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Vasopressin, but Not Fluid Resuscitation, Enhances Survival in a Liver Trauma Model with Uncontrolled and Otherwise Lethal Hemorrhagic Shock in Pigs

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Background: **The authors compared the effects of vasopressin *versus* fluid resuscitation on survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs.**

Methods: **A midline laparotomy was performed on 23 domestic pigs, followed by an incision, and subsequent finger fraction across the right medial liver lobe. During hemorrhagic shock, animals were randomly assigned to receive either 0.4 U/kg vasopressin (n = 9), or fluid resuscitation (n = 7), or saline placebo (n = 7), respectively. A continuous infusion of 0.08 $U \cdot kg^{-1} \cdot min^{-1}$ vasopressin in the vasopressin group, or normal saline was subsequently administered in the fluid resuscitation and saline placebo group, respectively. After 30 min of experimental therapy, bleeding was controlled by surgical intervention, and blood transfusion and rapid fluid infusion were subsequently performed.**

Results: **Maximum mean arterial blood pressure during experimental therapy in the vasopressin-treated animals was significantly higher than in the fluid resuscitation and saline placebo groups (mean ± SD, 72 ± 26 *vs.* 38 ± 16 *vs.* 11 ± 7 mmHg, respectively; $P < 0.05$). Subsequently, mean arterial blood pressure remained at approximately 40 mmHg in all vasopressin-treated animals, whereas mean arterial blood pressure in all fluid resuscitation and saline placebo pigs was close to aortic hydrostatic pressure (~15 mmHg) within approximately 20 min of experimental therapy initiation. Total blood loss was significantly higher in the fluid resuscitation pigs compared with vasopressin or saline placebo after 10 min of experimental therapy (65 ± 6 *vs.* 42 ± 4 *vs.* 43 ± 6 ml/kg, respectively; $P < 0.05$). Seven of seven fluid resuscitation, and seven of seven saline placebo pigs died within approximately 20 min of experimental therapy, while 8 of 9 vasopressin animals survived more than 7 days ($P < 0.05$).**

Conclusions: **Vasopressin, but not fluid resuscitation or saline placebo, ensured survival with full recovery in this liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs.**

RESUSCITATION of patients in hemorrhagic shock remains one of the most challenging aspects of trauma care. For the past 20 years, prehospital treatment of hypotensive trauma patients suffering from hemorrhagic shock included crystalloid and colloid solutions to maintain adequate tissue perfusion, and tissue oxygen delivery. Currently there is an ongoing discussion about resuscitation strategies in hemorrhagic shock, such as immediate *versus* delayed fluid resuscitation. For example, Roberts *et al.*[1] recently stated that there is no scientific evidence for the effectiveness of immediate fluid resuscitation in hemorrhagic shock. Also, in a large clinical study with penetrating torso trauma, patients receiving delayed fluid resuscitation had better chances of survival compared with patients receiving immediate fluid resuscitation.[2] Although delayed fluid resuscitation may be beneficial when cardiocirculatory function has not collapsed, this becomes a fundamental dilemma if a trauma patient suffers cardiac arrest at the scene. In this cohort of patients, the current international resuscitation guidelines recommend vasopressors, if pulseless electrical activity or bradyasystolic rhythm is imminent.[3,4]

In a clinical study, Shelly *et al.* reported that vasopressin may be useful for managing patients with massive intraabdominal bleeding.[5] In addition, we showed in a previous study the beneficial effects of vasopressin on short-term survival in a hemorrhagic shock model in pigs[6];however, a limitation of that study was the short postresuscitation observation period of 60 min only. Thus, we were unable to determine if lactate metabolism was working, and whether full recovery would have been possible beyond 1 h. Accordingly, this model was developed to determine the effects of vasopressin *versus* fluid resuscitation *versus* saline placebo on long-term survival. The null-hypothesis was that there would be no differences between groups regarding the study of endpoints.

Materials and Methods

This project was approved by the Austrian Federal Animal Investigational Committee, and the animals were managed in accordance with the American Physiologic Society, institutional guidelines, and Position of the American Heart Association on Research Animal Use, as adopted on November 11, 1984. Animal care and use was performed by qualified individuals, supervised by veterinarians, and all facilities and transportation complied with current legal requirements and guidelines. Anesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted. Our

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animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care.

