The effects of norepinephrine on hemodynamics and renal function in severe septic shock states

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Received: 3 March 1992; accepted: 16 October 1992

Abstract. Objective: To investigate the effect of norepinephrine (NE) on hemodynamics, oxygen metabolism and renal function in patients with severe septic shock.

Design: Prospective study.

Setting: Post-operative ICU in a municipal general hospital.

Patients: The study included 56 patients with extreme low resistance states due to abdominal sepsis, who remained hypotensive (MAP<60 mmHg) despite optimal fluid therapy and dopamine>20 µg/kg/min and cumulative doses of dopamine and dobutamine>30 µg/kg/min, respectively.

Interventions: After registration of baseline values dopamine was reduced to 2.5 µg/kg/min, and norepinephrine was administered starting at a dose of 0.05 µg/kg/min until a mean arterial pressure of more than 60 mmHg could be maintained.

Measurements and results: During norepinephrine infusion (dosage ranging between 0.1-2 µg/kg/min, mean dose rate: 0.4 µg/kg/min) mean arterial pressure and systemic vascular resistance index increased significantly (p < 0.001). After 8 h a significant increase in stroke volume (p < 0.05) and decrease in heart rate (p < 0.05) could be observed. There was no significant change in cardiac index (CI), oxygen delivery (O₂AVI) and oxygen consumption (VO₂I). Creatinine clearance increased significantly (p < 0.005) from a control value of 75 ± 37 ml/min to 102 ± 43 ml/min after 48 h NE-treatment.

Conclusion: Our results suggest that norepinephrine can be used safely in the treatment of severe septic shock states. Mean arterial pressure and glomerular filtration rate improved markedly without deleterious effects on CI, O₂AVI and VO₂I.

Key words: Vasoactive drugs – Norepinephrine – Sepsis – Hemodynamic – Hyperdynamic shock

Consequently supranormal values of oxygen delivery and consumption are the main therapeutic goals in septic shock to avoid tissue hypoxia [4–7]. However, besides these variables sufficient mean arterial pressures are also essential for optimal organ perfusion. In extreme low resistance states adequate perfusion pressure cannot be maintained despite extreme increases of cardiac output [8]. In this particular pattern of septic shock, associated with a poor prognosis [9–12], beneficial effects of norepinephrine, a mainly α-adrenergic catecholamine, were described not only in septic canine models [13] but also in clinical series [8, 14–16].

As norepinephrine (NE) is known to depress glomerular filtration rate and renal blood flow in healthy volunteers [17] and in animal experiments [18] we prospectively investigated the effect of norepinephrine on hemodynamics as well as peripheral perfusion with particular attention to renal function in abdominal sepsis.

Patients and methods

The study included 56 septic patients in extreme low resistance states (< 1300 dyne·s/cm²·m²) due to septic shock according to the criteria of Bone [19]. Cause of sepsis were: superinfected necrotizing pancreatitis (n = 14), diffuse peritonitis due to primary perforation of the gut, intra-abdominal abscess and anastomosis leakage (n = 36), miscellaneous post-operative septic cases (n = 6). Mean age of the investigated patient population was 60 years (ranged from 23–89 years). Within the period of study all patients received ventilatory support. Positive end-expiratory pressure (PEEP) levels and inspiratory to expiratory (I/E) ratio were adjusted to ensure an arterial oxygen tension (PaO₂) of at least 80 mmHg on the minimum possible inspired oxygen fraction (FIO₂). The Apache II classification system [20] was used to rate the severity of illness. This score was calculated from the sum of weighted points representing the extent of physiologic derangements (omitting points related to cerebral function, as all patients were sedated receiving ventilatory support), age, and pre-existing chronic illness.

The study entry criteria were: a mean arterial pressure of below 60 mmHg, or in chronic hypertensive patients, a decrease in systolic pressure of more than 50 mmHg compared to pre-illness values, despite volume optimization and dopamine>20 µg/kg/min and cumulative doses of dopamine and dobutamine>30 µg/kg/min. Cases with tachycardia>140 per min were also included in the study even if the
doses of inotropic catecholamines infused were lower than indicated. After registration of baseline values, dopamine was reduced to low dose dopamine (2.5 μg/kg/min), and norepinephrine was administered starting at a dose of 0.05 μg/kg/min until a mean arterial pressure of more than 60 mmHg could be maintained. Dobutamine was kept at the former dose range. A standardized fluid regimen was used for all patients. Fluid deficits were replaced with balanced electrolyte solutions to an optimal pulmonary capillary wedge pressure above which there were no further increases in cardiac index. Human albumin was added when plasma colloid osmotic pressure decreased to less than 10 mmHg [21]. A hematocrit less than 30% was restored by transfusion of packed red blood cells. Following this regimen a mean positive fluid balance of 8000 ml (range: 3000–21000 ml) was required within the first 24 h of study period.

