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The effects of prostacyclin on gastric intramucosal pH in patients with septic shock

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Abstract *Objective:* To investigate whether infusing prostacyclin (PGI_2) in patients with septic shock improves splanchnic oxygenation as assessed by gastric intramucosal pH (pHi).
Design: Interventional clinical study.
Setting: Surgical ICU in a university hospital.
Patients: 16 consecutive patients with septic shock according to the criteria of the ACCP/SCCM consensus conference all requiring norepinephrine to maintain arterial blood pressure.
Interventions: All patients received PGI_2 (10 ng/kg·min) after no further increase in oxygen delivery could be obtained by volume expansion, red cell transfusion and dobutamine infusion. The results were compared with those before and after conventional resuscitation. The patients received continuous PGI_2 infusion for 3–32 days.
Measurements and results: O_2 uptake was measured directly in the respiratory gases, pHi was determined by tonometry. Baseline O_2 delivery, O_2 uptake and pHi were 466 ± 122 ml/min·m^2, 158 ± 38 ml/min·m^2, and 7.29 ± 0.09, respectively. While O_2 uptake remained unchanged, infusing PGI_2 increased O_2 delivery (from 610 ± 140 to 682 ± 155 ml/min·m^2, $p < 0.01$) and pHi (from 7.32 ± 0.09 to 7.38 ± 0.08, $p < 0.001$) beyond the values obtained by conventional resuscitation. While 9 of 11 patients with final pHi > 7.35 survived, all patients with final pHi < 7.35 died ($p < 0.01$).
Conclusions: Infusing PGI_2 in patients with septic shock increases pHi probably by enhancing blood flow to the splanchnic bed and thereby improves splanchnic oxygenation even when conventional resuscitation goals have been achieved.

Key words Prostacyclin · Gastric intramucosal pH · Splanchnic blood flow · Splanchnic oxygenation · Septic shock

Introduction

Septic shock is characterized by hypoperfusion abnormalities and sepsis-induced hypotension despite adequate fluid resuscitation [1, 2]. Hypoperfusion abnormalities include oliguria, lactic acidosis or impaired splanchnic oxygenation [1] resulting in the development of multiple organ dysfunction syndrome [3]. Splanchnic oxygenation can be monitored by determination of gastric intramucosal pH (pHi) [4] which can be measured simply by

placing a balloon tonometer in the lumen of the stomach; from the PCO_2 of the balloon fluid after a suitable equilibration period pHi can be calculated by a modified Henderson-Hasselbalch equation with the arterial bicarbonate concentration. The result of this calculations correlates well with directly measured pHi using microelectrodes [5].

Subnormal pHi levels have been shown to be associated with morbidity and mortality in ICU patients [6, 7], and patients monitored and treated for falls in pHi had lower mortality than those monitored only for conventional endpoints of resuscitation such as blood pressure and urine output [8, 9]. Conventional resuscitation consisting of volume expansion and dobutamine infusion aims at increasing global oxygen delivery [10, 11], but the treatment lacks a clearly defined endpoint. In addition, although dobutamine increased pHi in patients with sepsis [12], adverse effects on pHi have been reported by others [13].

Infusing prostacyclin (PGI_2, 5 ng/kg·min), a vasodilator with antiplatelet aggregating [14] and cytoprotective [15–17] properties increased liver blood flow in healthy volunteers [18] and improved "nutrient" blood flow and thereby tissue oxygenation as documented enhanced global oxygen uptake in patients with septic acute respiratory failure [19]. Since PGI_2 selectively rose splanchnic blood flow in animal models of hemorrhagic [20] and endotoxic [15, 21] shock we hypothesized that PGI_2 infusion would increase pHi in patients with septic shock. Therefore we investigated the effects of infusing PGI_2 after conventional resuscitation goals had been achieved. The patients were treated with PGI_2 for up to 32 days.

