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Hepato-splanchnic metabolic effects of the stable prostacyclin analogue iloprost in patients with septic shock

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Abstract *Objective*: To evaluate the effects of the stable prostacyclin analogue iloprost on hepato-splanchnic blood flow, oxygen exchange and metabolism in patients with septic shock.
Design: Prospective clinical study.
Setting: Intensive care unit in a university clinic.
Patients: Eleven patients with septic shock requiring norepinephrine to maintain mean arterial pressure above 70 mmHg.
Interventions: Iloprost was incrementally infused to increase cardiac index by 15 %.
Measurements and main results: Splanchnic blood flow (Qspl) was measured using the steady-state indocyanine-green infusion technique and endogenous glucose production rate (EGP) using a stable isotope approach. Systemic and splanchnic oxygen consumption (VO_2), the hepato-splanchnic uptake rates of the glucose precursors lactate, pyruvate, alanine and glutamine, the hepatic venous redox state and gastric mucosal-arterial PCO_2 gradients were determined. After a baseline measurement, iloprost infusion was started. After 90 min all measurements were repeated and a third measurement was obtained after another 90 min following iloprost withdrawal. Qspl (baseline I: 0.82/0.75–1.08 l·min·m^2; iloprost: 0.94/0.88–1.29 l·min·m^2; baseline II: 0.87/0.74–1.09 l·min·m^2) and splanchnic oxygen delivery (baseline I: 122/103–166 ml·min·m^2; iloprost: 134/117–203 ml·min·m^2; baseline II: 130/98–158 ml·min·m^2) significantly increased. While systemic VO_2 significantly increased (baseline I: 139/131–142 ml·min·m^2; iloprost: 147/136–164 ml·min·m^2; baseline II: 143/133–154 ml·min·m^2) splanchnic VO_2 increased in 9 of 11 patients which, however, did not reach statistical significance. EGP significantly decreased (baseline I: 23/16–26 μmol·kg·min; iloprost: 16/14–21 μmol·kg·min; baseline II: 18/12–20 μmol·kg·min), whereas all other parameters of energy metabolism remained unchanged.
Conclusion: In patients with septic shock an iloprost-induced increase in cardiac index increased splanchnic blood flow and shifted oxygen utilization from the energy requiring de novo glucose production rate to other oxygen-demanding metabolic pathways.

Keywords Endogenous glucose production · Iloprost · Lactate/pyruvate ratio · Splanchnic blood flow · Tonometry

Table 1 Individual patient data (*m* male, *f* female, *s.* survivor (discharged from ICU), *n.s.* non-survivor)

	Diagnosis	Age	Gender	Norepinephrine (μg·kg·min)	Iloprost (ng·kg·min)	Microbiology	Outcome
Patient 1	Pancreatitis	77	m	0.24	3.7	*Corynebacterium*	s.
Patient 2	Spondylodiscitis	73	f	0.17	1.6	Coagulase-negative *Staphylococci*	s.
Patient 3	Infected hip endoprosthesis	68	f	0.07	1.8	*Candida albicans*	n.s.
Patient 4	Peritonitis	71	m	0.08	1.0	*Enterococcus faecium*	s.
Patient 5	Peritonitis	69	m	0.13	1.1	*Enterobacter*	n.s.
Patient 6	Pancreatitis	62	f	0.07	1.0	*Citrobacter*	s.
Patient 7	Pancreatitis	51	m	0.08	1.5	*Candida albicans*	s.
Patient 8	Peritonitis	68	m	0.10	1.0	*Klebsiella*	s.
Patient 9	Pancreatitis	32	m	0.03	1.7	Coagulase-negative *Staphylococci*	s.
Patient 10	Perforated ulcus duodeni	73	f	0.05	1.0	Negative	s.
Patient 11	Pleural empyema	52	f	0.21	0.9	*Streptococci*	n.s.

