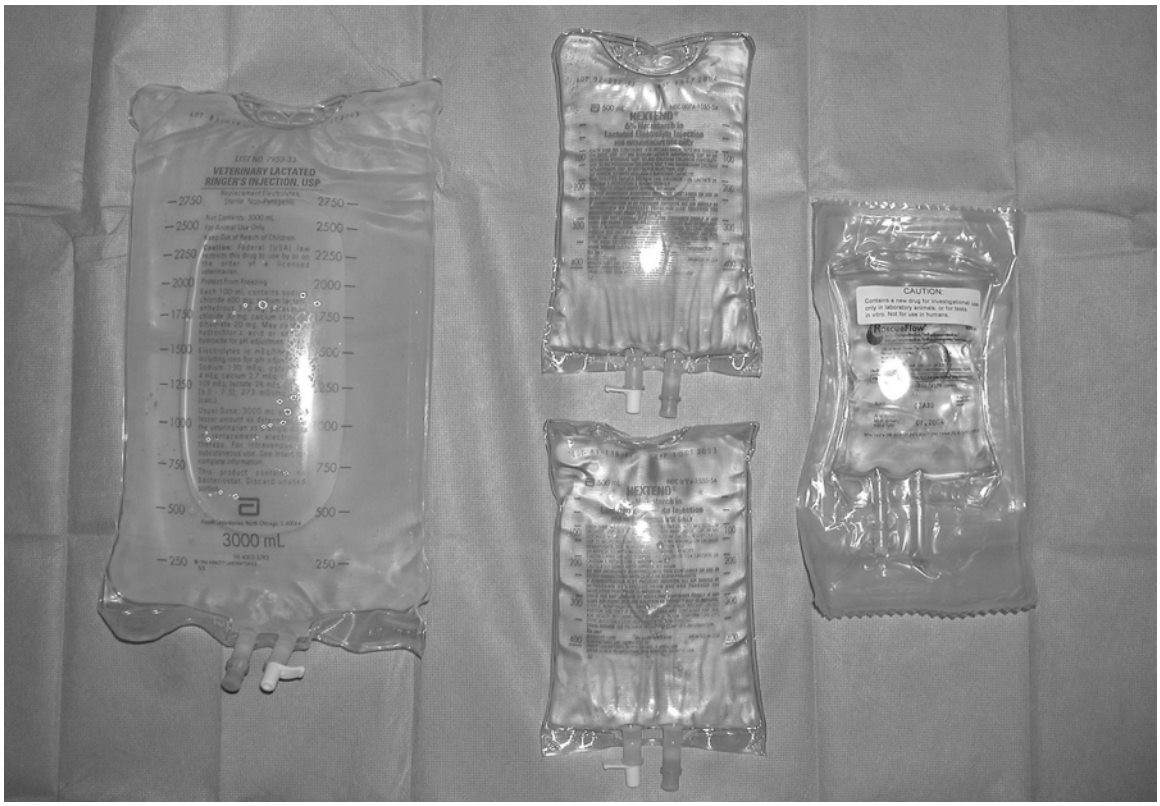


**Figure 1: Theoretical fluid volume requirements to achieve equal resuscitation after a 1L blood loss. Pictured are a 3L bag of LR, 2-500 ml bags of Hextend and a 250 ml bag of HSD.**

The treatment of significant hemorrhage requires fluid resuscitation, but it is recognized that the presence of hypotension, environmental and tactical conditions, limited expertise of the medic and/or the presence of mass casualties can lead to significant time delays and failures in gaining access to peripheral veins in the far-forward combat arena. Based on evidence to suggest that intraosseous (IO) infusion is a viable route for the emergency injection of drugs and fluids [28] and that the technique was easy to learn by military first responders,[29] the US Army, through in-house research activities and outside contracts, has examined the intraosseous route as an alternative means of infusing resuscitation fluids for the treatment of hemorrhagic hypotension in experimental animals [2,30-32]. These studies have focused on HSD and have observed that a single dose of HSD induced essentially identical hemodynamic effects through the IO route as the IV route [30-32]. In addition, where studies with IO infusion of isotonic crystalloids indicated that such administration could not resuscitate from hemorrhagic hypotension in a timely manner, [33] IO administration of HSD could be effective [31,32].

