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Comparison of Arginine Vasopressin, Terlipressin, or Epinephrine to Correct Hypotension in a Model of Anaphylactic Shock in Anesthetized Brown Norway Rats

Pascale Dewachter, M.D., Ph.D., Valérie Jouan-Hureaux, M.Sc.,† Isabelle Lartaud, Ph.D.,‡ Gaëlle Bello, M.Sc.,§ Nicole de Talancé, M.D.,‖ Dan Longrois, M.D., Ph.D.,# Paul Michel Mertes, M.D., Ph.D.***

Background: **Arginine vasopressin (AVP) and terlipressin were proposed as alternatives to catecholamines in shock states characterized by decreased plasma AVP concentrations. The endogenous plasma AVP profile in anaphylactic shock is unknown. In an ovalbumin-sensitized anesthetized anaphylactic shock rat model, the authors investigated (1) plasma AVP concentrations and (2) the dose *versus* mean arterial pressure response for exogenous AVP and terlipressin and compared them with those of epinephrine.**

Methods: **In a first series of rats (n = 12), endogenous plasma AVP concentrations were compared with a model of pharmacologically induced hypotension (nicardipine, n = 12). A second series was randomly assigned to three groups (AVP, n = 7; terlipressin, n = 7; epinephrine, n = 7) and dose (AVP: 8 doses, 0.03–100 U/kg; terlipressin: 7 doses, 0.03–30 μg/kg; epinephrine: 7 doses, 0.3–300 μg/kg)–response mean arterial pressure curves were plotted. Data are expressed as mean ± SD.**

Results: **Endogenous plasma AVP concentrations were significantly lower in anaphylactic shock (57 ± 26 pg/ml) than in the nicardipine group (91 ± 43 pg/ml; $P < 0.05$). The ED_{50} was 10.6 μg/kg (95% confidence interval, 7.1–15.9) for epinephrine and 4.1 U/kg (95% confidence interval, 3.0–5.6) for AVP. Terlipressin did not change mean arterial pressure, regardless of the dose used.**

Conclusions: **In a rat model, anaphylactic shock is associated with inadequately low plasma AVP concentrations. For clinically relevant doses, AVP and epinephrine had comparable effects on mean arterial pressure and heart rate values, whereas, unexpectedly, terlipressin was ineffective. These results are consistent with reports in humans experiencing anaphylaxis where AVP injection restored arterial pressure.**

ANAPHYLACTIC shock is a rare but potentially life-threatening complication during anesthesia.[1] Epinephrine is the first-line treatment for anaphylactic shock, and guidelines for the management of anaphylactic shock are derived from those developed for cardiac arrest and vasodilatory shock.[2,3] No controlled trial has been conducted to determine the best practice, and published guidelines on management of anaphylactic shock occurring during anesthesia essentially rely on pathophysiology, clinical cases, and expert opinion.††[2,4]

Alternatives to epinephrine have been proposed because in some situations characterized as "epinephrine resistance," this drug is ineffective. Therefore, pharmacologic agents that act on receptors other than the catecholaminergic and are able to restore vascular tone and arterial pressure could be an alternative to epinephrine in anaphylactic shock. One such agent is arginine vasopressin (AVP) and its derivative terlipressin. Arguments in favor of AVP infusion in shock states are derived from observations of low or inadequately low plasma endogenous AVP concentrations in patients with several forms of shock.[5–7] However, the profile of endogenous plasma AVP concentrations in anaphylactic shock is not known. In addition, the cardiovascular effects of exogenous AVP or terlipressin during anaphylactic shock are not documented. In an attempt to improve our understanding of the pathophysiology and therapy of anaphylactic shock, we investigated, in an anesthetized Brown Norway (BN) rat model of anaphylactic shock, the endogenous plasma AVP concentrations and compared them with those measured in a model of pharmacologically induced arterial hypotension.[8] We also investigated dose–response relations for exogenous AVP, terlipressin, and epinephrine on mean arterial pressure (MAP).

Materials and Methods

Animals and Sensitization Protocol

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 Helsinki Declaration. Therefore, these experiments were conducted in an authorized laboratory under the supervision of an authorized researcher (P.M.M.). Because the ovalbumin-sensitized BN rat is a suitable model for inducing specific immunoglobulin E responses,[9] we used 10-week-old BN rats weighing 290–340 g (Janvier, Le Genest-St-Isle, France). They were kept under standard conditions (temperature: 21° ± 1°C; lights from 6:00 AM to 6:00 PM) and given a standardized diet (A04; UAR, Villemoisson-sur-Orge,

