

# A Comparison of Epinephrine Only, Arginine Vasopressin Only, and Epinephrine Followed by Arginine Vasopressin on the Survival Rate in a Rat Model of Anaphylactic Shock

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**Background:** Epinephrine and more recently arginine vasopressin (AVP) alone or in combination have been proposed in patients with anaphylactic shock, but few experimental data exist. The authors investigated the effects of epinephrine only, AVP only, or epinephrine followed by AVP in a model of anaphylactic shock.

**Methods:** Ovalbumin-sensitized Brown Norway rats were anesthetized, intubated, and shock induced with ovalbumin. Rats (n = 6/group) were randomly allocated to receive 5 min after shock onset: (1) saline (no-treatment group); (2) two boluses of epinephrine followed by continuous infusion (epinephrine group); (3) AVP bolus followed by continuous infusion (AVP group); (4) epinephrine bolus followed by AVP continuous infusion (epinephrine + AVP group). Mean arterial pressure (MAP) and skeletal muscle oxygen pressure (P<sub>tiO<sub>2</sub></sub>) were measured. Continuous infusion rates were titrated to reach MAP values of 60 mmHg. Survival was analyzed.

**Results:** Without treatment, MAP and P<sub>tiO<sub>2</sub></sub> decreased rapidly with 0% survival. In the epinephrine group, MAP and P<sub>tiO<sub>2</sub></sub> recovered after an initial decrease, with 84% survival. In the AVP group, MAP was partially restored and subsequently decreased; P<sub>tiO<sub>2</sub></sub> values decreased to values similar to those in the no-treatment group; survival was 0%. In the epinephrine + AVP group, MAP and P<sub>tiO<sub>2</sub></sub> values increased more slowly as compared with the epinephrine group; survival was 100%.

**Conclusions:** In this model of anaphylactic shock, early treatment with epinephrine followed by continuous epinephrine or vasopressin infusion resulted in an excellent survival rate, whereas vasopressin only resulted in a 100% death rate. These experimental results suggest that epinephrine must still be considered as the first-line drug to treat anaphylactic shock.

ANAPHYLACTIC shock occurring during anesthesia is lethal in 3-10% of patients even in previously healthy

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individuals and despite therapy that is consistent with the current guidelines.<sup>1-3</sup> Epinephrine is considered in most guidelines<sup>4,5</sup> as the first-line treatment of anaphylactic shock. In some cases, alternative therapies are used, such as norepinephrine<sup>6</sup> or metaraminol,<sup>7,8</sup> or more recently arginine vasopressin (AVP).<sup>9-11</sup> Although, AVP has been used in several case reports and is considered as effective, there are many unanswered questions regarding its use in patients with anaphylactic shock and particularly in those with anaphylactic shock occurring during anesthesia. In a previous experimental study,<sup>12</sup> we demonstrated that AVP could increase mean arterial pressure (MAP) values in rats that underwent anaphylactic shock. This increase in MAP values after anaphylactic shock was comparable to that obtained with epinephrine, but at the highest AVP doses, it was associated with significantly lower skeletal muscle oxygen pressure (P<sub>tiO<sub>2</sub></sub>) values, a parameter that was shown in human and experimental shock states to be correlated with survival.<sup>13-16</sup>

The aims of the current study were (1) to compare, in a Brown Norway rat model of anaphylactic shock, epinephrine only to AVP only as therapy of anaphylactic shock occurring during anesthesia in terms of MAP, heart rate, P<sub>tiO<sub>2</sub></sub> values, and especially survival; and (2) to investigate, for the same parameters, a sequence that could mimic that recently reported in several clinical cases<sup>9,10</sup> where AVP was used only after epinephrine had been considered as ineffective, *i.e.*, epinephrine first followed by AVP. We demonstrate here that treatment with AVP only was associated with significantly lower survival as compared with epinephrine only. Interestingly, the sequence epinephrine first followed by AVP was associated with a survival rate comparable to that of epinephrine only. We hypothesize that epinephrine could attenuate the excessive vasoconstrictive effects of AVP.

## Materials and Methods

### Animals and Sensitization Protocol

The study was approved by the Animal Care Committee of the University Hospital (Nancy, France). This study, including care of the animals involved, was conducted according to the official edict presented by the French Ministry of Agriculture (Paris, France) and the recommendations of the Declaration of Helsinki. Therefore, these experiments were conducted in an autho-

