

ANAPHYLACTIC SHOCK DECREASES CEREBRAL BLOOD FLOW MORE THAN WHAT WOULD BE EXPECTED FROM SEVERE ARTERIAL HYPOTENSION

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ABSTRACT—The effects of acute reduction in arterial blood pressure in severe anaphylactic shock (AS) on cerebral blood flow are of paramount importance to be investigated. We studied cerebral circulation and oxygenation in a model of severe AS and compared it with a pharmacologically induced arterial hypotension of similar magnitude. Anaphylactic shock was induced by 1 mg intravenous ovalbumin (OVA) in sensitized rats. Rats were randomized to three groups: (i) no resuscitation (OVA; $n = 10$) (ii) intravenous volume expansion (10 mL in 10 min after OVA injection) (OVA + VE; $n = 10$); (iii) control hypotension (100 μ g of nicardipine followed by continuous infusion of 1 mg $\cdot$ 100 g⁻¹ $\cdot$ h⁻¹ intravenously; NICAR; $n = 10$). Mean arterial pressure (MAP), carotid blood flow (CBF), cardiac output, cerebral cortical blood flow (CCBF; estimated by laser Doppler technique), and cerebral tissue oxygen pressure (PtiO₂) were recorded over the 15 min following AS induction in all three groups. Results are expressed as mean (SD). One minute after OVA or nicardipine injection, there was a rapid and significant 50% decrease in MAP from basal values. In the OVA group, AS severely altered systemic and cerebral hemodynamics in 5 min: 93% (SD, 4%) decrease in CBF, 66% (SD, 8%) in CCBF, and 44% (SD, 8%) in PtiO₂; the decrease in CBF was significantly ($P < 0.05$) attenuated in the OVA + VE group; however, CCBF and PtiO₂ were not statistically different in the OVA versus OVA + VE groups. On the contrary, nicardipine-induced hypotension had only a limited impact on CBF, cardiac output, CCBF, and PtiO₂ for a similar MAP decrease. There was a linear relation between CCBF and blood pressure in the OVA (regression slope: 0.87 [SD, 0.06]; median $r^2 = 0.81$) but not in the NICAR group (regression slope: 0.23 [SD, 0.32]; median $r^2 = 0.33$). Anaphylactic shock resulted in severe impairment of cerebral blood flow and oxygenation, beyond what could be expected from the level of arterial hypotension.

KEYWORDS—Shock, anaphylaxis, cerebrovascular circulation, autoregulation

INTRODUCTION

Anaphylactic shock (AS) is a rapid, potentially fatal reaction within the spectrum of generalized immediate-type hypersensitivity (i.e., anaphylaxis) (1), which can lead to death even when the reaction is recognized rapidly and treated adequately. Although its epidemiology remains incompletely characterized, anaphylaxis is a relatively common problem (2). The mechanisms of anaphylaxis are thought to be immune (i.e., immunoglobulin E [IgE]- and/or IgG-mediated) or nonimmune (mediators released following nonspecific stimuli).

The most severe manifestation of anaphylaxis is AS. Its treatment is challenging because its pathophysiology remains largely obscure (3).

Central nervous system dysfunction associated with AS is considered generally to be secondary to hypotension (4). However, the response of cerebral vasculature to changes in blood pressure and cardiac output (CO) differs from other vascular territories (5, 6). Indeed, to maintain adequate cerebral blood flow despite frequent changes in systemic arterial blood pressure and to adjust constantly blood supply to the current metabolic demand dictated by neuronal electrical activity, the brain has developed a myriad of adaptive mechanisms. The mechanisms were probably formed during evolution to protect the central nervous system from potentially fatal consequences of shock states (hemorrhagic and septic) as well as other injuries such as hypoxia or energy substrate deficiency and are grouped under the term “cerebral autoregulation” (7).