* Staff Physician, Pôle d'Anesthésie-Réanimation, Centre Hospitalier Universitaire (CHU), Nancy, France. Institut National de la Santé et de la Recherche Médicale (INSERM) U 684, Université Henri Poincaré Nancy 1, Faculté de Médecine, Vandoeuvre-lès-Nancy, France. † Engineer, EA 3452, Université Henri Poincaré Nancy 1, Faculté de Pharmacie, Laboratoire d'Hématologie et de Physiologie, ‡ Professor, Université Henri Poincaré Nancy 1, Faculté de Pharmacie, Laboratoire de Pharmacologie, Nancy, France. § Ph.D. Candidate, INSERM U 684, Université Henri Poincaré Nancy 1, Faculté de Médecine, Vandoeuvre-lès-Nancy, France. ‖ Staff Physician, Laboratoire d'Explorations Fonctionnelles Métaboliques et Endocriniennes, CHU Brabois, Vandoeuvre-lès-Nancy France. # Professor, ** Professor, Pôle d'Anesthésie-Réanimation, CHU, Nancy, France. INSERM U 684, Université Henri Poincaré Nancy 1, Faculté de Médecine, Vandoeuvre-lès-Nancy, France.

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Address correspondence to Dr. Mertes: Service d'Anesthésie-Réanimation Chirurgicale, Centre Hospitalier Universitaire Hôpital Central, 29 Avenue du Maréchal de Lattre de Tassigny, 54035 Nancy, France. pm.mertes@chu-nancy.fr.

†† http://www.aagbi.org/pdf/Anaphylaxis.pdf. Accessed November 5, 2005.

France) and water (Aqua-clear; Culligan, Northbrook, IL) *ad libitum*. Rats were sensitized by subcutaneous administrations on days 0, 4, and 14 with grade VI chicken egg albumin (OVA, 1 mg; Sigma-Aldrich, Saint-Quentin Fallavier, France) and aluminum hydroxide (OHA_1, 3.5 mg; Merck Eurolab, Briare Le Canal, France) diluted in 1 ml saline solution (Chlorure de sodium, Cooper 0.9%; Melun, France).

Surgical Procedure, Measurement of Hemodynamic Parameters and $Ptio_2$, and Induction of Shock

The surgical procedure was performed during general anesthesia on day 21. Anesthesia was induced with 60 mg/kg intraperitoneal thiopentone sodium (Sanofi Santé animale, Libourne, France) and maintained with intravenous additional doses (2 mg/kg) when required. 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 ml · kg^{-1} · h^{-1}) with Ringer's solution (Braun Medical SA, Boulogne, France). The trachea was cannulated, and the lungs were mechanically ventilated with 100% oxygen using a Harvard Rodent respirator model 683 (Harvard Apparatus, Cambridge, MA).

Mean arterial pressure was recorded using a strain gauge pressure transducer (DA-100; Biopac Systems, Northborough, MA). The pressure transducer and the electrocardiogram were connected to a desktop computer for continuous data acquisition (Acqknowledge software and MP 100 hardware; Biopac Systems).

A flexible Clark-type polarographic oxygen electrode (diameter and length of the oxygen partial pressure–sensitive area of the probe: 0.5–0.6 mm and 1 mm, respectively) computer-supported Licox system (GMS, Mielkendorf, Germany) was introduced in one of the quadriceps muscles. For correction of tissue oxygen partial pressure ($Ptio_2$) measurements, temperature within the muscle was monitored, and $Ptio_2$ values were adjusted to quadriceps temperature by means of the computer software Licox. The electrode was calibrated before and after each experiment with room air. The Licox system was connected to a desktop computer for continuous data acquisition (Acqknowledge). Hemodynamic values were allowed to stabilize for 30 min (stabilization period) after surgery, and pre–anaphylactic shock values were recorded before shock induction. In each group, anaphylactic shock was induced by injecting 1 mg ovalbumin diluted in 250 μl saline solution intravenously in 1 min. Time 0 (T0) corresponds to the beginning of ovalbumin injection.

Plasma Endogenous Arginine Vasopressin Measurement

In a first series of rats, we compared ovalbumin-sensitized BN rats randomly allocated to the anaphylactic shock or to the nicardipine group in which hypotension of amplitude similar to that of the anaphylactic shock group was obtained by injecting 2 μg/100 g (by weight) nicardipine (Novartis Pharma SA, Rueil-Malmaison, France) intravenously in 1 min followed by a continuous intravenous infusion of nicardipine (500 $\mu g \cdot 100\ g^{-1} \cdot h^{-1}$), as previously done.[8] At the end of the experiments (1 h after shock induction), 3 ml blood was withdrawn from the arterial catheter, and endogenous plasma AVP measurements were performed with a standard radioimmunologic method.[10] A polyclonal antivasopressin antibody and a radioactivated vasopressin tracer (RIA; Amersham Biosciences, Orsay, France) were used. The lower limit of detection for this assay in our laboratory is 1.2 pg/ml. The intraassay and interassay variation coefficients were of 9.4% and 19.2%, respectively.