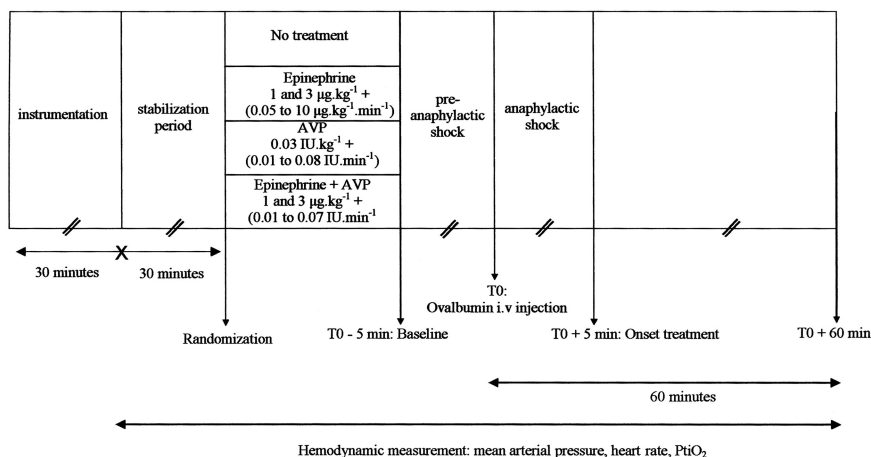


Fig. 1. Time course of measurements and treatment protocol according to the drug used for resuscitation: epinephrine and/or arginine vasopressin (AVP) in the different groups ( $n = 6/\text{group}$ ). Pre-anaphylactic shock values were recorded after randomization of the four groups of rats and before shock induction ( $T_0 - 5$  min). Time 0 ( $T_0$ ) corresponds to the injection of ovalbumin. Treatment was started 5 min after ovalbumin injection ( $T_0 + 5$  min).

alized laboratory and under the supervision of an authorized researcher (P.M.M.). We used 10-week-old Brown Norway rats weighing 266–314 g (Janvier, Le Genest-St-Isle, France). They were kept under standard conditions (temperature  $21^\circ \pm 1^\circ\text{C}$ ; light from 6 AM to 6 PM) and given a standardized diet (A04; UAR, Villemoisson-sur-Orge, France) and water (Aqua-clear; Culligan, Northbrook, IL) *ad libitum*. Rats were sensitized by subcutaneous administrations, at days 0, 4, and 14, with grade VI chicken egg albumin as previously described.<sup>12,17</sup>

#### Surgical Procedure, Measurement of Hemodynamic Variables, Tissue Oxygen Partial Pressure, and Induction of Shock

The surgical procedure was performed during general anesthesia on day 21 using 60 mg/kg intraperitoneal sodium pentobarbital (Pentobarbital Sodique; Ceva Santé Animale, Libourne, France) and maintained with intravenous additional doses (2 mg/kg) when required. Rectal temperature was maintained at  $38^\circ \pm 0.5^\circ\text{C}$  by intermittent warming with a heating pad. A fluid-filled polyethylene catheter (ID, 0.58 mm; OD, 0.96 mm; Biotrol Diagnostic, Chennevières Les Louvres, France) was inserted in the right common carotid artery for arterial pressure monitoring. Another fluid-filled catheter was inserted in the left external jugular vein for administration of drugs and fluid maintenance ( $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) with Ringer's solution (Braun Medical SA, Boulogne, France). The trachea was intubated, and the lungs were mechanically ventilated with 100% oxygen using a Harvard Rodent respirator model 683 (Harvard Apparatus, Cambridge, MA). MAP was recorded using a strain gauge pressure transducer (DA-100; Biopac Systems, Northborough, MA). A flexible Clark-type polarographic oxygen electrode (diameter and length of the oxygen partial pressure-sensitive area of the probe: 0.5–0.6 and 1 mm, respectively) computer-supported Licox system (GMS, Mielkendorf, Germany) was introduced in one of the quadriceps muscles. For correction of PtiO<sub>2</sub> measurements, temperature within the muscle was monitored,

and PtiO<sub>2</sub> values were adjusted to quadriceps temperature by means of the computer software. The electrode was calibrated before and after each experiment with room air. Hemodynamic values were allowed to stabilize for 30 min (stabilization period) after surgery, and pre-anaphylactic shock values were recorded just before shock induction ( $T_0 - 5$  min). The pressure transducer, the Licox system, and the electrocardiogram were connected to a desktop computer for continuous data acquisition (Acqknowledge software and MP 100 hardware; Biopac Systems). In each group, anaphylactic shock was induced by injecting 1 mg ovalbumin diluted in 500 µl saline solution intravenously in 1 min. Time 0 ( $T_0$ ) corresponded to the beginning of ovalbumin injection, and the study was performed for an additional 60 min after  $T_0$  ( $T_0 + 60$  min) (fig. 1).

#### Treatment with Epinephrine and/or Arginine Vasopressin and Evaluation of Survival

Animals were randomly allocated to four groups. In addition to a control group submitted to anaphylactic shock without any added therapy, three groups were designed according to the drug used for resuscitation: epinephrine (Aguettant, Lyon, France) only, AVP (Aguettant) only, and epinephrine followed by AVP (fig. 1). The investigator was not blinded to the drug used. The first bolus of epinephrine or AVP was injected 5 min after shock induction ( $T_0 + 5$  min). The second bolus of epinephrine was injected when the MAP began to decrease again after the initial increase following the first bolus. Doses of bolus were chosen according to our previous work.<sup>12</sup> Two bolus of AVP followed by a continuous infusion induced the death of the animals due to multiple organs infarction (data not shown). Therefore, only one bolus of AVP was injected. To avoid any excessive volume loading, both drugs were prepared at different dilutions (in saline solution), and the syringes were changed when necessary to preserve a volume rate infusion less than 4 ml/h. Epinephrine was therefore diluted at 0.5, 5, 25, or 50 µg/ml (maximum infusion rate,

