Blood Pressure at which Rebleeding Occurs after Resuscitation in Swine with Aortic Injury

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Background: The appropriateness of vigorous fluid resuscitation to normal blood pressure following hemorrhage in uncontrolled bleeding has recently been questioned due to the possibility of dislodging clots and exacerbating hemorrhage. To develop a rational blood pressure target that maximizes the metabolic benefits of resuscitation without causing increased blood loss, it was first necessary to determine whether there is a reproducible mean arterial pressure (MAP) at which rebleeding occurs. The purpose of this study was to explore the relationship between the rate and time of resuscitation after injury and the rebleeding MAP in an uncontrolled hemorrhage model.

Methods: Sixty-two anesthetized pigs were instrumented with catheters and splenectomized, and suction tubes were placed in the lateral peritoneal recesses to continuously capture shed blood. With the abdomen open, an aortotomy was made in the infrarenal aorta. At either 5, 15, or 30 minutes after the end of the initial hemorrhage, resuscitation with warmed lactated Ringer's solution was begun at either 100 or 300 mL/min. The rebleeding MAP was determined at the moment blood appeared in the suction tubes.

Results: The average pressure at the rebleeding point for all animals was MAP = 64 ± 2, Systolic = 94 ± 3, and Diastolic = 45 ± 2 mm Hg. The pressure at which rebleeding occurred in this aortotomy model was not affected by either time of resuscitation (5–30 min), nor was the rebleeding pressure affected by the rate (100 vs. 300 mL/min) of resuscitation.

Conclusions: There was a reproducible pressure at which rebleeding occurred in this model of uncontrolled hemorrhage. The optimal endpoint of resuscitation in patients without definitive hemorrhage control would then be below this rebleeding pressure.

Key Words: Hemorrhage, Uncontrolled hemorrhage, Resuscitation, Rebleeding, Trauma, Aorta, Arterial injury, Pig, Porcine.

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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 in 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]

Numerous animal studies of uncontrolled hemorrhage have shown that there is increased blood loss following resuscitation induced by an injury to a blood vessel or organ.[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 before hemorrhage control. Taken together, these studies suggest that resuscitation to a normal blood pressure may not be beneficial when attempted before definitive hemorrhage control. Clots may be dislodged from vascular injuries when the blood pressure is increased leading to further blood loss, hemodilution and death. 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 clear that increased blood loss is associated with increased mortality. To maximize the metabolic benefits of resuscitation without causing increased blood loss and mortality, it is essential to determine whether there is a reproducible point at which rebleeding occurs. The optimal endpoint of resuscitation in patients with truncal injury without definitive hemorrhage control would then be just below this rebleeding point. The purposes of this study were 1) to explore the relationship between a new model of uncontrolled aortic hemorrhage and the rate and time of resuscitation after injury; and, 2) determine whether there was a reproducible mean arterial blood pressure that was associated with the onset of rebleeding.

MATERIALS AND METHODS

All animals were maintained in an Association for Assessment and Accreditation of Laboratory Animal Care International accredited facility. The protocol was approved by the Animal Care and Use Committee of the USAISR. All animals received care in strict compliance with the 1996

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Guide for the Care and Use of Laboratory Animals by the National Research Council.

Surgical Procedure

Immature female Yorkshire cross pigs weighing 40.4 ± 0.4 kg were obtained from a local Class-A dealer (HDH Farms, Boerne, TX, U.S.A.). They were quarantined for two weeks before the experiment. The pigs were fasted overnight before surgery with water available *ad lib*. Animals were premedicated with an intramuscular injection of glycopyrrolate (1 mL/18 kg) and tiletamine-zolazepam (5 mg/kg) and maintained with isoflurane anesthesia in 47 - 49% oxygen and 50% nitrous oxide. Isoflurane was administered at 1.8% to 3.0% pre-injury and reduced to approximately 1.0% to 1.5% at injury, with the level increased during resuscitation, if needed, to maintain a surgical plane of anesthesia. Animal core body temperature was maintained at 37–39°C. Catheters were placed into the carotid artery, femoral artery and vein (8.5 Fr. Side-port/hemostasis valve catheter, Arrow International, Reading, PA). All catheter lumens were kept patent by infusion of normal saline through a uniflow flush device (3 mL/hr, Baxter Healthcare Corp, Irvine CA, U.S.A.) attached to an administration set inserted into a liter bag of saline pressurized at 300 mm Hg. No heparin was used at any time during this study.

