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EXPERIMENTAL

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Systemic pressure-flow reactivity to norepinephrine in rabbits: impact of endotoxin and fluid loading

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Abstract *Objective:* This study aimed to evaluate the impact of fluid loading on hemodynamics and vascular hypocontractility to norepinephrine (NE) in an endotoxic shock model.
Design: Mean arterial pressure (MAP), aortic blood flow velocity (AoV, 20 MHz Doppler) and aortic conductance (AoC = AoV/MAP) were studied during 180 min (T0–T180) in 41 anesthetized and ventilated rabbits.
Interventions: Shock was induced by a 600 μg/kg bolus injection of endotoxin. Fluid loading (20 ml/kg colloids) was infused from T90 to T120. Dose-response curves to NE were performed at T0, T60 and T120 in endotoxic and non-endotoxic animals with or without fluid loading.
Measurements and results: Endotoxin decreased pressure (–23 %, $p < 0.05$) and flow (–42 %, $p < 0.05$) corresponding to a decrease in conductance (–19 %, $p < 0.05$). Fluid loading did not improve hypotension but markedly increased systemic flow (+51 %, $p < 0.01$), corresponding to a hyperkinetic syndrome. Vascular reactivity to NE was impaired after endotoxin at T60 since the pressure response to NE was depressed ($p < 0.01$) and flow did not decrease. In non-fluid-loaded groups, the pressure response to NE recovered at T120, with no reduction in flow. In fluid-loaded endotoxic animals, however, the pressure response to NE was still impaired at T120 ($p < 0.05$), but with a decrease in flow.
Conclusions: Fluid loading transformed the hypodynamic profile of endotoxic shock into a hyperdynamic state without improving blood pressure. Depressed vascular reactivity to NE was observed in both hyperdynamic and hypodynamic states, suggesting that a reduced vascular reactivity does not necessarily imply systemic vasodilation.

Key words Endotoxin · Fluid loading · Doppler · Vascular reactivity · Vasoplegia · Norepinephrine

Introduction

The hemodynamic pattern of septic shock is widely presented as an association of systemic hypotension and high systemic blood flow, which implies a decrease in calculated systemic vascular resistances [1–5]. The decrease in arterial blood pressure during sepsis may result from a combination between a reset of high pressure baroreflex [6], an abnormal contractile response of the vessels [7–10], a release of various substances dilating the peripheral vasculature [11–13] or the use of sedation and general anesthesia as an additional factor impairing the cardiovascular adaptation [14].

The relation between systemic pressure and flow appears to be more complex since pressure is a regulated variable whereas flow is an adaptative variable. One

can then observe that hypotension might be associated with a high or a low systemic flow as shown in the literature [4, 11, 15]. The determinants of systemic flow can be schematically classified in cardiac and peripheral factors. Both factors have been shown to be altered during sepsis. Cardiac function [16] and contractility [3] are impaired, together with a reduced venous return in the absence of fluid resuscitation [17]. As a result, in the absence of resuscitation, a decreased systemic flow can be expected after a septic injury. Among the septic-induced hemodynamic alterations, vessel hypocontractility, defined as a decreased pressure (and/or flow) response to increasing doses of vasopressors such as norepinephrine (NE) [18, 19] or angiotensin [10], has been shown both in vivo [7–9, 18] and ex vivo [10, 18, 20]. Since vascular hyporeactivity and hyperkinetic syndrome often coexist, there has frequently been confusion between vessel hypocontractility to NE and vasodilatation or vasoplegia calculated from hemodynamic data.

The present study was designed to evaluate the role of fluid loading on the observed hyperdynamic patterns during endotoxic challenge and separate the concept of vascular hypocontractility from the decrease in vascular resistance. Finally, we tried better to understand the pressure/flow relationship following endotoxin injection, with and without fluid loading. The rabbit model used in the present study is well established and allows the measurement of hemodynamic variables for at least 3 h under stable conditions [11, 21, 22].

Materials and methods

Forty-one New Zealand rabbits (2–2.5 kg, Charles River, France) were studied in accordance with approved guidelines for the care and use of laboratory animals. The animals were housed in individual cages with free access to food and water up to the time of anesthesia.