Surgical Preparations and Measurements

This study was performed on 23 healthy, 12- to 16-week-old swine weighing 30 to 40 kg. The animals were fasted overnight, but had free access to water. The pigs were premedicated with azaperone (4 mg/kg intramuscular, neuroleptic agent, Stresnil™, Janssen, Vienna, Austria) and atropine (0.1 mg/kg intramuscular) 1 h before surgery, and anesthesia was induced with propofol (1 to 2 mg/kg intravenously). After tracheal intubation during spontaneous respiration, the pigs were ventilated with a volume-controlled ventilator (Draeger, EV-A Lübeck, Germany) with 35% oxygen at 20 breaths/min, and with a tidal volume adjusted to maintain normocapnia. Anesthesia was maintained with propofol (6–8 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) and a single injection of piritramide (30 mg, opioid with ~ 4 to 8 h half time, Dipidolor™, Janssen, Vienna, Austria).[7] Muscle paralysis was achieved with 0.2 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} pancuronium after tracheal intubation to facilitate laparotomy. Ringer's solution (6 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}), and a gelatin solution (4 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}, colloid solution including 40 g of gelatin (oncotic active mean molecular weight, Mn = 23200), Gelofusin™, Braun, Melsungen, Germany), was administered in the preparation phase. A standard lead III electrocardiogram was used to monitor cardiac rhythm; depth of anesthesia was judged according to arterial blood pressure, heart rate, and electroencephalography (Engström, Munich, Germany). If cardiovascular variables or electroencephalography indicated a reduced depth of anesthesia, additional propofol and piritramide was given. Body temperature was maintained between 38.0 to 39.0°C.

In addition, nine pigs were used for donation of pig-compatible blood. After induction of anesthesia as mentioned previously, a midline laparotomy was performed, and a needle was advanced into the abdominal aorta in an aseptic manner. Blood was collected in normal blood donation pouches, and leukocytes were subsequently depleted. When mean arterial blood pressure deteriorated and hypovolemic shock was imminent, these pigs were euthanized with an overdose of fentanyl, propofol, and potassium chloride.

In the 23 study animals, an 18-gauge catheter was advanced into the right femoral artery in an aseptic manner for withdrawal of arterial blood samples, and measurement of arterial blood pressure. In addition, a 5-French catheter was advanced into the femoral vein for drug and fluid resuscitation. Arterial blood pressure was measured with a saline-filled catheter attached to a pressure transducer (model 1290A, Hewlett Packard, Böblingen, Germany), that was calibrated to atmospheric pressure at the level of the right atrium; pressure tracings were recorded with a data acquisition system (Dewetron port 2000, Graz, Austria; and Datalogger, custom made software, Peter Hamm, Technician, Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens-University, Innsbruck, Austria). Blood gases were measured with a blood gas analyzer (Chiron, Walpol, MA); end-tidal carbon dioxide was measured using an infrared absorption analyzer (Multicap, Datex, Helsinki, Finland).

Experimental Protocol

After assessing baseline hemodynamic values, a midline laparotomy was performed. Propofol infusion was adjusted to 2 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, and infusion of lactated Ringer's and gelatin solution was stopped before induction of the experiment. An incision (width, 12 cm; depth, 3 cm), and subsequent finger fraction was performed across the right liver lobe. When mean arterial blood pressure was less than 20 mmHg, and heart rate declined progressively for more than 30% of its peak value, pharmacologic support was provided for 30 min to simulate a human prehospital phase before surgical intervention. Twenty-three animals were randomly assigned to receive at the point of experimental intervention (mean arterial pressure $<$ 20 mmHg; heart rate $<$ 30% of its peak value) either 0.4 U/kg vasopressin (Pitressin®, Parke-Davis/Pfizer, Karlsruhe, Germany; n = 9), an equal volume of saline placebo (n = 7), or fluid resuscitation (n = 7; 25 ml/kg Ringer's, and 25 ml/kg 3% gelatin solution), respectively. Pigs receiving vasopressin, fluid resuscitation, and saline placebo were flushed with 20 ml normal saline; subsequently, a continuous infusion of 0.08 U $\cdot$ kg^{-1} $\cdot$ min^{-1} vasopressin, or normal saline at an equal infusion rate was administered in each respective group. Pigs receiving fluid resuscitation received no further drug therapy, but only continuous fluid resuscitation. The investigators were blind to the treatment protocol. After 30 min of experimental therapy, bleeding was controlled by surgical intervention in all hemodynamically stable pigs at that point. Therefore, large liver blood vessels were sutured, and a fibrin adhesive (Tissucol Duo Quick 2 ml, Baxter Hyland Immuno, Baxter, Vienna, Austria) was applied to the bleeding surface. In addition, a transfusion of whole blood (~40 ml/kg) as well as fluid resuscitation (25 ml/kg Ringer's, and 25 ml/kg 3% gelatin solution) was performed in all surviving pigs. When arterial blood pressure, lactate values, acid-base, and metabolic function indicated normalization in the surviving pigs, they were weaned from the ventilator, extubated, and returned to their cages. In these pigs, neurologic evaluation according to a Neurologic Deficit Score[8] was performed 24 h and 7 days after successful resuscitation. Afterward, they were euthanized with an overdose of fentanyl, propofol, and potassium chloride.

