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Hyperthermia decreases the response to vasoconstrictors in rat portal veins

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Abstract

The rat portal vein is a useful pharmacological model to study the contractions of smooth muscle cells through both receptor-dependent and receptor-independent mechanisms. We previously showed that sepsis decreases the spontaneous and agonist-induced contractile response to angiotensin II in this model. To determine whether acidosis and hyperthermia, which occur in sepsis, might contribute to this vascular failure, rat portal veins were isolated from control rats and exposed to norepinephrine and angiotensin II. During the pharmacological tests, the rat portal vein were incubated at 37 or 39.5 °C or infused with a solution at low pH with normal or high pCO_2. Mild and severe acidosis had minor effects on the vascular response of rat portal vein to norepinephrine and angiotensin II. In contrast, hyperthermia decreased the response of both drugs. Nitric oxide (NO), carbon monoxide (CO), and prostaglandins were not responsible for the decreased response. Thus, acidosis observed during sepsis is not responsible for the vascular dysfunction of rat portal vein. In contrast, hyperthermia participates to the vascular failure but the mediator responsible remains unknown.

Keywords: Vascular reactivity; (Rat); Portal vein; Hyperthermia; Acidosis; Norepinephrine; Angiotensin

1. Introduction

Septic patients frequently exhibit a severe vascular failure associated with a decreased response to vasoconstrictors. Consequently, the perfusion of high concentrations of vasoconstrictors are necessary to restore a normal mean arterial pressure (Vincent et al., 2000, Landry and Oliver, 2001). In experimental septic shock, an impaired response to vasoconstrictors is also observed in various regional circulations. In anesthetized pigs infused with endotoxin, we previously showed that the renal circulation was hyporesponsive to norepinephrine (Pastor, 1999), whereas the response of the hepatic circulation was not modified (Mastrangelo and Pastor, 1999; Pastor et al., 2000).

Acidosis which is frequently associated with sepsis might contribute to the vascular failure. Thus, hypercapnic acidosis vasodilates the coronary circulation in anesthetized dogs (Gurevicius et al., 1995). A similar response is observed in the forearm circulation of normal subjects infused with a hypercapnic solution (Kontos et al., 1967). Moreover, in isolated rat mesenteric arteries, low pH decreases the contractility to norepinephrine (Ryan and Gisolfi, 1995). In contrast, in the perfused rat liver, normocarbic or hypercarbic acidosis had no effect on the response to norepinephrine (Pastor and Hadengue, 2001).

Hyperthermia is another abnormality observed during septic shock. When hyperthermia is moderate, mean arterial pressure is maintained by splanchnic contraction, while at a temperature >41.5 °C, the splanchnic contraction is lost and hypotension occurs (Massett et al., 1998). Similarly to acidosis, hyperthermia decreases the vascular response to constrictors in mesenteric arteries and thoracic aorta (Massett et al., 1999).

The rat portal vein has been used extensively in physiological and pharmacological studies. It is a large vein which has a spontaneous activity induced by local pacemaker cells and which is characterized by rhythmic contractions (Sutter, 1990). Besides this spontaneous activity, the rat portal vein is also reactive to vasoactive agents such as angiotensin II, norepinephrine, and neurokinin B which act on specific receptors as previously shown (Mastrangelo et al., 2000). In portal veins isolated

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from septic rats (24 h after cecal ligature and puncture), we previously showed that the contractile response to neurokinin B and angiotensin II is significantly decreased and that the vascular failure is correlated with the severity of the disease (Mastrangelo et al., 2000). In contrast, in this model, the vasoconstriction to norepinephrine was not modified. Because acidosis (Huber-Lang et al., 2001) and hyperthermia (Gourine et al., 1998) are both associated with this rat septic model of peritonitis, the aim of our study was to determine whether acidosis and hyperthermia may induce vascular failure in portal veins isolated from healthy rats.

