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Aerosolized prostacyclin and inhaled nitric oxide in septic shock – different effects on splanchnic oxygenation?

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Abstract *Objectives:* To compare the effects of inhaled nitric oxide and aerosolized prostacyclin (PGI_2) on hemodynamics and gas exchange as well as on the indocyanine-green plasma disappearance rate and gastric intramucosal pH in patients with septic shock.
Design: Prospective, randomized, interventional clinical study.
Setting: Intensive care unit in a university hospital.
Patients: Sixteen patients with pulmonary hypertension and septic shock according to the criteria of the ACCP/SCCM consensus conference all requiring norepinephrine and/or epinephrine to maintain mean arterial blood pressure above 65 mmHg.
Methods and interventions: Patients were randomly assigned to receive either nitric oxide or aerosolized prostacyclin. Nitric oxide was inhaled using a commercially available delivery system, prostacyclin was administered with a modified ultrasound nebulizer. Both nitric oxide and prostacyclin were incrementally adjusted to obtain a 15% decrease of mean pulmonary artery pressure. Hemodynamics and gas exchange as well as indocyanine-green plasma disappearance rate and gastric intramucosal pH were determined at baseline after 90 min in steady state, after 90 min of nitric oxide inhalation or prostacyclin aerosol administration had elapsed in stable conditions, and after 90 min in stable conditions after nitric oxide or prostacyclin withdrawal.
Results: Both inhaled nitric oxide and aerosolized prostacyclin selectively reduced the mean pulmonary artery pressure from 35 ± 4, 30 ± 4 mmHg ($p < 0.05$) and 34 ± 4 to 30 ± 3 mmHg ($p < 0.05$) respectively; after removal of nitric oxide and prostacyclin, the mean pulmonary artery pressure returned to the baseline values. Systemic hemodynamics remained unaltered during the vasodilator treatment. While the mean PaO_2 was not significantly influenced, it increased in 4/8 of the NO- and 3/8 of the PGI_2 – treated patients. Neither of the drugs influenced indocyanine-green plasma disappearance rate, but prostacyclin – unlike nitric oxide – significantly increased gastric intramucosal pH (from 7.26 ± 0.07 to 7.30 ± 0.05, $p < 0.05$) which remained elevated in four of these patients after prostacyclin removal, and decreased the arterial-gastric mucosal pressure of carbon dioxide gap from 19 ± 6 to 15 ± 4 mmHg ($p < 0.05$).
Conclusions: Our data suggest that aerosolized prostacyclin – unlike nitric oxide – has similar beneficial effects on splanchnic perfusion and oxygenation as intravenous prostacyclin without detrimental effects on systemic hemodynamics. The

different effects of prostacyclin and nitric oxide might be explained by the longer half-life of prostacyclin associated with a certain spillover into the systemic circulation.

Key words Septic shock · Nitric oxide · Prostacyclin · Gastric intramucosal pH · PCO_2 gap · Splanchnic oxygenation · Indocyanine-green extraction

Introduction

Septic shock is characterized by hypoperfusion abnormalities and sepsis-induced hypotension despite adequate fluid resuscitation [1, 2]. Intravenous prostacyclin allows for the normalization of tonometrically determined gastric intramucosal pH (pHi) [3], a mirror of both splanchnic perfusion and oxygenation as well as derangements of cellular energy metabolism [4]. However, its use is limited as intravenously administered prostacyclin reduces blood pressure and impairs arterial oxygenation [3, 5, 6]. In contrast, aerosolized prostacyclin (PGI_2) may even facilitate improvement in arterial PO_2 [7–9] without negative side effects on systemic hemodynamics.

We therefore investigated whether PGI_2 also allows for improvement in splanchnic perfusion and oxygenation in septic shock, as determined by pHi tonometry and indocyanine-green clearance. The effects of PGI_2 were compared to those of inhaled nitric oxide (NO) which has been shown to restore hepatic venous oxygen saturation in cases of right ventricular failure [10].

Patients and methods

The study protocol was approved by the local Ethics Committee, and the study was conducted according to the principles embodied in the Declaration of Helsinki.

Patients

Sixteen patients with septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine-Consensus Conference were included in the study and randomly assigned to receive either NO inhalation or PGI_2 aerosol.