Introduction

Sepsis and septic shock are usually associated with increased hepato-splanchnic blood flow and oxygen transport as a result of enhanced hepatic metabolic activity, in particular in carbohydrate and lactate metabolism [1, 2]. The concept that hepatic metabolic rate is directly related to oxygen or substrate availability, however, is not always valid: in bacteremic burn patients in whom complications developed the hepato-splanchnic oxygen uptake remained elevated despite a reduction both in regional blood flow and uptake of glucose precursors as well as glucose release [3]. The usual approach to improve hepato-splanchnic blood flow is fluid resuscitation and/or the use of catecholamines [4, 5, 6]. The latter, however, may per se impair splanchnic blood flow [7, 8] and thereby impair regional metabolism [7, 8]. Furthermore, during sepsis and septic shock the efficacy of catecholamines may progressively decline due to reduced receptor responsiveness [9, 10]

In both animals with endotoxic shock [11] and patients after mesenteric traction [12] the endogenous release of prostacyclin, a vasodilator prostaglandin with platelet aggregation inhibitor and cytoprotective properties [13], proved to be pivotal for the maintenance of hepato-splanchnic perfusion and intestinal mucosal integrity. In endotoxic pigs the infusion of the stable prostacyclin analogue iloprost restored hepato-splanchnic blood flow, reversed intestinal mucosal acidosis [14] and improved hepatic metabolic activity and energy balance [15]. Finally, in patients with septic shock iloprost restored the indocyanine-green dye removal by the liver independently of systemic hemodynamics [16].

We therefore tested the hypothesis that iloprost may increase hepato-splanchnic blood flow and thereby improve regional oxygen exchange as well as carbohydrate and energy metabolism in norepinephrine-dependent patients with septic shock.

Materials and methods

The study was approved by the ethics committee of the Ulm University Medical School and conducted according to the principles of the "Declaration of Helsinki". Eleven patients with septic shock were studied, all requiring norepinephrine to maintain mean arterial pressure above 70 mmHg (norepinephrine infusion rate (median/quartile): 0.08/0.06–0.14 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The patients fulfilled the following criteria: (1) age between 18–70 years, (2) cardiac index 3.0 $l \cdot min \cdot m^2$ or more, (3) temperature 38 °C or higher or 36 °C or lower and (4) leukocytes 4000 or below or 12,000 giga/l or above. Detailed patient data are presented in Table 1. In addition, a hepatic venous-mixed venous saturation gradient of more than 10%, a possible indicator of inappropriate hepato-splanchnic perfusion [5], was present in 9 of the 11 patients.

All studies were accomplished during volume-controlled mechanical ventilation (Servo 900 C, Siemens Solna, Sweden) and the patients were sedated and their pain relieved with continuous i.v. midazolam (Dormicum, Hoffmann LaRoche, Basel, Switzerland) and fentanyl (Janssen, Neuss, Germany) and relaxed with cis-atracurium (Nimbex, Glaxo Wellcome, Bad Oldesloe, Germany). During the protocol the patients were not fed enterally, all i.v. fluids were kept at maintenance infusion rates and no red blood cells were given. No H_2-receptor or proton pump blockers were given. Body temperature did not vary beyond ± 0.5 °C throughout the study period. Turning or other nursing procedures were prohibited in order to avoid manipulation-induced variations of global or splanchnic blood flow, oxygen demand or sympathetic tone. In addition to routine monitoring (radial and pulmonary artery catheters), a catheter was inserted into one hepatic vein. The correct position of this was verified before and after the study by fluoroscopy using a small amount of contrast dye. A nasogastric tube (TRIP NGS catheter, Tonometrics, Worcester, Mass.) was inserted in the stomach, the correct position of which was confirmed by X-ray.

Systemic and pulmonary hemodynamic measurements

Systemic and pulmonary vascular pressures as well as cardiac output (Vigilance, Baxter, München, Germany) were continuously measured. The data reported are the mean values of the last 10 min of each 90-min period of the study.

Splanchnic hemodynamic measurements

The total hepato-splanchnic blood flow (Qspl) was estimated using a primed, continuous infusion of indocyanine green (ICG) as described in detail previously [17]. Briefly, after a prime injection of ICG (12 mg; Cardiogreen, Becton-Dickinson Microbiology Systems, Cockeysville, Md.), the dye was infused at a constant rate (0.5 mg/min). At 20, 25 and 30 min of infusion, arterial and hepatic venous blood was sampled for the analysis of ICG levels and subsequent estimation of hepato-splanchnic blood flow. The means of the three blood flow values are reported. The mean ICG extraction at baseline was 32 (24–45)%, exceeding the limit of 10% as required for valid application of this method [17].

