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Improved Survival after Resuscitation with Norepinephrine in a Murine Model of Uncontrolled Hemorrhagic Shock

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Background: **Recent studies have challenged current guidelines on fluid resuscitation. However, studies on resuscitation using norepinephrine in uncontrolled hemorrhagic shock are lacking. The authors examined the effects of norepinephrine in combination with saline infusion in uncontrolled hemorrhage in rats.**

Methods: **Rats subjected to a 15-min controlled hemorrhage (withdrawal of 3 ml blood/100 g body mass) followed by a 60-min uncontrolled hemorrhage (75% tail amputation) were randomly assigned to one of several treatment groups (10 rats/group) receiving different doses of norepinephrine (0 [NE0], 5 [NE5], 50 [NE50], or 500 [NE500] $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$). In the four hypotensive resuscitation groups (n = 40), mean arterial pressure was not allowed to fall below 40 mmHg by titrated infusion of normal saline. In the four normotensive resuscitation groups (n = 40), it was not allowed to fall below 80 mmHg. The endpoint was survival at 210 min.**

Results: **There was a significant difference ($P < 0.05$) in survival rate among groups. Among the hypotensive rats, 6 (60%) survived in the NE0 and NE5 dose groups, 9 (90%) survived in the NE50 dose group, and none survived in the NE500 dose group. Among the normotensive rats, none survived in the NE0 group, 4 (40%) survived in the NE5 dose group, all 10 (100%) survived in the NE50 group, and none survived in the NE500 group.**

Conclusions: **The early use of norepinephrine in uncontrolled hemorrhagic shock in rats significantly improved survival when infused at a rate of 50 $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$ in normotensive and hypotensive resuscitation strategies.**

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RESUSCITATION of patients in hemorrhagic shock remains one of the most challenging aspects of trauma care.[1] Studies have brought current guidelines on fluid resuscitation into question.[2–4] Laboratory and clinical studies have shown that, even if a quantity of fluid should be given in the early treatment of hemorrhagic shock to avoid death from profound hypotension, aggressive fluid resuscitation to achieve normal mean arterial pressure during uncontrolled bleeding significantly increases blood loss, hemodilution, and mortality.[5–7] Delaying fluid administration until operative intervention improved outcome in hypotensive trauma patients with penetrating torso injuries.[2] These authors recommended delaying fluid infusion until bleeding is definitively controlled or until the hypotensive target blood pressure is reached.[2]

Administering vasopressor agents on fluid resuscitation can help rapidly achieve the target blood pressure and limit volume fluid requirements and hemodilution. Recently, vasopressin has been studied in experimental studies in various clinical situations including hemorrhagic shock.[8–14] Vasopressin has proven useful in treating patients with massive intraabdominal bleeding but is not marketed worldwide.[15] Conversely, norepinephrine has been rarely studied in uncontrolled hemorrhagic shock. Available studies are dated and have suggested an increase in mortality.[16–20] However, these studies used a model of controlled and not uncontrolled hemorrhagic shock.[16,17,21]

The aim of the current study was to examine the effects of norepinephrine on short-term survival in a model of uncontrolled hemorrhagic shock in rats.

Materials and Methods

This study complied with the recommendations of the Declaration of Helsinki on animal care, French regulations on the protection of animals used for experimental and other scientific purposes (D2001-406), and European Community regulations (Official Journal of European Community L358 12/18/1986). The study was conducted in an authorized animal care unit (agreement number A-93-008-01) under the supervision of authorized researchers (F.A., M.-P.P.). It was based on a model combining volume-controlled and uncontrolled hemorrhagic shock that has been used in several animal studies, including studies in rats.[7,22,23] As in previously pub-

lished models, our experimental design comprised three phases. Phase 1 (90 min; T0-T90) consisted of a volume-controlled hemorrhagic shock (T0–T30) followed by an uncontrolled hemorrhagic shock (T30–T90), with or without administration of saline, and with or without norepinephrine. Phase 2 (30 min; T90–T120), the recovery phase, consisted in controlling the hemorrhage and resuscitating the animals with shed blood. Phase 3 was a 90-min (T120–T210) observation period.