3.8 ml/h) and AVP at 0.4, 1.2, or 1.5 U/ml (maximum infusion rate, 3.2 ml/h). Continuous infusion of epinephrine or AVP was initiated immediately after the last bolus injection. The perfusion rate for the continuous infusion was adapted to reach MAP values of 60 mmHg. When the MAP goal was reached and stable during a 10-min period, drug infusion was progressively decreased and stopped. For each rat, the following measurements were performed: (1) average dose per minute of vasoconstrictor drugs, (2) duration of drug infusion, and (3) weight evolution in survivors. At the end of the data acquisition period, *i.e.*, 60 min after shock induction (T0 + 60 min), catheters were removed, cutaneous incisions were closed, and rats were extubated and moved to a regular cage with free access to food and water. Awakening was attentively observed. When rats were awake, a loading dose of paracetamol (10 mg/kg) was given orally, followed by a maintenance dose (60 mg/kg per day) *ad libitum* during 72 h.<sup>18</sup> Animals were observed at 12-h intervals for determination of survival. Surviving animals were killed on day 7 by an overdose of sodium pentobarbital.

#### Statistical Analysis

Results are expressed as mean  $\pm$  SD and survival as percentage. Intragroup and between-group comparisons were performed using one-way and two-way analysis of variance for repeated measures (Statview; SAS Institute Inc., Cary, NC). When a significant interaction was observed with two-way analysis of variance, paired comparisons were made with the Fisher *post hoc* test. Survival rate were compared with the Fisher exact test. Significance was assumed when *P* was less than 0.05. All tests were two-sided.

## Results

Twenty-four ovalbumin-sensitized Brown Norway rats (weight on the day of, but before shock induction:  $296 \pm 3$  g) were studied (six rats in each of the four groups; fig. 1). For the three measured variables (MAP, heart rate, PtiO<sub>2</sub>), values did not differ among the four groups at the following time points: preshock (T0 - 5 min/baseline), T0, and postshock (T0 + 5 min).

In the absence of treatment, after ovalbumin injection at T0, anaphylactic shock was characterized by a rapid and sustained decrease in MAP and PtiO<sub>2</sub> values, with most of the decrease occurring within the first 5 min after ovalbumin injection (decrease of 66% and 45% from baseline values, respectively). The initial rapid decrease was followed by a further, more gradual decrease over time for both variables (figs. 2A and B).

#### Effects of Epinephrine and/or AVP

The effects of epinephrine and/or AVP on MAP values are presented in figure 2A. After the initial arterial hypo-