Surgical procedures in peritonitis were: pre-planned re-laparatomies and, in case of unfluinenced septic course, open packing laparastomy with continuous lavage. The therapeutic concept in acute necrotizing pancreatitis consisted of necrosectomy, daily open lavage and continuous lavage of the peripancreatic space via retro-peritoneocystomy.

**Monitoring**
Mean arterial pressure was obtained through an intravascular line placed in the radial artery (20 G, British Vigo, Swindon, UK); pulmonary arterial pressures and right atrial pressure (RAP) were monitored via a Swan Ganz catheter (Thermodilution catheter AH-05000-H, Arrow, Pennsylvania). At fixed points of time (control values, and 1, 4, 8 and 24 h after norepinephrine administration) cardiac output was measured by thermodilution (cardiac output computer, Sirecust 404-1, Siemens) using 10 ml iced saline solution (0–5°C) as the indicator. At the same points of time pulmonary capillary wedge pressure (PCWP), RAP arterial and mixed venous blood samples were obtained for measurement of blood gas data, hemoglobin content and hemoglobin saturation (Instrumentation Laboratory CO-Oximeter 282). Pressures were zero referenced to the mid axillary line and read at end-expiration. Oxygen content in arterial and mixed venous blood was calculated by hemoglobin content, hemoglobin saturation and oxygen tension. Systemic and pulmonary vascular resistance, O2-delivery and O2-consumption were calculated using standard formulae.

Creatinine clearance (Ccr) and free-water clearance (CH2O) were calculated from the 24 h period before therapy and from the 0–24 h and the 24–48 h periods during norepinephrine treatment using standard formulae (CH2O (ml/h) = UF – Cosm; Cosm (ml/h) = (UF x Cosm)/Posm, where Cosm is osmolar clearance, Posm and Uosm are plasma and urine osmolality, respectively, and UF is urine volume/h). All calculations were done on an IBM-compatible personal computer using a statistical package (PC-Statistik; Top Soft, Hannover, Germany). Paired data at the different time points were compared with the control data using analysis of variance and t-test for statistical evaluation. All data were expressed as mean±SD. A p-value of less than 0.05 was considered as significant.

**Results**
Of the 56 patients investigated 31 survived. There were 25 patients who died due to intractable septic multiple organ failure (mortality: 44.6%). The duration of ICU stay was 3–12 weeks. The Apache II score at study entry varied between 12–31 (average: 16.8).

During the study period a norepinephrine (NE) dosage ranging between 0.1–2 μg/kg/min (mean dose rate 0.4 μg) was necessary to maintain a mean arterial pressure of more than 60 mmHg.

Table 1 gives a survey of hemodynamic changes following NE treatment. Mean arterial pressure (MAP) and systemic vascular resistance index (TPRI) showed marked, statistically significant increase of 37% and 53%, respectively, just after 1 h and remained above the initial values in the further course. After 8 h a statistically significant increase in stroke volume and decrease in heart rate could be observed. There was no significant change in cardiac index (CI), O2-delivery and O2-consumption. The indices of renal function are depicted in Table 2.

After 24 h, creatine clearance increased from an initial value of 75±37 ml/min to 89±39 ml/min. After 48 h it rose to 102±43 ml/min significantly exceeding baseline values. Urine flow and free water clearance did not change significantly. None of the 56 patients showed a decrease of creatinine clearance. Moreover, 5 of 7 patients suffering from non-oliguric acute renal failure at admission (Ccr < 20 ml/min, BUN > 80 mg%) regained sufficient renal function (Ccr > 60 ml/min) during NE-treatment (Table 3).

**Discussion**
The reluctance to use potent α-adrenergic substances in septic patients during the last decade can be referred to the fear that an increase in peripheral resistance could jeopardize maintenance of cardiac index and oxygen delivery thus leading to insufficient perfusion of vital organs. In particular, given the high risk of acute renal failure in septic patients [22] many physicians have been reluctant to use NE for fear of precipitating acute renal failure because of decreased renal blood flow. NE is known