However, during AS, the consequences of systemic hemodynamic alterations and the direct effects of mediators of anaphylaxis on cerebral vasculature and brain perfusion remain to be determined. Understanding the consequences of

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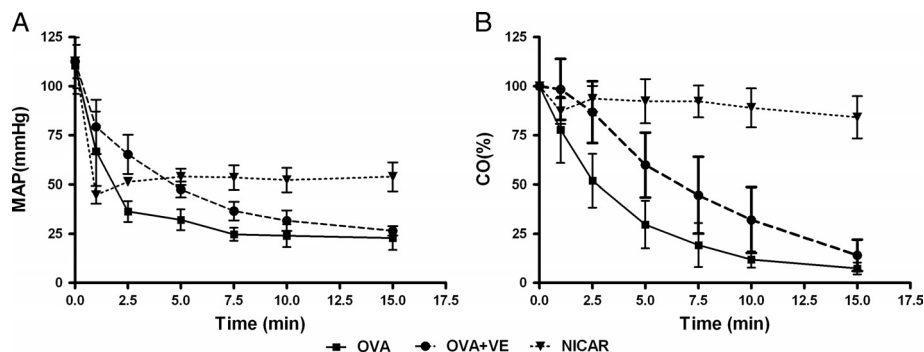


FIG. 1. Time course of systemic hemodynamic parameters: MAP (A) and CO (B) in NICAR, OVA, and OVA + VE groups. Results are expressed as mean (SD). Cardiac output results are expressed as percentage change from baseline. A, The time course of MAP values was significantly different among groups ($P < 0.05$). An initial sharp decrease in MAP was observed in the three groups. Mean arterial pressure remained stable in the NICAR group but not in rats receiving OVA (OVA and OVA + VE groups). The decrease in MAP was attenuated transiently by volume expansion (OVA + VE). B, A moderate but not significant decrease in CO was observed in rats treated with nicardipine (NICAR), whereas a very rapid and profound decrease in CO was observed in animals treated with OVA (OVA and OVA + VE groups). Once again, this decrease was attenuated transiently by volume expansion ($P < 0.05$).

AS on brain perfusion may be of critical importance in delineating optimal therapeutic goals and strategies (8).

We hypothesized that AS could impair cerebral blood flow beyond its characteristic arterial hypotension. To test this hypothesis, we measured several determinants of systemic and cerebral hemodynamics in an ovalbumin (OVA)-induced model of AS in Brown Norway rats. These results were compared with a model of pharmacologically induced arterial hypotension of similar magnitude (9).

MATERIALS AND METHODS

Animals and sensitization protocol

This study was approved by the Animal Care Committee of the University Hospital (Nancy, France) and was conducted according to the official recommendations of the French Ministry of Agriculture (Paris, France) and the recommendations of the Helsinki Declaration. Ten-week-old Brown Norway male rats weighing 250 to 300 g (Janvier, Le Genest-St-Isle, France) were used for these experiments. They were kept under standard conditions (temperature, 21°C [SD, 1°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, Ill) *ad libitum*. Rats were sensitized by subcutaneous administration of grade VI chicken egg albumin (OVA, 1 mg; Sigma-Aldrich, Saint-Quentin Fallavier, France) and aluminum hydroxide (OHA1, 4 mg; MercEurolab, Briare Le Canal, France) diluted in 1 mL 0.9% saline solution on days 0, 4, and 14, as previously described (9, 10).

Surgical procedure and measurement of hemodynamic variables

The surgical procedure was performed on day 21 following the initial sensitization. Anesthesia was induced using 3% isoflurane. The trachea was intubated, and the lungs were mechanically ventilated with 100% oxygen using a Harvard Rodent respirator model 683 (Harvard Apparatus, Cambridge, Mass) to maintain P_{aCO_2} between 38 and 42 mmHg. Maintenance of anesthesia was ensured with 1% isoflurane. Rectal temperature was maintained at 38°C (SD, 0.5°C) by intermittent warming with a heating pad. A fluid-filled polyethylene catheter (internal diameter, 0.58 mm; outer diameter, 0.96 mm; Biotrol Diagnostic, Chennevières Les Louvres, France) was inserted into the right femoral vein for administration of drugs and fluid maintenance (10 mL $\cdot$ kg⁻¹ $\cdot$ h⁻¹ of 0.9% saline solution). Mean arterial pressure (MAP) was monitored continuously with a fluid-filled polyethylene catheter (internal diameter, 0.58 mm; outer diameter, 0.96 mm; Biotrol Diagnostic) using a strain gauge pressure transducer (DA-100; Biopac Systems, Northborough, Mass) inserted into the right femoral artery. Cardiac output and carotid blood flow (CBF) were measured using perivascular ultrasonic flow probes (RB1 and RB2) (Transonic System Inc, Ithaca, NY) placed on the abdominal aorta and the right carotid artery, respectively.