As pigs have a contractile spleen, the spleen was removed via a midline laparotomy. The spleen was immediately weighed and the animals infused with warm lactated Ringer's solution at three times the splenic weight to replace the volume of blood contained in the removed spleen. The abdominal organs were inspected for evidence of past or present disease processes.

Experimental procedure

After the instrumentation was completed and stable mean arterial pressure (MAP) was obtained, a 10-minute baseline period was begun and hemodynamic measurements were made. Perforated sleeves (Via-Guard sump suction converter sleeve; SurgiMark, Inc., Yakima, WA, U.S.A.) were laid along the lateral dorsal abdominal walls bilaterally and suction tubes were placed in the sleeves. Preliminary experiments revealed that the suction catheters cleared 95% of the intraperitoneal blood. Blood could thus be suctioned into a canister placed on a balance (SR16000 Mettler Balance; Mettler-Toledo, Highstown, NJ, U.S.A.) and the weight of the blood recorded every 10 seconds. The balance was linked to a computerized data collecting system, providing real time quantification of the amount and rate of bleeding. With retraction of the intestines, the infra-renal aorta was exposed approximately 3 cm rostral to the bifurcation. A hole was then made in the aorta with either a 1.5 or 2.0-mm disposable skin biopsy punch (Acuderm, Inc., Ft. Lauderdale, FL, U.S.A.) or a 2.8-mm aortic-punch (Deknatel, Fall River, MA, U.S.A.). With the punch plugging the hole, the intestines were then restored to their natural position over the injury site. The punch was removed and bleeding was initiated. The weight of suctioned blood was continuously recorded throughout the hemorrhage and monitoring period. The hemorrhage volume per animal weight was calculated as total blood loss (g)/animal weight (kg). The specific gravity of blood was rounded to 1 mL/g for this study and all weights of blood were converted on a 1 g to 1 mL basis.

Treatment Groups

Seventy-six animals were instrumented. Six were excluded from the study due to technical failures (unsatisfactory aortic injury or retained retroperitoneal hematoma precluding the determination of an accurate onset of rebleeding). Five animals were excluded because they died before resuscitation was initiated. Three animals died during the onset of resuscitation before rebleeding: one animal in the 5 minute delay group and one of the two animals in the 30 minute delay group fibrillated during the onset of the resuscitation. The remaining 62 animals were randomly assigned to seven groups of animals. The animals received warm (37°C) lactated Ringers (LR) solution at either 100 or 300 mL/min IV. Resuscitation was begun either at 5, 15, or 30 minutes following the end of the initial hemorrhage at each rate of resuscitation. In addition, there was a group of animals that were hemorrhaged but received no resuscitation. Upon the expiration of the 120-minute observation period, the animal was euthanatized (Euthosol, Delmarva Laboratories, Midlothian, VA, U.S.A.).

In some animals, MAP reached a plateau with LR infusion alone without rebleeding occurring, and then started to decline. At the point where MAP started to decline, the LR infusion was halted and an IV infusion of norepinephrine (NE; Levophed, Winthrop, New York, NY, U.S.A.) was begun at 0.5 μg/kg/min at 3 mL/min with a syringe pump (Model 22; Harvard Apparatus, Holliston, MA, U.S.A.) until rebleeding occurred or until a MAP of 200 mm Hg was obtained. The rate of NE infusion was increased to produce higher MAPs, if required.