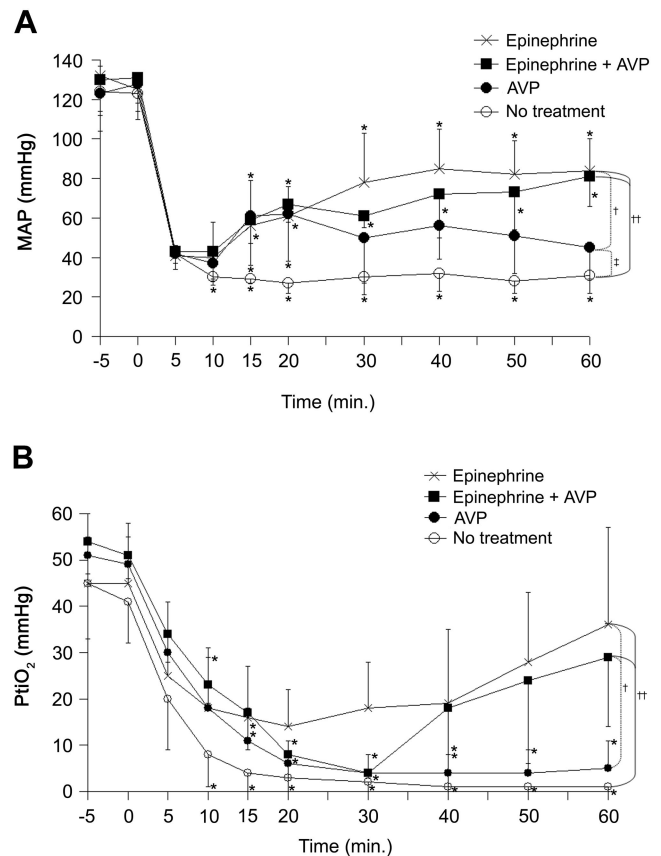


Fig. 2. (A) Mean arterial pressure (MAP) profiles after onset of treatment in the three treated groups and in the untreated group (n = 6 rats/group). Time 0 (T0) corresponds to the injection of ovalbumin. Treatment was started 5 min after ovalbumin injection (T0 + 5 min). \* *P* < 0.05 intragroup differences versus T0 + 5 min. † *P* < 0.05 between-group differences epinephrine only versus arginine vasopressin (AVP) only. ‡ AVP only versus untreated group. †† Epinephrine only or epinephrine + AVP versus untreated group. (B) Skeletal muscle tissue oxygen partial pressure (PtiO<sub>2</sub>) profiles after onset of treatment in the three treated groups and in the untreated group (n = 6 rats/group). Time 0 (T0) corresponds to the injection of ovalbumin. Treatment was started 5 min after ovalbumin injection (T0 + 5 min). \* *P* < 0.05 intragroup differences versus T0 + 5 min. † *P* < 0.05 between-group differences epinephrine only or epinephrine + arginine vasopressin (AVP) versus AVP only. †† Epinephrine only or epinephrine + AVP versus untreated group.

tension after shock induction, MAP values were partially restored in the three groups (epinephrine, epinephrine + AVP, and AVP) characterized by a similar profile until T0 + 20 min. After T0 + 20 min, profiles of MAP values were different among the three groups: (1) The epinephrine and epinephrine + AVP groups (*P* = not significant [NS] for comparisons between them) were characterized by significantly (*P* < 0.05) higher values as compared with the no-treatment group; (2) for the AVP group, MAP values were significantly lower (*P* < 0.05) as compared with the epinephrine and epinephrine + AVP groups, despite escalating doses of AVP, but not different from those of the untreated group (*P* = NS) (fig. 2A).

Heart rate values are presented in table 1. In the untreated group, HR values did not change significantly

**Table 1. Time Course of Heart Rate (beats/min) in the Four Groups**

Time	No Treatment	Epinephrine	AVP	Epinephrine + AVP
T0 - 5	413 ± 18	402 ± 27	437 ± 34	412 ± 37
T0	403 ± 26	392 ± 30	430 ± 33	408 ± 39
T0 + 5	380 ± 14	380 ± 33	397 ± 39	372 ± 53
T0 + 10	375 ± 72	443 ± 51	377 ± 48*	380 ± 42
T0 + 15	395 ± 30	470 ± 59*	340 ± 59*	364 ± 45*
T0 + 20	405 ± 45	463 ± 45*	367 ± 35*	372 ± 16
T0 + 30	388 ± 57	463 ± 23*	353 ± 35*	380 ± 18
T0 + 40	403 ± 22	463 ± 43*	357 ± 37*	396 ± 15
T0 + 50	393 ± 33	436 ± 29	363 ± 51*	400 ± 18
T0 + 60	375 ± 26	428 ± 45	377 ± 46*	404 ± 50

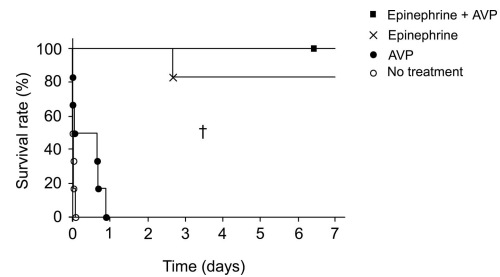
Time 0 (T0) corresponds to the injection of ovalbumin. First bolus of each drug was injected at T0 + 5 min. Values are expressed as mean ± SD (n = 6/group).

\*  $P < 0.05$  vs. T0 - 5 min.

AVP = arginine vasopressin.

over time. In the group treated with epinephrine, heart rate values were significantly increased as compared with baseline values from T0 + 15 min until T0 + 40 min. In contrast, in the AVP group, heart rate values were significantly lower after onset of treatment as compared with baseline values during the whole study period. In the epinephrine + AVP group, heart rate values were not significantly different from baseline values except at T0 + 15 min, when they were significantly decreased. As compared with the untreated group, for the period that followed shock induction, heart rate values were significantly higher for the epinephrine group, significantly lower for the AVP group, and unchanged for the epinephrine + AVP group. Interestingly, at T0 + 20 min, MAP values were similar in all treated groups (fig. 2A), but heart rate values were significantly higher for the epinephrine as compared with the AVP group.

The effects of epinephrine and/or AVP on  $P_{\text{tO}_2}$  values are presented in figure 2b. After onset of treatment in the three groups,  $P_{\text{tO}_2}$  decreased gradually until T0 + 15 min in the three groups with a similar profile. After T0 + 15 min,  $P_{\text{tO}_2}$  profiles differed among the groups. In the epinephrine group,  $P_{\text{tO}_2}$  remained stable ( $P = \text{NS}$  as compared with T0 + 5 min) after T0 + 10 min and slowly increased after T0 + 40 min, reaching values similar to preshock values at T0 + 60 min. In the epinephrine + AVP group,  $P_{\text{tO}_2}$  decreased gradually until T0 + 30 min to values significantly lower as compared with T0 + 5 min; subsequently at T0 + 50 min and T0 + 60 min,  $P_{\text{tO}_2}$  values increased and were not different from those measured at T0 + 5 min but remained significantly lower as compared with values measured at T0 - 5 min. Nevertheless, profiles of  $P_{\text{tO}_2}$  values were similar for the rest of study between the epinephrine and epinephrine + AVP groups ( $P = \text{NS}$ ) and significantly ( $P < 0.05$ ) different from those of the untreated group. In contrast in the AVP group,  $P_{\text{tO}_2}$  values continued to