Evaluation of Dose–Response Relations

Animals were randomly allocated into three groups (epinephrine, AVP, and terlipressin) according to a computer-generated randomization list. In each animal, post–anaphylactic shock values for MAP, heart rate, and $Ptio_2$ were recorded at T0 + 5 min corresponding to the time when MAP decreased at 40% of pre–anaphylactic shock values as previously described[8] (table 1). The first injection of the different vasoconstrictors was performed at T0 + 5 min (fig. 1). In each animal, a dose–response relation was obtained by injecting increasing doses (intravenous bolus in saline solution, 2 ml/kg) of seven doses of epinephrine (doses 1–7: 0.3–300 μg/kg, Adrénaline; Aguettant, Lyon, France), eight doses of AVP (doses 1–8: 0.03–100 U/kg, (Arginine[8])-Vasopressin Grade VI Solution APP; Sigma-Aldrich), or seven doses of terlipressin (doses 1–7: 0.03–30 μg/kg, Glypressine; kindly provided by Ferring, Gentilly, France). For each group, maximal MAP values obtained after each injection were averaged, then plotted (y-axis) against log dose (x-axis). Maximal MAP effect (Emax MAP) and ED_{50} were determined and expressed as mean and 95% confidence interval of the mean by using the four-parameter logistic equation according to the Hill model: $Y = \text{minimum} + (\text{Emax} - \text{minimum})/(1 + 10^{(\text{dose-logED50})})$, where minimum equals return to the hypotension level (Prism 3 algorithm for statistical analysis; GraphPad Software, San Diego, CA). For each rat, the following measurements were also performed: time interval in seconds between the end of the injection dose and (1) MAP maximal effect (peak) and (2) time required to return to hypotension values (recovery). Durations (in minutes) of the different experiments were recorded. At the end of the experiments, animals were killed by an overdose of thiopentone.

Table 1. Pre– (T0 − 5) and Post–Anaphylactic Shock (T0 + 5) Values for MAP, Heart Rate, and Skeletal Muscle $Ptio_2$ in the Epinephrine (n = 7), Arginine Vasopressin (n = 7), and Terlipressin (n = 7) Groups

Time, min	Epinephrine	Arginine Vasopressin	Terlipressin
MAP, mmHg			
T0 − 5	135 ± 14	133 ± 19	142 ± 15
T0 + 5	56 ± 5*	58 ± 6*	61 ± 8*
Heart rate, beats/min			
T0 − 5	473 ± 26	454 ± 32	425 ± 55
T0 + 5	399 ± 33*	411 ± 23*	445 ± 52
$Ptio_2$, mmHg			
T0 − 5	40 ± 5	47 ± 11	37 ± 7
T0 + 5	24 ± 5*	33 ± 11*	25 ± 13*

Values are expressed as mean ± SD. Time 0 (T0) corresponds to the injection of ovalbumin (* $P < 0.05$ *vs.* T0 − 5).

MAP = mean arterial pressure; $Ptio_2$ = tissue oxygen partial pressure.

Statistical Analysis

Results are expressed as mean ± SD for convenience, although several statistical tests were nonparametric. Endogenous plasma AVP measurements of anaphylactic shock and nicardipine groups were compared using a Mann–Whitney test. Intragroup and intergroup differences in epinephrine, AVP, or terlipressin groups were tested by 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, the mean values were compared with the postanaphylactic shock values by the Fisher exact test. The slopes of the MAP *versus* $Ptio_2$ value curves were compared using a Wilcoxon test. The criterion of significance was $P < 0.05$ (two tailed).

Results

Two series of experiments involving 45 ovalbumin-sensitized BN rats were performed. Endogenous plasma AVP concentrations were measured in a first series of rats (290 ± 16 g) randomly allocated to the anaphylactic shock (n = 12) or the nicardipine group (n = 12). Blood samples for AVP measurements were withdrawn 60 min after the induction of the anaphylactic shock or of the pharmacologic hypotension. A second series of 21 rats (317 ± 32 g) were randomly allocated to the epinephrine group (n = 7), the AVP group (n = 7), or the terlipressin group (n = 7). Endogenous plasma AVP concentrations were significantly lower ($P < 0.05$) in the anaphylactic shock group than in the nicardipine group: 57 ± 26 *versus* 91 ± 43 pg/ml, respectively.

Dose–Response Effects of Epinephrine, AVP, and Terlipressin on MAP Values

Pre–anaphylactic shock values (MAP, heart rate, $Ptio_2$) were not significantly different among the three groups (T0 − 5; table 1). Five minutes after induction of anaphylactic shock (post–anaphylactic shock values equivalent to mean values before the first dose of drug injection), a profound and similar reduction in MAP was observed in the three groups (table 1). The duration of the experiments was similar in the epinephrine (38 ± 22 min) and AVP (38 ± 20 min) groups, whereas it was significantly shorter (11 ± 5 min; $P < 0.05$) in the terlipressin group.