Measurements

Arterial blood samples (20 mL) were collected at baseline (-10 min), nadir, and rebleed for lactate (Vitros Chemistry System; Johnson and Johnson, Rochester, NY, U.S.A.), prothrombin time (PT), activated prothrombin time (aPTT), and fibrinogen (Electra 1600C Automatic Coagulation Analyzer; Medical Laboratory Automation, Pleasantville, NY, U.S.A.), complete blood count (CBC, System 9000 Hematology Series Cell Counter; Baker Instruments, Allentown, PA, U.S.A.), whole blood thromboelastogram (TEG, Thrombelastograph Coagulation Analyzer; Hemoscope Corporation, Morton Grove, IL, U.S.A.), blood gases (IL 1400 BG-Electrolyte Analyzer and IL 482 Co-oximeter System; Instrumentation Laboratory, Lexington, MA, U.S.A.), spun hematocrit (Hemostat Centrifuge Model C-70; Braintree Scientific Inc., Braintree, MA, U.S.A.), and plasma protein con-
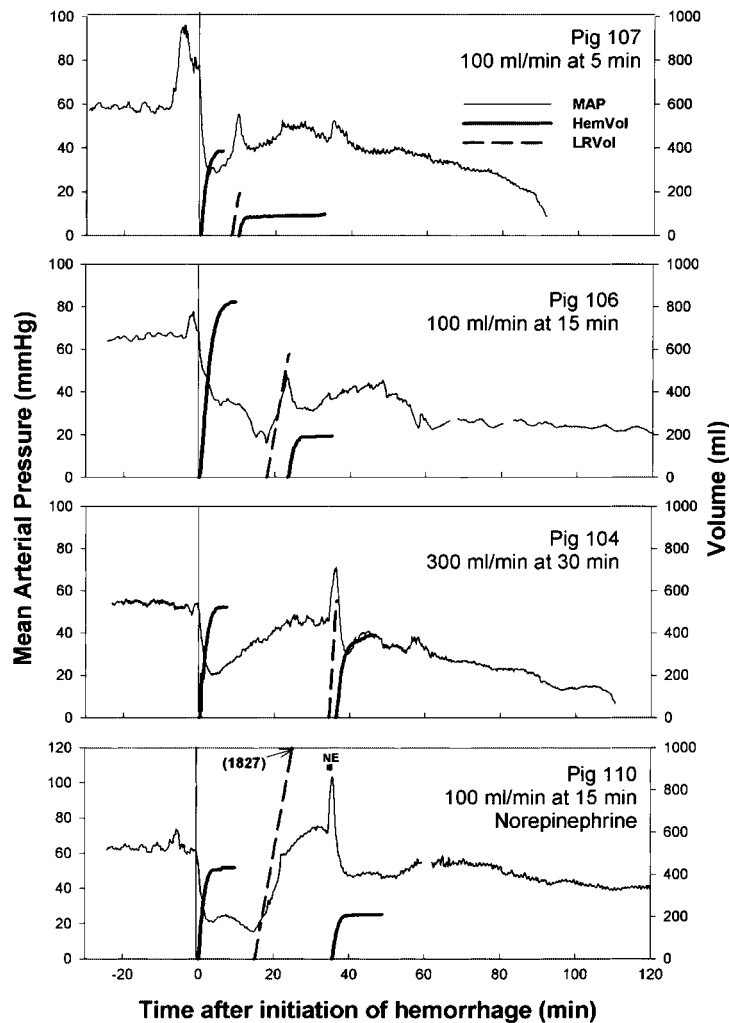
FIG 1. *Resuscitation procedure. Four representative experiments using a 1.5 mm skin biopsy punch are shown. The MAP is the thin black line (left axis). At time 0, the aortotomy is made and the hemorrhage volume is the first heavy black line (right axis). Resuscitation with LR (gray dashed line –right axis) is started either 5 (Pig 107), 15 (Pig 106), or 30 (Pig 104) minutes after the end of the initial hemorrhage. The rebleeding point is determined by when blood appears in the suction tubes (second heavy black line –right axis). In some animals (e.g. Pig 110), LR resuscitation alone only raised MAP to a certain level where it plateaued or started to decline. At that point, LR resuscitation was interrupted and an infusion of NE (0.5 µg/kg/min) was begun at 3 mL/min until rebleeding started, at which time NE was discontinued.*

centration (Refractometer, Reichert Scientific Instruments, Buffalo, NY, U.S.A.).

Carotid artery pressure was recorded using a polygraph (Gould Instruments, Valley View, CA). All analog data were continuously acquired on the MI^2 Modular Instruments, Inc. (Malvern, PA) data acquisition system.

Data Analysis

The data were analyzed by one-, two-, or three-factor analysis of variance with repeated measures on the time factor when appropriate. Student Newman-Keuls tests were used for post-hoc comparisons. Linear regression analyses were performed on the blood volume and survival time as well as on the rebleed pressures versus the pre-resuscitation

pressures. Differences were considered significant at $p <$ 0.05. Data are expressed as means $\pm$ SEM.

RESULTS

Figure 1 shows representative rebleeding experiments at the three times of resuscitation and two resuscitation rates. These figures demonstrate that the time and MAP at which rebleeding was detected is associated with an increase in hemmorhage volume (i.e., second heavy black line) and change in blood pressure. Some animals did not rebleed with LR resuscitation alone, and for those animals NE was infused to increase the pressure to the rebleed pressure (bottom panel of Fig. 1).