**Fig. 3. Survival rates in the four groups expressed as days (from day 1 to day 7). Survival rate was significantly higher in the epinephrine-only and epinephrine + arginine vasopressin (epinephrine + AVP) groups ( $\dagger P < 0.05$ ) as compared with the two other groups (AVP-only and no-treatment groups). Survival rates between the AVP-only and no-treatment groups were not different.**

decrease and were not different from those measured in the absence of treatment ( $P = \text{NS}$ ).

#### Total Drugs Consumption and Duration of Drug Infusion

Mean continuous infusion rates of AVP in the AVP-only group ( $0.064 \pm 0.007$  U/min;  $P < 0.05$ ) were significantly higher as compared with those in the epinephrine + AVP group ( $0.045 \pm 0.002$  U/min). The durations of drug infusion were similar for the epinephrine ( $54 \pm 1$  min) and AVP ( $47 \pm 7$  min) groups and significantly shorter in the epinephrine + AVP group ( $24 \pm 4$  min) ( $P < 0.05$ ).

#### Survival and Weight Follow-up after Recovery

Survival rates of all groups are presented in figure 3 (percentage survival analyzed with the Fisher exact test). All untreated rats and rats treated with AVP only died a few hours after extubation (0.26 and 8 h, respectively). Five of the six rats treated with epinephrine survived in very good conditions, and one died on day 3; the mean average of weight loss on day 7 (n = 5) was 23% as compared with baseline. All rats treated with epinephrine + AVP survived in very good conditions; weight loss on day 7 (n = 6) was 16%. No significant difference for survival and weight loss was observed between epinephrine and epinephrine + AVP groups.

#### Discussion

The main findings of this study were that in an anesthetized anaphylactic Brown Norway rat model, (1) when initiated 5 min after anaphylactic shock induction, therapy with epinephrine only was associated with a high rate of survival (84%), whereas therapy with AVP only had 100% mortality; and (2) interestingly, the sequence epinephrine followed by continuous AVP infusion, an experimental design that was chosen to mimic several recent clinical cases of use of AVP in patients

with anaphylactic shock, was associated with 100% survival.

Correction of excessively decreased mean arterial pressure and maintenance of adequate organ perfusion are the therapeutic goals during vasodilatory shock states including anaphylactic shock. These goals are also valid for treatment of anaphylactic shock occurring during anesthesia and the perioperative period. Epinephrine is considered as the first-line treatment in most guidelines on perioperative management of anaphylaxis.<sup>4,5,19</sup> These recommendations are based on experimental and clinical data obtained in the context of cardiac arrest and vasodilatory shock states other than anaphylactic.<sup>5,20</sup> However, there are few experimental and no methodologically correct clinical data to support these extrapolations to anaphylactic shock. Evidence in the literature suggests that a poor outcome during anaphylactic shock is associated with late administration of epinephrine<sup>21,22</sup> but also when epinephrine has been given inadequately. Recently, experimental work provided arguments for the possible use of AVP as therapy of anaphylactic shock.<sup>12,23,24</sup> In other respects, the most recent American guidelines on anaphylaxis<sup>5,25</sup> and several case reports suggested that adding AVP to standard therapy might be considered as a potential therapeutic approach in anaphylactic shock.<sup>9-11</sup> In the wake of these case reports and taking into account a possible AVP deficiency observed in experimental anaphylactic shock,<sup>12</sup> we compared, in an anesthetized Brown Norway rat model of anaphylactic shock, the survival rate according to the drug injected, epinephrine and/or AVP. Treatment of anaphylactic shock after a delay of 5 min was chosen because this period was considered as a delay consistent in clinical practice with the diagnosis and the preparation of the epinephrine. Doses for bolus injection of epinephrine and AVP were chosen according to our previous work,<sup>12</sup> doses for continuous infusion of epinephrine were chosen according to the literature,<sup>4,5</sup> and doses of AVP were chosen according to the indications of the manufacturer.

When comparing the epinephrine-only, epinephrine + AVP, and AVP-only groups, MAP and  $P_{\text{tO}_2}$  profiles were initially similar in the three groups but differing strikingly after  $T_0 + 20$  min and  $T_0 + 15$  min, respectively. The epinephrine-only and epinephrine + AVP groups were characterized by a partial restoration of MAP and full recovery of  $P_{\text{tO}_2}$  values associated with tachycardia and unchanged heart rate, respectively. In contrast, in the AVP group, MAP and  $P_{\text{tO}_2}$  values decreased over time, and this was associated with significantly lower heart rate values, despite escalating doses of AVP. Survival in the three groups differed with a high rate of survival in the epinephrine and epinephrine + AVP groups and 100% mortality in the AVP group.