Dose–response curves for epinephrine, AVP, and terlipressin *versus* MAP values are presented in figure 2. Injections of epinephrine and AVP induced dose-dependent increases in MAP values. Epinephrine injection resulted in higher Emax MAP values as compared with AVP ($P < 0.05$). ED_{50} was 10.6 μg/kg for epinephrine and 4.1 U/kg for AVP (table 2). Injections of terlipressin did not change MAP values, regardless of the dose used. We had previously performed experiments (n = 5) that revealed that terlipressin increased MAP values in non-shocked, ovalbumin-sensitized, anesthetized BN rats. Increases of 18%, 27%, and 29% as compared with the MAP baseline values were respectively obtained within 2–3 minutes after a terlipressin dose of 1 μg/kg and within 1 min after doses of 3 and 10 μg/kg (data not shown). Heart rate values for the epinephrine, AVP, and terlipressin groups before and after each dose injection are presented in table 3. Heart rate values before and after the highest two doses of epinephrine were significantly increased when compared with the post–anaphylactic shock values ($P < 0.05$). When high doses of epinephrine were injected, there were 3 out of 7 rats

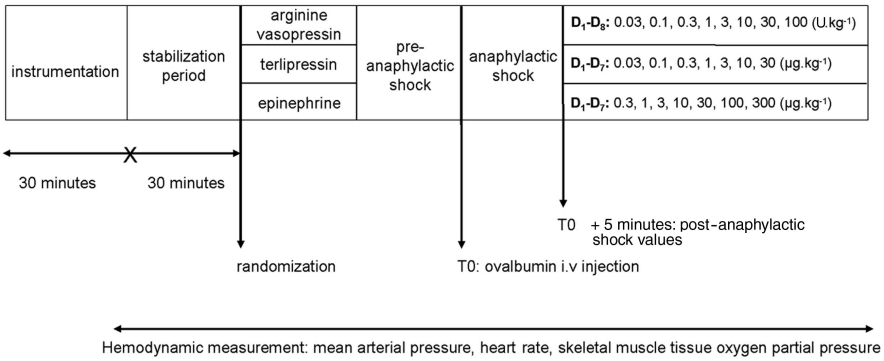

Fig. 1. Time course of the dose–response curves experiments. Time 0 (T0) corresponds to the injection of ovalbumin. Pre–anaphylactic shock values were recorded after randomization of the three groups of rats and before shock induction. Post–anaphylactic shock values were measured 5 min after shock induction (T0 + 5 min). The first dose of each drug was injected after the post–anaphylactic shock values were recorded. Each subsequent dose was injected when hypotensive values equivalent (P = not significant for each hypotension value before the subsequent injection *vs.* T0 + 5 min) to post–anaphylactic shock values were obtained. i.v. = intravenous.

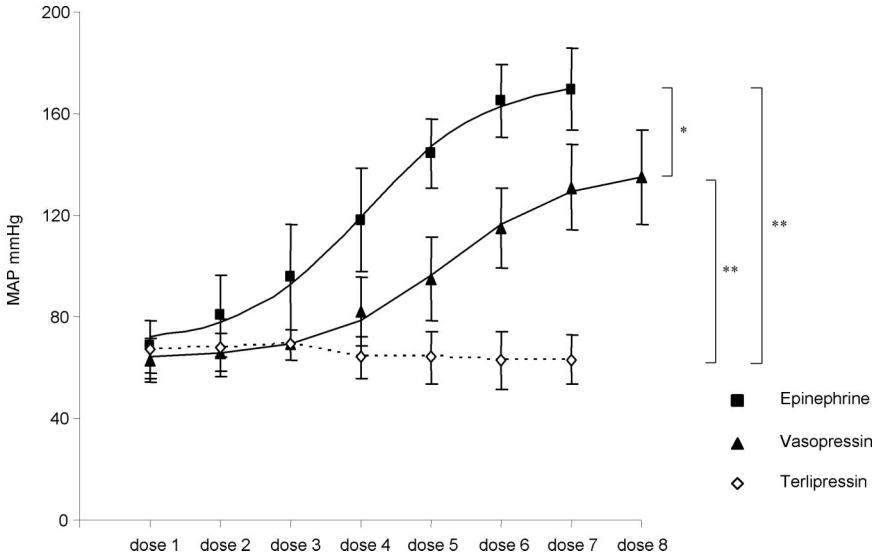

Fig. 2. Dose–response relations of increasing doses (seven or eight doses) of epinephrine, arginine vasopressin, or terlipressin on mean arterial pressure (MAP) in ovalbumin-sensitized Brown Norway rats after anaphylactic shock induction (n = 7 rats/group). The dose variable is plotted on the x-axis as logarithmic values. *Symbols* represent mean ± SD for peak MAP values reached after each injection, and *thin lines* were determined by using the four parameter logistic equation (Hill model) where minimum equals post–anaphylactic shock values. * $P < 0.05$ for the epinephrine *versus* AVP groups; ** for the epinephrine and AVP groups *versus* terlipressin group.

that presented episodes characterized by prolonged ventricular depolarization (QRS) complexes that lasted for approximately 50 s, which were reversible and consistent with episodes of ventricular tachycardia. These episodes of arrhythmia occurred at high doses of epinephrine (> 100 μg/kg) when MAP values were higher than 170 mmHg. In contrast, in rats that received AVP, there were no such episodes.

