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Perfusion Pressure Manipulation in Porcine Sepsis: Effects on Intestinal Hemodynamics

A. KROUŽECKÝ, M. MATĚJOVIČ, J. RADĚJ, R. ROKYTA JR., I. NOVÁK

Intensive Care Unit, First Medical Department, Faculty of Medicine and Teaching Hospital, Charles University, Plzeň, Czech Republic

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Summary

Limited information is available about selection of the threshold for arterial blood pressure in critically ill patients, particularly in sepsis when normal organ blood flow autoregulation may be altered. The present experimental study investigated whether increasing perfusion pressure using norepinephrine in normotensive hyperdynamic porcine bacteremia affects intestinal macro- and microcirculation. Nine pigs received continuous i.v. administration of *Pseudomonas aeruginosa* (PSAE) to develop hyperdynamic, normotensive (mean arterial pressure [MAP] ≥ 65 mm Hg) sepsis. Norepinephrine was used to achieve 10-15 % increase in MAP. Mesenteric arterial blood flow (Q_{gut}), ileal mucosal microvascular perfusion (LDF_{gut}) and ileal-end-tidal PCO_2 gap (PCO_2 gap) were measured before norepinephrine, after 60 min of norepinephrine infusion and 60 min after norepinephrine infusion had been discontinued. During a 12 h period of PSAE infusion all pigs developed hyperdynamic circulation with significantly decreased MAP. Although the mesenteric blood flow remained unchanged, infusion of PSAE resulted in a gradual fall of ileal microvascular perfusion, which was associated with progressively rising PCO_2 gap. Norepinephrine which induced a 10-15 % increase in perfusion pressure (i.e. titrated to attain near baseline values of MAP) affected neither Q_{gut} nor the intestinal blood flow distribution (Q_{gut}/CO). Similarly, norepinephrine did not change either LDF_{gut} or PCO_2 gap. In this hyperdynamic, normotensive porcine bacteremia, norepinephrine-induced increase in perfusion pressure exhibited neither beneficial nor deleterious effects on intestinal macrocirculatory blood flow and ileal mucosal microcirculation. The lack of changes suggests that the gut perfusion was within its autoregulatory range.

Key words

Sepsis • Shock • Perfusion pressure • Microcirculation • Norepinephrine

Introduction

Organ blood flow autoregulation is usually preserved over a wide range of mean arterial pressure (Johnson 1986). As far as MAP is decreased below a certain critical level (i.e. autoregulatory threshold), organ perfusion becomes pressure-dependent. There is an agreement that under physiological conditions this minimum of MAP is about 60-65 mm Hg. MAP ≥ 65 mmHg has been recommended as a goal for the vasopressor therapy in sepsis provided that the volume expansion is adequate (Dellinger *et al.* 2004). In sepsis,

Fax +420 241 062 164
E-mail: physres@biomed.cas.cz http://www.biomed.cas.cz/physiolres

however, vasoplegia and altered vascular reactivity may result in a shift of the autoregulatory threshold to higher values (Terborg *et al.* 2001). In addition, the autoregulatory threshold may vary between different organs (Bellomo and Giantomasso 2001). In this context, some clinicians advocate a higher MAP than is generally recommended (i.e. MAP ≥ 65 mmHg) presuming that it may further increase regional blood flow. This reasoning is supported by clinical and experimental studies showing that increasing perfusion pressure using norepinephrine in sepsis might be beneficial for renal perfusion and function (Martin *et al.* 1993, Bellomo *et al.* 1999, Di Giantomasso *et al.* 2003, Albanese *et al.* 2004). It should be stressed, however, that in most studies the intervention started clearly below the expected autoregulatory threshold, i.e. from levels of 50-60 mmHg. (Martin *et al.* 1993, Bellomo *et al.* 1999, Albanese *et al.* 2004). In contrast, recent clinical studies showed that renal functions, oxygen kinetics and selected metabolic variables were neither improved nor compromized when MAP was increased from 65 to 85 mmHg in septic shock patients (LeDoux *et al.* 2000, Bourgoin *et al.* 2005), suggesting that MAP of 60-65 mmHg may define autoregulatory threshold, at least for renal blood flow, in septic shock patients (Reisbeck and Astiz 2005). Nevertheless, as mentioned above, this threshold may vary between different organs. In this context, little or inconclusive data are available on intestinal autoregulation in sepsis (for review see Asfar *et al.* 2004). A small clinical study that attempted to address this issue failed to show any effect on gastric tonometry when increasing MAP from 65 to 85 mmHg in septic shock patients (LeDoux *et al.* 2000). Data from experimental studies are mostly derived from short-term (Treggiari *et al.* 2002), single endotoxin or bacteria bolus (Zhang *et al.* 1997, Di Giantomasso *et al.* 2003) or from hypodynamic rodent models of sepsis (Levy *et al.* 2003).