Animal preparation

This model has been described previously [11, 21]. The rabbits were anesthetized with sodium pentobarbital (15 mg/kg) injected into the marginal vein of the left ear. Adequacy of anesthesia was assessed by monitoring the responses of heart rate and blood pressure to external noxious stimuli. After the induction of anesthesia, the animals were paralyzed and anesthesia was maintained by additional intravenous injections of pentobarbital (3.5 mg/kg) and pancuronium (0.1 mg/kg). After tracheotomy, the trachea was intubated with an uncuffed 3 mm i.d. endotracheal tube, and the animals were mechanically ventilated on 100% oxygen (Harvard pump Model 638). During the stabilization period after surgical preparation, a tidal volume of 7–8 ml/kg and a breath frequency of 35–40 min were adjusted to obtain an arterial blood pH and carbon dioxide tension ($PaCO_2$) around 7.40 and 40 mm Hg, respectively (Radiometer ABL-30, Copenhagen). These settings were held constant for the rest of the study. Throughout the study, the animals were infused continuously (4 ml/kg) with a saline solution containing 0.2 mEq/ml bicarbonates. The animals were maintained at 38 °C (rectal temperature) by a warming pad.

A 14-gauge cannula (Critikon) was inserted into the right carotid artery to measure mean arterial pressure (MAP). The pressure transducers (Abbott, North Chicago, Ill.) were linked to a pressure monitor (CGR, Thomson, Telco, France). A 14-gauge cannula (Critikon) was inserted into the right jugular vein for drug infusion.

Through a limited superior sternotomy, a 20 MHz flow velocity probe (5 or 6 mm i.d.) was positioned around the aortic root to measure aortic blood flow velocity (AoV). The Doppler probe was connected by a microplug to a directional pulsed Doppler flowmeter (Engineering Department of Baylor College of Medicine, Houston, Texas) [23]. The Doppler signals were recorded as mean flow velocities (cm/s) and were the best obtained by varying the range of the flow probes. Zero flow was established by turning off the ultrasound signal. After a midline abdominal incision, a vascular tie was inserted around the inferior vena cava in a subset of animals, to induce a hypotension by atraumatically and reversibly occluding the vessel. The data were recorded on a Gould ES 1000 paper recorder (Ballainvilliers, France). After surgical preparation, the animals were allowed to recover for 45 min during which three consecutive measurements were performed and averaged to define the 100% control value.

Experimental procedure

Six hundred microgram per kilogram BW of a mixture of three types of endotoxin (Escherichia coli, Salmonella enteritidis and Salmonella minnesota; 400 μg each) was used intravenously to induce a reproducible endotoxic shock [11, 12, 21]. At T0, endotoxin or saline solution was injected. Then hemodynamic data were collected every 15 min over a 180-min period (designated throughout from T0 to T180).

In the subset of animals receiving fluid loading, this consisted of a 20 ml/kg infusion over 30 min (from T90 to T120) of a colloid solution (Plasmion, Bellon, France) 90 min after endotoxin or saline injection [24].

Norepinephrine dose-response curves were performed at T0 (before endotoxin or saline), T60 (after endotoxin or saline, before fluid loading) and T120 (after endotoxin or saline, immediately after the end of fluid loading). Five intravenous incremental boluses of NE were injected (0.5, 1, 2, 3, 4 mg/kg) and were all diluted with saline to an equal volume of 0.5 ml. Injections followed at 3 min intervals so that the hemodynamics returned to baseline values before each incremental dose. The 100% reference value was the one measured immediately before each incremental NE dose. Hemodynamic data were collected before and at the highest response to each NE dose. In five animals, a reversible, controlled hypotension was achieved by the occlusion of the inferior vena cava before each NE administration in order to test the impact of hypotension per se on the hemodynamic response to NE.

The hemodynamic measurements included MAP and AoV. To assess the peripheral vascular tone, aortic conductance (AoC) was calculated as the ratio of AoV and MAP. The use of conductance was preferred to resistance to assess peripheral vascular tone because conductance best reflects in vivo the vascular tone modifications primarily due to changes in flow [25]. Blood gases were measured at 30-min intervals and also before and after administering NE. Lactate concentrations were measured at T0, T60 and T180.