A pilot study was initiated to determine whether HSD, infused through the IO route, could be used in the context of permissive hypotension to resuscitate animals subjected to an uncontrolled hemorrhage [34]. Anesthetized, splenectomized animals were bled 25 ml/kg (about 37% of estimated blood volume) from the femoral artery over a 30 minute period. An uncontrolled hemorrhage was induced by pulling the aortotomy

wire, and the animal was left undisturbed for 15 minutes. Fluid resuscitation with HSD or LR was initiated through an IO sternal access device until a systolic blood pressure of 70 mmHg was achieved. Pressure was maintained at this level with the appropriate fluid over a 2-hour experimental period. The preliminary results of these studies indicated that the volume of HSD required to maintain systolic blood pressure at 70 mmHg was less than 10% of the volume of LR needed, similar to the data obtained with bolus infusions of HSD [23,24]. Although the IO technique appears relatively safe, [2,28,32] the safety of multiple infusions of hypertonic fluids has not been established [35].

## 4.0 CURRENT STUDIES

Currently in our laboratory, hypotensive resuscitation research has expanded to evaluate US FDA-approved fluids or other investigational products. In one study, anesthetized, splenectomized swine were hemorrhaged 20 ml/kg over a 4 min 40 sec period followed by an additional 8 ml/kg after a 30 min compensation period. The second hemorrhage was over the same time period and each hemorrhage period duplicated the blood loss profile of an uncontrolled aortotomy hemorrhage. Thus, the model mimics an uncontrolled hemorrhage, yet retains the reproducibility of a controlled hemorrhage. Also, this model is lethal if left untreated. Fluid resuscitation was begun 30 minutes after the first hemorrhage. The second hemorrhage was then begun to mimic rebleeding that may occur with resuscitation. Fluid resuscitation is continued as needed to achieve and maintain a systolic blood pressure of 80 mmHg. Animals were monitored for 3 hr after the start of fluid infusion or until death. Figure 2 illustrates preliminary results comparing LR resuscitation versus no treatment on blood pressure in these animals [36]. Of note, resuscitation with lactated Ringer's (LR) to a systolic blood pressure of 80 mmHg resulted in 75% survival from an otherwise lethal hemorrhage, and the volumes required were 3.4 times the shed blood volume, exceeding the typical 3:1 ratio of resuscitation fluid to blood volume loss often used in standard resuscitation. These results suggest that in hypotensive resuscitation, crystalloid fluid alone may be insufficient to properly resuscitate from severe hemorrhage. Other fluids under evaluation in this study include Hespan and Hextend as colloids, and a hemoglobin therapeutic as an oxygen carrier. It should be noted that Hextend is now carried by special forces medics. One of the goals of this study was to evaluate whether any of these fluids, when used in hypotensive resuscitation, was superior in improving hemodynamic and metabolic responses to severe hemorrhage. Preliminary results in table 2 show the volumes of the different fluids necessary to achieve and maintain a systolic blood pressure of 80 mmHg, and illustrates the expected volume sparing effects of colloids compared to a crystalloid. However, these colloids resulted in similar survival rates as LR in these experiments. As described above, similar volume sparing effects of colloids were observed in table 1 to maintain MAP at 70 mmHg after hemorrhage in rats.[16] In addition, there are parallel studies using these fluids in conscious pigs and rats to evaluate the effects of permissive hypotension for up to 24 hr. In the conscious pig model chronically instrumented, splenectomized pigs are hemorrhaged 37 ml/kg following the same uncontrolled hemorrhage profile described above. In this model, fluid resuscitation begins 10 min after hemorrhage and continues to achieve and maintain a systolic blood pressure of 80-82 mmHg. After 24 hr, the animals receive their shed blood back and are allowed to recover. Animals are monitored for up to 72 hr after start of resuscitation or until death to begin to evaluate potential complications of prolonged hypotensive resuscitation. In the conscious rat model, animals are hemorrhaged to 40 mmHg (MAP) and held there for 30 minutes. At this point they are given fluid as required to raise their MAP to 60 mmHg and they are given fluid as required to stay above this level for an additional 4 hours. Thereafter they are given sufficient fluid to raise their MAP to 80 mmHg and they are monitored for an additional 20 hours.