Therefore, in the present study we investigated whether the manipulation with perfusion pressure using norepinephrine, titrated towards near normal (i.e. still physiological) values of MAP affect intestinal macro- and microcirculation in hyperdynamic, well resuscitated, long-term live bacteria-induced porcine sepsis.

Methods

Animal preparation

The experiment was performed in adherence to "*Principles of Laboratory Animal Care*". The study protocol was approved by the University Animal Care Committee. Nine domestic pigs of either sex with a median body weight of 25 kg (range 22-28) were premedicated one hour before the experiment with intramuscularly administered atropine (Atropin Biotika; Hoechst-Biotika, Slovakia) and azaperone (Stresnil; Janssen Neuss, Germany). Anesthesia was induced by intravenous administration of thiopenthal (Thiopenthal; ICN, Czech Republic) and ketamine (Narkamon; Léčiva, Czech Republic) into an ear vein. Then the pigs were orotrachealy intubated and mechanically ventilated (FiO_2 0.4; PEEP 5 cmH_2O; Servo 900C; Siemens, Germany) with a tidal volume of 12 ml/kg and the respiratory rate was adjusted (14-18 bpm) to maintain end-tidal PCO_2 35-40 mm Hg (Tonocap, Datex-Ohmeda, Helsinki, Finland). The continuous anesthesia and analgesia were maintained by infusion of thiopenthal and repeated boluses of buprenorphine (Temgesic®, Schering-Plough, Great Britain) as described previously (Matějovič *et al.* 2004, 2005). The jugular veins as well as the femoral artery were surgically exposed to allow introduction of pulmonary artery (1 Corodyn TD-I, B. Braun Melsungen AG, Germany), central venous (Certofix ® Trio, B. Braun Melsungen AG, Germany) and arterial catheters (Secalon® Seldy, Becton Dickinson, Singapore), respectively. A midline laparotomy was performed, and a precalibrated ultrasound transit time flow probe (Transonic System, Ithaca, NY) was placed around the superior mesenteric artery. A catheter (Certofix® Duo Paed S 520, B. Braun Melsungen AG, Germany) for vein pressure measurements was inserted into the superior mesenteric vein. A loop-ileostomy was performed, which allowed simultaneous insertion of a tonometric tube (TRIP, Tonometrics, Finland) for intramusosal P_{CO2} measurements and a laser Doppler flowmetry probe (409-2.5, Perimed AB, Sweden) for monitoring ileal mucosal microcirculation. The abdominal wall was then closed. In addition, a cystostomy catheter for urine collection was percutaneously placed under ultrasound guidance. A postsurgical stabilization period of 6 h was allowed before baseline measurements were obtained.