Following this preparation, animals were placed in the prone position for craniotomy. A flexible Clark-type polarographic oxygen electrode (diameter of 0.5–0.6 mm, length of 1 mm) connected to a computer-supported Licox system (GMS, Mielkendorf, Germany) was inserted into the right cerebral cortex 2 mm lateral to the bregma for cerebral oxygen pressure monitoring (P_{tO_2}). Cerebral cortical blood flow (CCBF) was monitored using a PeriFlux PF 5010 laser

Doppler monitor (Perimed AB, Stockholm, Sweden) with a laser Doppler needle probe (reference 402, diameter of 0.45 mm, fiber separation of 0.14 mm) inserted into the skull on the surface of the right cerebral cortex 2 mm rostral to the oxygen electrode.

After a 20-min stabilization period, animals were randomly allocated into three groups according to a computer-generated randomization list. In (OVA) animals, shock was induced by injecting intravenously 1 mg of OVA diluted in 1 mL of 0.9% saline solution in 1 min, in the absence of any treatment (OVA; $n = 10$).

In (OVA + VE) rats, shock was induced with OVA in association with volume expansion (OVA + VE; $n = 10$). Volume expansion (3 mL of 0.9% saline solution over 10 min before, then 10 mL [30 mL/kg] over the first 10 min following shock induction) was chosen to partially attenuate the rapidity of the CO decrease, to allow us to study more precisely cerebral blood flow, brain oxygenation, and systemic blood pressure relationship. Volume expansion was preferred to epinephrine to avoid possible interactions between mediators of anaphylaxis and epinephrine on cerebral vascular reactivity. Furthermore, this experimental design may mimic a clinical situation where a patient has developed AS outside the hospital while waiting for medical treatment, and the only therapeutic intervention could be passive leg-raising-induced volume expansion.

The third group consisted of sensitized rats (NICAR; $n = 10$) in which arterial hypotension corresponding to a 50% decrease in MAP was obtained by intravenous injection of 100 μ g of nicardipine followed by a continuous intravenous infusion of 1 mg $\cdot$ 100 g⁻¹ $\cdot$ h⁻¹ (Novartis Pharma SA, Rueil-Malmaison, France), as described previously (10).

In all animals, mean arterial blood pressure, CO, CBF, CCBF, and P_{tO_2} were continuously monitored. Values were recorded at different times: before shock induction (T0); at T1, T2.5, and T5 min; and then every 5 min until the end of experiment.

Statistical analysis

Results are expressed as mean (SD). Intragroup and intergroup differences were tested by one- and two-way analyses 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.

For each animal, the linear regression curve for the relation between values of CCBF versus MAP was drawn, and r^2 was determined. For each group, mean slope, mean Y-intercept, and median r^2 (min–max) were determined and used to draw the mean linear regression curve of the group. Significance was assumed when $P < 0.05$.

RESULTS

Thirty OVA-sensitized Brown Norway rats were studied and allocated randomly to the OVA group (263.6 [SD, 16.3] g, $n = 10$), OVA + VE group (267 [SD, 14.0] g, $n = 10$), and NICAR group (283.6 [SD, 18.4] g, $n = 10$). For all measured variables, baseline values in the three groups did not differ during the stabilization period.