Although the punch size affected the initial hemorrhage volume, punch size did not affect the rebleeding MAP (Table

Table 1 Relationship of Punch Size with Initial Hemorrhage Volume

Punch size (mm)	All pigs including non resuscitated		No NE		NE	
	Hem. Vol. (ml/kg)	n	Rebleed MAP (mmHg)	n	Rebleed MAP (mm Hg)	n
1.5	10.5 ± 1.1*	14	62 ± 5	9	126 ± 13	3
2.0	16.6 ± 0.8	38	66 ± 3	20	134 ± 8	12
2.8	19.3 ± 1.4	10	61 ± 5	9	(none)	

NE, norepinephrine.

1). There was no difference among the groups with respect to punch size or initial hemorrhage volume (Table 2), confirming that the different punch sizes were equally distributed among the groups. There was no significant relationship between punch size and rebleed MAP ($R = 0.046$, $p = 0.794$, regression not shown) indicating that although there was a larger initial hemorrhage with the larger two punch sizes, it had no effect on the rebleed pressure.

The duration of active bleeding for the initial hemorrhage until a plateau was reached and no further bleeding occurred were not different among the groups and ranged from 2.8 to 7.2 minutes (Table 2). The groups had unequal sizes (see Table 2) because of the requirement to have at least n = 6 per group in those that did not receive NE and that lived long enough to rebleed.

The purpose of this study was to determine the rebleed pressure at the different combinations of delay (5, 15, and 30 minutes) and rate of resuscitation (100 and 300 mL/min). Figure 2 shows the rebleed systolic, mean, and diastolic pressures associated with each group. The mean and diastolic pressure in the 15-minute delay group at both the 100 and 300 mL/min rates of resuscitation was slightly but significantly lower than the two other delay groups at both rates of LR resuscitation. It was expected that, if the delay time had an effect on the rebleeding pressure, then the rebleeding pressures would increase with the increasing delay time as the clot presumably matured and strengthened. Likewise, if there was an effect of the rate of resuscitation, it was expected that the higher rate would cause rebleeding at a lower blood pressure. However, this did not prove to be the case since neither delay time or resuscitation rate consistently altered the rebleed MAP. Since resuscitation rate and delay time did not affect the rebleeding MAP, the data were therefore pooled

resulting in an average pressure at rebleed, for all animals not receiving NE, of MAP = 64 ± 2, Systolic = 94 ± 3, and Diastolic = 45 ± 2 mm Hg.

The relationship between the pressure at which resuscitation was begun and the rebleeding pressure was explored by performing a linear regression analysis on animals that did not receive NE. Figure 3 shows the scattergram of the rebleed MAP, systolic, diastolic, and pulse pressure against the corresponding pressures at the initiation of resuscitation. There was a significant relationship with the pressure at the initiation of resuscitation and the rebleed pressure, suggesting that the lower the pressure at which resuscitation is initiated, the more susceptible to rebleeding some animals are. Systolic and pulse pressure had stronger correlations than mean pressure. In the 38 animals that bled with LR, there were two animals that rebled at systolic pressures under 70 mm Hg, seven under 80 mm Hg, five under 90 mm Hg, twelve under 100 mm Hg, and twelve greater than 100 mm Hg. Thus, the majority of animals, 76% (83% if the NE animals are included), rebled at systolic pressures higher than 80 mm Hg.

Sixteen animals out of a total of 54 (30%) in the study did not rebleed with LR infusion alone and were treated with NE. One animal treated with NE did not rebleed despite obtaining a MAP of 200 mm Hg. The rebled MAPs for all groups, with and without NE for the rebleeders are shown in Figure 4.

The highest number of deaths before (5 of 5) or with the onset of resuscitation (2 of 3) was in the 30-minute delay group. Forty-nine of seventy animals (including the non-resuscitated animals (n = 8) and those that either that died before or with resuscitation, n = 8) compensated their MAP in the period between the end of hemorrhage and the beginning of resuscitation. All of the animals that died either

Table 2 The Punch Size, Initial Hemorrhage Volume, and the Time the Initial Hemorrhage Lasted (Bleed Time) Averaged Among the Seven Groups