Measurements and calculations

The measurement and calculations of systemic hemodynamics included cardiac output (CO), systemic vascular resistance (SVR) and filling pressures of both ventricles (PAOP, CVP) (66S monitor; Hewlett Packard, Palo Alto, CA, USA). The mesenteric arterial blood flow (Qgut) was recorded continuously (T206 flowmeter,

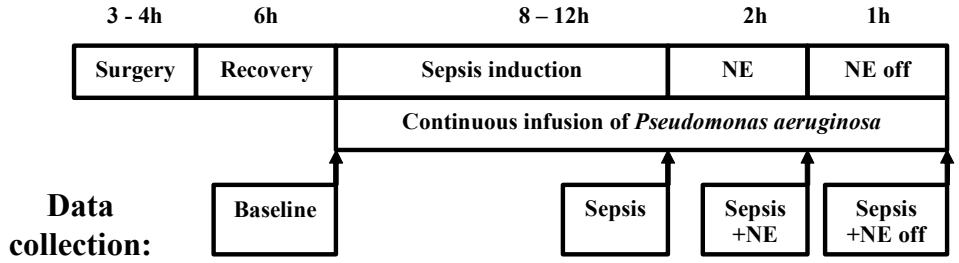

Fig. 1. Study protocol flowchart. NE = norepinephrine

Transonic Systems, Ithaca, NY, USA). Ileal mucosal PCO_2 was measured by automated air tonometry (Tonocap, Datex-Ohmeda, Helsinky, Finland) (time equilibration 10 min). The ileal-end-tidal PCO_2 gap, a surrogate index of gut perfusion/metabolism, was calculated (Uusaro *et al.* 2000a). The ileal mucosal microcirculation was monitored with a laser Doppler flowmeter (Periflux 5000, Perimed AB, Sweden) as described previously (Matějovič *et al.* 2004, 2005). Briefly, each measurement represented mean value of blood flow obtained from five randomly chosen locations, each recorded for 60 s with an optimal intensity of the backscattered light. The quality of laser Doppler signal was controlled on-line on a computer screen so that any motion disturbances as well as noise due to inadequate probe position could be detected before the measurement was started. The mesenteric vein pressure (MVP) was continuously recorded (66S monitor; Hewlett Packard, Palo Alto, CA, USA), and subsequently the mesenteric vascular resistance (MVR) was calculated according to the formula:

$$MVR = MAP\ (mmHg) - MVP\ (mmHg) / Q_{gut}\ (ml\ min^{-1}).$$

Protocol of the study (Fig. 1)

After the postoperative recovery period the baseline data were obtained (Baseline). Then the pigs received a central venous continuous infusion of *Pseudomonas aeruginosa* (1×10^9 colony forming units/ml determined by serial dilution and colony counts). The dose of *Pseudomonas aeruginosa* was titrated during the following 12 h to attain a decrease in MAP 20-25 % below the baseline value. The dose of *Pseudomonas aeruginosa* required to achieve this target was kept constant during the remainder of the study. The 10 % hydroxyethylstarch (Hemohes® 10 %, 200/0.5, B. Braun Melsungen AG, Germany) was infused to maintain MAP ≥ 65 mm Hg and to keep pulmonary artery acclusion pressure (PAOP) below 18 mm Hg. Moreover, all animals received 7 ml kg^{-1} $h^{-1}$of Ringer's lactate solution as a maintenance fluid. The second data set (Sepsis) was collected after 12 h of *Pseudomonas aeruginosa* infusion period. Thereafter, the norepinephrine was administered to achieve 10-15 % increase in MAP above the sepsis value and then after 60 min of steady state the third data set was collected (Sepsis+NE). Subsequently, the norepinephrine was switched off and after next 60 min the last measurements were collected (Sepsis+NE off). When the last set of data had been obtained, the animals were sacrificed by an intravenous potassium chloride injection under deep anesthesia.

Statistical analysis

All values shown are median and the interquartile range. Friedman repeated measures analysis of variance on ranks and a subsequent Dunn's test for multiple comparisons were used to evaluate within-group differences. $P<0.05$ was regarded as significant.

Results

The total dose of *Pseudomonas aeruginosa* infused was 19×10^9 (range 16-21 x 10^9) colony forming units/12 h. The cumulative amount of hydroxyethyl starch infused was 135 ml/kg (range 79-167). Systemic, pulmonary and some of regional and microcirculatory hemodynamic parameters are summarized in Table 1. All animals developed hyperdynamic circulation with reduced systemic vascular resistance within the first 12 h of the experiment. Despite a sustained increase in cardiac output, *Pseudomonas aeruginosa* infusion caused a significant gradual fall in mean arterial pressure. The increase in CO was not paralleled by the increase in Q_{gut} (Fig. 2). Thus, the contribution of mesenteric blood flow to total cardiac output (Q_{gut}/CO) was significantly

Table 1. Systemic, pulmonary and intestinal hemodynamic parameters.