Methods

The study protocol was approved by the institutional ethical committee, and the study was conducted according to the principles embodied in the Declaration of Helsinki.

Patients

Sixteen consecutive patients with septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [2] were included in the study: core temperature > 38.5 or < 35.5 °C; white blood cell count > 12000/µl, < 4000/µl, or > 10% immature (band) forms; presence of perfusions abnormalities such as oliguria, increased lactate levels; hypotension (systolic blood pressure < 90 mmHg) without the use of vasopressor agents despite adequate fluid replacement (pulmonary artery occluded pressure ≥ 12 mmHg). The type and amount of therapy was measured using the Therapeutic Intervention Scoring System [22], and the mean TISS-score was 52±3 (survivors 52±4, non-survivors 52±2, $p > 0.5$). In order to maintain arterial blood pressure, all patients received norepinephrine (0.21±0.14 µg/kg·min; survivors 0.23±0.17 µg/kg·min, non-survivors 0.18±0.07 µg/kg·min, $p > 0.5$), arterial lactate levels were 2.34±0.61 mmol/l (normal range in our laboratory 1.0–1.8 mmol/l). None of the patients received corticosteroids or nonsteroidal antiinflammatory drugs at least 24 h prior to the study. The patients' clinical characteristics including their major infection are shown in Table 1.

The patients were sedated with continuous i.v. fentanyl and methohexital and paralyzed with intermittent vecuronium. In addition to cardiovascular failure [23, 24] all patients had respiratory failure [23, 24] and were mechanically ventilated (mean FiO_2 0.53, range 0.35–0.70) in the pressure controlled-inversed ratio ventilation mode (Evita ventilator, Dräger, Lübeck, Germany) with application of positive end-expiratory pressure (mean PEEP 11.8 cmH_2O, range 8–16 cmH_2O). Acute renal failure [23] requiring continuous hemodiafiltration or hemodialysis was present in 8 patients, renal dysfunction with creatinine levels above 220 µmol/l in 4 additional patients (Table 1). Liver dysfunction as defined by bilirubin levels > 100 µmol/l and/or ASAT levels > 3 times the normal [23] was present in 5 patients. All patients, hence, had failure of two or more organ systems for at least two days, and therefore expected mortality was 60–95% [24].

Measurements

Routine clinical monitoring of the patients included a thermodilution pulmonary artery catheter (mo. 93A-754-7.5F. Baxter Healthcare, Irvine, CA) and a radial artery catheter. Mean systemic arterial pressure, mean pulmonary arterial, right atrial and pulmonary artery occluded pressure were measured with disposable transducers (Combitrans Monitoring Set, Braun, Melsungen, Germany) and a monitoring system together with a continuous lead II ECG. The zero reference for the supine position was the midaxilla. Cardiac output was measured with thermodilution (Explorer, Baxter Healthcare), the reported values being the mean of five injections of 10 ml ice-cold saline randomly spread over the respiratory cycle [25]. Arterial and mixed-venous blood samples were analyzed for blood gas tensions, pH, total hemoglobin and hemoglobin oxygen saturation with an ABL 510 blood gas analyzer (Radiometer, Copenhagen) equipped for spectrophotometry. Oxygen delivery and venous admixture were calculated from standard formulae.

Oxygen uptake ($\dot{V}O_2$) was directly measured in the respiratory gases with a Deltatrac® Metabolic Monitor (Datex, Finland). This device has been validated in critical care patients [26, 27]. Before each investigation gas equilibration was performed with a known gas mixture (approx. 95% O_2, 5% CO_2). The flow constant of the mixing chamber was calibrated before the study by burning 5 ml of ethanol 99% under a canopy and analyzing the exhaust gases. The average coefficient of variation of the $\dot{V}O_2$ measurements for the study period during minute-to-minute registrations was 6.9±1.9%. To minimize changes of oxygen delivery and uptake unrelated to the study protocol suctioning, turning or other manipulations of the patients were prohibited during the study, and it was checked that body temperature remained within 0.5 °C of baseline.