This is a model of very severe AS leading to the death of all untreated animals after approximately 20 min. The general time-dependent profile of changes in MAP was similar in the three

TABLE 1. Time course of MAP, CO, CBF, and CCBF in OVA, OVA + VE, and NICAR groups (n = 10 rats/group)

		OVA	OVA + VE	NICAR
MAP, mmHg	T0	110.5 (14.4)	112.5 (8.6)	112.6 (13.7)
	T1	66.8 (20.3)*	79.3 (13.8)*	44.8 (4.5)
	T2.5	36.3 (5.3)*,†	65.3 (9.9)*	51.3 (2.1)
	T5	32.1 (5.3)*,†	47.5 (4.0)*	53.9 (4.2)
	T7.5	24.7 (3.3)*,†	36.6 (4.7)*	53.5 (6.2)
	T10	24.0 (5.8)*,†	31.7 (5.3)*	52.3 (6.2)
	T15	22.8 (6.1)*	26.5 (2.4)*	53.9 (7.3)
CO, mL · min ⁻¹	T0	19.8 (2.1)	19.8 (5.6)	19.1 (2.3)
	T1	15.4 (4.0)	19.5 (3.6)	16.8 (3.0)
	T2.5	10.4 (3.4)*,†	17.2 (3.3)	17.8 (2.3)
	T5	6.0 (3.1)*,†	11.8 (3.0)*	17.6 (2.9)
	T7.5	4.0 (2.7)*,†	8.8 (3.7)*	17.5 (1.7)
	T10	2.4 (1.0)*,†	6.4 (3.2)*	16.9 (1.5)
	T15	1.5 (0.6)*	2.6 (1.1)*	16.0 (1.9)
CBF, mL · min ⁻¹	T0	5.6 (1.2)*	6.6 (1.5)*	4.2 (0.9)
	T1	2.8 (1.8)†	5.9 (1.5)*	3.4 (1.7)
	T2.5	0.9 (1.0)*	4.0 (1.2)*	4.1 (1.8)
	T5	0.4 (0.6)*,†	2.7 (1.4)*	4.2 (1.9)
	T7.5	0.2 (0.3)*,†	1.7 (0.7)*	3.9 (1.9)
	T10	0.1 (0.2)*	1.4 (0.7)*	3.6 (1.8)
	T15	0.1 (0.1)*	0.6 (0.4)*	3.4 (1.8)
CCBF, perfusion unit	T0	104 (42.9)	119.2 (27.3)	90.3 (23.7)
	T1	82.3 (31.1)	86.1 (22.3)	79.4 (15.4)
	T2.5	58.0 (29.6)*	73.7 (18.5)	88.4 (14.9)
	T5	35.3 (23.4)*,†	61.1 (16.7)*	84.8 (11.6)
	T7.5	27.5 (22.0)*	48.3 (16.2)*	82.8 (8.9)
	T10	22.0 (18.8)*	42.1 (19.4)*	80.6 (10.6)
	T15	15.4 (11.5)*	24.5 (17.0)*	84.6 (11.4)

T0: OVA injection. Values are presented as mean (SD).

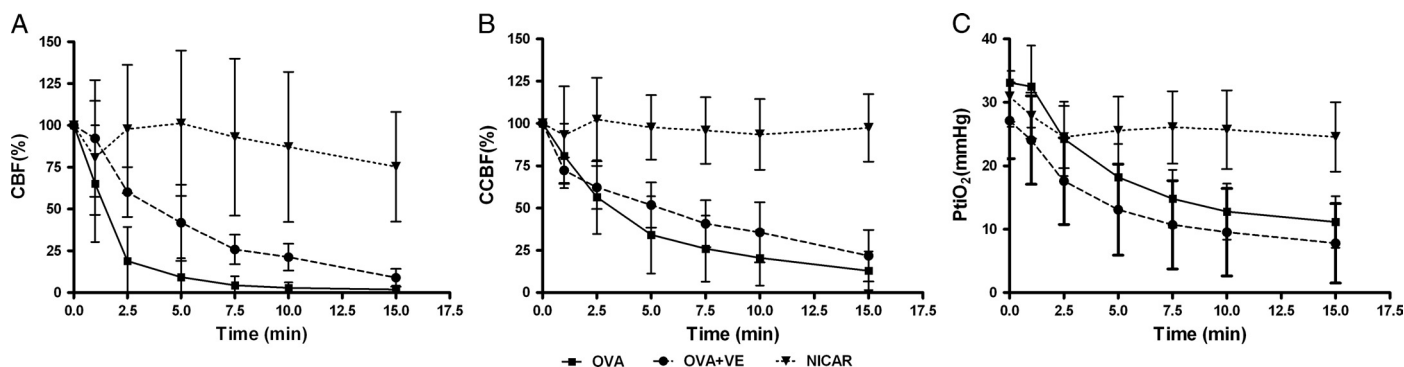
* $P \leq 0.05$ vs. NICAR group.† $P \leq 0.05$ vs. OVA + VE group.