2. Methods

2.1. Isolation of the rat portal vein

Male Sprague–Dawley rats (360–420 g) were used for the experiments. Following the sacrifice of the animals, the abdomen was opened and the rat portal vein was carefully removed (1 cm) and placed in Krebs–Henseleit bicarbonate (KHB) solution (in mM, NaCl 118.7, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2 and glucose 10.1). After removal of adherent fat and connective tissue, the rat portal vein was suspended via silk threads attached at both extremities in 150-μl thermostated chambers and connected to an isometric force transducer (Grass FT03, Quincy, MA, USA). In the chambers, the preparations were continuously infused at a flow rate of 1.5 ml min^{-1} with the KHB solution. Mechanical tension was amplified and recorded on a six-channel paper recorder (W + W, DCR 520, Syntrel Electronic, Basel, Switzerland) and on a personal computer through an analog-to-digital converter and a data acquisition system (MacPacq MP100; Biopac Systems, Goletta, CA). The protocol was approved by the animal welfare committee of the University of Geneva and the veterinary office and followed the guidelines for the care and use of laboratory animals.

2.2. Experimental protocol

After an equilibration period of 60 min during which basal tension was adjusted to 1 g (optimum tension determined in preliminary studies), the tissues were exposed to noncumulative concentrations of norepinephrine (3×10^{-8}–10^{-5} M) or angiotensin II (10^{-10}–3×10^{-7} M). Each agent was infused for 5 min and between each concentration, a drug-free KHB solution was infused during 30 min. To measure the spontaneous contractile activity, the mean tension was recorded over a 5-min period prior to the drug infusion. To obtain the value of drug-induced contraction, this value was subtracted from the mean tension measured during a 3-min period after the response had reached equilibrium. Spontaneous and drug-induced contractions were expressed in grams.

2.3. Norepinephrine- and angiotensin II-induced contraction of the rat portal vein incubated at 37 and 39.5 °C

To study the effect of temperature on the vascular reactivity of the rat portal vein, the concentration–response curves to norepinephrine (3×10^{-8}–10^{-5} M) and to angiotensin II (10^{-10}–3×10^{-7} M) were studied at 37 °C ($n = 13$) and 39.5 °C ($n = 13$). In the hyperthermic group, following a 1-h incubation time in KHB solution at 37 °C, the temperature was increased to 39.5 °C during the entire experiment.

2.4. Mediators involved in the decreased response to angiotensin II during hyperthermia

To determine the mediators involved in the decreased contractile activity of the rat portal vein observed at 39.5 °C, the concentration–response curves to angiotensin II were studied in the absence and in the presence of indomethacin (Ind, 10^{-5} M, $n = 9$), in the presence and in the absence of the combination of two nitric oxide (NO) synthase inhibitors [3×10^{-4} M N^{ω}-nitro-L-arginine (L-NNA) and 10^{-5} M N^{ω}-nitro-L-arginine methyl ester (L-NAME), $n = 10$], in the presence and the absence of the selective inhibitor of the heme oxygenase, tinn protoporphyrin IX (SnPP-IX, 10^{-5} M, $n = 9$), and in the presence of increased Ca^{2+} concentration in the KHB solution (Ca^{2+}: 2.5 or 7.5 mM, $n = 9$). SnPP was tested in a dark room. To ensure the absence of deterioration of the preparations over time, two consecutive concentration–response curves to angiotensin II were studied ($n = 9$). The effect of increased Ca^{2+} concentrations in the KHB solution in rat portal vein incubated at 37 °C was also studied ($n = 7$).

2.5. Norepinephrine- and angiotensin II-induced contraction of the rat portal vein during hypercarbic acidosis

After isolation, rat portal veins were incubated in a KHB solution equilibrated with normal pCO_2, pH, and pO_2. Two consecutive concentration–response curves to norepinephrine were studied in the presence of normal pCO_2, pH, and pO_2 ($n = 10$) and two consecutive concentration–response curves to norepinephrine were studied in the presence of mild (6.5 kPa < pCO_2 < 7.5 kPa) and severe hypercarbic acidosis (9.5 kPa < pCO_2 < 10.5 kPa) ($n = 10$). High pCO_2 was obtained by bubbling increased % CO_2 in the KHB solution. Concomitantly, pH decreased while pO_2 was kept constant during all tests. Similar experiments were performed with angiotensin II ($n = 20$).