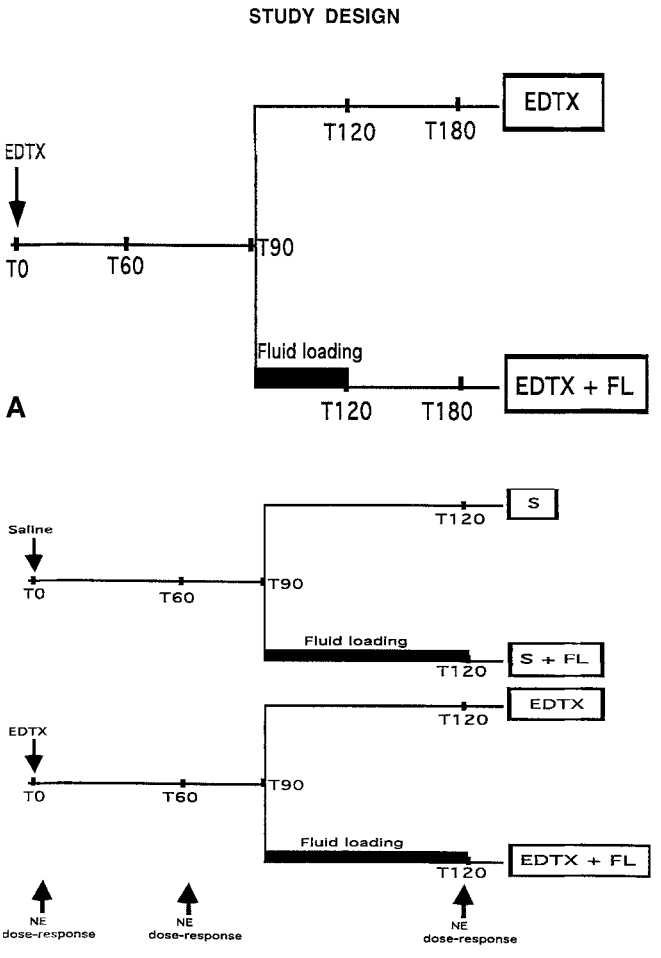

Fig. 1 **A** Protocol used for endotoxic (EDTX) groups receiving or not receiving fluid loading (FL), to evaluate the effects of fluid loading on hemodynamics in endotoxic animals. **B** Protocol used for the norepinephrine groups, to evaluate the vascular reactivity to norepinephrine (NE) in saline (S) and endotoxic animals (EDTX), receiving or not receiving fluid loading (FL)

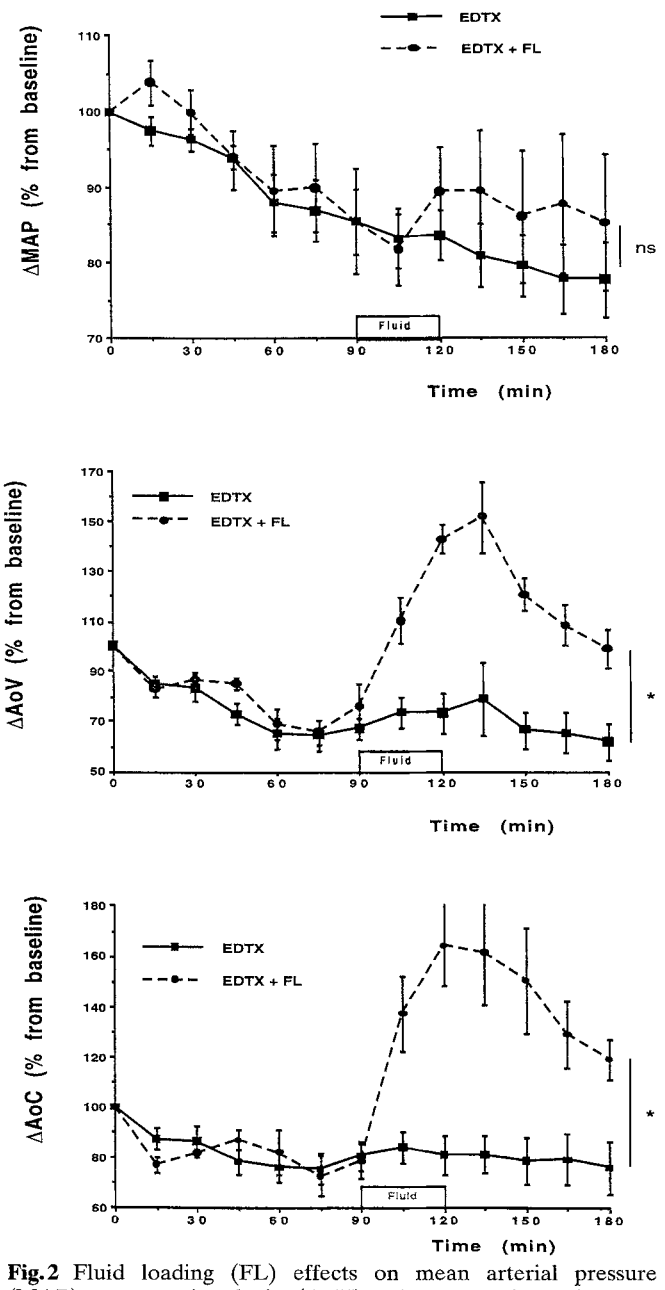

Fig. 2 Fluid loading (FL) effects on mean arterial pressure (MAP), mean aortic velocity (AoV) and mean aortic conductance (AoC) in non-fluid-loaded endotoxic group *(black square)* and in FL endotoxic group *(black circle)* (*: $p < 0.01$, 2-way ANOVA interaction, FL vs non-FL endotoxic groups)

Study design

The study consisted of two parts:
Part one evaluated the effects of fluid loading on systemic hemodynamics in EDTX-treated animals (Fig. 1 a):

Group EDTX: endotoxin administration without fluid loading ($n = 10$);
Group EDTX + FL: endotoxin administration with fluid loading ($n = 6$).