Statistical Analysis

Values are expressed as mean ± SD. The comparability of weight and baseline data were verified using one-way

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Table 1. Arterial Blood Gas Variables during Liver Injury

			Experimental Therapy		Fluid Resuscitation	
	Baseline	Hypovolemic Shock	5 min after DA	30 min after DA	15 min	60 min
pH, Units	—	—	—	—	—	—
Vasopressin	7.52 ± 0.03	7.48 ± 0.08	7.44 ± 0.11	7.15 ± 0.11	7.18 ± 0.09	7.36 ± 0.07
Fluid resuscitation	7.49 ± 0.02	7.51 ± 0.07	7.27 ± 0.05*	NA	NA	NA
Saline placebo	7.52 ± 0.02	7.56 ± 0.05	7.57 ± 0.12	NA	NA	NA
$Paco_2$, mmHg	—	—	—	—	—	—
Vasopressin	37 ± 2	28 ± 3	26 ± 7	35 ± 5	39 ± 3	37 ± 2
Fluid resuscitation	38 ± 3	27 ± 6	36 ± 8	NA	NA	NA
Saline placebo	37 ± 2	23 ± 6	15 ± 6†	NA	NA	NA
Pao_2, mmHg	—	—	—	—	—	—
Vasopressin	128 ± 12	157 ± 95	199 ± 161	310 ± 185	256 ± 174	191 ± 118
Fluid resuscitation	140 ± 24	169 ± 22	179 ± 37	NA	NA	NA
Saline placebo	140 ± 15	108 ± 48	124 ± 44	NA	NA	NA

Data shown as mean ± SD.

Baseline, measurements before liver trauma; Hypovolemic Shock, values at the point of experimental intervention (mean arterial pressure < 20 mmHg; heart rate < 30% of its peak value); Experimental Therapy, vasopressin or fluid resuscitation or saline placebo administration without bleeding control; DA, drug administration; NA, not applicable due to death of fluid resuscitation and saline placebo animals.

*$P < 0.05$ for fluid resuscitation *vs.* vasopressin and saline placebo; †$P < 0.05$ for saline placebo *vs*. vasopressin and fluid resuscitation. No statistical comparison was performed after 20 min of experimental therapy due to death of all fluid resuscitation and saline placebo pigs, respectively.

analysis of variance. To identify significant differences during the periods of no therapy and the experimental protocol, repeated measure two-way analysis of variance was used, and if necessary, followed by a Tukey *post hoc* test to indicate the significant differences between the three groups. Survival rates were compared using Fisher exact test, and were corrected with the Bonferroni method for multiple comparisons. Differences with a two-tailed P value of less than 0.05 were considered significant.

Results

After 30 min of uncontrolled bleeding, total blood loss per kg body weight in vasopressin *versus* fluid resuscitation *versus* saline placebo animals was 42 ± 5 *versus* 37 ± 5 *versus* 41 ± 4 ml/kg, respectively (NS). Pharmacologic intervention was started 31 ± 7 min in the vasopressin group *versus* 32 ± 6 and 32 ± 7 min in the fluid resuscitation, and saline placebo group (NS). Arterial blood gas variables were comparable in all groups at baseline and before initiation of experimental therapy (table 1). Lactate values were comparably high (~6.5 mM) in all groups at the time of experimental therapy, indicating tissue hypoxia (table 2). Maximum mean arterial blood pressure during experimental therapy in the vasopressin-treated animals was significantly higher than in the fluid resuscitation and saline placebo groups (mean ± SD, 72 ± 26 *vs.* 38 ± 16 *vs.* 11 ± 7 mmHg, respectively; $P < 0.05$). Subsequently, mean arterial blood pressure remained at approximately 40 mmHg in all vasopressin-