FIG. 2. Time course of cerebral perfusion parameters: CBF (A), CCBF (B), and tissue oxygen partial pressure (PtiO₂) (C) in NICAR, OVA, and OVA + VE groups. Results are expressed as mean (SD). Carotid blood flow and CCBF results are expressed as percentage change from baseline values. The evolution of the three cerebral perfusion parameters was significantly different among groups ($P < 0.01$). A, Carotid blood flow was relatively preserved in the NICAR group, whereas a dramatic decrease in CBF was observed in the OVA groups, reaching an almost complete interruption of perfusion at 5 min (OVA). This decrease was attenuated significantly by volume expansion; however, CBF reached 50% of the baseline value as of 5 min, and complete interruption of CBF occurred at 15 min (OVA + VE). B, Cerebral cortical blood flow was relatively preserved in the NICAR group, whereas a dramatic decrease in CCBF was observed following OVA injection (OVA and OVA + VE). C, Tissue oxygen partial pressure was relatively preserved in the NICAR group, whereas a dramatic and similar decrease in PtiO₂ was observed following OVA injection (OVA and OVA + VE).

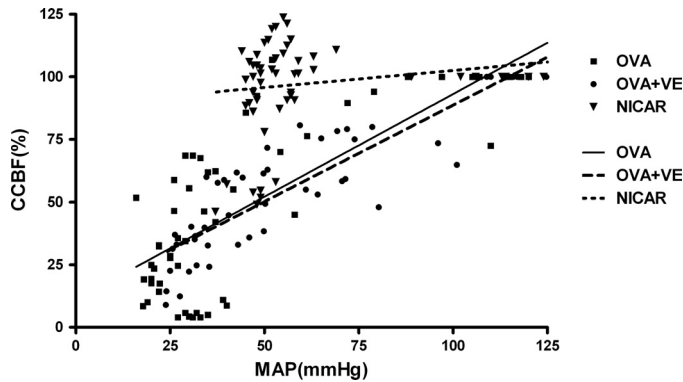


FIG. 3. Mean linear regression of the relation between CCBF changes versus MAP in NICAR, OVA, and OVA + VE groups. Slopes were statistically different between NICAR group and both other groups ($P < 0.001$), whereas they were not between the OVA and OVA + VE groups ($P > 0.05$).

groups with slight but significant differences among groups for MAP values ($P < 0.05$). In rats receiving nicardipine, an initial sharp decrease of 50% of MAP was observed as soon as 1 min after nicardipine injection, followed by a plateau until the end of experiment (Fig. 1A). A similar sharp decrease in MAP was observed when shock was induced with OVA injection (OVA and OVA + VE groups), but this initial decrease was transiently attenuated by volume expansion (OVA + VE) (Fig. 1A, Table 1). Subsequently, a further progressive decrease in MAP was observed in animals that received OVA. Changes in CO, on the other hand, showed a completely different profile in the three groups ($P < 0.001$). A moderate but insignificant decrease in CO was observed in rats treated with nicardipine (Fig. 1B, Table 1), whereas a very rapid and profound decrease in CO was observed in animals receiving OVA. Once again, this decrease was transiently attenuated by volume expansion ($P < 0.05$).

Cerebral perfusion parameters exhibited a completely different profile among the groups ($P < 0.01$) (Fig. 2, A–C; Table 1). In the NICAR group, limited decreases from baseline in CBF (26% [SD, 9%]), CCBF (10% [SD, 6%]), and P_{tO_2} values (21% [SD, 5%]) were observed, suggesting that brain perfusion was preserved throughout the experiment (Fig. 2, A–C; Table 1). In rats receiving OVA, in the absence of volume expansion, rapid

decreases in carotid (93% [SD, 4%] decrease from baseline values in 5 min) and cerebral blood flow (66% [SD, 8%] decrease in 5 min) and P_{tO_2} (44% [SD, 8%] decrease in 5 min) were observed (Fig. 2, A–C; Table 1), reaching ischemic thresholds values within 5 min following OVA injection. The decrease in CBF was significantly attenuated by volume expansion ($P < 0.05$) (OVA + VE); however, CCBF and P_{tO_2} were not statistically different in the OVA versus OVA + VE groups.