On admission to the study a tonometer (Trip® TGS catheter, Tonometrics Inc., Bethesda, MD) was placed in the patients' stomach and correct positioning confirmed by radiography. Patients with oesophageal or nasopharyngeal obstructions and bleeding and/or recent surgical anastomoses of the upper gastrointestinal tract were excluded. Gastric intramucosal pH (pHi) was assessed with the method of Fiddian-Green [28]: The silicone balloon of the tonometer was anaerobically filled with 2.5 ml 0.9% saline. After 90 min of equilibration between the saline and the gastric mucosa and lumen samples of the tonometer saline and of arterial blood were taken simultaneously and analyzed for PCO_2 and bicarbonate content, respectively (ABL 510). pHi was then calculated with a modified Henderson-Hasselbalch equation as

$$pHi = 6.1 + \log\left(\frac{\text{arterial bicarbonate}}{PCO_2 \cdot 1.12 \cdot 0.03}\right)$$

where 6.1 is the pK of carbonic acid, 1.12 the correction factor provided by the manufacturer for 90 min of equilibration time, and 0.03 the solubility of CO_2 in saline.

The method has been validated in animals by comparison of intramucosal pH measured tonometrically and with a needle pH microelectrode [5]. To increase precision in the measurement of pHi all patients received histamine-receptor-blocking agents or omeprazole throughout their whole ICU stay [29].

Protocol

After the diagnosis of septic shock a first set of measurements was obtained when the patients had stabilized under norepinephrine infusion. Then the patients were treated according to a protocol developed in-house to achieve supranormal levels of oxygen delivery while the norepinephrine infusion was maintained. The treatment consisted of dobutamine infusion in incremental dosage together with volume expansion with fresh frozen plasma in boluses of 250 ml to maintain pulmonary artery occluded pressure ≥ 12 mmHg and packed red cell transfusion if total hemoglobin was < 100 g/l until no further increase in oxygen delivery could be achieved. A mean of four boluses of plasma (range 3–7) and 32 ± 10 µg/kg·min of dobutamine (34 ± 8 and 29 ± 11 µg/kg·min in survivors and non-survivors, respectively, $p > 0.4$) of dobutamine were required to achieve this goal. After 90 min had elapsed in stable hemodynamic conditions, a second set of measurements was obtained. Then prostacyclin (PGI_2, 10 ng/kg·min) was added, and 90 min later a third set of data was obtained. The order of the conventional resuscitation and the PGI_2 administration was not randomized since PGI_2 infusion without a preceding volume expansion was expected to result in pronounced hypotension [19].

After the study all patients were treated with prolonged continuous PGI_2 infusion (3–10 ng/kg·min) for 3–32 days. Measurements of pHi were performed twice daily. PGI_2 treatment was terminated when inotropic or vasopressor support was no longer necessary and/or organ failure had resolved.

Statistical analysis

All date are expressed as mean ± SD. The Friedman rank sign analysis of variance and the Wilcoxon-Wilcox test for multiple comparisons were used to analyze the response to conventional resuscitation and the prostacyclin infusion. The patients were followed for 28 days or until death, and outcome was tested with Fisher's exact test. Differences in the initial physiological measurements between survivors and non-survivors were sought with a Wilcoxon rank sign test for unpaired samples, distribution of organ system failure was analyzed with Fisher's exact test.