Our experimental results demonstrate that in this model of anaphylactic shock, epinephrine cannot be

replaced by AVP as the first-line treatment. Nevertheless, when treatment is initiated with epinephrine, continuous infusion with either epinephrine or AVP may be chosen to maintain arterial pressure. The effects on survival of our experimental design (two boluses of epinephrine followed by either epinephrine or AVP or the single bolus of AVP followed by AVP) should be interpreted cautiously and take into account (1) the different plasma half-life values: a few minutes for epinephrine and 10–35 min for AVP<sup>26</sup>; and (2) the different sequences bolus/continuous infusion in the three resuscitated groups. It is difficult, therefore, to isolate the impact on survival of the bolus *versus* continuous infusion, but this study design was chosen because drug injection (bolus/infusion) was titrated on MAP values. The cardiovascular effects of epinephrine and AVP are complex.<sup>27</sup> Epinephrine is a direct-acting  $\alpha$ - and  $\beta$ -adrenergic agonist, and restores in most clinical situations the global hemodynamics during anaphylactic shock. Its beneficial effects in anaphylactic shock are mediated by the  $\alpha_1$ -adrenergic effects, which increase the left ventricular preload by reducing venous capacitance, whereas  $\beta$ -adrenergic effects reverse bronchoconstriction and increase cardiac inotropy and chronotropy.<sup>28,29</sup> A few experimental studies have been conducted to study the hemodynamic effects of epinephrine in whole animals experiencing anaphylactic shock.<sup>30-32</sup> The main results showed that a single bolus of epinephrine caused a transient increase in MAP accompanied by simultaneous increases in cardiac output and mean pulmonary capillary wedge pressure compared with the control group,<sup>31</sup> whereas a titrated intravenous infusion of epinephrine produced a sustained improvement of hemodynamics and seemed to act by increasing cardiac output and stroke work.<sup>32</sup> The beneficial effects of continuous infusion epinephrine have therefore been attributed to its cardiac  $\beta$ -adrenergic effects that resulted in increased cardiac output and stroke work.<sup>32</sup>

The precise mechanism of the vasopressor action induced by AVP remains unclear. In vasoplegic shock states, AVP restores vascular tone by at least four mechanisms: (1) activation of  $V_1$  receptors, (2) ability to close adenosine triphosphate-sensitive  $K^+$  channels ( $K_{\text{ATP}}$ ) while activation of  $K_{\text{ATP}}$  channels produces cellular hyperpolarization resulting in vasodilatation, (3) modulation of nitric oxide, and (4) potentiation of adrenergic and other vasoconstrictor agents.<sup>33,34</sup> In addition, AVP could act during anaphylactic shock as an “antiinflammatory agent” by antagonizing the effects of nitric oxide. Increased synthesis of nitric oxide contributes to the hypotension and resistance to vasopressor drugs that occur in vasodilatory shock,<sup>34</sup> and AVP directly decreases intracellular concentrations of the nitric oxide second messenger, cyclic guanosine 3',5'-monophosphate.<sup>35</sup>

In contrast to what was observed in the group treated

with epinephrine only, treatment with AVP only was associated with 100% mortality. Despite the initial increase of MAP, a further decrease over time was associated with significantly lower heart rate values and a significant decrease of  $P_{\text{tO}_2}$  values. Comparable hemodynamic changes induced by AVP have been reported in experimental and clinical investigations. The absence of tachycardia in the AVP-only group, in our experiments, could be attributed to its interaction with central  $V_1$  receptors. Laszlo *et al.*<sup>36</sup> demonstrated that AVP administration reduces heart rate and cardiac index because of an increase in vagal and a decrease in sympathetic tone. Controversial results have been reported with AVP during experimental or clinical studies according to the dosage infusion and leading either to an impairment of myocardial function<sup>37-39</sup> or to a maintained cardiac index.<sup>40</sup> In addition, several recent studies have demonstrated controversial effects of AVP on tissue oxygen pressure depending on the experimental model.<sup>41</sup>

In the current study, the mean average of AVP infusion was  $0.064 \pm 0.007$  U/min and could have contributed to a potential myocardial dysfunction. Only two studies have been conducted in whole animals using AVP during anaphylactic shock.<sup>12,24</sup> In a rabbit model, vasopressin at 0.08 U/kg improved survival rate and corrected hypotension provoked by systemic anaphylaxis, as compared with 0.8 U/kg. Nevertheless, in the experimental model of Hiruta *et al.*,<sup>24</sup> rabbits were treated 1 min after allergen challenge when MAP was 100 mmHg and survival was 35% in the absence of resuscitation. Our model is characterized by 100% mortality in the absence of resuscitation, and vasopressors were injected when animals were severely hypotensive.