2.6. Norepinephrine- and angiotensin II-induced contraction of the rat portal vein during normocarbic acidosis

In additional groups ($n = 10$ each), pH was gradually decreased by replacing $HCO3^-$ with equivalent amount of NaCl such as the osmolality and the Na^+ concentration of the KHB solution did not change. The concentration–

response curves to norepinephrine were studied during mild (pH ≈ 7.28) and severe (pH ≈ 7.12) normocarbic acidosis. Two additional consecutive concentration–response curves to angiotensin II were studied in the presence of mild and severe normocarbic acidosis.

2.6.1. Statistics

All results were expressed as mean ± S.D. The vasoconstrictive responses to increasing doses of agonists were analyzed by a two-way analysis of variance with repeated measurements to assess the overall difference between groups with increasing drug concentrations. To compare the spontaneous contractile activities between two groups, a *t* test was used.

3. Results

3.1. Norepinephrine- and angiotensin II-induced contraction of the rat portal vein incubated at 37 and 39.5 °C

Incubation of the rat portal vein at 39.5 °C decreased the vasoconstrictive response to both norepinephrine and angiotensin II (Fig. 1, line graphs) and the spontaneous activity of the rat portal vein (Fig. 1, bar graphs).

3.2. Mediators involved in the decreased response to angiotensin II during hyperthermia

To determine the mediators involved in the decreased response to angiotensin II during hyperthermia, we added indomethacin during the test. Indomethacin did not restore a normal response to angiotensin II. The response to angiotensin II was unchanged but indomethacin further decreased the spontaneous contractile activity (Fig. 2A).

The role of NO in inducing the hyporesponsiveness of the rat portal vein was investigated by testing the veins in the presence of two NO synthase inhibitors N^{ω}-nitro-L-arginine (L-NNA, 3×10^{-4} M) and N^{ω}-nitro-L-arginine methyl ester (L-NAME, 10^{-5} M) (Fig. 2B). NO synthase inhibition did not correct the decreased response to angiotensin II but further reduced the response. The spontaneous contractile activity was not significantly modified by NO synthase inhibition.

The contractile responses (spontaneous and agonist-induced) were similar in the presence and in the absence of the selective inhibitor of the heme oxygenase, 10^{-5} M tinn protoporphyrin IX (Fig. 2C).

We also increased Ca^{2+} concentration in the KHB solution and found that 7.5 mM Ca^{2+} further decreased the response to angiotensin II, whereas the spontaneous contractile activity was increased (data not shown). When rat portal vein were incubated at 37 °C, high [Ca^{2+}] concentration did modify neither the contractile response to angiotensin II at 37 °C or the spontaneous contractile activity (data not shown).