Patients were eligible for entry into the study if they fulfilled the following criteria: core temperature more than 38.5 or less than 35.5 °C; white blood cell count more than 12000/μl or less than 4000/μl, or more than 10% immature forms; the presence of perfusion abnormalities such as oliguria (urine < 500 ml/die · 1.73 m^2 BSA) or increased lactate levels (> 2.2 mmol/l); pulmonary artery occlusion pressure (PAOP) more than 12 mmHg; cardiac index (CI) more than 2.5 l/min per m^2. The mean pulmonary artery pressure (MPAP) was 35 ± 4 mmHg in the PGI_2 and 34 ± 4 mmHg in the NO group. In order to maintain mean arterial pressure (MAP) at more than 65 mmHg, they received norepinephrine (NO: 0.14 ± 0.21 μg/kg per min, PGI_2: 0.24 ± 0.48 μg/kg per min; NS) and/or epinephrine (NO: 0.17 ± 0.21 μg/kg per min, PGI_2: 0.17 ± 0.28 μg/kg per min; NS). The patient's clinical characteristics including their major germ are presented in Table 1. Arterial lactate levels were 2.7 ± 1.4 mmol/l (NO: 3.0 ± 1.3 mmol/l; PGI_2: 2.3 ± 1.5 mmol/l, NS). The type and amount of therapy was evaluated using the Therapeutic Intervention Scoring System [TISS] [11] (NO: 50 ± 3, PGI_2: 53 ± 4; NS). None of the patients had received corticosteroids or nonsteroidal anti-inflammatory drugs within at least 24 h prior to the study. Patients with upper gastrointestinal bleeding within the last 72 h and patients with recently performed surgical anastomoses of the upper gastrointestinal tract, as well as patients unlikely to survive longer than 24 h following the initiation of the study, were excluded.

The patients were sedated with a continuous infusion of fentanyl in combination with midazolam and paralyzed with pancuronium. They were mechanically ventilated FIO_2: NO: 0.49 ± 0.13, PGI_2: 0.55 ± 0.24, NS) in the pressure-controlled/inversed-ratio mode (Servo Ventilator 300, Siemens, Erlangen, Germany) combined with a positive end-expiratory pressure (PEEP) (NO: 9.6 ± 1.4 cm H_2O, PGI_2: 9.1 ± 1.9 cm H_2O; NS). Acute renal failure requiring hemodiafiltration was present in 11 patients (NO: $n = 6$; PGI_2: $n = 5$; NS), renal dysfunction with creatinine levels above 170 μmol/l [12–14] in all other patients. Liver dysfunction, defined by bilirubin values of more than 60 μmol/l, and/or ASAT/ALAT/γGT values more than three times the normal were present in seven patients (NO: $n = 3$; PGI_2: $n = 4$; NS) [12–14], disseminated intravascular coagulation (DIC), defined as platelet count less than 100000/μl or a fall of more than 50% and partial thromboplastin time of more than 60 s without therapeutic heparinization or thromboplastin time (Quick) less than 50% of a reference, in eight patients (NO: $n = 3$, PGI_2: $n = 5$, NS) [12–14]. All patients, therefore, had failure of two or more organ systems for at least 24 h, and so the expected mortality was 50–95% [12, 13]. There was no difference between the two groups regarding the extent of organ system failure other than cardiorespiratory (Table 1+2).

Methods

Measurements of hemodynamic and oxygen transport

Routine clinical monitoring of the patients included a thermodilution pulmonary artery catheter (93 A 754 7.5 F, Baxter Healthcare, Irvine, CA) and an arterial cannula. The mean systemic arterial pressure, right atrial pressure (RAP), MPAP and PAOP were measured using standard disposible pressure transducers (Medex MX 80, Medex Inc. Hillard, Ohio) together with a lead II/V5 ECG for the derivation of heart rate. The zero reference for the supine position was the mid axilla. Cardiac output was determined by thermodilution (Explorer, Baxter, Healthcare, Irvine, CA), the values reported being the mean of 4–5 injections of 10 ml ice-cold saline randomly spread over the respiratory cycle [15]. Arterial and mixed-venous blood samples were analyzed for PO_2, PCO_2, and pH (NOVA Stat 5, Biomedical, Waltham, MA) as well as total hemoglobin and hemoglobin oxygen saturation (IL 482 CO-Oximeter, Lexington, MA). Oxygen uptake was calculated using the standard formula according to the reversed Fick principle. Oxygen delivery and venous admixture were calculated from standard formulae. In order to minimize changes in oxygen delivery and oxygen uptake unrelated to the study protocol, none of the patients were turned or otherwise manipulated during the observation period. Body temperature did not vary beyond 0.5 °C of the baseline value.