In contrast to what was observed in the AVP-only group, when AVP was injected as a continuous infusion after an initial bolus of epinephrine (epinephrine + AVP group), AVP restored MAP in the same way as epinephrine only but was associated with an unchanged heart rate, whereas tachycardia was observed in the epinephrine group. When comparing the epinephrine + AVP group with the AVP-only group in terms of survival, it is striking that (1) despite lower infusion rates of AVP ( $0.045 \pm 0.002$  U/min) in the epinephrine + AVP group, MAP values and  $P_{\text{tO}_2}$  were significantly higher in this group; and (2) the duration of drug infusion was significantly shorter in the epinephrine + AVP group. Therefore, our results suggest that two bolus injections of epinephrine before the continuous AVP infusion result in a major change of the effects of AVP that probably explains the highly improved survival in the epinephrine + AVP group as compared with the AVP-only group. The design of our study does not allow us to elucidate the mechanisms of the beneficial effects of the epinephrine bolus that precedes the continuous infusion of AVP. It is tempting to speculate that (1) the two bolus injections of epinephrine attenuate/abrogate the negative inotropic

and chronotropic effects of AVP; and (2) the lack of a bolus infusion of AVP in the epinephrine + AVP group, before the onset of AVP continuous infusion, could have avoided possible deleterious effect of excessive AVP concentrations on organs other than the heart.

In conclusion, we provide information on the survival rate in a rat model of anaphylactic shock treated with epinephrine and/or AVP and demonstrate that treatment with AVP only was associated with significantly lower survival as compared with epinephrine only. Interestingly, the sequence epinephrine first followed by AVP was associated with a survival rate comparable to that of epinephrine only. Based on these experimental results, epinephrine must still be considered as the first-line drug to treat anaphylactic shock. Nevertheless, these data support use of vasopressin as reported in case reports,<sup>9,10</sup> *i.e.*, after (or in addition to) epinephrine. Further studies are necessary to determine whether administration of a continuous small dose of AVP added to classic treatment with epinephrine could be clinically relevant.<sup>42</sup>

## References

- Mitsuhashi H, Matsumoto S, Hasegawa J: The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan. *Masui* 1992; 41:1664-9
- Currie M, Webb R, Williamson J, Russell W, Mackay P: The Australian Incident Monitoring Study. Clinical anaphylaxis: An analysis of 2000 incident reports. *Anaesthesia Intensive Care* 1993; 21:621-5
- Lienhart A, Auroy Y, Pequignot F, Benhamou D, Warszawski J, Bovet M, Jouglé E: Survey of anesthesia-related mortality in France. *ANESTHESIOLOGY* 2006; 105:1087-97
- Longrois D: Quel est le traitement de la réaction allergique survenant en cours d'anesthésie et en particulier du choc anaphylactique? *Ann Fr Anesth Reanim* 2002; 21 (suppl 1):168-80
- American Heart Association: Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: 10.6. Anaphylaxis. *Circulation* 2005; 112:IV143-5
- Sneyd JR: Catecholamine-resistant cardiovascular collapse after propofol, atracurium and gentamicin. *Eur J Anaesthesiol* 1998; 15:600-2
- Heytman M, Rainbird A: Use of alpha-agonists for management of anaphylaxis occurring under anaesthesia: Case studies and review. *Anaesthesia* 2004; 59:1210-5
- Hepner DL: From the laboratory to the bedside: Searching for an understanding of anaphylaxis. *ANESTHESIOLOGY* 2005; 103:1-2
- Kill C, Wranze E, Wulf H: Successful treatment of severe anaphylactic shock with vasopressin. *Int Arch Allergy Immunol* 2004; 134:260-1
- Schummer W, Schummer C, Wippermann J, Fuchs J: Anaphylactic shock: Is vasopressin the drug of choice? *ANESTHESIOLOGY* 2004; 101:1025-7
- Williams SR, Denault AY, Pellerin M, Martineau R: Vasopressin for treatment of shock following aprotinin administration. *Can J Anesth* 2004; 51:169-72
- Dewachter P, Jouan-Hureaux V, Lartaud I, Bello G, de Talancé N, Longrois D, Mertes PM: Comparison of arginine vasopressin, terlipressin or epinephrine to correct hypotension in a model of anaphylactic shock in anesthetized Brown Norway rats. *ANESTHESIOLOGY* 2006; 104:734-41
- Niinikoski J, Halkola L: Skeletal muscle  $PO_2$ : Indicator of peripheral tissue perfusion in haemorrhagic shock. *Adv Exp Med Biol* 1977; 94:585-92
- van der Kleij A, de Koning J, Beerhuizen G, Goris R, Kreuzer F, Kimmich H: Early detection of hemorrhagic hypovolemia by muscle oxygen pressure assessment: Preliminary report. *Surgery* 1983; 93:518-24
- Drucker W, Pearce F, Glass-Heidenreich L, Hopf H, Powell C, Ochsner M, Frankel H, Murray D, Nelson M, Champion H, Rozycki G, Silva J, Malcom D, DeNobile J, Harviel D, Rich N, Hunt TK: Subcutaneous tissue oxygen pressure: A reliable index of peripheral perfusion in humans after injury. *J Trauma* 1996; 40:S116-22
- Ragheb J, Buggy DJ: Tissue oxygen tension in anaesthesia and perioperative medicine. *Br J Anaesth* 2004; 464-8
- Dewachter P, Jouan-Hureaux V, Franck P, Menu P, de Talancé N, Zannad F, Laxenaire MC, Longrois D, Mertes PM: Anaphylactic shock: A form of distrib-