Splanchnic and systemic oxygen exchange measurements

Blood samples were taken at the 30-min time point of ICG sampling, and blood gases and hemoglobin oxygen saturations (SaO_2) were measured using a blood gas analyzer (Nova Stat Profile M, Nova Biomedical, Rödermark, Germany). The arterial oxygen content was calculated as:

$$Hb \times SaO_2 \times 1.36 + PaO_2 \times 0.0031$$

The systemic (DO_2sys) and regional oxygen delivery (DO_2spl) were calculated as the product of the arterial oxygen content (CaO_2) and cardiac index (CI) and Qspl, respectively. Systemic oxygen uptake (VO_2sys) was continuously measured from the inspired and expired respiratory gases by open-circuit indirect calorimetry (Deltatrac, Datex-Engstroem, Helsinki, Finland) [18]. Splanchnic oxygen consumption was calculated as the product of Qspl and the arterial-hepatic venous oxygen content difference.

Metabolic parameters

Endogenous glucose production rate (EGP) was determined using stable, non-radioactive isotope-labeled 6,6-$^2H_2$-glucose (Cambridge Isotope Laboratories, Woburn, Mass.) as described previously [19]. The glucose rate of appearance (Ra) was derived from the arterial plasma isotope enrichment (atom percentage excess, APE) according to the non-steady state version of the Steele equation [20]:

$$Ra = F \times APE_{pl} - (dAPE_{pl}/dt) \times V \times c/APE_{pl}$$

where APE_{pl} is the isotope enrichment in the plasma, F the infusion rate of the labeled glucose, V the volume of distribution of 0.22 l/kg [21] and c the glucose plasma concentration. This equation corrects for a drift with time in the measured tracer enrichment values. The drift with time ($dAPE_{pl}/dt$) was determined for each study phase from a linear regression curve drawn through five measurement values sampled over a time interval of 30 min. The EGP was subsequently calculated as the difference between Ra and the infusion rate of unlabelled glucose [19]. Glucose concentrations were determined using a glucose and lactate analyzer (YSI Model 2300 Stat, Yellow Springs Instrument, Yellow Springs, Ohio). Adopting the formulae described by Fong et al. [2] enabled us to determine the splanchnic glucose extraction fraction (EF) as well as the splanchnic glucose uptake (R_{dspl}) and release (R_{aspl}) according to the following equations:

$$EF = 1 - ((HV) \times APE_{hv})/((A) \times APE_a) \quad (1)$$

$$R_{dspl} = Qspl \times (A) \times EF \quad (2)$$

$$R_{aspl} = Qspl \times (V) \times (1 - APEv/APEa) \quad (3)$$

where (A) and (HV) are the arterial and hepatic venous substrate concentrations, Qspl the splanchnic blood flow, and APE_{hv} and APE_a the hepatic venous and the arterial isotope enrichments, respectively. Assuming that the kidney is the only organ other than the liver capable of adding glucose to the circulation, we calculated the renal glucose release (RGR) as the difference between the overall rate of appearance of glucose and splanchnic glucose release [22].

Arterial and hepatic venous alanine and glutamine levels were assessed in duplicate with the ninhydrine-reaction after separation by high-performance liquid chromatography (Amino Acid Analyser LC 3000, BiotroniK, Hamburg, Germany) [7, 19]. For the determination of the arterial and hepatic venous lactate/pyruvate ratios, the lactate and pyruvate concentrations were measured in duplicate spectrophotometrically as described previously [19]. The regional substrate turnover rates for lactate, pyruvate, glucose, alanine and glutamine were then calculated as:

$$\text{substrate balance}_{spl} = ((A) - (HV)) \times Qspl$$

where (A) and (HV) are the arterial and hepatic venous substrate concentrations and Qspl the splanchnic blood flow.

Hepatic venous acetoacetate and β-OH-butyrate levels were measured for the calculation of the ketone body ratio (β-OH-butyrate/acetoacetate) using an enzymatic method as described previously [19]. Plasma adrenaline and norepinephrine concentrations where measured using reversed-phase high-performance liquid chromatography with electrochemical detection as described previously, the detection limit being 15 pg/ml [23].