Part two focussed on the cardiovascular response to NE in EDTX-treated and saline-treated animals, receiving or not receiving fluid resuscitation (Fig. 1 b):

Group S: saline administration without fluid loading ($n = 5$);
Group S + FL: saline administration with fluid laoding ($n = 5$);
Group EDTX: endotoxin administration without fluid loading ($n = 4$);
Group EDTX + FL: endotoxin administration with fluid loading ($n = 6$).

An additional group was studied to assess the impact of hypotension alone on vascular reactivity ($n = 5$).

Statistical analysis

The results were expressed as the mean ± SEM (percent changes compared to reference value). Intra-group differences were tested by one-way analysis of variance for repeated measures and referred to T0 or T90 for the fluid loading effects. Inter-group differences (i. e. effect of endotoxin or fluid loading on the time course evo-

Table 1 Hemodynamic effect of fluid loading on endotoxic and saline animals

Parameters (m ± SEM)	Time	Group S	Group S + FL	Group EDTX	Group EDTX + FL
MAP (mm Hg)	T0	89 ± 2	84 ± 3	86 ± 4	87 ± 3
	T60	86 ± 2	80 ± 3	71 ± 7*†	71 ± 3*†
	T120	82 ± 5	82 ± 7	62 ± 14*†	67 ± 7*†
AoV (cm/s)	T0	19 ± 1	21 ± 3	20 ± 3	20 ± 3
	T60	18 ± 2	19 ± 3	13 ± 2*†	15 ± 3*†
	T120	15 ± 2	28 ± 3*@	14 ± 2*†	27 ± 5*$
AoC (cm/s. mm Hg)	T0	0.20 ± 0.02	0.24 ± 0.01	0.24 ± 0.04	0.23 ± 0.04
	T60	0.21 ± 0.01	0.24 ± 0.01	0.16 ± 0.03*	0.17 ± 0.03*
	T120	0.19 ± 0.01	0.36 ± 0.02*@	0.19 ± 0.03	0.39 ± 0.04*$

(*MAP* mean arterial pressure, *AoV* aortic blood flow velocity, *AoC* aortic conductance, *S* saline, *FL* fluid loading, *EDTX* endotoxin)
*: $p < 0.05$ vs T0 intragroup
†: $p < 0.05$ EDTX vs saline groups
@: $p < 0.05$; group S + FL vs group S
$: $p < 0.05$; group EDTX + FL vs group EDTX

lution of hemodynamics, impact of timing on NE dose-response curves) were tested by two-way analysis of variance for repeated measures with one grouping factor. When a significant interaction was observed with two-way analysis of variance, the mean values were compared to the reference value by the Fisher test. A p value less than 0.05 was considered significant.

Results

Effects of fluid loading on hemodynamics after EDTX

The baseline values in the two groups (EDTX and EDTX + FL) did not differ (Table 1). Figure 2 shows the evolution of systemic hemodynamic parameters after the administration of EDTX, in the absence or presence of fluid loading. Until the time of fluid loading (T90), the two groups evidenced similar decreases in MAP (−23 %, $p < 0.01$ vs T0), systemic blood flow velocity (−42 %, $p < 0.01$ vs T0) and vascular conductances (−19 %, $p < 0.05$ vs T0). Fluid loading administered from T90 to T120 did not improve MAP, but increased the systemic blood flow velocity compared to the control point ($p < 0.01$ between groups). These modifications corresponded to an increased vascular conductance after fluid loading ($p < 0.01$ between groups). In the non-fluid-loaded group the decrease in pressure, flow and conductance reached a plateau.

Therefore endotoxin, in the absence of fluid loading, induced a stable hypokinetic shock. In animals receiving fluid loading, a hyperkinetic profile with an intense vasodilation was observed. Endotoxin induced acidosis in both groups at T180 (Table 2), related to a marked increase of the concentration in lactate. Only the fluid-loaded group elicited a significant increase in $PaCO_2$ after fluid challenge ($p < 0.05$ vs T0, intra-group) compared to T0, but did not significantly differ from the non-fluid-loaded group.