The relation between CCBF versus MAP values showed significant differences among the groups (Fig. 3). In the NICAR group, the mean linear regression slope was 0.23 (SD, 0.32) (median $r^2 = 0.33$; 0–0.99), significantly lower than those in the OVA group (0.87 [SD, 0.19]; $P < 0.001$) (median $r^2 = 0.81$; 0.67–0.99) and in the OVA + VE group (0.94 [SD, 0.22]; $P < 0.001$) (median $r^2 = 0.94$; 0.83–1.00) (Fig. 3). The mean slopes of OVA and OVA + VE groups were not significantly different ($P > 0.05$). In the NICAR group, cortical blood flow was preserved when MAP remained higher than 50 mmHg, and the low r^2 value reflected a nonlinear model consistent with preserved autoregulation. In contrast, in the OVA and OVA + VE groups, cortical blood flow decreased as soon as shock was induced, and the r^2 values close to 1 showed that the MAP–cerebral blood flow relation was linear, suggesting a profound alteration in cerebral blood flow autoregulation (Fig. 3).

Blood gas parameters are presented in Table 2. No differences were observed among groups before OVA or nicardipine injection (T0). Fifteen minutes after onset of shock, the levels of pH and P_{aCO_2} in the groups suffering from anaphylaxis were significantly lower than those in the group NICAR, whereas lactate levels were significantly increased when compared with the NICAR group.

DISCUSSION

The main findings of this study were that AS induced by OVA in sensitized rats impaired dramatically both systemic and cerebral hemodynamics. In addition, in this model of AS, cerebral blood flow decreased linearly with the decrease in MAP. Taken together, these observations suggest that, during AS, cerebral blood flow and oxygenation impairments are more severe than

TABLE 2. Biochemistry variables in OVA, OVA + VE, and NICAR groups (n = 10 rats/group)

		OVA	OVA + VE	NICAR
pH	T0	7.38 (0.04)	7.39 (0.07)	7.41 (0.03)
	T15	7.17 (0.07)* [†]	7.16 (0.02)* [†]	7.40 (0.07)
P_{aCO_2} , mmHg	T0	39.6 (0.9)	40.3 (1.6)	38.9 (1.9)
	T15	10.7 (4.5)* [†]	15.2 (6.4)* [†]	39.4 (3.1)
P_{aO_2} , mmHg	T0	291.3 (26.7)	309.7 (49.8)	295.2 (34.6)
	T15	193.3 (35.9)* [†]	343.2 (54.6)*	287.0 (33.7)
Lactate, mmol · L ⁻¹	T0	2.7 (0.6)	2.3 (0.4)	2.9 (1.0)
	T15	13.1 (2.8)* [†]	6.9 (2.7)* [†]	3.4 (1.2)
Hemoglobin, g · dL ⁻¹	T0	12.1 (1.0)	12.7 (1.1)	12.4 (1.3)
	T15	14.3 (2.0)* [†]	14.7 (1.4)* [†]	12.1 (0.9)

T0: OVA injection. Values are presented as mean (SD).

* $P \leq 0.05$ vs. T0.

[†] $P \leq 0.05$ vs. NICAR group.

what could be anticipated from the simple decrease in MAP. Volume expansion did not appear to correct the alterations in cerebral hemodynamics.

The OVA-sensitized Brown Norway rat model has been previously characterized as a suitable model of lethal AS (10) resulting from sensitization associated with the presence of circulating antibodies, which belong to a class of immunoglobulins analogous to human IgE (11). Its comparison with a pharmacologically induced arterial hypotension state (nicardipine infusion) allowed us to investigate the specific consequences of anaphylaxis, considered as a complex hemodynamic and inflammatory process, on cerebral perfusion for a similar acute decrease in MAP. Nicardipine was chosen because its effects on the cerebral vasculature are relatively well documented. It has direct cerebral vasodilating effects and therefore would produce arterial hypotension and cerebral vasodilation without a significant decrease in CO (12) in the absence of any inflammatory component. This model has been characterized previously by our group (10, 13, 14).