Table 1 Diagnosis and clinical characteristics of the patients as well as major germ and outcome. Other organ failure designates organ system failure other than respiratory or cardiovascular; *DIC* refers to disseminated intravascular coagulation

Patient	Age/sex	Diagnosis	Major germ	Arterial lactate (mmol/l)	FIO_2/ PEEP (cmH_2O)	Other organ failure*	TISS-score	Survival
Nitric oxide-inhalation								
V.T.	65/M	Mitral valve replacement, postoperative pneumonia	*Haemophilus influenza*	4.1	0.35/10	Liver, kidney	50	Yes
M.S.	71/F	Cholangiosepsis	*Enterobacter cloacae*	3.4	0.50/10	Liver, DIC	47	Yes
M.I.	66/F	Necrotizing pancreatitis	*Streptococcus faecalis*	3.1	0.45/9	DIC, kidney	53	No
M.M.	51/F	Perforated appendix, peritonitis	*Streptococcus viridans, Bacteriodes fragilis*	1.8	0.34/12	Liver, kidney	47	Yes
E.D.	77/M	Peritonitis after hemicolectomy	*Echerichia coli, Streptococcus faecalis*	5.5	0.60/7	Kidney	51	Yes
O.M.	52/M	Endocarditis, mitral valve replacement	*Streptococcus viridans*	1.2	0.48/9	Cerebral	50	Yes
G.G.	67/M	ARDS after femoral fracture	*Staphylococcus aureus*	2.5	0.75/10	DIC, kidney	50	No
L.W.	47/M	Necrotizing pancreatitis	*Proteus vulgaris, Candida albicans*	1.9	0.45/10	Kidney	55	No
Prostacyclin-aerosol								
M.Z.	70/M	Ruptured abdominal aortic aneurysm	*Pseudomonas fluorescens*	1.0	0.35/7	DIC. kidney	52	Yes
W.M.	67/M	Endocarditis, mitral valve replacement	*Streptococcus epidermidis*	5.8	0.45/8	Kidney, liver, DIC	58	Yes
P.E.	40/M	Necrotizing pancreatitis	*Candida albicans*	1.8	0.40/12	Kidney, liver, DIC	53	No
W.G.	70/M	Coronary artery bypass graft, bowel ischemia	*Bacteroides fragilis*	1.5	1.0/7	Liver, kidney	59	No
E.C.	61/M	Bowel perforation, peritonitis	*Candida albicans*	1.5	0.45/10	Liver	49	No
A.S.	57/M	Necrotizing pancreatitis	*Enterobacter cloacae, Candida albicans*	2.7	0.35/8	DIC	49	No
H.L.	68/M	Myocardial infarction, aspiration pneumonia	*Pseudomonas fluorescens*	2.5	0.85/10	Kidney	53	No
W.E.	69/M	Necrotizing pancreatitis	*Klebsiella pneumoniae*	1.8	0.60/11	DIC	50	No

Gastric intramucosal pH (pHi)

After admission to the study a tonometer (TRIP® NGS catheter, Tonometrics Inc., Bethesda, MD) was inserted into the patient's stomach via the nasogastric route and the position was confirmed by Roentgenogram. For each measurement of pHi 2.5 ml of a buffer solution (NaH_2PO_4/Na_2HPO_4) were anaerobically filled into the balloon [16]. After at least 90 min of equilibration of PCO_2 between buffer, lumen and gastric mucosa, the balloon fluid was sampled anaerobically and simultaneously with an arterial blood sample and then immediately analyzed with a blood gas analyzer (NOVO STAT 5). Thereafter, the pHi was calculated according to the following formula (for the derivation of the formula see Appendix):

$$pHi = pHa + \log (PaCO_2/PiCO_2 \cdot F)$$

where $PaCO_2$ = arterial PCO_2, pHa = arterial pH, $PiCO_2$ = PCO_2 of the tonometer sample and 1.07 = correction factor for the equilibration period more than 90 min provided by the manufacturer [17].

The reproducibility and validity of the tonometric intramucosal PCO_2 measurements with the phosphate buffer solution using a NOVA STAT 5 had been validated in a previous study [16] and, based on these measurements, a change in pHi exceeding 0.03 pH units was regarded free from measurement error. In addition to the pHi calculation, we evaluated the PCO_2 gap between the $PaCO_2$ and $PiCO_2$. Neither H_2-blockers nor omeprazol were administered for the study purpose.