Table 2 Time evolution of arterial blood gas and lactates concentrations in non-fluid-loaded (EDTX) and in fluid-loaded endotoxic animals (EDTX + FL)

Parameters	Time	Group EDTX	Group EDTX + FL
pH (UI)	T0	7.45 ± 0.02	7.39 ± 0.02
	T60	7.32 ± 0.02*	7.25 ± 0.02*
	T120	7.25 ± 0.04*	7.15 ± 0.03*
	T180	7.17 ± 0.06*	7.19 ± 0.04*
$PaCO_2$ (mm Hg)	T0	37.5 ± 2.5	39.6 ± 1.5
	T60	36.3 ± 1.0	40.1 ± 3.6
	T120	39.9 ± 2.6	49.1 ± 3.6*
	T180	45.1 ± 6.3	46.9 ± 3.7*
HCO3- (mEq/l)	T0	25.9 ± 2.2	24.6 ± 1.3
	T60	18.6 ± 1.1*	16.9 ± 1.4*
	T120	17.6 ± 1.8*	16.8 ± 1.6*
	T180	18.1 ± 2.1*	17.3 ± 1.5*
Lactates (mmol/l)	T0	4.6 ± 0.8	5.5 ± 0.5
	T60	7.7 ± 0.6*	13.3 ± 1.6*
	T120	10.9 ± 1.3*	9.6 ± 3.5*
	T180	11.1 ± 1.4*	12.3 ± 1.8*

Endotoxin-induced metabolic acidosis with an increase in lactate concentration in both groups (*: $p < 0.05$ vs T0, intra-group)

Pressure-flow reactivity to norepinephrine

Since NE dose-response curves at T0 did not differ in the four NE groups, they were pooled together to define the T0 NE control curve. For the same reason, at T60, NE dose-response curves were pooled in non-EDTX animals and in EDTX animals, respectively.

The baseline values of the four groups studied did not differ (Table 1). Hemodynamics, arterial blood gas and lactate concentration remained stable in saline-treated animals throughout the study. Interestingly, endotoxic and non-endotoxic groups had a similar response to fluid loading, since blood pressure did not change and systemic flow largely increased. However,