Table 2. End-tidal Carbon Dioxide, Hemoglobin, and Lactate Values during Liver Injury

			Experimental Therapy		Fluid Resuscitation	
	Baseline	Hypovolemic Shock	5 min after DA	30 min after DA	15 min	60 min
$Petco_2$, mmHg	—	—	—	—	—	—
Vasopressin	39 ± 2	13 ± 2	16 ± 3	24 ± 3	38 ± 2	36 ± 2
Fluid resuscitation	38 ± 2	12 ± 2	20 ± 10	NA	NA	NA
Saline placebo	39 ± 1	13 ± 4	9 ± 7†	NA	NA	NA
Hemoglobin, g/dl	—	—	—	—	—	—
Vasopressin	9.1 ± 0.6	8.3 ± 0.7	7.8 ± 0.7	7.1 ± 1.8	6.4 ± 1.2	5.3 ± 0.5
Fluid resuscitation	8.5 ± 1.0	7.8 ± 1.1	3.4 ± 1.0*	NA	NA	NA
Saline placebo	8.4 ± 0.8	7.9 ± 0.6	7.4 ± 0.7	NA	NA	NA
Lactate, mM	—	—	—	—	—	—
Vasopressin	1.3 ± 0.5	7.3 ± 3.2	9.5 ± 3.1	12.7 ± 3.2	10.8 ± 2.9	7.5 ± 3.2
Fluid resuscitation	1.6 ± 0.7	5.3 ± 2.2	9.0 ± 0.7	NA	NA	NA
Saline placebo	1.5 ± 0.4	6.0 ± 3.0	9.2 ± 1.6	NA	NA	NA

Data shown as mean ± SD.

Baseline, measurements before liver trauma; Hypovolemic Shock, values at the point of experimental intervention (mean arterial pressure < 20 mmHg; heart rate < 30% of its peak value); Experimental Therapy, vasopressin or fluid resuscitation or saline placebo administration without bleeding control; DA, drug administration; NA, not applicable due to death of fluid resuscitation and saline placebo animals.

*$P < 0.05$ for fluid resuscitation *vs.* vasopressin and saline placebo; †$P < 0.05$ for saline placebo *vs*. vasopressin and fluid resuscitation. No statistical comparison was performed after 20 min of experimental therapy due to death of all fluid resuscitation and saline placebo pigs, respectively.

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treated animals, whereas mean arterial blood pressure in all fluid resuscitation and saline placebo pigs was close to aortic hydrostatic pressure (~15 mmHg) within approximately 20 min of experimental therapy initiation. Total blood loss did not change in the vasopressin or saline placebo animals, but was significantly higher in the fluid resuscitation group after 10 min of experimental therapy (fig. 1). Hemoglobin levels were significantly lower in the fluid resuscitation group compared with the vasopressin, or saline placebo group 5 min after starting the experimental protocol (table 2). Pigs treated with vasopressin had relatively stable hemodynamic variables during pharmacologic intervention, while cardiocirculatory status in seven of seven fluid resuscitation and seven of seven saline placebo animals deteriorated, and resulted in pulseless electrical activity before surgical intervention was initiated ($P < 0.05$). Nine of nine vasopressin, but no fluid resuscitation or saline placebo animals, could be extubated 7 ± 1.5 h after induction of liver trauma, and were returned to their cages. Neurologic evaluation 24 h after successful resuscitation revealed an unsteady gait in all vasopressin-treated animals with a neurologic deficit score of 10/400. Nine of nine vasopressin pigs were drinking and eating 24 h after successful resuscitation and had normal levels of consciousness, respiratory pattern, and behavior. One of nine pigs died after 48 h because of intraabdominal bleeding that was confirmed by necropsy; the remaining eight pigs had a neurologic deficit score of 0/400 7 days after treatment.