Surgical Preparations and Measurements

One hundred healthy rats (Elevage Janvier, Le Genest Saint Isles, France) weighing 300–400 g were allowed access to food and water *ad libitum* until the day of surgery, when they were anesthetized by intraperitoneal injection of 35 mg/kg pentobarbital, followed by intramuscular injection of 60 mg/kg ketamine. The spontaneously breathing, anesthetized rats were kept in a supine position on a heating pad to monitor temperature (rectal Thermistor, D-79232; Harvard Apparatus, March-Hugstetten, Germany). Polyethylene catheters (PE-50; Becton-Dickinson, Franklin Lakes, NJ) were introduced into the carotid artery and external jugular vein for arterial blood pressure measurement and intravenous infusion of drug or saline. Continuous monitoring of electrocardiography, blood pressure, and heart rate was performed using a Biopac acquisition device (Biopac® MP30; Biopac Systems Inc., Goleta, CA) run on a Macintosh G4 personal computer (Apple Inc., Cupertino, CA). The arterial line contained a calibrated pressure transducer directly linked to the acquisition system. The femoral artery was isolated through an incision in the right groin and cannulated with a PE-50 catheter for blood withdrawal, sampling, and infusion. Blood samples were drawn at baseline, 30 min, and 90 min to measure hematocrit and blood gases (ABL-500; Radiometer, Copenhagen, Denmark). Blood lactate levels were determined using the I-stat device (Abbott Point of Care Inc., East Windsor, NJ).

Experimental Protocol

The first step of Phase 1 was induction of volume-controlled hemorrhagic shock. Blood was withdrawn at a rate of 1 ml · 100 g^{-1} · 5 min^{-1} through the femoral arterial line from T0 to T15 (total of 3 ml/100 g). At T30, after a 15-min period of equilibration, an uncontrolled hemorrhagic shock was provoked by amputation of the tail at 75% of its length measured from the tip. The bleeding tail was directed into a graduated tube and the amount of blood shed was recorded. Fluid resuscitation started immediately after the tail was cut and was continued for 60 min (T30–T90).

The rats were randomly assigned to one of 10 treatment groups (n = 10 for each group): a control group undergoing no resuscitation; 4 hypotensive resuscitation groups (BP40, n = 40) infused with saline at a rate to prevent mean arterial pressure (MAP) falling below 40 mmHg and infused with norepinephrine in saline at a constant rate of 5 ml · 100 g^{-1} · h^{-1} over 60 min (doses of 0 [NE0, n = 10], 5 [NE5, n = 10], 50 [NE50, n = 10], or 500 [NE500, n = 10] $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$); 4 normotensive resuscitation groups (BP80, n = 40) infused with saline to prevent MAP falling below 80 mmHg and receiving the same norepinephrine doses as the hypotensive rats; or a sham group without hemorrhage and without resuscitation.

Phase 2 began at T90 after the uncontrolled hemorrhagic shock. The tail cut was cauterized and ligated. Intravenous resuscitation was continued for 30 min (T90–T120) with fresh donor blood to achieve a hematocrit value of 30% plus intravenous saline to achieve a MAP above 80 mmHg. Donor blood had been stored in standard citrate phosphate:glucose solution, 1:4. The surviving rats at the end of this phase had their catheters removed and incisions closed. During phase 3, the animals were allowed to recover from the anesthetic and were placed in individual cages with free access to food and water (T120–T210). The endpoint was survival at T210 as in most animal studies on fluid resuscitation strategies.[23]

Statistical Analysis

The rats were randomly assigned to groups using a PLAN procedure (SAS Institute Inc., Cary, NC). Values are expressed as either mean ± 1 SD or median (25th–75th percentiles). To detect a 60% difference in survival (probability 0.8 *vs.* 0.2, power 0.8), the estimated minimum sample size was 10 animals per group. To avoid inflation of α risk due to multiplicity, we used hierarchical procedures for testing differences among groups. We first compared the five groups (controls, fluid + NE0 or NE5, NE50, or NE500) for both the hypotensive and normotensive strategies by a global test at a 0.05 two-sided significance level. If the null hypothesis that the five groups were similar was rejected, we compared each group of treated rats with the control group using appropriate adjustment for multiplicity.