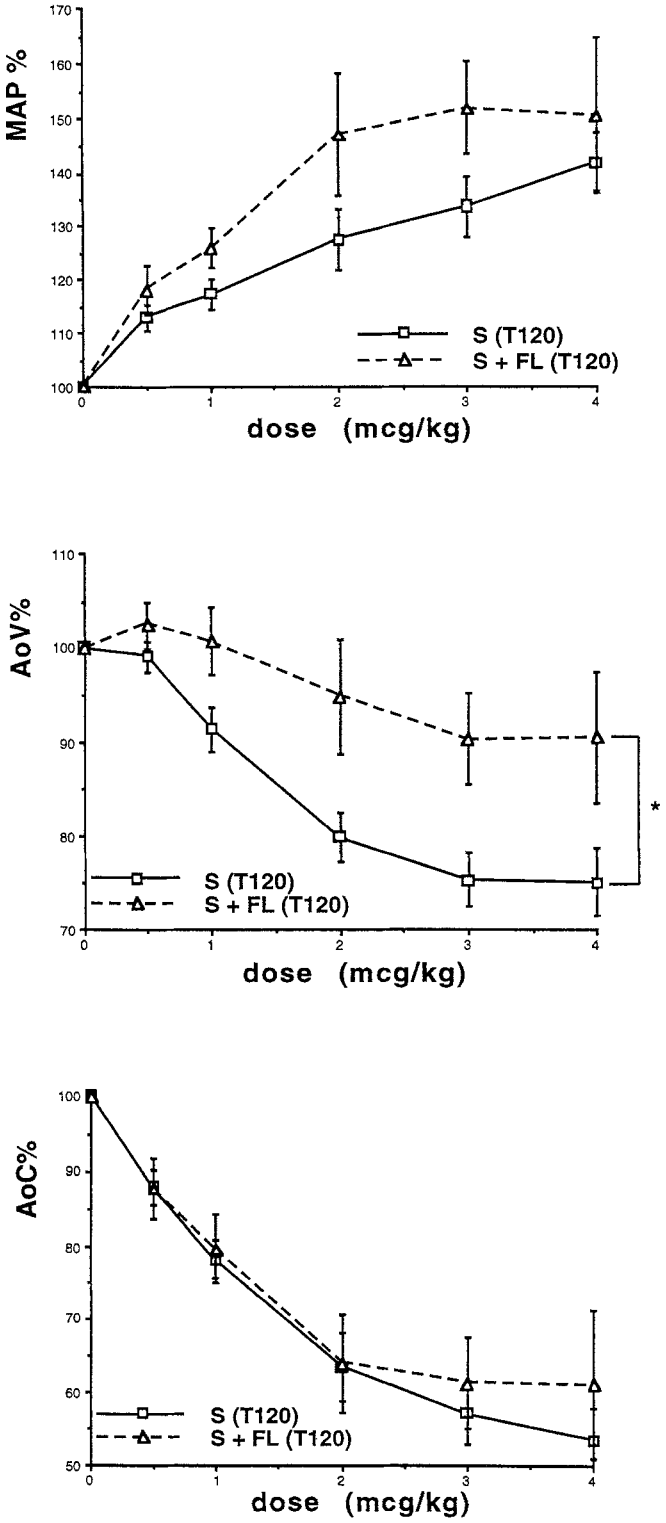

Fig. 3 Fluid loading (FL) effects on vascular reactivity to norepinephrine (NE) in saline animals (S). (*MAP* mean arterial pressure, *AoV* aortic blood flow velocity, *AoC* aortic conductance. *Open square:* animals who did not receive fluid loading, *open triangle:* animals who received fluid loading) (*: $p < 0.05$, between both groups, 2-way ANOVA interaction)

such an increase in flow was higher in endotoxic than in non-endotoxic animals (+83% vs +49%, respectively, $p < 0.05$).

Figure 3 shows the NE dose-response curves at T120 with special attention to fluid loading in non-endotoxic animals (group S and group S + FL). Blood pressure increased similarly in the two groups, while systemic flow variations were different ($p < 0.05$). In the group made hypotensive by mechanical occlusion of the vena cava, MAP decreased to 63 ± 3 mmHg ($p < 0.05$) with an associated decrease in AoV to 14 ± 2 cm/s ($p < 0.05$). Norepinephrine dose-response curves were similar for MAP, AoV and AoC to the normotensive control group (data not shown).

Figure 4 shows the NE dose-response curves in endotoxic and non-endotoxic animals with or without fluid loading. In the absence of fluid loading (Fig. 4, top), EDTX decreased the NE pressure effect ($p < 0.05$, T60 vs T0), with no decrease in AoV ($p < 0.05$, T60 vs T0). These blunted pressure and flow responses are consistent with the attenuated effect on systemic conductance ($p < 0.05$), T60 vs T0). At T120, the pressure response to NE was normalized compared to T0, whereas the flow response remained altered ($p < 0.05$, T120 vs T0). Consequently, AoC remained less reactive than in the controls ($p < 0.05$, T120 vs T0). Fluid loading in endotoxic animals (Fig. 4, bottom; T120) induced an altered pressure response to NE compared to the fluid loading saline group ($p < 0.05$ vs saline group). The flow and AoC response to NE were decreased similarly to those observed in the fluid loading saline group.

Inter-group comparisons at T120 between fluid-loaded and non-fluid-loaded endotoxic groups showed that only the flow response to NE was significantly different ($p < 0.01$, fluid-loaded vs non-fluid-loaded endotoxic groups).

Discussion

In the present study, endotoxin induced a hypokinetic shock corresponding to hypotension with a low systemic blood flow and low systemic conductance. Fluid loading did not correct hypotension but increased the systemic blood flow velocity above the pre-endotoxin level, thus transforming the hypodynamic profile of endotoxic shock into a hyperdynamic state.

Despite the increase in systemic flow, systemic arterial blood pressure did not increase, thus raising a question concerning the use of this variable as a goal for fluid resuscitation. The absence of any effect of fluid loading on systemic blood pressure needs further investigations on the regulatory factors. It is noteworthy that blood pressure did not vary in either control or endotoxic animals, although the initial pressure levels were different. Since blood pressure is a regulated variable, this obser-