The gastric mucosal PCO_2 was measured semi-continuously (at 10-min intervals) via the nasogastric tube with a Tonocap (Tonocap TC 200, Datex-Ohmeda, Helsinki, Finland) using air to inflate the balloon.

Protocol

Before the baseline measurement of systemic and regional blood flow, cardiac index and vascular pressures were monitored for a 60-min period to assure stable conditions. During this period no changes were made in the ventilator settings or any other treatment. The hepato-splanchnic blood flow was determined during the following 30 min. After the baseline measurement an iloprost (Ilomedin, Schering AG, Germany) infusion was started and the infusion rate was incrementally adjusted until a 15% (8–21%) increase in CI had been obtained. The iloprost infusion rate was reduced if the mean arterial pressure declined by more than 15%, heart rate increased by more than 20% or transcutaneous SaO_2 fell below 90%. Dose limitation of iloprost was due to a fall in arterial oxygenation in three patients and increased heart rate in one patient, and therefore infusion rates of 1.28 (1.04–1.69) $ng \cdot kg^{-1} \cdot min^{-1}$ were administered. After 60 min of stabilization the regional blood flow measurement was repeated during a 30-min period and a second set of data was collected. Then the iloprost infusion was withdrawn. The third set of data was collected after at least another 90 min of stabilization. The total duration of the study, therefore, was 280–300 min, depending on the time to titrate the infusion rate of iloprost.

Table 2 Systemic and regional hemodynamic response to iloprost (*CI* cardiac index, *HR* heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *PAOP* pulmonary arterial occlusion pressure, *SV* stroke volume, *Qspl* splanchnic blood flow, *Qspl/CI* fraction of splanchnic blood flow to cardiac index) Data are median/25/75 percentiles

	Baseline	Iloprost	Baseline
CI (l·min·m^2)	3.9/3.5–4.6	4.7/4.0–5.0*	3.9/3.6–4.5
HR (beat/min)	91/84–96	104/94–111*	97/95–108
MAP (mmHg)	83/80–89	79/74–83	81/73–84
CVP (mmHg)	13/12–14	12/11–13	12/10–13
PAOP (mmHg)	16/15–17	15/14–17	16/14–18
SV (ml)	43/41–47	42/40–48	42/38–46
Qspl (l·min·m^2)	0.82/0.75–1.08	0.94/0.88–1.29*	0.87/0.74–1.09
Qspl/CI (%)	22/19–27	24/21–30	22/20–24

* indicates significance ($p < 0.05$; difference to baseline)

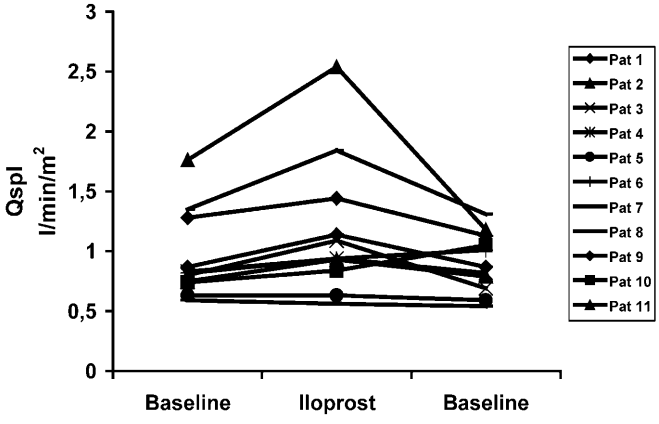

Fig. 1 Individual responses of splanchnic blood flow. Each symbol refers to an individual

Statistical methods

The data are presented as median and 25/75 percentiles unless otherwise stated. After exclusion of normal distribution the data were analyzed using a Friedman rank sign analysis of variance and a subsequent Student-Newman-Keuls test for multiple comparisons. Statistical significance was considered at p less than 0.05.