Indocyanine-green plasma disappearance rate (ICG_{PDR})

Hepatic blood flow and function were evaluated by measuring the indocyanine-green (ICG-PULSION®, München) plasma disappearance rate (ICG_{PDR}) using the Pulsion-COLD system, which calculates the ICG_{PDR} from the optical and thermal signals registered by a 3 F arterial thermal-dye-dilution probe (Pulsiocath®, Pulsion) inserted into the femoral artery. The data reported are the mean of three ice-cold boluses of ICG (0.3 mg ICG/kg BW) injected via a central venous line randomly spread over the respiratory cycle. The ICG_{PDR} values were converted into ICG half-life ($ICG_{1/2}$) data using the formula [18]:

$$ICG_{t1/2} = \ln 2 \cdot 100/ICG_{PDR}.$$

Table 2 Hemodynamic and gas exchange data of the two patient groups at baseline, during NO of PGI_2 administration, respectively, and after withdrawal of the vasodilator treatment

	Before NO-inhalation	After NO-inhalation	NO-inhalation	Before prostacyclin-aerosol	Prostacyclin-aerosol	After prostacyclin-aerosol
Heart rate (1/min)	96±15	94±9	99±16	106±22	106±21	102±18
Mean systemic arterial pressure (mmHg)	77±9	79±10	79±12	79±14	79±16	82±16
Mean pulmonary artery pressure (mmHg)	35±4	30±4*	35±3	34±4	30±2*	35±3
Central venous pressure (mmHg)	18±6	16±6	17±5	16±4	15±3	16±4
Pulmonary artery occluded pressure (mmHg)	18±5	18±5	17±5	17±4	17±5	17±5
Cardiac index (l/min per m^2)	3.4±0.5	3.4±0.6	3.5±0.9	3.6±0.5	3.6±0.7	3.7±0.6
Stroke volume index (ml/m^2)	36±6	37±5	36±7	35±7	35±11	37±9
Right ventricular ejection fraction (%)	28±5	31±5	31±7	28±6	28±9	30±10
Right ventricular enddiastolic volume (ml/m^2)	129±27	121±17	118±13	130±23	132±40	130±36
Arterial PO_2 (mmHg)	87±11	95±14	90±13	83±16	87±14	83±14
Arterial PCO_2 (mmHg)	42±5	40±5	40±2	39±5	38±7	38±6
Arterial pH	7.41±0.08	7.41±0.07	7.41±0.08	7.42±0.06	7.44±0.06	7.45±0.07
Mixed venous PO_2 (mmHg)	40±3	40±4	40±2	37±4	38±4	38±6
Oxygen delivery (ml/min per m^2)	488±110	492±99	498±144	527±95	513±73	524±100
Oxygen uptake (ml/min per m^2)	138±16	147±20	139±21	152±27	149±30	146±30
Venous admixture (%)	29±10	27±7	31±10	29±10	28±8	31±8

*$p<0.05$ vs baseline

Using this technique the normal range for the ICG plasma half-life in healthy volunteers is 2.6±0.4 min, while in patients with chronic aggressive hepatitis it has been reported to be 6.3±3.3 min [18].

Administration of prostacyclin

Prostacyclin (Epoprostenol, Glaxo Wellcome, Hamburg, Germany) dissolved in a glycine buffer (10 µg/ml; pH: 10.5) was continuously infused into the nebulizer chamber of a modified ultrasound nebulizer (Siemens, Germany) switched into the inspiratory limb of the ventilating circuit. This nebulizer delivers particles with a diameter of 1.5–5.5 µm (80% of the spectrum; diameter was determined by phase Doppler anemometry).

Administration of nitric oxide

Inhaled NO was administered into the inspiratory limb of the ventilating circuit using the Pulmonox system (Messer Griesheim, Duisburg, Germany), which allows for the administration of NO in a respiratory gas flow-proportional manner controlled by a microprocessor unit. The online analysis of NO and NO_x was carried out using an integrated chemiluminiscence unit. NO_x concentrations were always below 0.1 ppm.

Protocol

The patients were randomly assigned to receive either NO inhalation or aerosolized PGI_2. The baseline data set was collected after at least 90 min had elapsed in stable hemodynamic condition (i.e. constant vascular pressures, CI and arterial blood gas analyses). Each data set including hemodynamics (MPAP, MAP, HR, CO, CVP, PAOP) and oxygenation (arterial and mixed venous blood gas analyses, hemoglobin oxygen saturation) as well as measurements of pHi and ICG_{PDR}. Then the patients received either NO inhalation or PGI_2 aerosol in incremental doses until a 15% decrease of MPAP was achieved and/or a maximum dose of 25 ppm NO or 40 ng/kg per min PGI_2 was reached. A mean dose of 19±10 ppm NO and 18±9 ng/kg per min PGI_2 was required to attain this goal. After another 90 min in stable condition a second data set was obtained. Thereafter the treatment was discontinued, and a third data set was collected after 90 min had elapsed in stable condition after withdrawal of PGI_2 or NO. During the study period neither drug infusion nor the ventilatory therapy was altered.