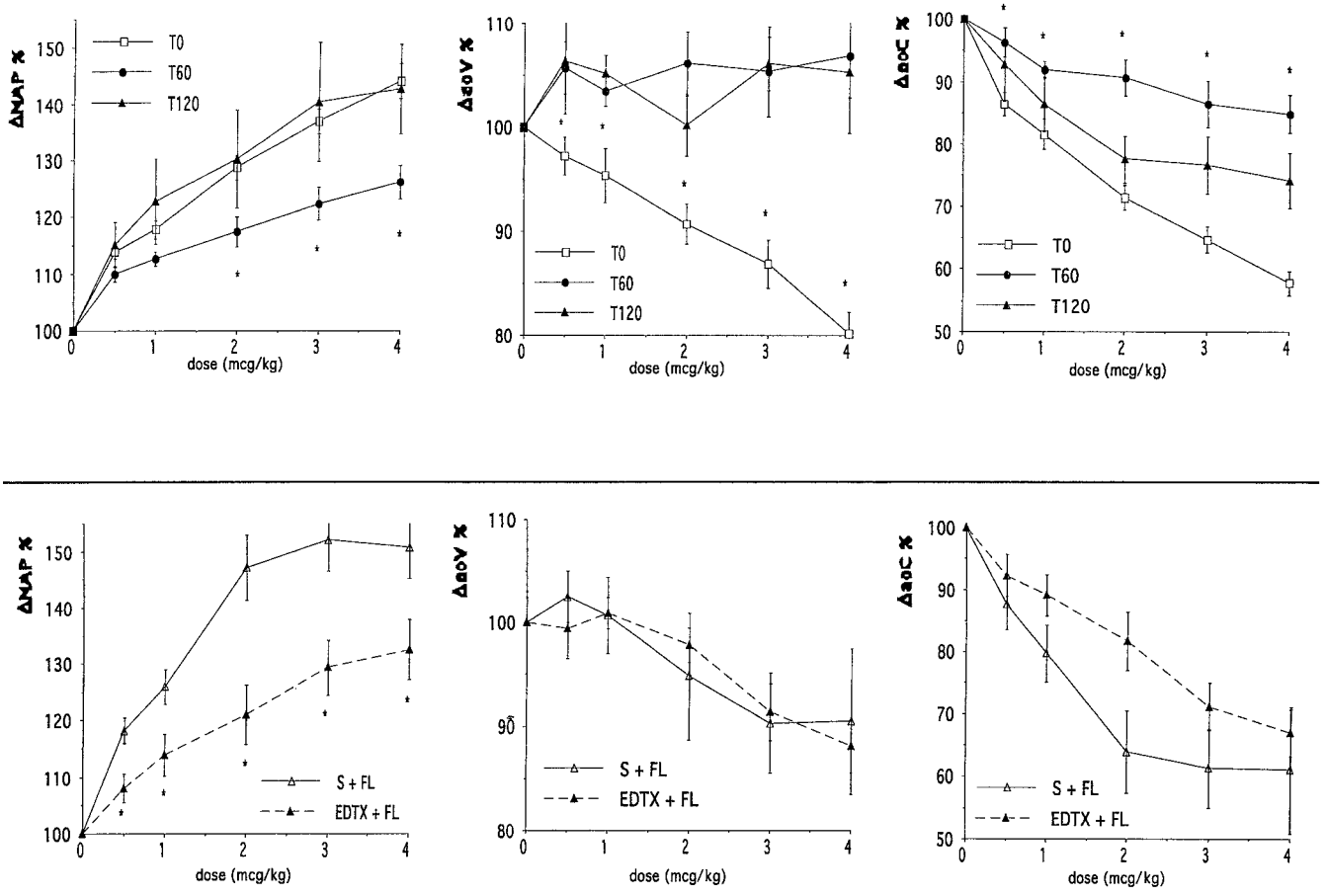

Fig. 4 Norepinephrine (NE) dose-response curves after endotoxic *(black signs)* or saline *(open signs)* administration. The upper part represents time evolution of NE dose-response curves in non-fluid-loaded endotoxic animals. The bottom part represents the effect of fluid loading (at T120) on NE dose-response curves in endotoxic and control animals. *(MAP* mean arterial pressure, *AoV* aortic blood flow velocity, *AoC* aortic conductance) (*: $p < 0.05$ inter-groups, 2-way ANOVA interaction)

vation suggests that the sensing level of a "normal" blood pressure was reset to a lower value in endotoxic animals than in controls, as previously described [6]. This modification in blood pressure regulation may result from several mechanisms, such as an abnormal response to the high pressure baroreflex [6, 26], a release of flow-dependent vasodilatators. Using the same model, we have shown that, in the absence of fluid resuscitation, nitric oxide donors can induce similar hemodynamic patterns to fluid loading [11, 12].