Results

Evaluation of baseline measurements in the 16 patients with septic shock revealed no difference between survivors and non-survivors in any measured or calculated variable of systemic and pulmonary hemodynamics, gas

Table 1 Clinical characteristics of the patients

Patient	Age/sex	Diagnosis and surgical intervention	Major germ	Organ dysfunction[a]	Survival
W.B.	72/M	Abdominal aortic aneurysm, nephrectomy, splenectomy	*Streptococcus faecalis*	Kidney, liver	No
R.E.	52/M	Polytrauma: multiple fractures, thoracic contusion	*Haemophilus influenzae, Pneumococcus*	Kidney, liver	No
R.Z.	43/F	ARDS after aorto-mesenteric bypass graft	*Bacteroides fragilis*	None	Yes
K.W.	71/M	Appendicitis, peritonitis, subhepatic abscess	*Streptococcus faecalis, Candida albicans*	Kidney	No
H.D.	78/M	Abdominal aortic aneurysm, ileus, postoperative pneumonia	*Klebsiella pneumoniae, Escherichia coli*	Kidney	Yes
W.J.	77/M	Aorto-coronary bypass graft, bowel ischema	*Streptococcus faecalis, Escherichia coli*	Kidney	No
B.A.	69/M	Ruptured abdominal aortic aneurysm	*Pseudomonas aeruginosa*	Kidney	No
W.K.	65/M	Aorto-coronary bypass graft, postoperative pneumonia	*Pseudomonas aeruginosa, Candida albicans*	None	Yes
E.M.	81/M	Ruptured abdominal aortic aneurysm	*Staphylococcus aureus*	Kidney, liver	No
W.P.	52/M	Aorto-coronary bypass graft, postoperative pneumonia, pseudomembraneous colitis	*Klebsiella pneumoniae*	Kidney	Yes
K.R.	68/M	Aorto-bifemoral bypass graft, renal artery desobliteration	*Klebsiella pneumoniae*	Kidney, liver	Yes
P.T.	75/M	Ruptured abdominal aortic aneurysm, postoperative pneumonia	*Enterobacter cloacae*	Kidney, liver	No
E.C.	58/F	Graft infection after aorto-bifemoral bypass	*Staphylococcus aureus, Proteus mirabilis*	None	Yes
W.T.	64/M	Aorto-coronary bypass graft, postoperative pneumonia	*Streptococcus faecalis, Proteus mirabilis*	None	Yes
F.S.	67/M	Aorto-coronary bypass graft, postoperative pneumonia	*Streptococcus faecalis*	Kidney	Yes
H.K.	71/M	Aneurysm of ascending aorta, postoperative pneumonia	*Escherichia coli, Proteus mirabilis*	Kidney	Yes

[a] Organ dysfunction other than respiratory or cardiovascular

exchange, arterial pH, bicarbonate and lactate levels, and pHi; the presence of organ system failure other than respiratory or cardiovascular were similar as well. Table 2 summarizes the results of the baseline physiological measurements in survivors and non-survivors immediately prior to the study.

Infusing PGI_2 usually produced an increase in pHi (Fig. 1) concomitant with enhanced oxygen delivery (Fig. 2, left panel) beyond the levels obtained with conventional resuscitation, while oxygen uptake (Fig. 2, right panel) remained unchanged. Table 3 presents the immediate hemodynamic and gas exchange responses to the conventional resuscitation and the subsequent PGI_2 infusion. While conventional treatment increased oxygen delivery from 466 ± 122 to 610 ± 140 ml/min·m^2 ($p < 0.001$) without a significant change in pHi (from 7.29 ± 0.09 to 7.32 ± 0.09, $p > 0.2$) subsequent PGI_2 infusion resulted in a further increase of oxygen delivery (to 682 ± 155 ml/min·m^2, $p < 0.01$) associated with a significantly higher pHi (7.38 ± 0.08, $p < 0.001$). Global oxygen uptake did not change throughout the study period.

PGI_2 infusion was continued in all patients for a total of 3–32 days. In 9 of the 11 patients in whom pHi was restored to normal levels at the end of the protocol (i.e. pHi > 7.35) pHi values stayed within the normal range on the following days. These 9 patients survived. In the two remaining patients (patients R.E. and W.J., Table 1) pHi subsequently fell to subnormal levels, and these patients died 3 and 16 days, respectively, after completion of the study protocol.