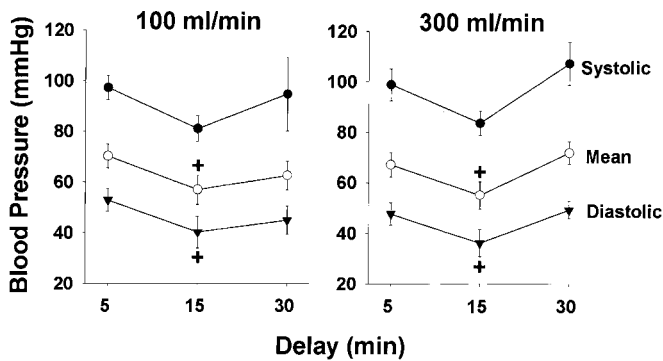| Treatment	n	Punch size (mm)	Hem. Vol. (ml/kg)	Initial Bleed Time (min)
No resuscitation	8	2.0 ± 0.1	15 ± 1	4.8 ± 0.3
100 ml/min at 5 min	10	2.0 ± 0.1	13 ± 2	4.4 ± 0.2
100 ml/min at 15 min	12	2.0 ± 0.1	15 ± 2	5.1 ± 0.3
100 ml/min at 30 min	9	1.9 ± 0.1	13 ± 2	4.4 ± 0.3
300 ml/min at 5 min	8	2.3 ± 0.1	18 ± 2	4.5 ± 0.3
300 ml/min at 15 min	7	2.0 ± 0.1	19 ± 2	5.1 ± 0.4
300 ml/min at 30 min	8	2.0 ± 0.1	17 ± 2	5.2 ± 0.4

FIG 2. *The rebleed systolic, mean, and diastolic pressures in the No NE groups. The mean and diastolic, but not the systolic pressure, at the 15-minute delay time in both the 100 and 300 mL/min rate groups were significantly lower than the 5- and 30-minute times (+p < 0.05).*

before resuscitation or with the onset of resuscitation were not able to compensate their MAP indicating that failure to compensate to a hemorrhage leads to early death. An example of this decompensation can be seen in the second panel in Figure 1. Twelve of the sixteen animals that required NE were ones which had been able to compensate their MAP.

The 300 mL/min rate resulted in a significantly higher volume of LR at the rebleed pressure than the volume with the 100 mL/min rate because the time it took to rebleed was

similar in both groups (Table 3). Those animals that received NE had a significantly higher volume at rebleed and took longer to reach the rebleed MAP (Table 3). However, in those animals, the volume given did not cause the animals to rebleed.

Various indices of coagulation and extent of dilution were measured to determine whether differences were present between those animals that did and did not require NE. There was no correlation of hematocrit, hemoglobin, platelets, fibrinogen, PT, aPTT, plasma protein concentration, arterial lactate, pH, base excess, partial pressure of carbon dioxide, or arterial bicarbonate on rebleed MAP and no difference between those that rebled with LR resuscitation alone and those that required NE (regression data not shown). There was a significant reduction in hematocrit, hemoglobin, protein concentration, fibrinogen concentration, platelet number, maximum amplitude of the TEG, and the base excess at the rebleed point (Table 4) compared with baseline values. Likewise, a significant reduction in the rebleed hematocrit, hemoglobin, and protein concentration at the 300 versus the 100 mL/min resuscitation rate was demonstrated (Table 4). An increase in plasma lactate concentration at the rebleed point compared with the baseline was found (Table 4).

DISCUSSION

The major contribution from this study is the finding that there was a reproducible blood pressure at which rebleeding
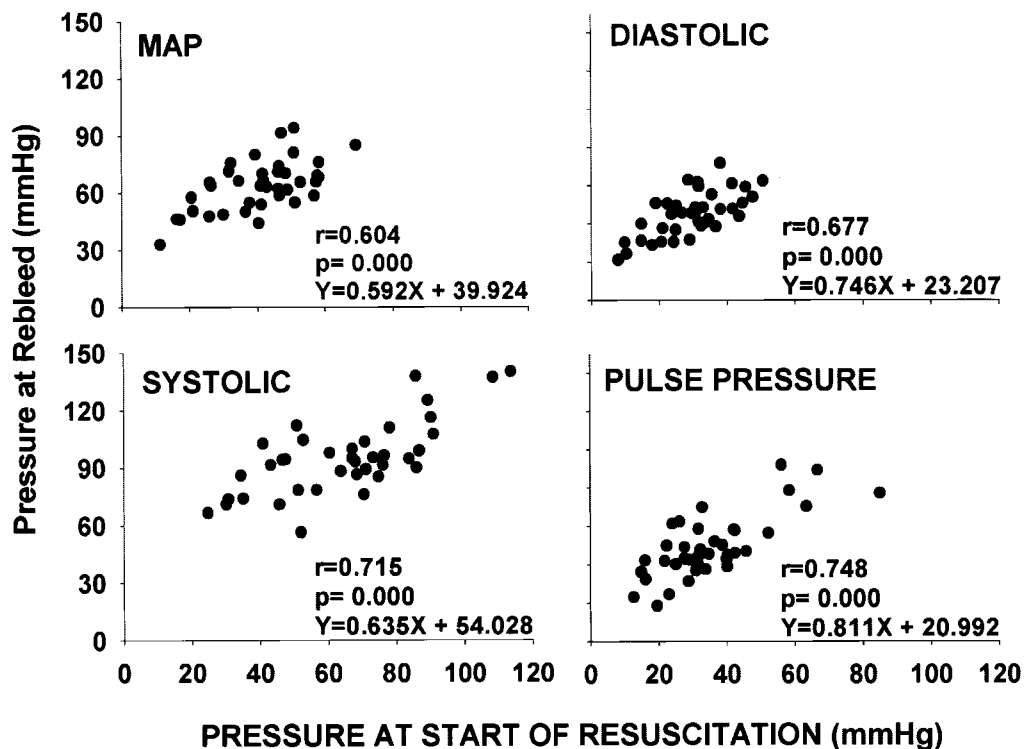