Statistics

All data are given as the mean±standard deviation (SD). Statistical evaluation was performed with a Wilcoxon rank sign analysis for paired samples with α-adjustment according to Bonferroni for the testing of differences between baseline values and treatment, and a Mann-Whitney rank sign analysis for unpaired samples for the comparisons between the two groups; $p<0.05$ was regarded as significant.

Results

Baseline measurements did not show any differences between the NO and the PGI_2 groups regarding systemic

and pulmonary hemodynamics, gas exchange, blood gas analysis of pHi and $ICGP_{DR}$.

Table 2 presents the results of hemodynamic and oxygenation measurements of both group at baseline, during NO or PGI_2 administration, and after withdrawal of the treatment. Both aerosolized PGI_2 and inhaled NO produced a significant ($p < 0.05$) reduction of MPAP from 34±4 to 30±3 mmHg (PGI_2) and from 35±4 to 30±4 mmHg (NO). After NO or PGI_2 removal, MPAP returned to pretreatment values in both groups. In six of eight patients in each of the two groups the fall in MPAP was at least 15%, in the other two patients of each group it was reduced by 3 mmHg. Neither of the drugs produced any effect on systemic hemodynamics. While the mean PaO_2 did not change significantly in the two groups, 3/8 (37%) patients in the PGI_2 group and 4/8 (50%) in the NO group showed an increased PaO_2.

The results of indocyanine-green and pHi measurements are demonstrated in Figs. 1 and 2: neither of the drugs significantly influenced ICG_{PDR} expressed as $ICG_{t1/2}$ (Fig. 1) although the mean $ICG_{t1/2}$ declined from 6.7 to 4.8 min during PGI_2 aerosol. While PGI_2 significantly increased pHi from 7.26±0.07 to 7.30±0.05 ($p < 0.05$) (Fig. 2, lower panel), the pHi remained uninfluenced (7.28±0.06 to 7.26±0.06) during NO inhalation (Fig. 2, upper panel). In four of eight patients receiving PGI_2, the pHi remained elevated or even further increased after the aerosol removal (Fig. 2).

The results of the determination of the arterial – gastric intramucosal PCO_2 difference are shown in Fig. 3: while during PGI_2 aerosol the PCO_2 difference significantly dropped from 19±6 to 15±4 mmHg ($p < 0.05$) (Fig. 3, lower panel) and returned to 16±6 mmHg after withdrawal of PGI_2, NO inhalation had no significant effect (from 15±5 to 18±6 mmHg and 14±6 after withdrawal) (Fig. 3, upper panel).

Discussion

There is evidence that inhaled NO and intravenous PGI_2 may lead to the amelioration of hepatic and splanchnic oxygenation in critically ill patients: intravenous PGI_2 restored pHi in patients with septic shock after conventional resuscitation goals had been achieved [3], and in-

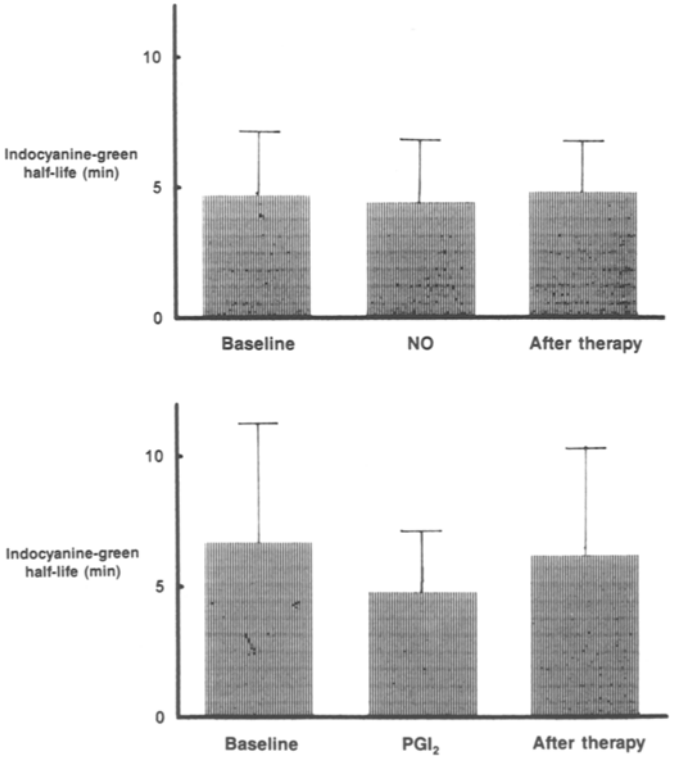

Fig. 1 Effect of NO inhalation (*upper panel*) and PGI_2 aerosol (*lower panel*) on indocyanine-green clearance presented as ICG half-life (mean±SD). Note that while mean $ICG_{t1/2}$ did not change during NO inhalation, it declined from 6.7 to 4.8 min during PGI_2 aerosol. This difference, however, did not reach statistical significance