Several studies have shown a low systemic blood flow [11, 15, 21, 22], rather than a high systemic blood flow [1, 4, 5, 16], in septic shock, that might be related to fluid resuscitation [1, 22, 27]. Considering the pathophysiology of endotoxic shock, it is admitted that endotoxin induces a peripheral vascular hypocontractility [7–10, 18], considerable vasodilation [4, 5, 7], an altered cardiac function [2–4], relative hypovolemia resulting from capillary leak [28, 29] and increased resistance to venous return [17]. Consequently, the pathophysiologic determinants of the high systemic blood flow observed in the early phase of shock remain unclear. It can reasonably be concluded that this hyperdynamic profile mainly results from the fluid resuscitation [1, 22, 26], as suggested by our results. Fluid loading induced similar effects on flow in endotoxin and non-endotoxin animals, although the fluid-induced vasodilatation was more pronounced in endotoxic animals than in controls. This amplification has not been described previously and may result from complex interactions between metabolic, hormonal and endothelial factors, such as glucose level [21], prostaglandins [30], and nitric oxide (NO) [13, 31]. This "hypersensibility" to fluid after endotoxin administration might also result from the vascular hypocontractility induced by the acute inflammation [31].

In the present study, reduced vascular reactivity to NE was confirmed 60 min after the injection of endotoxin (i.e. before fluid administration), in the absence of any vasodilatation. This depressed pressure-response to NE recovered 2 h after endotoxin, while the systemic hypotension persisted. Depressed vascular reactivity to NE was observed in both hyperdynamic and hypodynamic states, suggesting that a reduced vascular reactiv-

ity does not necessarily imply systemic vasodilation, with a dissociation between vasodilatation and vascular hyporeactivity.

The sepsis-induced vascular hyporeactivity has been previously demonstrated in different conditions [18, 20, 32, 33]. The recovery in vascular reactivity may result from the administration of the endotoxin as a bolus. The model used concerned a short period of time after endotoxin injection, which does not allow for any conclusions about the mechanisms of this recovery of vascular contractility. Little information is available in the literature on the chronology of cardiovascular abnormalities, particularly hypotension and its related causes. The contrast between a recovered vascular contractility and a persistent hypotension may be related to a longer alteration in the systemic pressure regulation system [6]. In addition, vascular tissue exposed to endotoxin may have a heterogeneous ability to counter the effect of endotoxin on vascular reactivity [34]. Finally, persistent release of vasodilating substances [13, 31] such as NO and/or prostaglandins may participate in this sustained hypotension.

Blood pressure variations induced by vasoconstrictors are not only related to the induced vasoconstriction, since the cardiac function might intervene in the pressure variations. Because of this, in addition to pressure response, we also evaluated the flow response to vasoconstrictors. After endotoxin, the impact of NE on flow was persistently altered, confirming the sustained alteration of vascular reactivity following endotoxemia. Interestingly, the depressed pressure and flow responses to NE were observed independently of a systemic vasodilation, since aortic pressure and flow were both decreased at that time. This demonstrates that systemic vasodilation is not the main cause of vascular hyporeactivity, since vascular hyporeactivity could be observed even in the absence of vasodilation.

In contrast to the non-fluid-loaded endotoxic animals, the pressure response to NE remained depressed after fluid loading in endotoxic animals. This strongly suggests a role of fluid loading after endotoxin, which may theoretically concern vascular [22] and/or cardiac [3] effects. In this regard, the study of the flow response after fluid loading in these animals gave significant information. At T120 after endotoxin injection, the confrontation of the absence of flow reduction in non-fluid-loaded animals with the flow reduction observed in fluid-loaded animals suggests an effect of fluid loading per se. This decrease in blood flow was also observed in saline animals after fluid loading, but with a normal pressure response.

The association of an abnormal pressure response and a flow reduction after NE in endotoxic fluid-loaded animals raised a question concerning the additional role of impaired ventricular function. It is reasonable to consider that fluid loading shifted the heart function curve to a better point, and that the addition of NE induced an abrupt increase in afterload which might have precipitated the impairment in systolic function. This hypothesis is in accordance with the previously published concept of cardiac dysfunction in sepsis [3, 4, 26]. Consequently, if the heart fails to pump against a moderate increase in afterload, the pressure response to NE should then be altered. This point is clinically relevant since NE is frequently used to improve severe hypotension in sepsis [35], but sometimes fails to improve the systemic pressure in the presence of associated heart dilatation [3]. This situation may then lead to the choice of a more inotropic therapy such as dobutamine or adrenaline.

In conclusion, fluid loading transformed the non-resuscitated hypodynamic profile of endotoxic shock into a hyperdynamic profile without improvement in hypotension. Endotoxin induced a depression of the pressure response to NE associated with small effects on flow and systemic conductance. Depressed vascular reactivity was observed with both hypodynamic and hyperdynamic profiles, suggesting that vascular hyporeactivity and systemic vasodilation may be dissociated. Fluid loading did not modify the vasomotor reactivity to NE during endotoxic shock but might have precipitated systolic cardiac dysfunction. These observations would suggest caution is necessary in the use of both fluid loading and NE in the resuscitation of septic shock.

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