The time to peak MAP values and the time to return to hypotensive values for the three groups are presented in table 4. There were significant time-dependent increases in both the delay to peak and the delay to return to arterial hypotension values for both the epinephrine and AVP groups. The time to peak effect increased significantly after the seventh dose (300 μg/kg) in the epinephrine group ($P < 0.05$) and after the fourth dose (1 U/kg) in the AVP group ($P < 0.05$). The time to recovery increased dose dependently and was significantly longer in the epinephrine group ($P < 0.05$) after the seventh dose (300 μg/kg) and in the AVP group after the sixth dose (10 U/kg).

$Ptio_2$ Profiles

The $Ptio_2$ profiles for the three groups are presented in figure 3. $Ptio_2$ values decreased significantly ($P < 0.05$) after induction of anaphylactic shock in the three groups (table 1). $Ptio_2$ decreased after the first injection in the AVP group and after the second injection in the epinephrine and terlipressin groups ($P < 0.05$ *vs.* $Ptio_2$ measured before injection of the first dose of each drug). $Ptio_2$ decreased rapidly in the terlipressin group, whereas MAP values did not change. The slopes of the MAP *versus* $Ptio_2$ values were significantly different ($P < 0.05$) between the epinephrine and AVP groups and for the epinephrine and AVP groups *versus* the terlipressin group.

$Ptio_2$ values measured at MAP values (below 120 mmHg) observed after injections of 1–10 μg/kg epinephrine or after injections of 1–10 U/kg AVP were not significantly different between groups, whereas they remained higher ($P < 0.05$) in the epinephrine group at MAP values obtained after injections of 30 μg/kg epinephrine or 30–100 U/kg AVP.

Table 2. Emax MAP and ED_{50} in the Epinephrine (n = 7) and AVP (n = 7) Groups

	Emax MAP, mmHg	ED_{50}
Epinephrine, μg/kg	173 (165–181)*	10.6 (7.1–15.9)
AVP, U/kg	138 (133–143)	4.1 (3.0–5.6)

Data are expressed as mean (95% confidence interval).

* $P < 0.05$, epinephrine *vs.* arginine vasopressin (AVP).

Emax MAP = mean arterial pressure maximum effect.

Discussion

The main findings of this study were that (1) anaphylactic shock occurring in anesthetized BN rats, as compared with a model of nicardipine-induced arterial hypotension of similar magnitude,[8] was characterized by significantly lower concentrations of endogenous plasma AVP; (2) the effects of exogenous AVP and epinephrine on MAP, heart rate, and skeletal muscle $Ptio_2$ values were comparable at low doses and differed for the highest doses; (3) the ED_{50} values for epinephrine and AVP were 10.6 μg/kg and 4.1 U/kg, respectively; and (4) terlipressin, even at very high doses, did not increase MAP.

Epinephrine is the first-line vasopressor to treat cardiovascular collapse in most guidelines on perioperative management of anaphylaxis.††[2,4] However, epinephrine is not always successful, and situations where epinephrine does not restore cardiovascular homeostasis are considered as "epinephrine resistant," although no clear criteria define this term. In other situations of catechol-

Table 3. Time Course of Heart Rate in Epinephrine (n = 7), Arginine Vasopressin (n = 7), and Terlipressin (n = 7) Groups

Epinephrine		Arginine Vasopressin		Terlipressin	
Dose, μg/kg	Heart Rate, beats/min	Dose, U/kg	Heart Rate, beats/min	Dose, μg/kg	Heart Rate, beats/min
Dose 1: 0.3		Dose 1: 0.03		Dose 1: 0.03	
Before	399 ± 33	Before	416 ± 32	Before	445 ± 40
After	399 ± 38	After	394 ± 47	After	425 ± 72
Dose 2: 1		Dose 2: 0.1		Dose 2: 0.1	
Before	390 ± 35	Before	411 ± 38	Before	435 ± 65
After	403 ± 45	After	386 ± 40	After	410 ± 70*
Dose 3: 3		Dose 3: 0.3		Dose 3: 0.3	
Before	413 ± 62	Before	403 ± 34	Before	435 ± 65
After	411 ± 57	After	403 ± 34	After	415 ± 74*
Dose 4: 10		Dose 4: 1		Dose 4: 1	
Before	407 ± 42	Before	407 ± 52	Before	435 ± 65
After	416 ± 59	After	407 ± 42	After	405 ± 59*
Dose 5: 30		Dose 5: 3		Dose 5: 3	
Before	407 ± 54	Before	403 ± 45	Before	420 ± 63
After	410 ± 59	After	394 ± 63	After	405 ± 59*
Dose 6: 100		Dose 6: 10		Dose 6: 10	
Before	437 ± 64*	Before	416 ± 47	Before	420 ± 63
After	433 ± 60*	After	403 ± 52	After	405 ± 59*
Dose 7: 300		Dose 7: 30		Dose 7: 30	
Before	433 ± 67*	Before	411 ± 59	Before	425 ± 69
After	433 ± 57*	After	416 ± 53	After	400 ± 62*
		Dose 8: 100			
		Before	420 ± 42		
		After	416 ± 36		

Values are expressed as mean ± SD.