Survival rates were compared using the Fisher exact test. The comparison with controls was made using a significance level of less than 0.0125 (level adjusted for multiplicity by the Bonferroni procedure). For volume of saline and blood loss, groups were compared using nonparametric one-way analysis of variance (*i.e.*, Kruskal-Wallis) because the statistical distribution is non-Gaussian. All tests were performed with use of SAS 9.13 software (from SAS Institute).

Results

Mean physiologic variable values at baseline and at different time points (T0, T30, T90) during the study are given in table 1. Mean baseline weight was 376 ± 61 g.

Changes in MAP are shown in table 2 for each group of rats. After the tail was cut, MAP remained in the 29- to 35-mmHg range in control (no-resuscitation group) rats. In

Table 1. Variable Values at Baseline and at T30 (15-min Volume-controlled Hemorrhage) and T90 (60-min Uncontrolled Hemorrhage)

Variable	Before Hemorrhage, T0	After Equilibration, T30	T90
MAP, mmHg	121 ± 16	38 ± 22	NC
Heart rate, beats/min	402 ± 47	388 ± 70	445 ± 112
Hematocrit, %	40 ± 5	32 ± 4	NC
pH	7.39 ± 0.04	7.27 ± 0.07	7.27 ± 0.07
$Paco_2$, mmHg	47 ± 5	40 ± 9	35 ± 5
Pao_2, mmHg	73 ± 20	84 ± 10	84 ± 10
BE, mM	2.6 ± 1.6	−8.9 ± 3.8	−8.0 ± 6.8
HCO_3, mM	28.3 ± 1.3	17.1 ± 2.7	16.7 ± 2.8
$Sato_2$, %	95 ± 2	95 ± 4	94 ± 2
Blood lactate, mM	1.0 ± 0.3	7.8 ± 1.6	4.8 ± 2.2

n = 10 in each group at T0. Values are expressed as mean ± SD.

BE = base excess; HCO_3 = serum bicarbonate; MAP = mean arterial pressure; NC = mean value was not displayed because there was a significant difference among groups (see text); $Paco_2$ = arterial carbone dioxide pressure; Pao_2 = arterial oxygen pressure; $Sato_2$ = arterial oxygen saturation.

hypotensive rats (BP40 rats; table 2), MAP ranged from 49 to 58 mmHg in the NE0 group and from 54 to 64 mmHg in the NE5 group. In the NE50 group, MAP remained above 80 mmHg for the first 30 min and then decreased to 78 to 81 mmHg over the next 30 min. In the NE500 group, MAP was above 130 mmHg for the first 20 min. However, all the rats in this high dose group died before 90 min. In normotensive rats (BP80 rats; table 2), MAP increased transiently in the NE0 group but, despite aggressive fluid resuscitation, decreased after 30 min, leading to death in all but one rat. This animal's MAP reached 88 mmHg, and the animal survived until the end of phase 2. In the NE5 group, MAP reached 80 mmHg in 15 min in eight rats and remained above this value in only five rats despite aggressive fluid resuscitation. MAP ranged from 87 to 98 mmHg in the NE50 group. In the highest dose group (NE500), all normotensive rats died as the hypotensive rats had done.

Survival rates are shown in figure 1. All rats survived the first 30 min of the experiment. All rats of the sham group survived throughout the study. Only 2 control rats (20%) survived until T90 (end of phase 1). At T90, there was a significant difference in survival rates in both normotensive and hypotensive rats ($P < 0.05$). In hypotensive rats (BP40 rats; fig. 1A), 8 (80%) survived in the NE0 and NE5 groups, 9 (90%) survived in the NE50 group, and none survived in the NE500 group. In normotensive rats (BP80 rats; fig. 1B), 1 (10%) survived in the NE0 group, 5 (50%) survived in the NE5 dose group, all 10 (100%) survived in the NE50 group, and none survived in the NE500 group.