- utive shock without inhibition of oxygen consumption. *ANESTHESIOLOGY* 2005; 103:40-9
18. St A Stewart L, Martin WJ: Evaluation of postoperative analgesia in a rat model of incisional pain. *Contemp Top Lab Anim Sci* 2003; 42:28-34
  19. Practice Parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology: The diagnosis and management of anaphylaxis: An updated practice parameter. *J Allergy Clin Immunol* 2005; 115:S483-523
  20. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM, for the Surviving Sepsis Campaign Management Guidelines Committee: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858-73
  21. Sampson H, Mendelson L, Rosen J: Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327:380-4
  22. Pumphrey R: Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30:1144-50
  23. Tsuda A, Tanaka KA, Huraux C, Szlam F, Sato N, Yamaguchi K, Levy JH: The *in vitro* reversal of histamine-induced vasodilatation in the human internal mammary artery. *Anesth Analg* 2001; 93:1453-9
  24. Hiruta A, Mitsuhashi H, Hiruta M, Horikawa Y, Takeuchi H, Kawakami T, Saitoh J, Seo N: Vasopressin may be useful in the treatment of systemic anaphylaxis in rabbits. *Shock* 2005; 24:264-9
  25. Treschan TA, Peters J: The vasopressin system: Physiology and clinical strategies. *ANESTHESIOLOGY* 2006; 105:599-612
  26. Czaczkes JW: Physiologic studies of antidiuretic hormone by its direct measurement in human plasma. *J Clin Invest* 1964; 43:1625-40
  27. Kam PCA, Williams SR, Yoong FFY: Vasopressin and terlipressin: Pharmacology and its clinical relevance. *Anaesthesia* 2004; 59:993-1001
  28. Smith PL, Kagey-Sobotka A, Bleecker ER, Traystman R, Kaplan AP, Gralnick H, Valentine MD, Permutt S, Lichtenstein LM: Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980; 66:1072-80
  29. Muelleman RI, Pribble JP, Salomone JA: Blood pressure effects of thyrotropin releasing hormone and epinephrine in anaphylactic shock. *Ann Emerg Med* 1988; 17:309-13
  30. Mink SN, Bands C, Becker A, Elkin J, Sharma S, Unruh H, Kepron W: Effect of bolus epinephrine on systemic hemodynamics in canine anaphylactic shock. *Cardiovasc Res* 1998; 40:546-56
  31. Bautista E, Simons FER, Simons KJ, Becker AB: Epinephrine fails to hasten hemodynamic recovery in fully developed canine anaphylactic shock. *Int Arch Allergy Immunol* 2002; 128:151-64
  32. Mink SN, Simons FER, Simons KJ, Becker AB, Duke K: Constant infusion of epinephrine, but not bolus treatment, improves hemodynamic recovery in anaphylactic shock in dogs. *Clin Exp Allergy* 2004; 34:1776-83
  33. Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA: Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; 25:1279-82
  34. Landry D, Oliver J: The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; 345:588-95
  35. Nambi P, Whitman M, Gessner G, Aiyar N, Crooke S: Vasopressin-mediated inhibition of atrial natriuretic factor-stimulated cGMP accumulation in an established smooth muscle cell line. *Proc Natl Acad Sci* 1986; 83:8492-5
  36. Laszlo FA, Laszlo FJ, De Wied D: Pharmacology and clinical perspectives of vasopressin antagonists. *Pharmacol Rev* 1991; 43:73-108
  37. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27:1416-21
  38. Westphal M, Stubbe H, Sielenkämper AW, Ball C, Van Aken H, Borgulya R, Bone HG: Effects of titrated arginine vasopressin on hemodynamic variables and oxygen transport in healthy and endotoxemic sheep. *Crit Care Med* 2003; 31:1502-8
  39. Ouattara A, Landi M, Le Manach Y, Lecomte P, Leguen M, Boccard G, Coriat P, Riou B: Comparative cardiac effects of terlipressin, vasopressin, and norepinephrine on an isolated perfused rabbit heart. *ANESTHESIOLOGY* 2005; 102:85-92
  40. Patel BM, Chittock DR, Russell JA, Walley KR: Beneficial effects of short-term vasopressin infusion during severe septic shock. *ANESTHESIOLOGY* 2002; 96:576-82
  41. Knotzer H, Pajk W, Maier S, Ladurner R, Kleinsasser A, Wenzel V, Dunser M, Ulmer H, Hasibeder W: Arginine vasopressin reduces intestinal oxygen supply and mucosal tissue oxygen tension. *Am J Physiol Heart Circ Physiol* 2005; 289:H168-73
  42. Dunser MW, Lindner KH, Wenzel V: A century of arginine vasopressin research leading to new therapeutic strategies. *ANESTHESIOLOGY* 2006; 105:444-5