* $P < 0.05$ *vs.* values measured before injection of the first dose of each drug.

amine resistance (*i.e.*, in septic shock), exogenous AVP and terlipressin have been proposed and used.[5,6,11–14]

Part of the rationale for the use of exogenous AVP in several shock states is based on the observation that under those conditions, endogenous plasma AVP concentrations are inadequately low.[5,6] In the current study, we demonstrate that during the short period of time of this experimental anaphylactic shock, endogenous plasma AVP concentrations are significantly lower as compared with a nicardipine-induced model of arterial hypotension of similar profile. In response to arterial hypotension during hemorrhage or severe sepsis, endogenous AVP is released from the neurohypophysis, and its concentration in plasma increases (20- to 200-fold).[15] As shock worsens, the initially high plasma concentrations of endogenous AVP decrease. This was reported both in animal models during hemorrhagic shock[16] and in patients with septic shock[5,7] or presenting with arterial hypotension refractory to catecholamines after left ventricular assist device implantation.[17,18] Different mechanisms have been proposed to explain the late decrease of endogenous plasma AVP concentrations, such as (1) depletion of neurohypophyseal stores of AVP in advanced shock, (2) impaired baroreceptor-mediated AVP secretion,[5] and (3) increased norepinephrine levels responsible for central inhibitory effect on AVP release.[19] A causal role for a relative AVP deficiency in several forms of shock is suggested by studies that reported a correlation between the endogenous plasma AVP concentrations and the magnitude of arterial hypotension[5,7] and between the endogenous plasma AVP concentrations and survival after resuscitation of cardiopulmonary arrest.[20]

Because measurement of endogenous plasma AVP concentrations requires 3–4 ml blood per sample withdrawn, whereas the total blood volume in our rat model is approximately 18–20 ml, we could not perform a time-dependent profile of endogenous plasma AVP during anaphylactic shock. Therefore, further studies are needed to investigate whether lower endogenous plasma AVP concentrations in anaphylactic shock animals are preceded by a transient increase. A likely cause of decreased endogenous plasma AVP concentrations could be the increase of endogenous norepinephrine concentrations.[19] We previously demonstrated that a stronger sympathetic response was observed in the anaphylactic shock group as compared with a nicardipine-induced arterial hypotension of similar amplitude.[8] This could support the mechanism proposed by Day *et al.*[19] Nevertheless, we cannot exclude the fact that our results could be related to the choice of nicardipine as the hypotensive drug, and therefore, our results require confirmation with different hypotensive drugs before the profile of endogenous AVP during anaphylactic shock can be clearly defined.

The cardiovascular effects of epinephrine, AVP, and terlipressin are complex,[21] but in the context of resuscitation of anaphylactic shock occurring during anesthe-

Table 4. Time (in Seconds) between End of Injection and (1) Mean Arterial Pressure Maximal Effect (Peak) and (2) Time to Return to Hypotension Values (recovery) in the Epinephrine (n = 7) and Arginine Vasopressin (n = 7) Groups

Epinephrine, μg/kg	Peak	Recovery	Arginine Vasopressin, U/kg	Peak	Recovery
Dose 1: 0.3	10.9 ± 3.4	32 ± 19	Dose 1: 0.03	13.6 ± 2.1	22 ± 7
Dose 2: 1	10.7 ± 1.4	32 ± 13	Dose 2: 0.1	14 ± 4	32 ± 12
Dose 3: 3	11.3 ± 2.6	37 ± 14	Dose 3: 0.3	19 ± 5	54 ± 28
Dose 4: 10	12.1 ± 1.1	55 ± 21	Dose 4: 1	21 ± 9	76 ± 56
Dose 5: 30	16 ± 4	82 ± 20	Dose 5: 3	32 ± 14‡	130 ± 39
Dose 6: 100	15 ± 3	213 ± 80	Dose 6: 10	35 ± 11‡	322 ± 201‡
Dose 7: 300	29 ± 15*	1,081 ± 419*	Dose 7: 30	38 ± 9‡	532 ± 264‡
			Dose 8: 100	30 ± 10‡	636 ± 233‡

Values are expressed as mean ± SD.

* $P < 0.05$ *vs.* dose 0.3 of epinephrine. ‡ $P < 0.05$ *vs.* dose 0.03 of arginine vasopressin.

sia, the therapeutic target is restoration of flow and function of vital organs. In the clinical context, MAP values are an acceptable surrogate because they can be measured with minimum effort. Therefore, the current study focused on MAP values to construct dose–response curves. The heart rate response was investigated because it is one of the determinants of left ventricular minute work and its increase is associated with decreased diastolic time, possibly impairing left ventricular myocardial perfusion. Because we recently demonstrated that anaphylactic shock in anesthetized BN rats is associated with intense vasoconstriction and rapidly decreased $Ptio_2$ values in skeletal muscle,[8] we investigated this compartment, which rapidly responds to changes in the central and peripheral circulation, to compare the effects of the three drugs on the oxygen delivery–oxygen consumption balance.