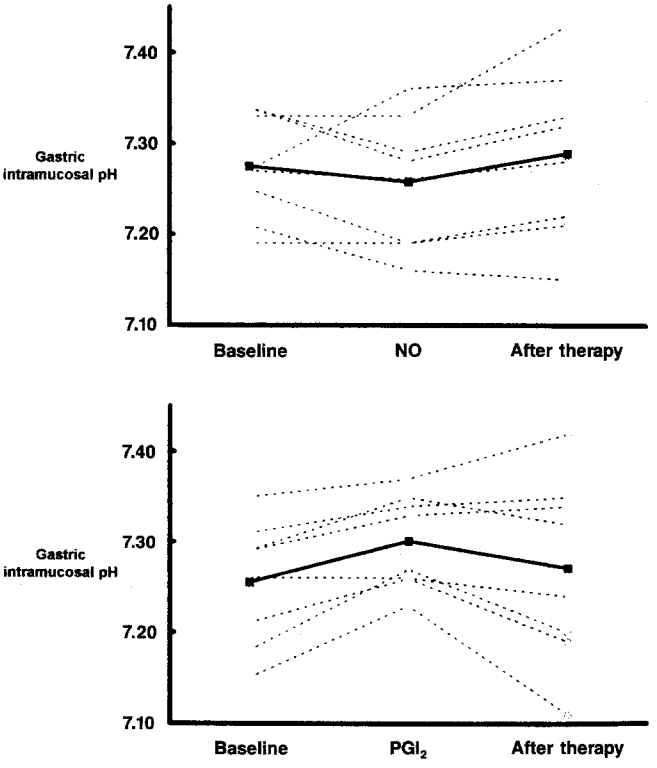

Fig. 2 Individual (*dotted lines, open circles*) and mean (*bold solid line, solid squares*) responses of gastric mucosal pH to NO inhalation (*upper panel*) and PGI_2 aerosol (*lower panel*). Note that while NO inhalation did not influence the mean pHi, PGI_2 aerosol resulted in a significant increase of pHi ($p < 0.05$) when compared to the pretreatment level. Intramucosal pH remained elevated after PGI_2 withdrawal in four of eight patients

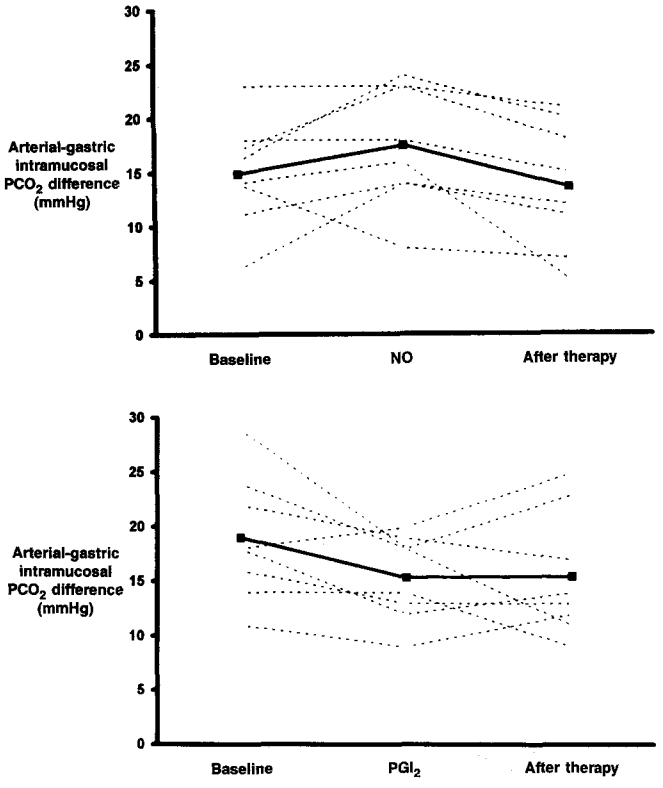

Fig. 3 Individual (*dotted lines, open circles*) and mean (*bold solid line, solid squares*) responses of arterial-gastric mucosal PCO_2 difference to NO inhalation (*upper panel*) and PGI_2 aerosol (*lower panel*). During the latter the PCO_2 gap significantly decreased when compared to the pretreatment value corresponding to the time course of pHi