	Baseline	Sepsis	Sepsis+NE	Sepsis+NE off
MAP (mm Hg)	97 (86;104)	74 (68;83) [a]	83 (79;94) [a,b]	72 (67;76) [a,c]
HR (beats/min)	112 (100;118)	107 (104;122)	121 (111;129)	111 (96;125)
CO (ml/min/kg)	121 (112;133)	180 (159;223) [a]	212 (194;237) [a,b]	145 (130;173) [a,b,c]
SVR (dyn/s/cm^{-5})	2633 (2403;3148)	982 (905;1168) [a]	1011 (947;1201) [a]	1060 (946;1339) [a]
MPAP (mm Hg)	25 (24;26)	34 (33;36) [a]	35 (32;36) [a]	32 (31;35) [a,b]
PAOP (mm Hg)	12 (11;13)	17 (16;19) [a]	17 (16;17) [a]	17 (16;17) [a]
CVP (mm Hg)	11 (9-12)	18 (17-19) [a]	17 (16-18) [a]	16 (15-18) [a]
Qgut (ml/min/kg)	9 (6;12)	9 (8;13)	10 (9;14)	9 (7,12)
MVR (dyn/s/cm^{-5})	25.1 (22.9;40.4)	17.7 (12.3;19.1) [a]	18.1 (13.3;22.4) [a]	18.6 (10.2;27.4) [a]

MAP= mean arterial pressure, HR= heart rate, CO= cardiac output, SVR= systemic vascular resistance, PAOP= pulmonary artery occlusion pressure, CVP= central venous pressure, MPAP= mean pulmonary artery pressure, Qgut= superior mesenteric artery blood flow, MVR= mesenteric vascular resistance. Values are median and interquartile range. [a] p<0,05 versus Baseline, [b] p<0.05 versus Sepsis, [c] p<0.05 versus Sepsis+NE

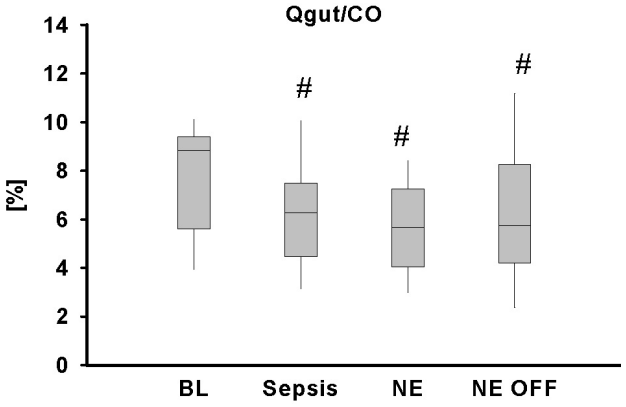

Fig. 2. Mesenteric arterial blood flow as a fraction of cardiac output (Qgut/CO). Data are median, 25/75 % quartiles and 5th and 95th quantile range. # denotes significant differences versus BL, BL= Baseline, NE= Sepsis+ NE, NE OFF= Sepsis+NE off.

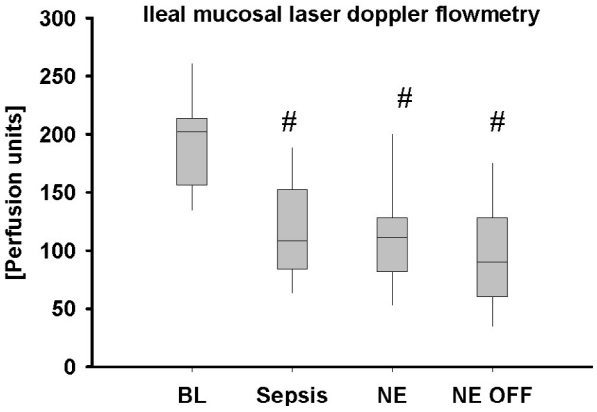

Fig. 3. Ileal mucosal laser Doppler flowmetry. Data are median, 25/75 % quartiles and 5th and 95th quantile range. # denotes significant differences versus BL, BL= Baseline, NE= Sepsis+ NE, NE OFF= Sepsis+NE off