We chose also to investigate the effects of volume expansion for the following reasons: (i) AS occurs most often in a non-medical setting, where in a recumbent patient, passive leg raising, an equivalent of volume expansion, may represent the single treatment measure available (while waiting for an epinephrine injection or advanced medical therapy). In addition, this experimental design allowed us to investigate possible mechanisms that could explain why nonanesthetized patients with AS die rapidly when standing (15); (ii) vasoactive drugs such as epinephrine could alter by themselves vascular reactivity and therefore the MAP versus cerebral blood flow relation.

The classic description of an AS is that of a distributive shock during which several regional circulations, i.e., brain, could be (at least in part) preserved by a change in the proportion of blood flow distribution (16, 17). However, this classic view of the hemodynamic consequences of the AS has been challenged recently in several reports; a severe decrease in blood perfusion in an adaptive compartment such as skeletal muscles combined with a persistence of a high level of energy consumption, resulting in a rapid and irreversible failure of energy production, has been reported recently (10). In addition, the idea of an initially preserved CO has also been challenged in several animal models of AS. Although several interspecies differences may exist, impaired myocardial contractility has been demonstrated in lethal models of anaphylaxis (18, 19), whereas less severe myocardial depression was observed in nonlethal models (20). In addition, an increase in venous tone in the splanchnic and portal vascular beds, with a presinusoidal contraction within the liver, as well as in the pulmonary veins resulting in a rapid decrease in preload and CO has been reported recently (21–23). In our model, we observed a rapid decrease in CO, which may be related to decreased venous return, as well as to a direct depressing effect of mediators on myocardial contractility.

Maintaining cerebral blood flow in any type of shock represents a major treatment end point. Based on the unexpected diversity of regional hemodynamic responses to anaphylaxis shown in experimental models, we hypothesized that, contrary to the canonical view, the classic protective “brain-sparing

effect” thought to exist in all shock states could be altered very rapidly in severe anaphylaxis. Indeed, anaphylaxis in the OVA group in this model of rapidly lethal AS resulted in a rapid and dramatic decrease in CO, thus precluding any redistribution of blood flow to the brain. This does not allow us to further investigate any possible simultaneous effects on cerebral blood flow autoregulation.

As could be expected, volume expansion in the OVA + VE group attenuated the sharp decrease in CO observed in the OVA group, allowing us to investigate more precisely the relation between systemic arterial pressure and cerebral perfusion.

This allowed us to demonstrate the possibility that altered cerebral perfusion observed in our model of AS was not only related to decreased CO. Our results suggest also an altered relation between MAP and cerebral blood flow, as seen by the linear relation between MAP and cerebral blood flow in the OVA and OVA + VE groups, by the increased threshold of pressure dependence observed in OVA + VE rats (Fig. 3), and by the rapid decrease in cerebral P_{tO_2} . This contrasts with the apparently preserved autoregulation of cerebral blood flow and brain oxygenation observed in the NICAR group (Figs. 2 and 3), at least for MAP values greater than 50 mmHg. These results are consistent with our previous report obtained in adaptive compartments such as skeletal muscles, demonstrating a relatively well-preserved oxygen delivery in the presence of decreased systemic oxygen transport in nicardipine-induced shock, in contrast to a profound decrease in tissue oxygenation resulting from AS (10). They are in agreement with the recent report of an initial loss of cerebral diastolic perfusion assessed by transcranial Doppler monitoring observed in a patient with a penicillin-induced AS (24). They differ from those reported by Kapin et al. (25), showing a fall in cerebral vascular resistance in a model of canine AS with relatively preserved cerebral metabolism. However, in this experimental model, AS induced with horse serum was not lethal, and a spontaneous recovery was observed. As observed in the clinical setting, an antigen challenge can result in different reaction severity. This suggests that, in mild forms of anaphylaxis, cerebral brain perfusion and metabolism can be preserved relatively, whereas severe anaphylaxis leading to death is characterized by altered brain perfusion.