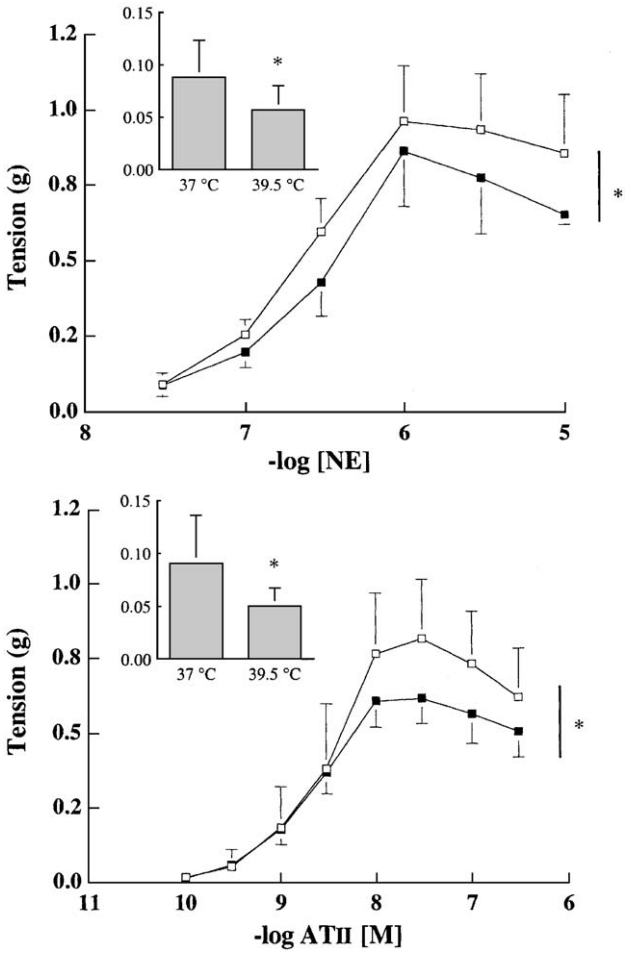

Fig. 1. Norepinephrine (NE)- and angiotensin II (ATII)-induced contractile activity in rat portal veins incubated at 37 °C (□) and 39.5 °C (■). Bars are means ± S.D. Two-way ANOVA found a significant difference between the two groups over the repeated measurements for NE and ATII. $N = 13$ in each group. The spontaneous contractile activities are illustrated in the bar graphs. $^{*}p < 0.05$.

3.3. Norepinephrine- and angiotensin II-induced contraction of the rat portal vein during hypercarbic acidosis

When rat portal veins were studied in a normal KHB solution, pCO_2, pH, and pO_2 remained constant during each test. In contrast, when % CO_2 increased in the KHB solution, pCO_2 increased and pH decreased. During mild hypercarbic acidosis, pH and pCO_2 were 7.28 ± 0.01 and 6.65 ± 0.24 kPa (3×10^{-8} M norepinephrine) and 7.25 ± 0.01 and 7.12 ± 0.01 kPa (10^{-5} M norepinephrine). During severe hypercarbic acidosis, pH and pCO_2 were 7.11 ± 0.01 and 9.76 ± 0.10 kPa (3×10^{-8} M norepinephrine) and 7.08 ± 0.01 and 10.77 ± 0.18 kPa (10^{-5} M norepinephrine). pO_2, Na^{+}, K^{+}, $HCO3^{-}$ and Ca^{2+} remained similar in all groups.

The concentration–response curves to angiotensin II were similar when two consecutive tests were performed at normal pH and pCO_2. Mild and severe hypercarbic