FIG 3. *Scattergram of the mean (top left), systolic (bottom left), diastolic (top right), or pulse pressure (bottom right) plotted against the respective mean, systolic, diastolic, or pulse pressure pressure just before the iniation of resuscitation for each animal. The Spearmans correlation coefficient, significance, and linear regression equation are given for each scattergram.*
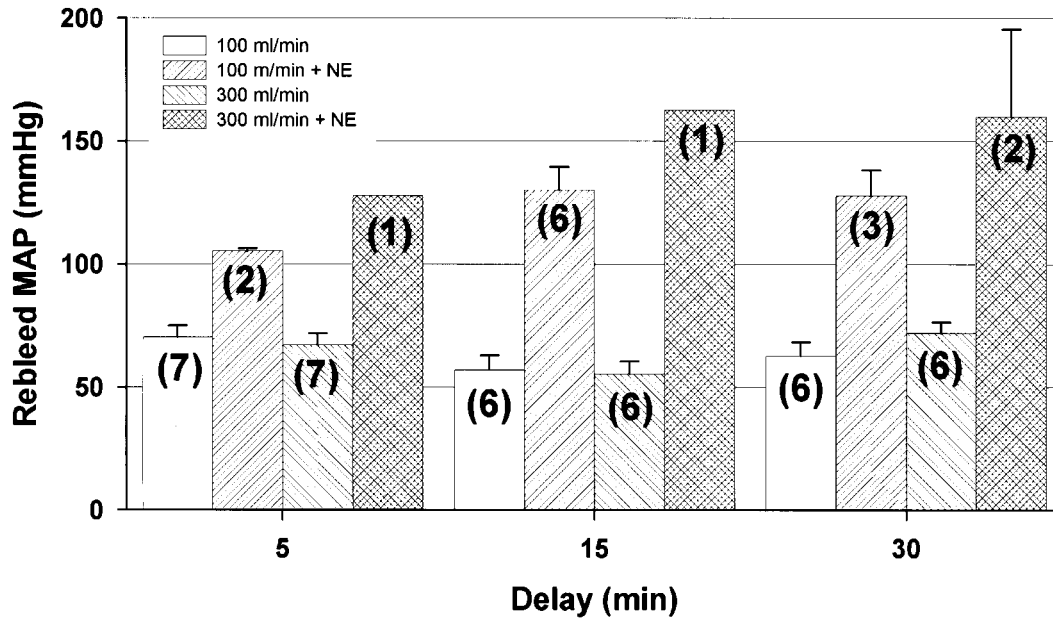
FIG 4. *Rebleed MAP of animals that rebled with LR resuscitation alone and with NE across delay, rate, and ± NE. There was a significant difference (p < 0.001) between NE and No NE groups, but no difference with NE treatment with rate or delay.*

occurred. The rebleed systolic (94 ± 3), mean (64 ± 2), and diastolic (45 ± 2 mm Hg) pressures in the no NE group were similar to those pressures recommended for resuscitation by Walter B. Cannon[22] and Henry K. Beecher[23] in WWI and WWII, respectively. As Beecher wrote: "A further principle that we established is that if surgery cannot be undertaken at once...The patient will not suffer as long as the systolic pressure is 80 mm Hg and the skin warm and of good color. Neither will he lose as much hemoglobin by renewed bleeding as he will if plasma, say, is used to raise the blood pressure higher than necessary during this waiting period..." The rebleeding pressures in this study are also consistent with the results found by other investigators who showed that resuscitation to MAPs of 40 or 60 mm Hg was associated with less rebleeding than full resuscitation to normal baseline MAPs.[4,7] The unique design of the current study permitted