Results

Global hemodynamics

Iloprost increased cardiac index (3.9/3.5–4.6 vs 4.7/4.0–5.0 l·min^{-1}·m^2) due to both increased heart rate (91/84–96 vs 104/94–111 min, $p < 0.01$) and stroke volume (44/41–47 vs 48/41–51 ml/m^2, $p < 0.01$). Neither mean arterial pressure (MAP) nor the filling pressures were significantly affected by iloprost (Table 2).

Regional hemodynamics

While the increased cardiac index resulted in a significant increase in Qspl (0.82/0.75–1.08 vs 0.94/0.88–1.29 vs 0.87/0.74–1.09 l·min^{-1}·m^2, $p < 0.01$) (Fig. 1; Table 2), the fractional contribution of Qspl to cardiac index was not significantly altered during iloprost infusion (Table 2), even though it increased in 8 of 11 patients.

Metabolism and gas exchange

Because of the significant fall in PaO_2 (13.1/12.4–15.3 vs 10.0/8.7–11.1 kPa) and SaO_2 (98/97–99 vs 93/89–97 %) the increase of DO_2sys did not reach statistical significance (565/473–642 vs 634/513–699 ml·min^{-1}·m^2, $p = 0.059$; Table 3) whereas splanchnic DO_2 (DO_2spl) increased in all patients (Table 3) (122/103–166 vs 134/117–203 ml·min·m^2, $p = 0.035$). VO_2sys increased significantly (139/131–142 vs 147/136–164 ml·min·m^2, $p = 0.036$; Fig. 2), whereas VO_2spl was not significantly affected although it rose in 9 of 11 patients ($p = 0.066$) (Table 3). The respiratory quotient significantly decreased during iloprost infusion (Table 3) as a result of the unchanged systemic VCO_2 (Table 3). The gradient between mixed venous and hepatic venous oxygen saturation did not change (19/11–31 vs 21/5–25 %) significantly (Table 3), and neither the mean gastric mucosal-arterial nor the gastric mucosal-hepatic venous PCO_2 gradient were significantly altered (Table 3).

Iloprost decreased the endogenous glucose production rate (EGP; 23/16–26 vs 16/14–22 vs 18/12–20 μmol·kg^{-1}·min^{-1}, $p = 0.001$), which remained lower after iloprost withdrawal (Fig. 3). By contrast, it did not significantly affect the splanchnic uptake rates of the glucose precursors alanine, pyruvate and lactate, or the splanchnic glutamine release (Table 4). Splanchnic glucose uptake and release were not influenced either (Table 4). Consequently, the decreased EGP was associated with a significantly reduced renal glucose release (RGR; Table 4). Neither the hepatic venous lactate/

Table 3 Systemic and regional oxygen exchange response to iloprost (PaO_2 arterial oxygen partial pressure, $PhvO_2$ hepatic venous oxygen partial pressure, DO_2 oxygen delivery, VO_2 oxygen consumption, VCO_2 carbon dioxide production, RQ respiratory quotient, Q_{VA}/Q_t venous admixture, $PaCO_2$ arterial carbon dioxide partial pressure, $PgmCO_2$ gastric mucosal carbon dioxide partial pressure, $PhvCO_2$ hepatic venous carbon dioxide partial pressure, S_{mv}–S_{hv} mixed venous saturation–hepatic venous saturation) Data are median/25/75 percentiles

	Baseline	Iloprost	Baseline
PaO_2 (kPa)	13.1/12.4–15.3	10.0/8.7–11.1*	14.0/12.8–15.5
$PhvO_2$ (kPa)	5.5/5.4–6.0	5.2/5.1–5.6	5.7/5.3–6.2
Systemic DO_2 (ml·min·m^2)	565/473–642	634/513–699	524/472–651
Splanchnic DO_2 (ml·min·m^2)	122/103–166	134/117–203*	130/98–158
Splanchnic VO_2 (ml·min·m^2)	58/49–67	59/57–71	56/52–65
Systemic VCO_2 (ml·min·m^2)	111/103–128	113/103–121	113/103–126
RQ	0.83/0.76–0.90	0.80/0.67–0.87*	0.80/0.69–0.91
Q_{VA}/Q_T (%)	13/9–18	29/17–34*	14/9–18
$PaCO_2$ (kPa)	6.4/5.4–6.8	6.5/5.6–7.3	6.4/5.7–7.1
S_{mv}–S_{hv} (%)	19/13–32	21/10–26	21/15–32
$P_{gm}CO_2$–$P_{art}CO_2$ (kPa)	0.4/–0.1–1.3	1.2/0.5–1.4	1.3/0.8–2.4
$P_{gm}CO_2$–$P_{hv}CO_2$ (kPa)	–0.2/–0.5–0.3	0.3/–0.2–0.6	0.6/–0.4–1.5