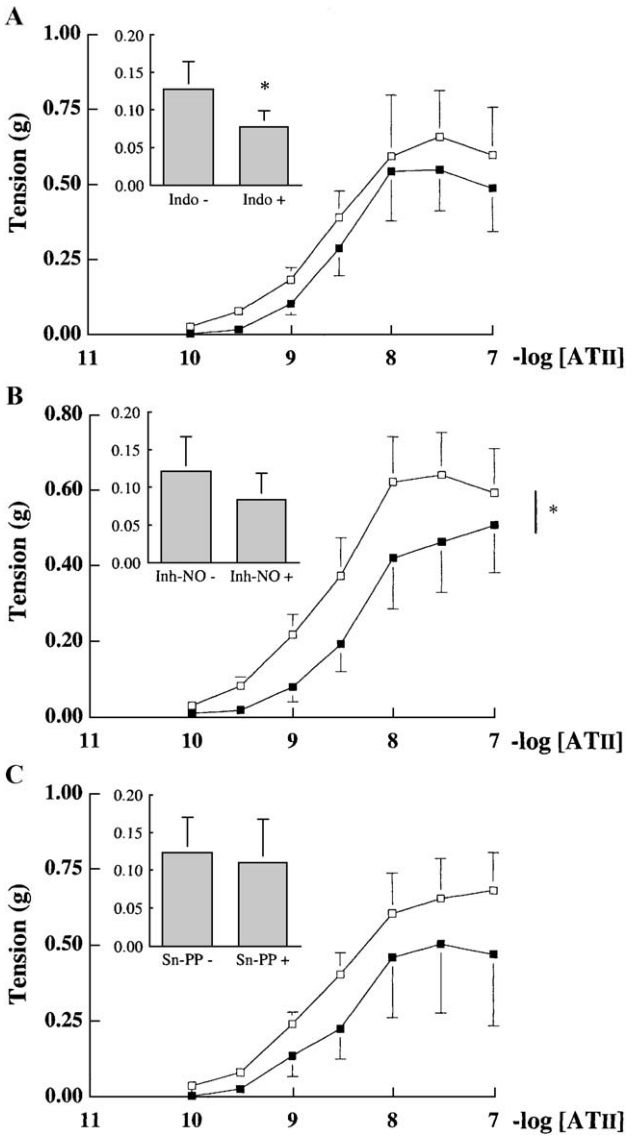

Fig. 2. Angiotensin II (ATII)-induced contractile activity in rat portal veins incubated at 39.5 °C in (A) Krebs–Henseleit bicarbonate buffer (KHB) $\pm 10^{-5}$ M indomethacin (Ind, $n=9$ in each group), (B) KHB $\pm 3\times10^{-4}$ M N^{ω}-nitro-L-arginine and 10^{-5} M N^{ω}-nitro-L-arginine methyl ester (Inh-NO, $n=7$), or (C) KHB buffer $\pm 10^{-5}$ M tinn protoporphyrin IX (SnPP-IX, $n=9$). Rat portal veins are incubated at 39.5 °C in KHB buffer (□) or KHB + selective inhibitors (■). Bars are means ± S.D. Two-way ANOVA found: (A) no significant difference between 0 or 10^{-5} M Ind over the repeated measurements, (B) a significant difference between the presence or the absence of Inh-NO over the repeated measurements, and (C) no difference between 0 or 10^{-5} M SnPP-IX. The spontaneous contractile activities are illustrated in the bar graphs. *$p<0.05$.

acidosis modify neither the angiotensin II-induced contraction of the rat portal vein (Fig. 3) or the spontaneous contractile activity (data not shown).

Similar conclusions were obtained with norepinephrine perfusion (data not shown). Emax were respectively 1.18 ± 0.08 and 1.12 ± 0.06 g during the two consecutive tests at normal pH and pCO_2. Mild and severe hypercarbic acidosis did not modify the norepinephrine-induced contraction of the rat portal vein (1.16 ± 0.08 and 1.18 ± 0.08 g, respectively).

3.4. Norepinephrine- and angiotensin II-induced contraction of the rat portal vein during normocarbic acidosis

When NaCl replaced $HCO3^{-}$ in the KHB solution, pH decreased and pCO_2 was not modified. During mild normocarbic acidosis, pH and pCO_2 were 7.31 ± 0.01 and 4.3 ± 0.1 kPa (3×10^{-8} M norepinephrine) and 7.29 ± 0.02 and 4.3 ± 0.2 kPa (10^{-5} M norepinephrine). During severe normocarbic acidosis, pH and pCO_2 were 7.14 ± 0.01 and 4.1 ± 0.1 kPa (3×10^{-8} M norepinephrine) and 7.09 ± 0.05 and 4.1 ± 0.4 kPa (10^{-5} M norepinephrine).

Mild and severe normocarbic acidosis induced slight differences with the control groups (Fig. 4), while the spontaneous contractile activity was not modified by decreasing pH in the KHB perfusion. When norepinephrine-induced contractions were tested, no difference was found