Our results differ from those obtained in cardiogenic shock during which cerebral cortical microcirculatory flow was fully preserved, demonstrating that the brain was selectively protected during severe states of cardiogenic shock and CO reduction in the absence of cardiac arrest (26). Similar results have been reported in a rat graded pressure-controlled hemorrhagic shock model, showing that cerebral microvascular flow was preserved during moderate and severe blood losses as long as MAP was kept greater than 40 mmHg (27). It should be noticed that, in both cardiogenic (26) and hemorrhagic (27) shock models, rats were anesthetized. This suggests that the severe alteration of cerebral blood flow regulation we observed in AS was not induced by anesthesia. Our results are also in agreement with data obtained recently in septic shock, a model of shock characterized, like anaphylaxis, by a strong inflammatory reaction, which showed that cerebral microcirculation was also impaired (28).

This suggests that, in addition to arterial hypotension, the release of mediators of anaphylaxis acting on the vascular wall (such as histamine, tryptase, nitric oxide, platelet-activating factor, etc.) may affect cerebral perfusion (29, 30). Indeed, the effects of histamine, tryptase, chymase, bradykinin, prostanooids, leukotrienes, and other substances released classically during anaphylaxis on cerebrovascular resistance and blood-brain barrier permeability have long been recognized (31). In addition, the potentially deleterious role of mast cells resident within the cerebral microvasculature in the very early phase of brain injury, by their rapid action on cerebral vessels, has been emphasized recently in other models of cerebral ischemia and hemorrhage (32). Furthermore, strong evidence suggests that platelet-activating factor and nitric oxide are key mediators in AS (29, 33). Platelet-activating factor was shown also to reduce cerebral blood flow and to increase cerebral metabolic rate for oxygen in rats (34). This could explain both the decrease in cerebral blood flow during AS in our model and the absence of lag time before the decrease in P_{tO_2} . In addition, the rapid decrease in arterial P_{aCO_2} observed during AS represents another major characteristic of severe anaphylaxis, which might have also played a significant role in the reduction in CBF we observed. Indeed, CO_2 , although produced, is not transported because the perfusion of many organs is stopped. This may occur in refractory forms of AS in humans. It is possible that preserved ventilation (in the presence of a very decreased CO) resulted in very high ventilation-perfusion ratio, thus contributing to the very low P_{aCO_2} . In recommendations for resuscitation of AS in humans, no expert ever provided a specific recommendation on the way ventilation/ P_{aCO_2} should be managed. It is conceivable that, in the presence of a severe decrease in CO, preserved ventilation may result in a very low P_{aCO_2} , thus providing a second insult resulting in very low brain perfusion. However, in our model, brain P_{tO_2} decreased very rapidly, as early as 1 min following onset of shock (Fig. 2C), whereas blood gas values were measured at later time points (15 min). We therefore hypothesize that low P_{aCO_2} values are not an initial (within 1 min) contributor to brain hypoperfusion in severe AS but may be a later, secondary, insult. Whether this secondary insult contributes to the low survival in this severe model of AS will require further investigation.

There are several limitations of this study that should be taken into account: (i) the rats were not senescent and did not have chronic systemic arterial hypertension or chronic medication that may have interfered with regulation of cerebral blood flow as could be the case in humans with AS; (ii) the mechanisms and mediators of the immune reaction during AS may be different among species, and extrapolation to humans should be done with caution; (iii) the MAP–cerebral blood flow relation was investigated during anesthesia, and it is not known whether the same relation could be valid in awake animals.

CONCLUSIONS

Treatment of AS remains based mainly on experts' opinions (35), and several treatment failures have been reported even

when anaphylaxis is diagnosed rapidly and treated according to international guidelines. These failures are a strong incentive to continue to design new therapeutic strategies. In this regard, our results indicate clearly that, at least in this animal model, cerebral blood flow and oxygenation impairments are more severe than what could be anticipated from the simple decrease in MAP we observed.

Clinical implications

Despite the previously mentioned limitations, our results, analyzed together with those of other investigators (26–28), demonstrate an “etiology of shock”—specific effects on cerebral perfusion. The specific alteration triggered by AS could explain why nonanesthetized patients with AS can die rapidly when in the upright position (15).

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