decreased. While MVR significantly decreased, sepsis caused a marked deterioration of ileal mucosal perfusion (ileal mucosal laser Doppler flowmetry) (Fig. 3). These sepsis-induced microcirculatory changes were associated with a progressive rise in ileal mucosal-end-tidal PCO_2 gap (Fig. 4).

The dose of norepinephrine needed to achieve the intended goal was 0.1 μg kg^{-1} min^{-1} (range 0.04-0.42). Norepinephrine-mediated increase in MAP affected neither Q_{gut} nor Q_{gut}/CO (Fig. 1). Similarly, norepinephrine did not modify MVR, intestinal mucosal microcirculation (Fig. 3) nor ileal mucosal-end-tidal PCO_2 gap (Fig. 4). After the cessation of norepinephrine infusion most of measured variables returned to the pre-treatment values, except for a significant fall in cardiac output.

Discussion

The main result of our study demonstrates that in hyperdynamic, volume-resuscitated, normotensive porcine bacteremia, norepinephrine-induced 10-15 % increase in perfusion pressure, titrated to maintain MAP at near normal values, did not affect either intestinal macrocirculatory blood flow or ileal mucosal microcirculation.

Despite the widespread clinical use of vasopressor therapy in vasodilatory hypotension, limited data still exist to guide selection of the threshold for arterial blood pressure (Vincent 2001). Recent guidelines recommend to maintain MAP $\geq$ 65 mmHg (Dellinger *et al.* 2004). However, blood flow autoregulation could

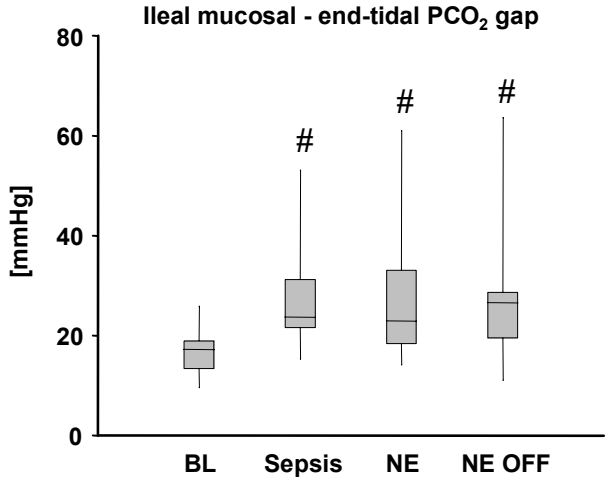

Fig. 4. Ileal mucosal - end-tidal PCO_2 gap. Data are median, 25/75 % quartiles and 5th and 95th quantile range. # denotes significant differences versus BL, BL= Baseline, NE= Sepsis+ NE, NE OFF= Sepsis+NE off

be lost in sepsis, resulting in almost linear pressure-flow relationship in the "at-risk" organs (Terborg *et al.* 2001). In this context, little or no data exist on intestinal autoregulation in sepsis (Asfar *et al.* 2004). In addition, due to the countercurrent microvascular architecture, the villus is particularly sensitive to changes in regional blood flow and oxygenation (Hassoun *et al.* 2001). Therefore, in the present study we tested the hypothesis whether the manipulation with MAP (titrated towards higher but still physiological values of MAP) could affect intestinal macro- and microcirculation in hyperdynamic live bacteria-induced porcine sepsis. We intentionally started the titration of norepinephrine in a normotensive hyperdynamic situation (although a 20 % decrease in mean arterial blood pressure from the baseline was thus achieved) for the following reason. The autoregulatory threshold for the mammalian kidney is above 80 mmHg (Bellomo and Giantomasso 2001). Although two recent clinical studies failed to demonstrate any improvement in renal function when MAP increased from 65 to 85 mmHg in patients with septic shock (Bourgoin *et al.* 2005, LeDoux *et al.* 2000), a higher threshold of MAP (i.e. above 80 mmHg) is still advocated in patients with history of hypertension as well as in patients with advanced chronic kidney or atherosclerotic vascular disease (Marik 2004). Since the relationship between arterial pressure and organ blood flow is non-linear and differs among vascular beds (Pinsky 1995), the increase in arterial pressure that might be of potential benefit for the kidney, may in fact jeopardize the perfusion of other organs (e.g. intestine). Therefore, our intention was to simulate this clinical scenario.