haled NO improved hepatic venous oxygen saturation in a patient with right heart failure [10]. Since aerosolized PGI_2 is exempt from the limiting systemic side effects [7–9], the present study was designed to compare the effects of aerosolized PGI_2 and inhaled NO on pHi and ICG_{PDR} in patients with septic shock. The major finding of our study was that while both aerosolized PGI_2 and inhaled NO induced comparable hemodynamic and gas exchange effects, only aerosolized PGI_2 improved splanchnic perfusion and oxygenation, as documented by increased pHi.

In our patients the mean baseline pHi was subnormal (PGI_2: 7.26±0.07, NO: 7.28±0.06) despite adequate volume resuscitation and norepinephrine and/or epinephrine therapy. These results seem in contrast to data collected in patients with septic shock by Ruokonen et al. who found restored splanchnic blood flow and oxygen uptake after conventional resuscitation [19]. A more profound septic shock probably accounts for this discrepancy in baseline pHi: despite a more aggressive resuscitation (PAOP > 12 in our, versus 8–12 mmHg in the quoted, study) the mean baseline global oxygen delivery as well as cardiac index were lower (507 vs 574 ml/min per m^2 and 3.5 vs 4.3 l/min per m^2) and lactate levels higher (2.7 vs 1.7 mmol/l) in our patients.

The finding of increased pHi during PGI_2 aerosol was underscored by the significantly reduced arterial-mucosal PCO_2 gap (Fig. 3), which has been reported to describe more appropriately ameliorated splanchnic perfusion and oxygenation [20, 21] and to reflect gastric mucosal hypoxia more precisely than pHi calculated according to the method of Fiddian-Green: in animal models of hemorrhagic and anaphylactic shock Tang [20] and Schlichtig [21] reported that the increase in gastric PCO_2 was more closely correlated to a decrease in gastric blood flow and seems to be more valid for detecting tissue hypoxia than the calculated gastric intramural pH.

It is noteworthy that in four of the eight patients treated with PGI_2 aerosol the pHi remained elevated or even further increased after withdrawal of the aerosol. The appearance of such a prolonged effect of a therapeutic interaction on pHi is comparable with recent data from Smithies et al. [22], who evaluated the effects of dopexamine on systemic and splanchnic perfusion in critically ill patients: during dopexamine infusion the pHi rose significantly and remained elevated after the dopexamine infusion had been discontinued.

We can only hypothesize about the difference between PGI_2 and NO in regard to splanchnic oxygenation, especially since global hemodynamics and the gas exchange effects were comparable. In this context the main pharmacologic difference is the longer half-life of PGI_2, which probably resulted in a spillover of the aerosolized prostanoid into the systemic circulation, whereas NO is assumed to be restricted to the lung vasculature because of instantaneous binding to hemoglobin and inactivation on entry into the vascular compartment [23, 24]. By this process further properties of PGI_2 (e.g. diminution of platelet aggregation, inhibition of neutrophil and macrophage activation, increased erythrocyte flexibility) [25–27] might assume importance and thereby contribute to the improved splanchnic oxygenation.

Although inhalation of NO did not have any beneficial effect on the overall mean pHi, it resulted in a substantial rise of pHi in one individual patient. This patient was suffering from pulmonary artery hypertension and right ventricular failure after mitral valve replacement for endocarditis. This individual finding agrees with a case report recently published by Gatecel et al. [10] showing that inhaled NO was able significantly to improve impaired hepatic tissue oxygenation monitored by continuous hepatic venous saturation. This improvement of hepatic venous oxygenation was explained by increased liver perfusion due to improved right ventricular function. Inhaled NO, therefore, may facilitate improvement in splanchnic perfusion and oxygenation in situations of right ventricular failure.

In addition to pHi, we also determined the indocyanine-green (ICG) plasma disappearance rate and half-

life, respectively, as a global measure of hepatic blood flow and function [18]. Neither NO nor PGI_2 significantly influenced the mean ICG half-life, a result which agrees with data from Smithies and coworkers [22], who did not find a parallel response of $ICG_{t1/2}$ and pHi either when they tried to improve splanchnic oxygenation by infusing dopexamine. It has to be noted, however, that in our patients the mean $ICG_{t1/2}$ decreased from 6.7 to 4.8 min during PGI_2 aerosolization, although this result did not reach statistical significance.