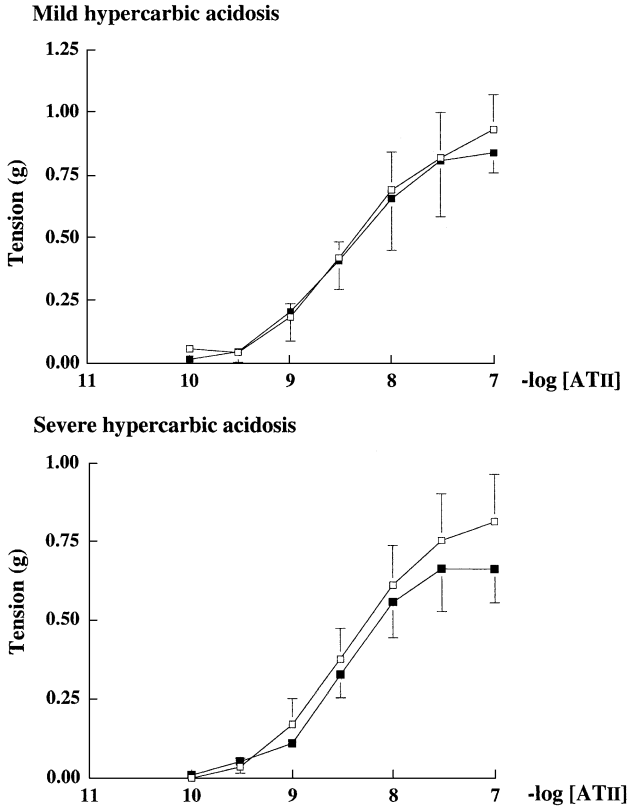

Fig. 3. Angiotensin II (ATII)-induced increase contraction of the rat portal vein during mild and severe hypercarbic acidosis. pCO_2 was 6.5 kPa < pCO_2 < 7.5 kPa (mild) or 9.5 kPa < pCO_2 < 10.5 kPa (severe) and pH decreased to $\approx 7.26\pm0.2$ and $\approx 7.10\pm0.2$, respectively. Rat portal veins are incubated in KHB buffer with normal pCO_2 (□) or in KHB buffer with high pCO_2 (■). Bars are means ± S.D. Two-way ANOVA found no difference between the two groups over the repeated measurements for mild and severe hypercarbic acidosis. $N=10$ in each group.

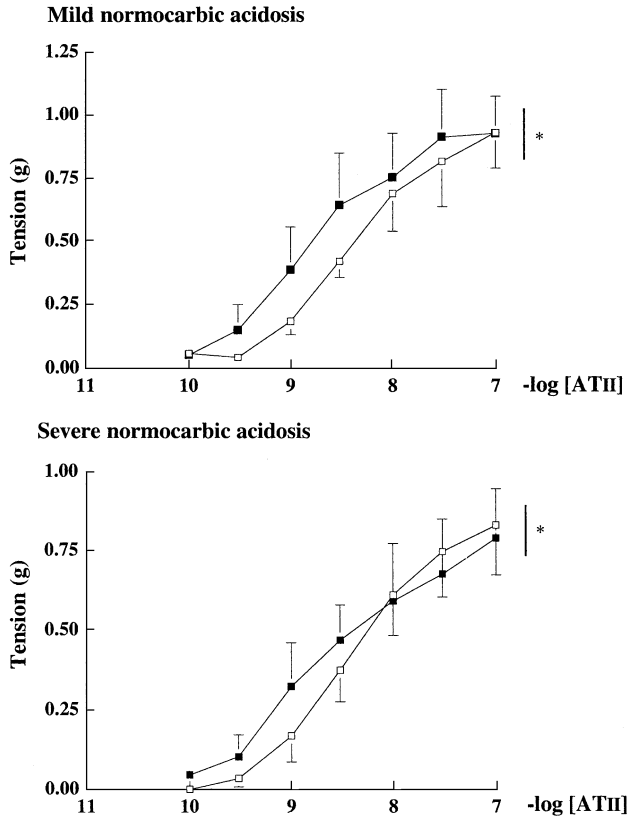

Fig. 4. Angiotensin II (ATII)-induced increase contraction of the rat portal vein during mild and severe normocarbic acidosis. $7.28 < pH < 7.31$ (mild) or $7.09 < pH < 7.14$ (severe), while pCO_2 remained constant. Rat portal veins are incubated in KHB buffer with normal pH (□) or in KHB buffer with low pH (■). Bars are means ± S.D. Two-way ANOVA found a slight difference between the two groups over the repeated measurements for mild and severe acidosis. $N = 10$ in each group. $^*p < 0.05$.

between the control group and mild or severe normocarbic acidosis.