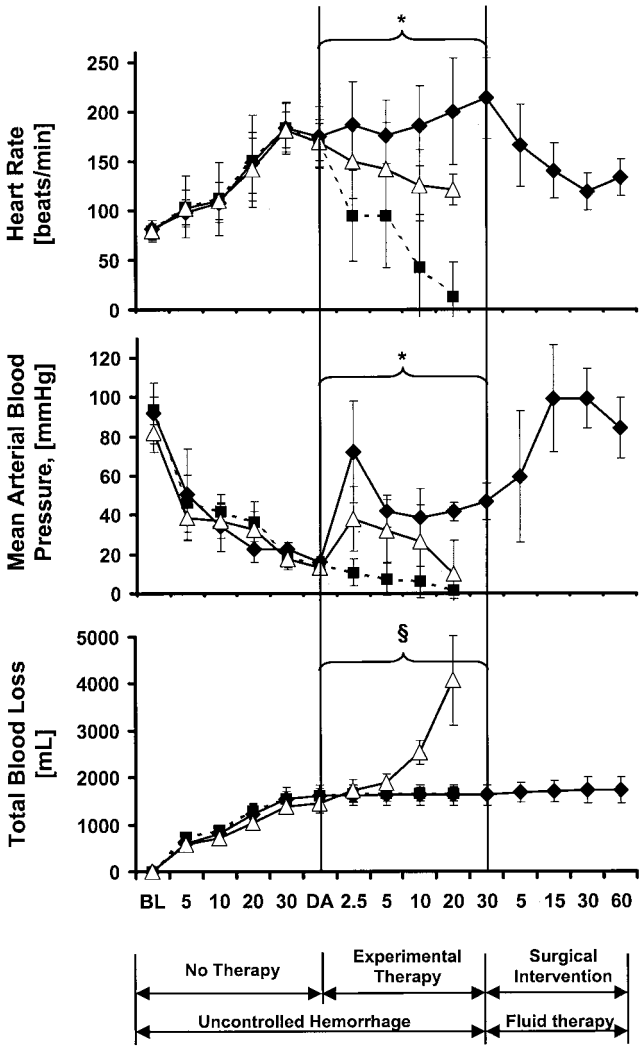

Fig. 1. Mean ± SD heart rate, mean arterial blood pressure, and total blood loss before, during, and after administration of a 0.4 U/kg bolus dose, and 0.08 U · kg^{-1} · min^{-1} continuous infusion of vasopressin (closed diamond, continuous line) *versus* fluid resuscitation (closed triangle, continuous line) with 25 ml/kg lactated Ringer's solution and 25 ml/kg 3% gelatin solution *versus* saline placebo (closed square, dotted line). Uncontrolled hemorrhage = the nonintervention interval after liver injury; experimental therapy = vasopressin or fluid resuscitation or saline placebo administration without bleeding control; surgical intervention = surgical management of the liver lobe to control bleeding; fluid therapy = infusion of lactated Ringer's solution, 3% gelatin solution, and transfusion of blood; BL = baseline; DA = drug administration; *$P < 0.05$ between groups for differences between all groups during the experimental protocol; §$P < 0.05$ for differences between the fluid resuscitation, and vasopressin and saline placebo group during the experimental protocol. No statistical comparison was performed after 20 min of experimental therapy because of death of all fluid resuscitation and saline placebo pigs, respectively.

Discussion

Vasopressin, but not fluid resuscitation or saline placebo, ensured long-term survival with full recovery in this liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. Although cumulating blood loss remained relatively stable at approximately 40 ml/kg in all vasopressin and saline placebo animals during experimental therapy, a significantly higher blood loss of approximately 65 ml/kg was observed in the fluid resuscitation group within 10 min after starting experimental therapy.

The fact that vasopressin, but not fluid resuscitation or saline placebo, increased mean arterial blood pressure in this model may be because of a profound vasopressin-mediated peripheral vasoconstriction *via* V1-receptors in the vasculature, which shifts blood primarily from the skeletal muscle, cutaneous, and splanchnic bed to the heart and brain.[9,10] As shown in both cardiopulmonary resuscitation and hemorrhagic shock studies, vasopressin temporarily impairs he mesenteric artery, and subsequently, portal vein blood flow, while arterial reperfusion of the liver and kidneys was immediately restored.[6,11–13] In a comparable liver trauma model with hemorrhagic shock, mean arterial blood pressure was significantly improved, but no further liver bleeding was observed. Although we measured regional abdominal blood flow in that model,[6] we were unable to determine whether restoration of sufficient cardiocirculatory function would result in long-term survival, since mesenteric artery blood