In contrast, the 5 patients in whom pHi could not be normalized during the protocol, pHi remained in the subnormal range throughout the whole period of PGI_2 administration. All these patients died. Hence, survival was significantly higher ($p < 0.01$) in the patients with pHi restored to normal.

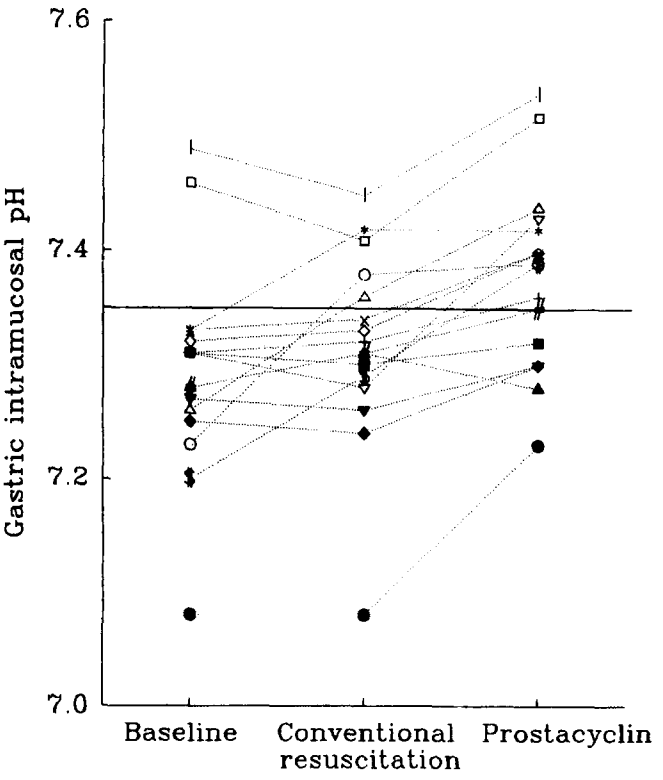

Fig. 1 Individual responses of gastric intramucosal pH to conventional resuscitation and prostacyclin administration. The *horizontal line* designates a pHi of 7.35, the lower limit of the normal range. All patients with final pHi < 7.35 (*solid symbols*) died. Note that in two patients (▽ and △) in whom pHi was restored to normal at the end of the initial study protocol it fell to subnormal levels on the following days despite resuscitative measures. These two patients died 3 and 16 days after completion of the study protocol, respectively

Table 2 Baseline physiological measurements in the 16 patients according to outcome

	9 Survivors	7 Non-survivors
Heart rate [beats/min]	104 ± 19	96 ± 16
Mean systemic arterial presssure [mmHg]	85 ± 15	74 ± 11
Mean pulmonary artery pressure [mmHg]	33 ± 9	28 ± 3
Right atrial pressure [mmHg]	15 ± 3	13 ± 3
Pulmonary artery occlusion pressure [mmHg]	16 ± 4	15 ± 3
Cardiac index [l/min·m^2]	2.8 ± 0.6	3.3 ± 1.0
Arterial PO_2 [mmHg]	107 ± 56	81 ± 11
Arterial PCO_2 [mmHg]	46 ± 6	51 ± 11
Arterial pH	7.46 ± 0.07	7.42 ± 0.05
Arterial bicarbonate [mmol/l]	32.2 ± 5.6	31.7 ± 3.2
Mixed-venous PO_2 [mmHg]	33 ± 5	34 ± 5
Venous admixture [%]	19 ± 6	23 ± 9
Oxygen delivery [ml/min·m^2]	458 ± 98	476 ± 155
Oxygen uptake [ml/min·m^2]	154 ± 34	161 ± 44
Arterial lactate [mmol/l]	2.36 ± 0.63	2.33 ± 0.63
Gastric intramucosal pH	7.33 ± 0.10	7.25 ± 0.08

All values are mean ± SD. Note that there were no significant differences in baseline physiological variables between survivors and non-survivors