4. Discussion

Mild and severe acidosis (metabolic and hypercarbic) had little effect on the vascular response of the rat portal vein to norepinephrine and angiotensin II. In contrast, hyperthermia decreased the response of both drugs. NO, carbon monoxide (CO), and prostaglandins were not responsible for the decreased response observed in rat portal vein incubated at 39.5 °C. Thus, acidosis is unlikely to induce the vascular hyporeactivity of the rat portal vein induced by sepsis, whereas hyperthermia participates to the vascular failure. The mediator responsible for this dysfunction remains unknown.

4.1. Vascular failure and pathology

Vasoconstriction of the peripheral circulation is the normal response to conditions in which the arterial pressure is too low to maintain an adequate tissue perfusion as observed in acute hemorrhagic or cardiogenic shock. In contrast, during septic shock, hypotension occurs because vascular smooth muscle cells fail to constrict. Such vasodilatory shock is characterized not only by hypotension due to peripheral vasodilatation but also by a decreased response to vasoconstrictors (Landry and Oliver, 2001). In experimental septic shock, an impaired response to vasoconstrictors is observed in various regional circulations. In anesthetized pigs infused with endotoxin during 18 h, we previously showed that the renal circulation was hyporesponsive to norepinephrine (Pastor, 1999). In the same model, although the increase in arterial pressure induced by norepinephrine was decreased over time, the response of the portal vein blood flow was not modified (Mastrangelo and Pastor, 1999). At the end of the in vivo experiment, transversal strips of portal veins were isolated and tested. The in vitro response of portal veins isolated from pigs infused during 18 h with endotoxin to norepinephrine was also decreased. Finally, in a rat model of cecal ligature and puncture, the spontaneous activity and the contractile responses of rat portal vein to angiotensin II and neurokinine B were decreased (Mastrangelo et al., 2000). Interestingly, we showed that the magnitude of the vascular failure was correlated to the severity of sepsis (Mastrangelo et al., 2000). Acidosis (Huber-Lang et al., 2001) and hyperthermia (Gourine et al., 1998) are both associated with this model of peritonitis. However, in rat portal veins isolated from septic rats and incubated in vitro at 37 °C (Mastrangelo et al., 2000), the response to norepinephrine was unchanged in contrast to the response obtained in portal veins isolated from control rats and incubated at 39.5 °C. Consequently, the hyporesponsiveness induced by hyperthermia does not fully explained the modifications induced by sepsis in vivo.

Heat stroke is another pathology associated with abnormal vascular reactivity. During heat stroke, the mean arterial pressure is maintained up to 41.5 °C because the splanchnic resistances increase (Kregel et al., 1988). Over 41.5 °C, the vasoconstriction of the regional circulation fails and hypotension occurs. Concomitantly, over 41.5 °C, the in vivo response of the arterial pressure to norepinephrine and angiotensin II infusions are significantly attenuated (Kregel and Gisolfi, 1990; Massett et al., 1998). Interestingly, the response to $BaCl_2$ which substitutes to Ca^{2+} is not altered by heat shock, suggesting that the vascular dysfunction is related to the receptor dysfunction. The response of the mesenteric, renal, and hindlimb blood flows to norepinephrine and angiotensin II is also altered over 41.5 °C (Massett et al., 1998). In contrast, no modification was found at 39 °C. In isolated rat mesenteric and thoracic aorta, increasing temperature (up to 43 °C) had no effect on the baseline tension but significantly increased the phenylephrine-induced vasoconstriction (Massett et al., 1999). In a similar model, the response to norepinephrine was not modified (Ryan and Gisolfi, 1995). Besides septic shock and heat

shock, inflammation is another clinical situation during which body temperature is increased. Vascular hyporesponsiveness might also occur in such situation.