At T210, there was a significant difference in survival rates among treatment groups under both hypotensive and normotensive conditions ($P < 0.05$). One control rat survived. Among the hypotensive rats (fig. 1A), 6 (60%) survived in the NE0 and NE5 dose groups, 9 (90%) survived in the NE50 dose group, and none survived in the highest NE500 dose group. The difference with respect to controls was significant for the NE50 dose group only ($P < 0.05$ adjusted for multiplicity).

Among normotensive rats (fig. 1B), none survived in the NE0 group, 4 survived in the NE5 dose group, all 10 (100%) survived in the NE50 group, and none survived in the highest NE500 dose group. The difference with controls was significant for the NE50 dose group only ($P < 0.05$ adjusted for multiplicity).

In both hypotensive and normotensive rats, the volume of saline given to rats surviving after the uncontrolled hemorrhagic shock (T30–T90) was significantly different in the various treatment groups ($P < 0.05$; table 3). The volume of blood shed from the tail of treated rats during this time was significantly higher than that in controls in normotensive rats ($P < 0.05$) but not in hypotensive rats.

At T90, there was no significant difference in heart

Table 2. Mean Arterial Blood Pressure (mmHg) in Each Group

Group	T0	T15	T30	T40	T50	T60	T70	T80	T90
Control	123 ± 15	24 ± 5	28 ± 8	25 ± 9	28 ± 6	32 ± 10	32 ± 10	35 ± 6	32 ± 3
BP40 groups									
BP40 NE0	132 ± 14	27 ± 7	32 ± 12	49 ± 14	48 ± 19	56 ± 12	58 ± 18	58 ± 18	57 ± 14
BP40 NE5	121 ± 16	27 ± 6	33 ± 14	54 ± 9	61 ± 6	57 ± 9	62 ± 7	61 ± 7	64 ± 7
BP40 NE50	115 ± 14	25 ± 3	30 ± 6	85 ± 25	86 ± 21	81 ± 17	78 ± 13	78 ± 14	81 ± 14
BP40 NE500	126 ± 17	30 ± 17	42 ± 24	135 ± 32	137 ± 3	NA	NA	NA	NA
BP80 groups									
BP80 NE0	116 ± 12	27 ± 4	30 ± 8	59 ± 22	55 ± 24	67	86	88	80
BP80 NE5	116 ± 18	27 ± 4	28 ± 3	76 ± 14	84 ± 5	84 ± 5	86 ± 4	76 ± 22	77 ± 23
BP80 NE50	109 ± 16	25 ± 15	35 ± 15	95 ± 16	98 ± 12	92 ± 9	90 ± 11	87 ± 10	87 ± 8
BP80 NE500	128 ± 9	33 ± 10	39 ± 14	144 ± 26	124 ± 58	NA	NA	NA	NA

n = 10 at T0. Values are expressed as mean ± SD. The BP40 groups (n = 40) comprise the four hypotensive resuscitation groups that were infused with saline at a rate given to prevent mean arterial pressure falling below 40 mmHg and with norepinephrine in saline at a constant rate of 5 ml · 100 g^{-1} · h^{-1} over 60 min (doses of 0 [NE0, n = 10], 5 [NE5, n = 10], 50 [NE50, n = 10], or 500 [NE500, n = 10] $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$). The BP80 groups (n = 40) comprise the four normotensive resuscitation groups infused with saline to prevent mean arterial pressure falling below 80 mmHg and receiving the same norepinephrine doses as the hypotensive rats. T0–T30: volume-controlled hemorrhagic shock; T30–T90: uncontrolled hemorrhagic shock with or without administration of saline, and with or without norepinephrine.

NA = not applicable (all rats died within 90 min).