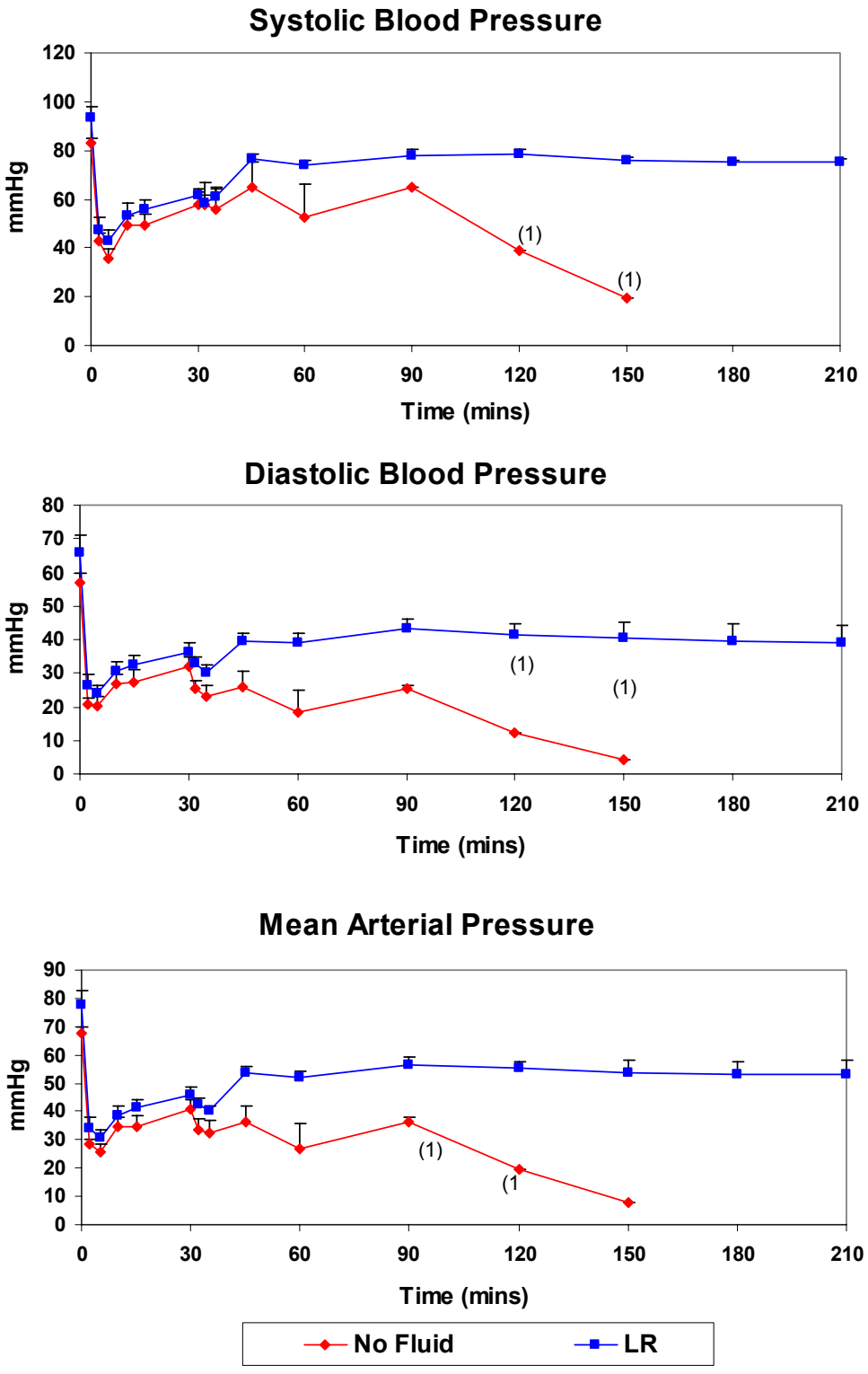


**Figure 2: Systolic, diastolic and mean arterial pressure in hemorrhaged swine receiving either no treatment or fluid resuscitation with lactated Ringer's (LR). Data represent mean ± standard error for 3-5 animals per group.**

**Table 2: Infusion volume of each fluid to maintain systolic blood pressure of 80 mmHg after hemorrhage in pigs**[1]

| | No Resuscitation | LR[2] | Hespan | Hextend |
|---|---|---|---|---|
| Volume infused (ml/kg) | 0 | 88.8±17.7 | 33.2±16.3* | 33.6±9.7* |

| | 5% NaCl | HSD[3] | HBOC[4] |
|---|---|---|---|
| Volume infused (ml/kg) | 16.0±5.9* | 10.4±2.8* | 29.7±0.8* |

[1]Data expressed as mean ± SEM of n=2-5/group

[2] Lactated Ringer's group

[3] Hypertonic saline dextran

[4] Hemoglobin oxygen carrier fluid

* p< 0.05 from lactated Ringer's group

## 5.0 CONCLUDING REMARKS

Current studies now investigate fluid resuscitation practices under the concept of permissive hypotension. However, much remains to be investigated to determine the optimal fluid that can be used in small volumes, yet improve outcomes even in situations where definitive care is delayed for many hours after injury. It is interesting to note that after years and resuscitation of thousands of patients for the treatment of hemorrhage, little reliable evidence exists to suggest how much fluid to give or the clinical endpoints to guide resuscitation [37]. Although the results of some animal studies seem promising, the long-term effects of permissive hypotension and the lasting superiority of one type of fluid over another are unknown. To this end, other studies under the Resuscitation task area of the Combat Casualty Care research program investigate the genetic responses to hemorrhage and resuscitation. Employing state-of-the-art microarray technology, these studies use genomics to evaluate the metabolic consequences of hemorrhage to provide a better understanding of the potential complications of prolonged hypotensive