In our experimental model, hyperthermia (39.5 °C) decreased the spontaneous contractile activity and the response to both norepinephrine and angiotensin. We chose to investigate the effect of temperature at 39.5 °C rather than 40–43 °C to mimic the modifications of temperature observed during sepsis. However, at this temperature, the decreased response to drugs was moderate (−28.2% for norepinephrine and −24.3% for angiotensin II) and mostly observed at high concentrations. Although it might be very interesting to compare the concentrations of vasoactive drugs used in our study to those observed in patients, no clinical study, to our knowledge, reported the serum concentrations of norepinephrine and angiotensin measured in septic patients.

Our results contrast with previous studies performed in isolated vessels. However, in the study published by Massett et al. (1999), isolated mesenteric arteries were incubated with phenylephrine and the tension was measured following increasing steps of temperature. In our study design, the temperature was maintained constant during the experiments (39.5 °C) and the response to increased doses of agonists was measured. Moreover, the level of hyperthermia chosen in our study parallel that observed during septic shock while the degree of temperature studied by Massett et al. 1999) parallels that observed in heat stroke. Additionally, when dog isolated cutaneous veins were vasoconstricted by norepinephrine, the increased temperature in the organ bath lowered the vessel tension (Vanhoutte and Shepherd, 1970). Changes in the vascular reactivity may greatly vary between veins and arteries and between various types of veins. Cutaneous veins, whose primary function is to regulate temperature might behave differently that other types of veins without such regulation.

4.2. Mediators involved in the decreased response to angiotensin II during hyperthermia

Because hyperthermia increases heat shock proteins, such as the heme-oxygenase-1 with the concomitant release of carbon monoxide (CO), rat portal vein were incubated at 39.5 °C in the presence of the selective inhibitor of the heme oxygenase, SnPP-IX (Sammut et al., 1998). The tests were performed in a dark room because, at room light, the spontaneous activity and most of the contractile activity were abolished in the presence of SnPP-IX, suggesting a toxic effect of the drug, as previously published (Zygmunt et al., 1994). SnPP-IX had no effect on the decreased response to angiotensin II or the decreased spontaneous contractile activity induced by hyperthermia.

Similarly, prostanoids were not involved in the decreased responses induced by hyperthermia. The fact that indomethacin did not prevent the decreased response to angiotensin II induced by hyperthermia has been reported in rat portal vein isolated from rats with cecal ligation and puncture (Mastrangelo et al., 2000). Additionally, indomethacin further reduced the spontaneous contractile activity. Although the reason of this effect is unknown, a reduced contraction of the lower esophageal sphincter in humans in the presence of indomethacin is also described (Cao et al., 2000).

Moreover, NO synthase inhibition did not prevent the decreased response to angiotensin II induced by hyperthermia (eliminating NO as a potential mediator of the abnormal response) but further decreased the response to angiotensin II. In longitudinal preparations of rat portal veins, NO inhibition already showed no effect (Mastrangelo et al., 2000; Feletou et al., 1989) or a decreased response (Mastrangelo et al., 2000) to vasoactive drugs. Because blockade of the NO synthase activity might not have been effective enough with a single NO synthase inhibitor, we used a combination of L-NNA and L-NAME, as previously described (Mastrangelo et al., 2000). However, differences between the longitudinal and circular muscle preparations have been pointed out in rat portal vein and, in contrast to longitudinal preparations, circular preparations may be regulated by endogenous NO (Shimamura et al., 2000).

4.3. Acidosis and vascular reactivity

Acidosis vasodilates the coronary circulation in anesthetized dogs (Daugherty et al., 1967) and the forearm circulation of healthy humans (Kontos et al., 1967). Acidosis also decreases the response to norepinephrine in isolated rat mesenteric arteries (Ryan and Gisolfi, 1995) and in rat aorta (Fukuda et al., 1990). However, in accordance with our results obtained in the rat perfused liver (Pastor and Hadengue, 2001), acidosis (normo or hypercarbic) had little effect on the reactivity to norepinephrine and angiotensin II in rat portal vein. The reason why acidosis does not vasodilate the rat hepatic circulation as observed in other circulations remains unclear.

In conclusion, acidosis observed during cecal ligature and puncture is not responsible for the vascular dysfunction of the rat portal vein. In contrast, hyperthermia participates to the vascular failure but the mediator responsible remains unknown.

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