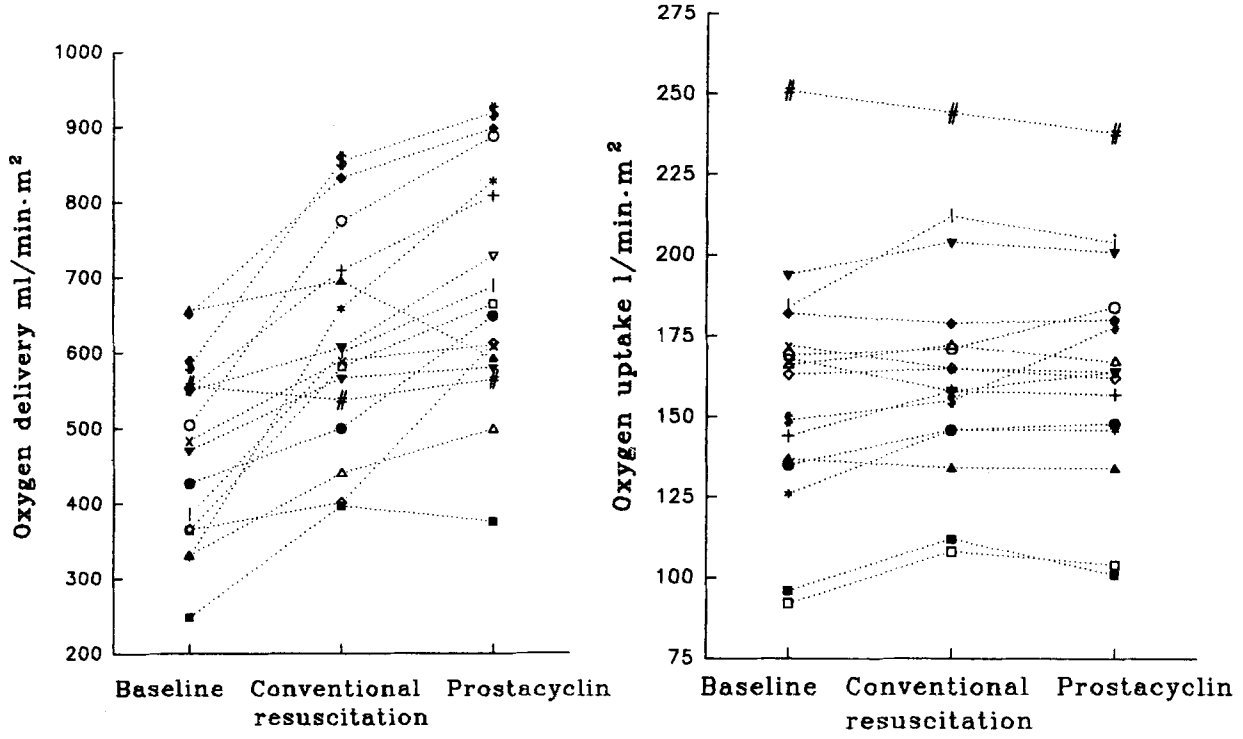

Fig. 2 Individual responses of oxygen delivery (*left panel*) and oxygen uptake (*right panel*) to conventional resuscitation and prostacyclin administration. The different *symbols* correspond to the same patients as in Fig. 1. Note that similar to the baseline evaluation (see also Table 2) there were no differences between survivors and non-survivors in oxygen delivery or uptake

Discussion

In 1987 Bihari et al. [19] demonstrated that infusing PGI_2 can increase systemic oxygen delivery and potentially improve "nutrient" blood flow in patients with septic acute respiratory failure, thereby revealing covert tissue hypoxia. Our study suggests that PGI_2 may restore splanchnic oxygenation as monitored by tonometric gastric intramucosal pHi even after conventional resuscitation goals have been achieved.