resuscitation, and to provide potential ways to recognize casualties that are not tolerating the prolonged hypotension. Other studies are also aimed at the early recognition of casualties that may require alternative resuscitation strategies or priority evacuation from the battlefield. In addition, working under the premise that hemorrhagic shock results in complement activation, preliminary studies in our laboratory suggest that early use of a complement inhibitor may reduce fluid needs and improve outcome in hemorrhaged rats [38]. Although evidence suggests that resuscitation to a systolic blood pressure of 80 mmHg may be inadequate to improve cerebral perfusion after head injury, [39,40] the addition of adjuncts or a "designer" fluid might improve outcome when used with permissive hypotension. As noted, to date most fluid resuscitation studies evaluating permissive hypotension have generally utilized crystalloids such as LR or normal (physiologic) saline. Recently, Burris et al. [41] suggested that at least short term outcome can be improved by resuscitating to a lower blood pressure with a hypertonic saline-hetastarch fluid than with LR.

## 6.0 SUMMARY

In summary, research in our laboratory over the years with HSD and the IO administration route, as part of the Combat Casualty Care fluid resuscitation task area, suggest that innovative means can be explored in resuscitating injured soldiers from severe hemorrhage in the far-forward combat environment. It is anticipated that our research in the area of permissive hypotensive resuscitation will help identify therapeutic windows and complication rates with currently available fluids. The successful implementation of hypotensive resuscitation strategies for far-forward treatment of severe hemorrhage will conserve the limited resources available, decrease rebleeding complications and improve the likelihood that injured soldiers will reach medical treatment facilities, thereby reducing the number killed in action.