Both exogenous AVP and epinephrine injections resulted in increased MAP values, and for both drugs, there was a wide 95% confidence interval. When investigating the time to peak effect on MAP and the delay to return to arterial hypotension after repeated bolus injection, we observed that for both drugs, at higher doses there was a statistically significant increase in time to peak effect. The design of our experiments does not allow us to identify the causes of the increase of the time to peak effect. In addition, for the lowest doses of the two drugs, the delays to return to arterial hypotension were short, thus suggesting the interest for both drugs of a continuous infusion.

At the highest doses, there were differences in the hemodynamic effects of epinephrine and exogenous AVP. These differences are as follows: (1) MAP values were significantly higher with epinephrine as compared with AVP; (2) episodes of ventricular arrhythmia occurred with epinephrine, a proarrhythmogenic effect that was not observed in animals treated with AVP; and (3) AVP injection was associated, at higher doses (30 and 100 U/kg), with lower $Ptio_2$ values ($P < 0.05$) as compared with epinephrine (30 μg/kg) at equivalent MAP values. When MAP values after either epinephrine or AVP was in the range of 80–120 mmHg, $Ptio_2$ values were not significantly different between the two groups.

The interpretation of the skeletal muscle $Ptio_2$ values

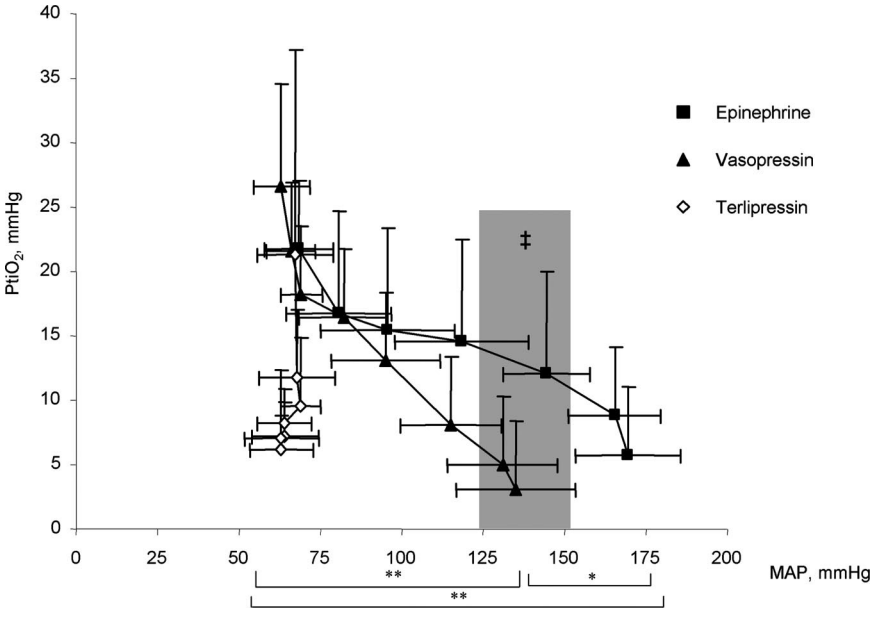

Fig. 3. Changes in skeletal muscle tissue oxygen partial pressure ($Ptio_2$) according to peak mean arterial pressure (MAP) values reached after injections of increasing doses of epinephrine, arginine vasopressin, or terlipressin in ovalbumin-sensitized Brown Norway rats after induction of anaphylactic shock (n = 7 rats/group). *Symbols* represent mean ± SD for $Ptio_2$ values reached after each injection. The slopes of the MAP *versus* $Ptio_2$ values were different (* $P < 0.05$ for the epinephrine *versus* AVP groups; ** for the epinephrine and AVP groups *versus* terlipressin group). $Ptio_2$ values measured in the epinephrine group were higher (‡ $P < 0.05$) at MAP values obtained after injections of 30 μg/kg if compared with the AVP group after injections of 30–100 U/kg.

in shock states is complex. In a previous study of anaphylactic shock in anesthetized rats, we associated measurements of skeletal muscle $Ptio_2$ values with measurements of interstitial lactate and pyruvate concentrations. We demonstrated that the most likely interpretation of low $Ptio_2$ values and increased lactate/pyruvate ratios in this model of anaphylactic shock was rapid failure of energy production in the skeletal muscle.[8] We interpret the lower $Ptio_2$ values in rats resuscitated with high doses of AVP as the effect of excessive vasoconstriction, increased oxygen consumption, or both, and we consider the lower $Ptio_2$ values as a potential deleterious effect of AVP. Nevertheless, AVP was associated with significantly lower $Ptio_2$ values only at the highest doses, which will probably never be used in clinical practice. However, at lower AVP doses, for similar increased on MAP values, AVP and epinephrine resulted in comparable $Ptio_2$ values.