Assessment of gastric intramucosal pH by tonometry has recently been introduced into clinical practice [28]. This indirect technique for the assessment of gut intramural pH has been extensively validated in different animal models of intestinal hypoperfusion by direct pH measurement with microelectrodes [5]. Recently, Boyd et al. [32], however, argued that tonometric pHi could be easily replaced by the assessment of bicarbonate levels and base excess from routine arterial blood-gas analysis. In all our

Table 3 Hemodynamic and gas exchange responses of the 16 patients to conventional resuscitation and subsequent prostacyclin infusion

	Baseline	Conventional resuscitation	Prostacyclin
Heart rate [beats/min]	100±18	112±14**	119±11**
Mean systemic arterial pressure [mmHg]	80±14	86±17	72±10**
Mean pulmonary artery pressure [mmHg]	31±8	32±6	29±5
Pulmonary artery occlusion pressure [mmHg]	15±4	16±4	15±4
Right atrial pressure [mmHg]	14±3	13±3	13±3
Cardiac index [l/min·m²]	3.0±0.8	3.9±0.9***	4.7±0.9***
Arterial PO_2 [mmHg]	96±44	101±54	70±25*
Arterial PCO_2 [mmHg]	48±9	50±8	49±10
Arterial bicarbonate [mmol/l]	31.9±4.3	32.3±4.2	32.6±4.7
Arterial pH	7.44±0.06	7.43±0.06	7.44±0.06
Mixed-venous PO_2 [mmHg]	33±5	38±4*	36±5
Venous admixture [%]	21±7	25±7*	35±10***
Oxygen delivery [ml/min·m²]	466±122	610±140***	685±155**
Oxygen uptake [ml/min·m²]	158±38	165±35	165±36
Gastric intramucosal pH	7.29±0.09	7.32±0.09	7.38±0.08***

All values are mean±SD.
*$p<0.05$, **$p<0.01$, ***$p<0.001$ for the comparison with the preceding value

patients with septic shock, no matter whether pHi was normal or subnormal, baseline arterial bicarbonate levels were within the normal range and base excess positive. Consequently, baseline arterial pH was normal in all patients as well (Tables 2, 3). No changes in any of these variables occurred throughout the study (Table 3), which clearly demonstrates that pHi yielded a monitoring parameter which could not be replaced by any other physiological measurement.

Baseline pHi was subnormal in all but two patients despite resuscitation with volume expansion and norepinephrine. This finding seems to contrast with data recently published by Ruokonen et al. [31]: in patients with septic shock correction of hypotension with vasopressors restored splanchnic blood flow and oxygen uptake. A more profound septic shock in our patients might account for this discrepancy: despite a more aggressive fluid resuscitation (pulmonary artery occluded pressure > 12 mmHg in our versus 8 – 12 mmHg in the quoted study) mean baseline global oxygen delivery as well as cardiac index were lower (466 and 3.0 versus 574 ml/min·m^2 and 4.3 l/min·m^2, respectively) and arterial lactate levels higher (2.34 versus 1.7 mmol/l) in our patients.

The major factor limiting splanchnic oxygenation is blood flow [4, 5, 32]. Therefore we tried to augment intestinal oxygen delivery by rising global oxygen transport after conventional resuscitation goals had been achieved. Prostacyclin was chosen to increase oxygen supply for a number of reasons: Prostacyclin (PGI_2) is a potent endogenous vasodilator [14] prostaglandin with anti-platelet [14] and cytoprotective [15, 16, 17] properties. Furthermore, PGI_2 has been shown to improve the distribution of microcirculatory flows in patients with sepsis [34] and to increase liver blood flow in healthy volunteers [18]. Finally, PGI_2 inhibits activation of macrophages and leucocyte adherence to injured endothelium [35], phenomena which might further promote endothelial injury [19].