## 7.0 REFERENCES

1. Bellamy RF. The causes of death in conventional land warfare: Implications for combat casualty care research. *Mil Med.* 1984; 149:55-62.

2. Dubick MA and GC Kramer. Hypertonic saline dextran (HSD) and intraosseous vascular access for the treatment of hemorrhagic hypotension in the far-forward combat arena. *Annals Acad Med Singapore.* 1997; 26:64-69.

3. Mehrotra M, Mehrotra S. Provisions of trauma resuscitation and anesthesia service in an advance field military hospital in northern India. *Trauma Care J* 2002;12:18-21.

4. Butler FK, Hagmann JH, Richards DT. Tactical management of urban warfare casualties in special operations. *Mil Med.* 2000; 165(suppl 1):1-48.

5. Nelson AW, Swan H. Hemorrhage: Responses determining survival. *Circ Shock.* 1974; 1:273-285.

6. Mabry RL, Holcomb JB, Baker A, et al. US Army Rangers in Somalia: An analysis of combat casualties on an urban battlefield. *J Trauma*. 2000;49:515-529.

7. Cannon WB, Fraser J, Cowell EM. The preventive treatment of wound shock. *JAMA.* 1918; 70:618.

8. Beecher HK. Preparation of battle casualties for Surgery. *Ann Surg* 1945; 121:769-792.

9. Bickell WH, Waal MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *New Engl J Med.* 1994; 331:1105-1109.

10. Shoemaker WC, Peitzman AB, Bellamy R, et al. Resuscitation from severe hemorrhage. *Crit Care Med.* 1996; 24:12S-23S.

11. Hambly PR, Dutton RP. Excess mortality associated with the use of a rapid infusion system at a level 1 trauma center. *Resuscitation* 1996;31:127-133.

12. Dries DJ. Hypotensive resuscitation. *Shock.* 1996; 6:311-316.

13. Owens TM, Watson WC, Prough DS, Uchida T, Kramer GC. Limiting initial resuscitation of uncontrolled hemorrhage reduces internal bleeding and subsequent volume requirements. *J Trauma.* 1995; 39:200-207.

14. Capone AC, Safar P, Stezoski W, Tisherman S, Peitzman AB. Improved outcome with fluid restriction in treatment of uncontrolled hemorrhagic shock. *J Am Coll Surg.* 1995; 180:49-56.

15. Stern SA, Wang X, Mertz M, et al. Under-resuscitation of near-lethal uncontrolled hemorrhage: Effects on mortality and end-organ function at 72 hours. *Shock.* 2001; 15:16-23.

16. Liu L-M, Ward JA, Dubick MA. Effect of crystalloid and colloid resuscitation on hemorrhage-induced vascular hyporesponsiveness to norepinephrine in the rat. J Trauma. 2003 54(5 Suppl):S159-168

17. Michell MW, Rafie AD, Shah A, et al. Hypotensive and normotensive resuscitation of hemorrhagic shock with Hextend or lactated Ringers (LR). *Crit Care Med* 2003;12(Suppl):A41.

18. Wu X, Stezoski J, Safar P, Tisherman SA. During prolonged (6 h) uncontrolled hemorrhagic shock (UHS) with hypotensive fluid resuscitation, mean arterial pressure (MAP) must be maintained above 60-70 mmHg in rats. *Crit Care Med* 2003;12(Suppl):A40.

19. Stern SA, Dronen SC, Birrer P, Wang X. Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. *Ann Emerg Med.* 1993; 22:155-163.

20. Kowalenko T, Stern S, Dronen S, Wang X. Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. *J Trauma.* 1992; 33:349-362.

21. Siegel JH, Fabian M, Smith JA, Kingston EP, Steele KA, Wells MR. Oxygen debt criteria quantify the effectiveness of early partial resuscitation after hypovolemic hemorrhagic shock. *J Trauma* 2003; 54:862-880.

22. Smith JG, Kramer GC, Perron P, Nakayama S-I, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscition of bled sheep. *J Surg Res.* 1985;39:517-528.