Terlipressin is a synthetic derivative of vasopressin. It is a prodrug that is converted to lysine vasopressin in the circulation after the N-triglycyl residue is cleaved by endothelial peptidases.[21] This results in a rapid and sustained release of the structural analog lysine vasopressin. The reason for which terlipressin was investigated in the current study is that despite differences with AVP for its hemodynamic effects, terlipressin has been used as an alternative to exogenous AVP, especially in France, where AVP is not commercially available.[12,22–25] Unexpectedly, terlipressin, which has been reported to be effective in catecholamine-resistant septic shock in adults[12,24,26,27] and in children,[28] did not increase MAP values during anaphylactic shock, regardless of the dose injected. The lack of increase of MAP in terlipressin-treated animals explains the shorter duration of the experiments as compared with the two other groups. The explanations for this lack of MAP effect are not clear. In experimental studies, terlipressin significantly increased MAP values without decreasing aortic blood flow in fluid-challenged endotoxic rats but not in hypodynamic rats[29] or in an endotoxemic sheep,[30] where MAP increase was accompanied by a progressive decrease in cardiac index. The authors concluded that it might therefore be advantageous to infuse terlipressin gradually instead of administering it as a bolus.[30] In an isolated rabbit heart model, terlipressin induced coronary blood flow reduction and, consequently, myocardial depression, only at supratherapeutic concentrations ($\geq$ 30 nM).[31] The lack of effect of terlipressin is not strain related because, as stated in the Results section, we could observe an increase in MAP values after terlipressin infusion in the absence of anaphylactic shock. Therefore, we propose two possible explanations for the lack of effect of terlipressin in this experimental model: (1) hypovolemia occurring after onset of anaphylactic shock and (2) a deleterious effect of terlipressin bolus infusion on cardiac output.

The $Ptio_2$ profile in rats injected with terlipressin is unexpected. In the absence of an increase of MAP values upon terlipressin injection, one would have expected a $Ptio_2$ profile comparable to that observed in rats with unresuscitated anaphylactic shock.[8] Nevertheless, as compared with a nonresuscitated model, terlipressin injections resulted in a faster decrease of skeletal muscle $Ptio_2$. One possible explanation of these results could have been increased skeletal muscle oxygen consumption (Vo_2) in the absence of an increased blood flow and oxygen transport. This hypothesis is not supported by several published articles that showed that terlipressin-induced a decrease of global Vo_2 in an endotoxemic sheep[30] or pig model[32] and in patients treated with renin-angiotensin system inhibitors receiving terlipressin to counteract the anesthesia-induced hypotension.[25] Therefore, the mechanisms of the rapidly decreasing $Ptio_2$ values in anaphylactic shock rats injected with terlipressin require further studies.

Our results provide experimental arguments for the possible use of AVP in humans with anaphylactic shock, as already reported by several authors.[33–35] Another experimental argument favoring the use of exogenous AVP, in addition to the lower endogenous plasma AVP concentrations demonstrated in our study, could be the fact that an *in vitro* study showed that whereas epinephrine only partially reversed histamine-induced vasodilatation in human internal mammary arteries, vasopressin leads to a complete reversal of the vasculature relaxation.[36]

The ED_{50} value calculated for AVP in our study was approximately 4 U/kg. A possible explanation of these ED_{50} values calculated in the current experiments may be due to the use of cumulative doses. Hiruta *et al.*[37] reported that the highest increase in MAP values in a rabbit model of anaphylactic shock was observed with 0.8 U/kg AVP, but the highest survival was observed with 0.08 U/kg AVP. The detrimental effect of the higher AVP dose was assumed by the authors to be related to decreased AVP-induced myocardial function. Taken together, the results of Hiruta *et al.*[37] are consistent with our observations in that lower doses of AVP seem to have the most favorable results in the experimental setting.

Arguments against the use of exogenous AVP in anaphylactic shock, but also in other forms of shock, could be due to excessive vasoconstriction in the splanchnic circulation[38] as well as other territories.[39,40] Indeed, in the current experiments, high doses of exogenous AVP that will probably never be used in clinical practice did decrease $Ptio_2$ values in skeletal muscle. Nevertheless, for lower doses, there were no differences for skeletal muscle $Ptio_2$ values between AVP and epinephrine. Whether this observation can be extrapolated to other organs in rats or to patients with comorbidities is not known. Our results should be interpreted by taking into account the species in which they were performed, the model of induction of anaphylaxis (ovalbumin), and also

the model that was used to induced the arterial hypotension in the control group, *i.e.*, the injection of nicardipine.

In conclusion, we provide information on dose–response curves for epinephrine and AVP and demonstrate that in this experimental model, AVP, but not terlipressin, may restore blood pressure during anaphylactic shock, corroborating recent clinical reports.[33–35] Further work is needed to study the optimal role of AVP in treatment of patients experiencing anaphylactic shock.

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