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flow was temporarily impaired. As such, we observed comparable results in the current study, but could show that vasopressin given during uncontrolled and otherwise lethal hemorrhagic shock resulted indeed in long-term survival with full recovery. Thus, vasopressin may be beneficial when a penetrating injury occurs below the diaphragm, because it simply shifts blood away from the injury and therefore, from the bleeding site. Another beneficial effect may be that exogenously administered vasopressin increases exhausted endogenous vasopressin plasma levels, which was reported to be beneficial during the late phase of hypovolemia with refractory peripheral vascular failure. This was suggested by Morales *et al.*, who identified vasopressin as an uniquely effective vasopressor in the irreversible phase of hemorrhagic shock in dogs that was unresponsive to volume replacement, and catecholamines.[14] Although the physiologic role of vasopressin in the regulation of arterial blood pressure during hemorrhagic shock is still to be identified comprehensively, it was widely accepted that vasopressin is one of the important endogenously released stress hormones; especially during cardiac arrest and vasodilatory shock.[15]

Our observation is in full agreement with recent experimental studies showing that aggressive fluid resuscitation in hemorrhagic shock could worsen bleeding[16,17] caused by impairing the formation of new blood clots, or dislodge existing ones.[18] Although no further blood loss was observed after initiation of experimental treatment in our vasopressin and saline placebo group, we found a sharp increase of total blood loss from approximately 40 to approximately 65 ml/kg in the fluid resuscitation group within 10 min of experimental therapy. Thus, an important adverse effect of fluid resuscitation was increasing blood loss, and significant hemodilution that was unable to meet oxygen delivery requirements. This mismatch in oxygen consumption *versus* oxygen delivery ultimately resulted in rapidly deteriorating mean arterial blood pressure, and subsequently, pulseless electrical activity in fluid resuscitation and saline placebo pigs.

It is surprising that the standard of care fluid resuscitation resulted in death within approximately 20 min after initiation of experimental treatment in this model. Interestingly, it does not seem to matter whether fluid resuscitation increases blood loss resulting in cardiac arrest, or saline placebo not preventing cardiocirculatory collapse. Thus, this time interval of 30 to 60 min after suffering major trauma may reflect in many cases the approximate arrival time in the emergency room, when patients with hemorrhagic shock and collapsing arterial blood pressure can often not be saved despite fundamental efforts. In strong contrast, vasopressin enabled us to maintain arterial blood pressure for an additional 30 min, which may be a significant advantage when arriving in the emergency room and/or operating room with a beating heart, and not while undergoing chest compressions. Quickly after surgical repair and concurrent blood transfusion and fluid resuscitation, blood gas analysis in our vasopressin pigs indicated a development toward normalization, requiring weaning of ventilatory and vasopressor support. Although we did not perform laboratory tests to assess exact organ function and inflammatory response parameters, we did not observe clinical surrogates for organ failure such as kidney failure, or sepsis in the immediate postresuscitation phase, and after extubation. It is further remarkable that full neurologic recovery could be achieved despite the fact that brain perfusion was most likely severely decreased during the liver trauma phase. Whether this is because of preconditioning or enough oxygenation due to an F_{IO_2} of 1.0 during experimental therapy cannot be explained with our data, and should be investigated in future studies.

While nine of nine vasopressin-treated pigs survived for 2 days following the experiment, one of these swine died because of intraabdominal bleeding 48 h after the experiment. It is surprising that we had critical care problems with this single pig only; in a clinical setting our pigs would have received rigorous coagulation monitoring and titration with fresh frozen plasma, and clotting factors. In contrast, we only infused our pigs after surgical intervention 40 ml/kg of whole blood because of a lack of pig-compatible blood products. In our study, laboratory measurements and blood component therapy were by far not equivalent to a human trauma setting; such a level of intervention may have prevented the single vasopressin death.

There are several limitations to this study that should be noted. First, organ blood flow was not measured due to preventing an additional infection source in this study. Second, we were unable to perform coagulation monitoring, and no fresh frozen plasma or clotting factors were administered because of limitations in laboratory and hematology resources. Also, there may be some varieties caused by species differences; for example, different vasopressin receptors in pigs (lysine vasopressin) and humans (arginine vasopressin) may result in a different hemodynamic response to exogenously administered arginine vasopressin. Also, more needs to be known about the effects of vasopressin on the circulation within the liver. The current model reflects fundamental, but local, trauma; whether our experience can be extrapolated to patients with additional trauma such as profound bone injuries should be investigated. In addition, it mimics more a penetrating than a blunt trauma. Also, we do not know the effects of anesthesia, which may be cerebro-protective, on long-term survival in this animal study. Finally, we are unable to determine whether fluid resuscitation and saline placebo pigs could have survived had we initiated surgical management previously.

In conclusion, vasopressin, but not fluid resuscitation or saline placebo, ensured long-term survival with full

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recovery in this liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs.

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