23. Wade CE, Hannon JP, Bossone CA, Hunt MM, Loveday JA, Coppes RI, Gildengorin VL. Resuscitation of conscious pigs following hemorrhage. Comparative efficacy of small volume resuscitation. *Circ Shock.* 1989; 29:193-204.

24. Hannon JP, Wade CE, Bossone CA, Hunt MM, Loveday JA. Oxygen delivery and demand in conscious pigs subjected to fixed-volume hemorrhage and resuscitated with 7.5% NaCl in 6% dextran. *Circ Shock.* 1989; 29:205-217.

25. Wade CE, Dubick MA, Vassar MJ, Perry CA, Holcroft JW. Plasma dextran concentrations in trauma patients administered hypertonic saline-dextran 70. *Clin Chem.* 1996; 42:779-780.

26. Mattox KL, Maningas PA, Moore EE, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The USA multicenter study. *Ann Surg.* 1991; 213:482-491.

27. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. *Arch Surg.* 1991; 126:1065-1072.

28. Dubick MA, Holcomb JB. Intraosseous vascular access in adults: Current status and military application. *J Spec Ops Med* 2003; 3(2):22-33.

29. Calkins MD, Fitzgerald G, Bentley TB, Burris D. Intraosseous infusion devices: A comparison for potential use in special operations. *J Trauma.* 2000; 48:1068-1074.

30. Dubick MA, JW Pfeiffer, CB Clifford, Kramer GC Comparison of intraosseous and intravenous delivery of hypertonic saline/dextran (HSD) in anesthetized, euvolemic pigs. *Ann Emerg Med.* 1992; 21:498-503.

31. Runyon DE, SP Bruttig, MA Dubick, Clifford CB, Kramer GC. Resuscitation from hypovolemia in swine with intraosseous infusion of a saturated salt-dextran solution. *J Trauma.* 1994; 36:11-19.

32. Kramer GC, Mertens SC, Halvorsen L, Holcroft JW, Perron PR, Gunther RA. Intraosseous infusion of hypertonic saline dextran: Effects on pulmonary function and the histology of bone marrow. *Circ* Shock 1989; 27:348.

33. Hodge D III, Delgado-Paredes C, Fleisher G: Intraosseous infusion flow rates in hypovolemic "pediatric" dogs. *Ann Emerg Med.* 1987; 16:305-7.

34. Watson WC, Ryan DM, Dubick MA, Simmons DJ, Kramer GC. High pressure delivery of resuscitation fluid through bone marrow. *Academic Emerg Med.* 1995; 2:402.

35. Alam HB, Punzalan CM, Koustova E, Bowyer MW, Rhee P. Hypertonic saline: Intraosseous infusion causes myonecrosis in a dehydrated swine model of uncontrolled hemorrhagic shock. *J Trauma* 2002;52:18-25.

36. Dubick MA, Sondeen JL, Szebeni J. Effects of hypotensive resuscitation with lactated Ringers (LR) solution on complement (C) activation after hemorrhage (H) in swine. *FASEB J*. 2003; 17:A1237.

37. Roberts I, Evans P, Bunn F, Kwan I, Crowhurst. Is the normalization of blood pressure in bleeding trauma patients harmful? *Lancet*. 2001; 357:385-387.

38. Szebeni J, Baranyi L, Savay S, Bentley T, Bunger R, Esser D, Smith RA, Gotzeo O, Mongan PD, Alving CR. Complement activation during hemorrhagic shock in pigs and rats: Beneficial effect of complement inhibition with APT070. *Shock* 2004; 21(Suppl):25.

39. Henry S, Scalea TM. Resuscitation in the new millennium. *Surg Clin NA.*1999; 79:1259-1267.

40. Revell M, Porter K, Greaves I. Fluid resuscitation in pre-hospital trauma care: A consensus view. Emerg Med J. 2002; 19:494-498.

41. Burris D, Rhee P, Kaufmann C, et al. Controlled resuscitation for uncontrolled hemorrhagic shock. *J Trauma* 1999;46:216-223.