the quantification of blood loss every 10 seconds which allowed for the determination of the blood pressure at which rebleeding occurred. In a recent study by Holmes et al.[11] in which MAP and rebleeding was measured every 5 minutes, rebleeding commenced at comparable pressures to those observed in this study; that is, hemorrhage volume increased when MAP was between 40 and 65 mm Hg in a group which received resuscitation after a 15-minute delay and at a MAP between 44 and 78 mm Hg in a group that received resuscitation after a 30-minute delay. Taken together these studies support the data presented herein of a reproducible rebleeding point. However, it should be noted that the model presented herein is the only model to date specifically designed to determine the pressure at which rebleeding occurs.

The pressure at which rebleeding occurred in this aortotomy model was not affected by either a delay of resuscitation

Table 3 **The Volume of LR at the Point of Rebleeding and the Time Until Rebleeding**

Treatment	NE	LR Vol at Rebleed (ml/kg)	Time to Rebleed (min)
100 ml/min at 5 min	No	19 ± 4	7.7 ± 1.8
100 ml/min at 15 min	No	8 ± 2	3.4 ± 0.6
100 ml/min at 30 min	No	10 ± 2	3.7 ± 0.7
300 ml/min at 5 min	No	27 ± 8*	3.8 ± 1.1
300 ml/min at 15 min	No	19 ± 4*	2.5 ± 0.6
300 ml/min at 30 min	No	23 ± 6*	3.3 ± 1.0
100 ml/min at 5 min	Yes	74 ± 18	49 ± 12
100 ml/min at 15 min	Yes	55 ± 6	25 ± 3
100 ml/min at 30 min	Yes	44 ± 2	21 ± 1
300 ml/min at 5 min	Yes	81	15
300 ml/min at 15 min	Yes	106	20
300 ml/min at 30 min	Yes	96 ± 3	16 ± 1

LR, lactated Ringer's solution; NE, norepinephrine.

Table 4 Variables for Formed Elements and Plasma Protein Concentration, Coagulation Profile, Arterial Plasma Lactate Concentration, Arterial Blood Gases, and Thromboelastogram

Variable	Rate (ml/min)	n	Baseline	Nadir	Rebleed
Hematocrit (%)	100	30	32.9 ± 0.5	31.5 ± 0.5	25.2 ± 0.7*
	300	22	32.0 ± 0.7	29.6 ± 0.9	20.4 ± 0.9*†
Hemoglobin (g/dL)	100	29	11.1 ± 0.2	10.4 ± 0.2	8.1 ± 0.2*
	300	22	10.5 ± 0.3	10.1 ± 0.2	6.6 ± 0.3*†
Protein Concentration (g/dl)	100	28	5.2 ± 0.1	5.1 ± 0.1	3.8 ± 0.1*
	300	20	5.3 ± 0.1	5.0 ± 0.1	3.3 ± 0.2*†
White Blood Cells ($10^3/mm^3$)	pooled	51	15.4 ± 0.8*	11.7 ± 0.7	13.8 ± 0.7
Fibrinogen (mg/dL)	pooled	48	181 ± 6	185 ± 6	136 ± 7*
Platelets ($10^3/mm^3$)	pooled	50	529 ± 20	516 ± 21	396 ± 22*
Prothrombin Time (sec)	pooled	47	11.1 ± 0.2	11.2 ± 0.2	11.6 ± 0.2
Partial Thromboplastin Time (sec)	pooled	29	17.2 ± 0.4	17.4 ± 0.4	17.4 ± 0.4
Lactate (mmol/L)	pooled	51	1.8 ± 0.1	2.1 ± 0.1	5.5 ± 0.3*
PH	pooled	51	7.45 ± 0.01	7.49 ± 0.01	7.37 ± 0.01
PCO2 (mmHg)	pooled	51	43 ± 1	39 ± 1	44 ± 1
HCO3 (mmol/L)	pooled	51	29.5 ± 0.3	28.2 ± 0.3	24.8 ± 0.4
Base Excess (mmol/L)	pooled	51	5.4 ± 0.3	5.1 ± 0.3	−0.1 ± 0.4*
TEG R (mm)	pooled	44	9.6 ± 0.5		10.5 ± 1.1
TEG K (mm)	pooled	43	2.1 ± 0.1		2.4 ± 0.3
TEG MA (mm)	pooled	44	73 ± 1		69 ± 1*
TEG Angle (degrees)	pooled	44	77 ± 1	75 ± 2	
TEG 30 minute Lysis (%)	pooled	44	2.5 ± 0.2	2.1 ± 0.2	
TEG 60 minute Lysis (%)	pooled	43	5.4 ± 0.4		5.3 ± 0.4