It could be argued that the physiologic significance of our main finding, namely that the aerosol administration improved pHi, is limited because there was no significant effect on $ICG_{t1/2}$. It has to be noted, however, that our technique for the assessment of $ICG_{t1/2}$ was relatively sensitive to random measurement errors and, hence, obtaining a statistically significant effect was difficult in a relatively small group of patients: first, we used a bolus injection technique, which is certainly less reliable than the more cumbersome steady-state infusion approach [28]. Furthermore, we had to limit the amount of dye injected per bolus in order to obtain triplicate measurements at every time point while respecting the maximum dosage for ICG. Finally, for ethical reasons we were not allowed to insert hepatic venous catheters and therefore correction of ICG_{PDR} for hepatic extraction, which considerably improves the ICG data [28], was not possible. The latter probably assumed particular importance, since liver failure was present in eight of the patients.

The discrepancy between the results of the pHi-determinations and those of the ICG_{PDR} measurements clearly raise the question of the clinical interpretation of our findings, particularly when taking into account the fact that the mortality in the PGI_2 group was about twice as high as that in the NO group (75 vs 38%). Clearly, given the size of the two treatment groups, the non-significant difference in mortality is not a valid measure for the clinical significance of our findings. Furthermore, comparing the two groups in terms of outcome is not justified since the whole study period lasted for only about 5–6 h and the PGI_2 aerosol could not be used as a continuous treatment because no technical device was available for reliable long-term aerosol administration. Finally, while the aerosol administration was always discontinued after the investigation period, NO inhalation was maintained in those patients who had exhibited increased PaO_2 and/or improved right ventricular function, and patients in the aerosol group who showed this response were switched to long-term NO inhalation.

Neither inhaled NO nor aerosolized PGI_2 improved the mean PaO_2. This finding might be regarded as contradictory to data from Rossaint et al. and Walmrath et al., both of whom reported a gas exchange response to the treatment in more than 50% of their patients [6, 29]. We can only speculate about the reasons for this discrepancy: on the one hand, we may not have used the appropriate dose of NO necessary to improve gas exchange, since we increased the inspiratory NO concentration until a target effect for MPAP (15% decline) was achieved. In fact, Gerlach et al. [30] have demonstrated in patients with ARDS that improved gas exchange is attained at lower concentrations of inhaled NO than those needed for the reduction of MPAP. On the other hand, the different patient population may play an important role in this different reaction. While Rossaint et al. [29] and Walmrath et al. [6] employed inhaled NO and PGI_2 aerosol in patients with ARDS and pneumonia mostly in the absence of septic shock, other authors have reported a clearly lower responder-quota to NO inhalation of about 36% and 41% when sepsis or septic shock was present [5]. This argument is underlined by the higher inspiratory NO concentrations necessary to achieve improved arterial oxygenation when non-septic and patients with septic shock are compared [31].

In conclusion, the results of our study suggest that both aerosolized PGI_2 and inhaled NO reduced MPAP without detrimental effects on systemic hemodynamics in patients with septic shock. Similar to intravenously administered PGI_2, aerosol administration of this drug – unlike inhaled NO – allows for the improvement of pHi in patients with septic shock. The difference between the two treatments may be due to the longer half-life and the further pharmacologic qualities of PGI_2 in association with its spillover into the systemic circulation. Further studies are warranted to determine whether a minute i.v. PGI_2 dosage may exert comparable effects.

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Appendix

Arterial pH can be calculated as:

$$pHa = pK + \log ([HCO_3^-]_a / PaCO_2 \cdot \alpha\text{-plasma}) \quad \text{(Eq. 1)}$$

where pK is the pK of carbonic acid, $[HCO_3^-]_a$ is the arterial bicarbonate concentration, $PaCO_2$ the arterial PCO_2 and α_{plasma} the CO_2 solubility in plasma.

Gastric intramucosal pH can be calculated according to the Fiddian-Green formula as:

$$pHi = pK + \log ([HCO_3^-]_a / PiCO_2 \cdot F \cdot \alpha_{buffer} \quad \text{(Eq. 2)}$$

where $PiCO_2$ is the PCO_2 in the balloon sample, α_{buffer} the CO_2 solubility in the phosphate buffer and F the correction factor 1.07 provided by the manufacturer for an equilibration period of ≥ 90 min.

Assuming that α_{plasma} and α_{buffer} are nearly identical and inserting Eq. 1 into Eq. 2 after solving Eq. 1 for $[HCO_3^-]$ then yields:

$$pHi = pHa + \log (PaCO_2 / PiCO_2 \cdot F)$$

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