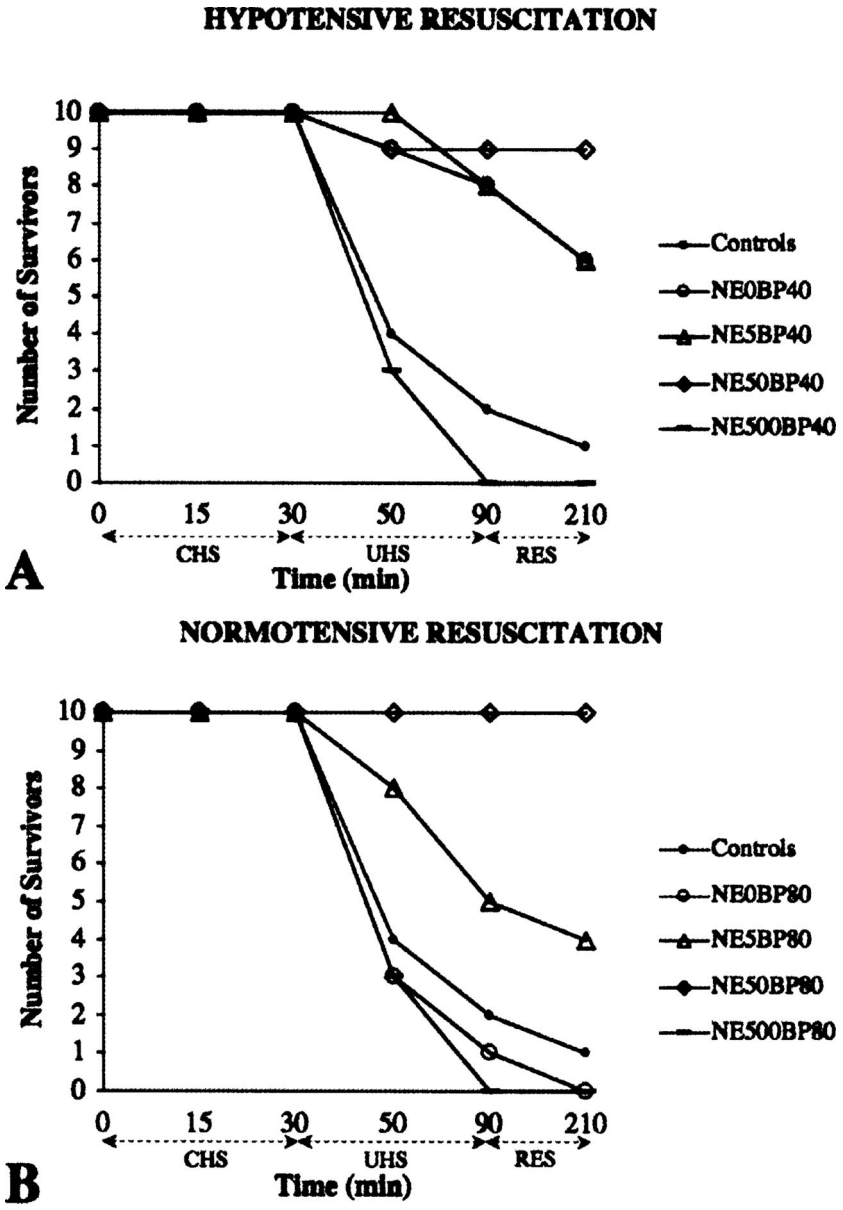

Fig. 1. Number of survivors (y-axis) over time (x-axis) in each group. (*A*) Hypotensive resuscitation groups; (*B*) normotensive resuscitation groups. The BP40 groups (n = 40) comprise the four hypotensive resuscitation groups that were infused with saline at a rate given to prevent mean arterial pressure falling below 40 mmHg and with norepinephrine in saline at a constant rate of 5 ml · 100 g^{-1} · h^{-1} over 60 min (doses of 0 [NE0, n = 10], 5 [NE5, n = 10], 50 [NE50, n = 10], or 500 [NE500, n = 10] $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$). The BP80 groups (n = 40) comprise the four normotensive resuscitation groups infused with saline to prevent mean arterial pressure falling below 80 mmHg and receiving the same norepinephrine doses as the hypotensive rats. T0–T30: volume-controlled hemorrhagic shock (CHS); T30–T90: uncontrolled hemorrhagic shock (UHS) with or without administration of saline, and with or without norepinephrine; T90–T210: resuscitation (RES) phase.

rate, arterial oxygen saturation, pH, arterial carbone dioxide pressure, arterial oxygen pressure, base excess, serum bicarbonate, or blood lactate among the treated groups (the highest dose groups [NE500] were excluded because all rats had died by T90). Mean values for surviving rats are given in table 1. However, normotensive rats (BP80) had a significantly lower hematocrit value than hypotensive rats (BP40) at T90 ($P < 0.05$). Hemat-