TEG, thromboelastogram; R, reaction time; K, clot formation time; MA, maximal amplitude.

(5–30 minutes) or the rate (100 vs. 300 mL/min) of resuscitation. If early clot maturation were a factor in the animal's ability to resist dislodgement of the thrombus, one would expect that the proportion of animals that rebled with LR alone would decrease as the delay time increased, but this did not occur in these animals; this observation is in agreement with other investigators.[10,11,13]

A possible criticism of this study is the use of different punch sizes. However, the finding that punch size had no effect on rebleed pressure, despite the observation that larger punch sizes were associated with larger initial hemorrhage volumes, strengthens the conclusion that there is a reproducible rebleeding MAP, not dependent on only one hole size. Furthermore, the reproducible rebleeding MAP was demonstrated using three different times of resuscitation and two rates of resuscitation.

Delay of resuscitation to 30 minutes resulted in some animals dying before resuscitation was begun. There was an initial compensation of blood pressure that started as soon as the initial hemorrhage stopped at the nadir point in 69% of the animals. The initial hemorrhage was large (23 ± 2 mL/kg) in eight animals and the blood pressure did not compensate, and they died before the 30-minute delay period or before rebleeding occurred, despite receiving resuscitation. The tendency for non-survival of the severely hemorrhaged animals by 30 minutes confirms that early resuscitation is beneficial in those that do not compensate. These incidental findings support the observation that an initially low or a downward trend of systolic blood pressure is an appropriate criterion on which to base triage of scarce resources.[27]

The two rates of resuscitation that were used in the current study were chosen because they represented the most rapid rates that could be achieved on the battlefield, 100 mL/min (2.5 mL/kg/min) with a wrist-sized peristaltic pump and the 300 mL/min (7.5 mL/kg/min) with a pressure bag inflated to 300 mm Hg. The rate used by Holmes et al.[11] was 2 mL/kg/min and they found similar results to ours, in that rebleeding occurred with both a 15- and 30-minute delay in starting resuscitation.

A regression analysis demonstrated a significant correlation between the pressure at the initiation of resuscitation and the rebleeding pressure. Although it is as yet unclear what increases the susceptibility for rebleeding when the initial resuscitation pressure is lower, our study indicates that more care should be taken in resuscitating the more severely hypotensive patient in the uncontrolled hemorrhage situation. Resuscitation strategies (e.g. slow or low volume) that minimize pulse/blood pressure increases may be beneficial in reducing the incidence of rebleeding. Small volume resuscitation to a hypotensive level has been shown to increase survival compared with aggressive resuscitation in a number of studies using uncontrolled hemorrhage models.[4,7,12,14,18,28]

Fifteen percent of animals only demonstrated rebleeding at supra-physiologic MAPs obtained with the administration of NE. When standard coagulation factors and acid/base status were correlated with the rebleeding pressures, no significant covariate was discovered (data not shown). The presence of this subpopulation of animals resistant to rebleeding suggests that an unknown protective mechanism or genetic predisposition may exist for reduced rebleeding.[29]

CONCLUSION

The metabolic benefit of resuscitation after hemorrhagic shock is widely accepted. The question that is currently facing those who are resuscitating patients in the field, ER, and OR is "What is the optimal endpoint of resuscitation?" To maximize the benefits of resuscitation, there first should be no further harm caused. The initial effect of fluid resuscitation is to raise the blood pressure. This rise in blood pressure should not cause further bleeding. We have shown that a MAP of 64 ± 2 is the reproducible bleeding point in a model of uncontrolled hemorrhage model with an aortic tissue defect. These data are consistent with recommendations made by Cannon from WWI and Beecher from WWII. Therefore, we recommend that patients without definitive hemorrhage control should not be resuscitated beyond a MAP of 60 mm Hg or a systolic pressure of 80–90 mm Hg.

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