In our patients with septic shock infusing PGI_2 improved pHi beyond the values obtained with conventional resuscitation. Since our data are uncontrolled we cannot exclude that this improved pHi during PGI_2 infusion was actually a delayed time-related phenomenon following adequate resuscitation with fluids and adrenergic drugs. It has to be noted, however, that in all of the 5 patients in whom pHi could not be restored to normal during the protocol pHi remained in the subnormal range throughout the whole period of PGI_2 infusion lasting from 3 to 19 days. Furthermore, other mechanisms than the enhanced global oxygen delivery may have caused the rise of pHi: Animal experiments showed that PGI_2 may redistribute blood flow to the splanchnic bed and thereby improve blood flow to gut [15, 20, 21, 35] and liver [21] after hemorrhagic [20, 35] and endotoxic [15, 21] shock.

Our finding that PGI_2 increased global oxygen delivery ($\dot{D}O_2$) without altering global oxygen uptake ($\dot{V}O_2$) raises the question whether our patients exhibited pathological supply dependency of oxygen uptake such as described in septic acute respiratory failure [19] or in septic patients with increased lactate levels [36]. When the $\dot{V}O_2$ data were plotted against $\dot{D}O_2$ no relationship could be identified. This result agrees with data recently published by Ronco et al. [37] in a comparable group of patients with sepsis: when oxygen delivery was increased with incremental dosages of dobutamine to an extent similar to that in our study, no supply dependency of directly measured oxygen uptake could be detected, no matter whether lactate levels were normal or increased.

Infusing PGI_2 produced a substantial rise in systemic oxygen delivery and improved pHi despite increased venous admixture and a concomitant fall in arterial PO_2. This impaired gas exchange probably reflected an increased intrapulmonary right-to-left shunt such as described in patients with adult respiratory distress syndrome receiving PGI_2 [38, 39]. The impaired gas exchange together with the reduced mean arterial blood pressure might limit the use of PGI_2 in patients with septic shock, and particular since these patients are often characterized by a high cardiac output-low perfusion pressure hemodynamic profile in combination with increased venous admixture [40]. It has to be noted, however, that in only one of our patients mean blood pressure fell below 55 mmHg and the inspired oxygen fraction had to be increased because of arterial hypoxemia (PO_2 = 43 mmHg) induced by the prostacyclin infusion. The relatively minor side effects of the PGI_2 infusion are due to the low infusion rate (10 ng/kg·min) confirming the findings in patients with septic acute respiratory failure [19] or the adult respiratory distress syndrome [41].

In addition to the study protocol PGI_2 infusion was continued in all patients for 3 – 32 days with pHi determinations twice daily. In two of the patients in whom pHi could be restored to normal during the initial investigational protocol pHi values fell to subnormal levels on the following days despite resuscitative measures. These two patients subsequently died. Nevertheless, survival was significantly higher in the patients with normalized pHi. Since there was no statistically significant difference in baseline pHi levels between survivors and non-survivors this result contrasts with other reports [6, 8, 9] inasmuch pHi-guided resuscitation lacked success when the initial pHi was pathologically low. Possible explanations for this discrepancy could be a more aggressive resuscitation protocol in our study (fluid administration as well as dobutamine infusion rates were higher; the conventional treatment was titrated until there was no further increase in global oxygen delivery) and a protective effect of PGI_2 against putative reperfusion injury: once the gut mucosa has been damaged restoring perfusion might also have deleterious effects mediated by oxygen free radicals [8]. PGI_2, however, has been shown to prevent organ dysfunction after ischemic injury due to endotoxic shock [16] or aortic cross clamping [43].

In a preliminary and uncontrolled study in a limited number of patients with septic shock we have shown that infusing PGI_2 in addition to conventional resuscitation restored pHi and thereby probably improved splanchnic oxygenation which was associated with increased survival. We can only speculate whether PGI_2 therapy would improve outcome in a larger group of patients. Therefore our findings, in particular when taking into account the potentially limiting side effects, have to be confirmed by a prospective controlled trial to determine whether PGI_2 treatment can raise pHi and thereby improve the outcome of patients with septic shock.

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