Table 3. Fluid Requirements and Blood Loss in Surviving Rats at T90

	Volume of Saline (ml/100 g)		Blood Loss (ml/100 g)	
	Hypotensive (BP40)	Normotensive (BP80)	Hypotensive (BP40)	Normotensive (BP80)
Control	0		0.18 ± 0.21	
NE0	5.24 ± 3.16	17.40	0.42 ± 0.69	1.88
NE5	4.21 ± 1.26	11.13 ± 5.88	0.30 ± 0.23	0.81 ± 0.71
NE50	3.37 ± 0.13	5.10 ± 2.46	0.45 ± 0.41	0.70 ± 0.39

n = 10 for each group at T0. Results are significantly different ($P < 0.05$) among the different treatment groups (analysis of variance global test for the four groups). The BP40 groups (n = 40) comprise the four hypotensive resuscitation groups that were infused with saline at a rate given to prevent mean arterial pressure falling below 40 mmHg and with norepinephrine in saline at a constant rate of 5 ml · 100 $g^{-1} \cdot h^{-1}$ over 60 min (doses of 0 [NE0, n = 10], 5 [NE5, n = 10], 50 [NE50, n = 10], or 500 [NE500, n = 10] $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$). The BP80 groups (n = 40) comprise the four normotensive resuscitation groups infused with saline to prevent mean arterial pressure falling below 80 mmHg and receiving the same norepinephrine doses as the hypotensive rats.

ocrit values were 8 ± 2% (NE0), 14 ± 3% (NE5), and 27 ± 6% (NE50) in normotensive rats, compared with 21 ± 4% (NE0), 31 ± 6% (NE5), and 28 ± 5% (NE50) in hypotensive rats.

Discussion

Our study has clearly shown that early infusion of 50 $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$ norepinephrine significantly improved early survival of rats in uncontrolled hemorrhagic shock when normotensive and hypotensive resuscitation strategies were used. All of the rats receiving the highest norepinephrine dose (500 $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$) died within 90 min regardless of resuscitation strategy. All showed transient hypertension and early bradyarrhythmia, followed by cardiac arrest with pulseless electrical activity. These results call for comments on three points: degree of fluid resuscitation, type of strategy (normotensive or hypotensive), and choice of substance.

Currently, fluid resuscitation with crystalloid solutions is recommended in hypotensive trauma patients, but colloid administration is advocated by French clinical practice guidelines in the case of massive hemorrhage.[1,24] However, in experimental studies, restoration of normal blood pressure by crystalloids results in an increased hemorrhage volume and increased mortality,[25] probably as a result of an increase in blood loss and hemodilution.[2,23,26] Moreover, the increase in blood pressure before clot formation is complete might increase the likelihood of clot disruption.[27] Hemodilution also decreases blood viscosity, which will increase blood flow at the injured site.[6] Studies on fluid resuscitation in hypotensive trauma patients have confirmed these experimental data.[2,26] In a review of 6,855 trauma patients, half receiving fluid resuscitation and half not, fluid resuscitation was found to have no impact on survival, whereas rapid transport and surgical control of hemorrhage were considered to be key factors in reducing mortality.[26] In a study of 598 patients with traumatic penetrating torso injuries resulting in systolic blood pressures of 90 mmHg or less who were randomly assigned to either early or delayed fluid resuscitation, survival rate was significantly higher in the delayed resuscitation group.[2]

On the basis of experimental studies, current practice guidelines recommend permitting hypotension when managing uncontrolled hemorrhagic shock in patients without brain injury but with the risk, however, of inducing tissue hypoperfusion.[3,4,28] Moreover, the risk of cardiac arrest and early death in cases of severe hemorrhagic shock without fluid resuscitation should be considered, especially in patients with coronary disease.[29]