In our model, due to aggressive volume resuscitation, the intestinal blood flow was well maintained during the course of sepsis. Norepinephrine-induced increase in MAP exerted no additional effect on mesenteric blood flow, which is in agreement with other experimental studies (Di Giantomasso *et al.* 2003, Zhang *et al.* 1997). However, since the unchanged mesenteric blood flow does not rule out changes in intestinal microcirculation, we also assessed mucosal micro-vascular perfusion using laser Doppler flowmetry and tonometry, the latter being considered a surrogate marker of both mucosal perfusion and energy metabolism (Tugtekin *et al.* 2001). Nevertheless, increasing the perfusion pressure neither improved nor jeopardized intestinal mucosal microcirculation and ileal mucosal acidosis. Only one clinical study has attempted to address this issue showing that MAP between 65-85 mm Hg was associated with no difference in organ perfusion variables in septic shock (LeDoux *et al.* 2000). It should be stressed, however, that in this study the impact of the increased MAP on splanchnic perfusion was only evaluated using the gastric tonometry, an indirect and equivocal marker of splanchnic perfusion (Uusaro *et al.* 2000b). In a porcine model of acute endotoxemia, Treggiari *et al.* (2002) administered norepinephrine to gradually increase MAP first from 52 to 65 mm Hg and then to 77 mm Hg. During the first arterial pressure increment they observed an increase in portal venous blood flow and jejunal microvascular perfusion. Second increment in perfusion pressure, however, did not further influence the intestinal perfusion. The effect of the first MAP increment was likely, since the intervention started clearly below the expected autoregulatory threshold. Nevertheless, despite obviously different experimenttal design (i.e. short-term, acute endotoxemia and early intervention versus 12 h of Gram-negative sepsis with delayed intervention in our study), our results are in accordance with those observed during the second step of Treggiari´s study.

There are some limitations of this study. First, the final effect of tissue perfusion pressure manipulation using norepinephrine depends on the relative contribution of multiple interrelated factors, including metabolic effects of such interventions. Therefore, without assessing metabolic consequences of vasopressor therapy, no definitive conclusions on the effects of MAP changes on tissue functions can be drawn (Träger *et al.* 2003a,b). Second, although our model mimics many of the features

of human hyperdynamic sepsis, the duration of the intervention was short. Thus, we cannot exclude that more prolonged application of norepinephrine would yield different findings. Third, since the increase in median MAP was only 9 mm Hg, we cannot rule out that a higher increment in MAP would change the results. Furthermore, our findings might not be transferable to other vasopressor agents. Finally, since we studied previously healthy young animals, our results may not be applicable to elderly patients with atherosclerosis and/or history of serious hypertension. We are currently conducting such clinical study that seeks to address these important questions.

In conclusion, our results show that in hyperdynamic, fluid resuscitated porcine sepsis a „better" MAP achieved by titrating norepinephrine to restore near-normal perfusion pressure neither improved nor adversely affected the mesenteric perfusion and intestinal mucosal microcirculation. Within the limitations of the present study, the lack of changes observed over the range of 70-85 mmHg in MAP suggests that the gut perfusion was, at least in this model, within its autoregulatory range.

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Reprint requests

Aleš Kroužecký, Intensive Care Unit, First Medical Department., Charles University Medical School and Teaching Hospital, Alej Svobody 80, CZ-304 60 Plzeň, Czech Republic. E-mail: krouzecky@fnplzen.cz