Vasopressors increase blood pressure by increasing peripheral vascular resistance.[30] This decreases tissue perfusion, which in turn aggravates the deleterious effects of hypovolemic shock. For this reason, older studies condemned the use of vasopressors for hemorrhagic shock, although more recent findings on phenylephrine and vasopressin have led to a revision of this opinion.[8,9,13–15,31] When uncontrolled hemorrhagic shock was combined with brain injury in swine, infusion of phenylephrine improved mean arterial pressure and systemic and cerebral perfusion pressure in the initial phase, although it did not reduce secondary neuronal ischemia.[32] In porcine models of liver injury with uncontrolled and otherwise lethal hemorrhagic shock, vasopressin, unlike epinephrine and saline placebo, improved short-term survival when surgical intervention and fluid replacement were delayed or even led to full recovery and survival.[13,33] When administered to dogs in controlled hemorrhagic shock, it either increased or did not influence mortality.[17,34] Moreover, like other vasoconstrictors, norepinephrine can, by constricting capacitance vessels, shift blood from unstressed to stressed volume and, thereby, increase venous return.[35] The mechanism involves a decrease in splanchnic venous outflow resistance and an increase in fractional blood flow to regions with fast time constants. However, unlike vasopressin or terlipressin, norepinephrine has been shown to increase myocardial performance in isolated perfused rabbit heart.[36]

We chose to study norepinephrine rather than vasopressin because norepinephrine is widely available and widely used in clinical practice. Vasopressin is not marketed worldwide. Our results on the use of norepinephrine in uncontrolled hemorrhagic shock in rats fully support experimental studies showing that aggressive fluid resuscitation without vasopressors can worsen bleeding by probably impairing the formation of new blood clots or dislodging existing ones.[7,37] None of the rats that did not receive norepinephrine in the normotensive group survived at T210. Blood loss, which was highest in this group, was much reduced on infusing 50 $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$ norepinephrine (BP80 NE50; 0.70 ± 0.39 ml/100 g *vs.* 1.88 ml/100 g; $P < 0.05$). Survival at T210 was also best in this group. This suggests that supplementation with norepinephrine might be useful in patients, such as those with head injuries, in whom a normotensive resuscitation strategy is indicated, although it should not be forgotten that α stimulation (phenylephrine) has been shown to reduce blood volume expansion in sheep.[38] In our hypotensive strategy of fluid resuscitation, survival in the group receiving norepinephrine at 50 $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$ with a very low fluid requirement was better than that of the group receiving no norepinephrine, suggesting that norepinephrine may be useful in the hypotensive strategy. However, in this group, mean arterial pressure values were dramatically higher than the target value in the hypotensive groups and closer to the target value in the normotensive groups. This "overshoot" in correction of blood pressure for the BP40 NE50 group is directly linked to the norepinephrine infusion rate. Our results also suggest that survival is better after a normotensive strategy with reduced fluid loading in which 50 $\mu g \cdot 100$

$g^{-1} \cdot h^{-1}$ norepinephrine is administered than after a hypotensive strategy with fluid loading only.

Although we used a well-known model, there are potential limitations to our study. The anesthesia we gave to control pain and limit suffering may have interfered with the rats' cardiovascular response to hemorrhage. Animals anesthetized with ketamine have shown better survival rates than those given other anesthetics.[39] Moreover, ketamine acts favorably on cardiac output and tissue perfusion in rats subjected to hemorrhage by increasing perfusion to organs such as the heart, kidneys, and brain.[40] However, ketamine induces higher blood lactate concentrations than thiopental in rats in hemorrhage shock.[41] This possible interference by ketamine does not necessarily detract from the clinical relevance of our results. Use of intravenous anesthetics is routine in the emergency setting and during intensive care of patients with hemorrhagic shock even if it may interfere with the cardiovascular compensation to hemorrhage. Combinations using nitrous oxide and halogenated anesthetics cannot be used routinely in the emergency department.

In conclusion, attempts to achieve normal MAP without using norepinephrine during uncontrolled bleeding increased blood loss and mortality in rats. All of the rats treated with high norepinephrine doses died early. Using an intermediate norepinephrine infusion rate, in either a hypotensive or a normotensive strategy of resuscitation during uncontrolled hemorrhage, resulted in significantly improved survival.

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