* indicates significance ($p < 0.05$; difference to baseline)

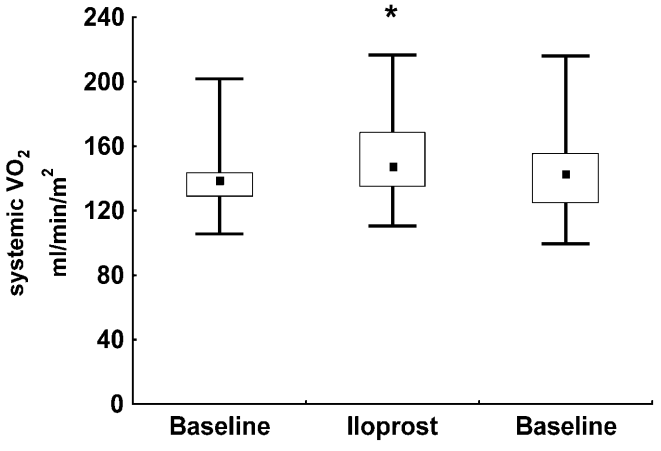

Fig. 2 Calorimetric oxygen uptake (systemic VO_2) before, during and after iloprost infusion. Data are median, 75/25 and 95/5 percentiles. * indicates significant difference to baseline value ($p < 0.05$)

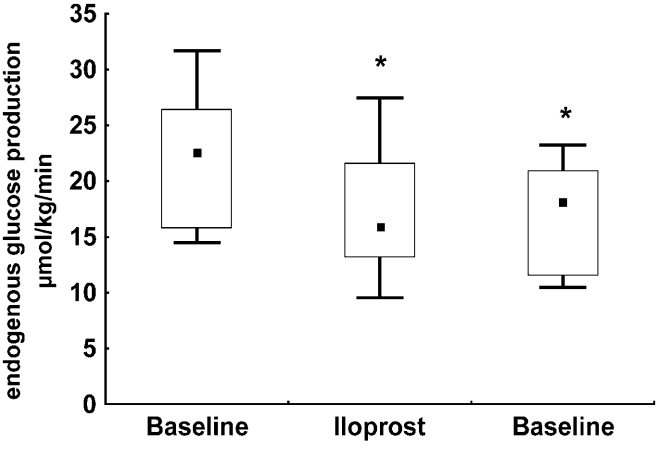

Fig. 3 Endogenous glucose production before, during and after iloprost infusion. Data are median, 75/25 and 95/5 percentiles. * indicates significant difference to baseline value ($p < 0.05$)

pyruvate and ketone body ratios nor the plasma catecholamine levels were significantly affected (Table 4.).

Discussion

This study was designed to test the hypothesis that the stable prostacyclin analogue iloprost could improve hepato-splanchnic blood flow as well oxygen exchange, and thereby carbohydrate metabolism, in patients with hyperdynamic septic shock requiring norepinephrine to maintain mean arterial blood pressure. Iloprost was chosen to increase regional perfusion because (1) endogenous prostacyclin is pivotal for the maintenance of gastrointestinal perfusion [12] and mucosal integrity [11], (2) i.v. prostacyclin improved gastric mucosal pH [24] in patients with sepsis or septic shock and (3) i.v. prostacyclin had made possible an increase in glucose oxidation in insulin-dependent patients with sepsis who did not receive vasopressor treatment [25]. The key findings were that iloprost resulted in an increased cardiac index, regional oxygen availability, and systemic oxygen uptake, without changes in regional oxygen uptake. In addition, endogenous glucose production decreased without significant changes in the hepato-splanchnic uptake of glucose precursors and in hepatic venous redox state.

In good agreement with previous studies using prostacyclin [24, 25], iloprost increased cardiac output and hepato-splanchnic blood flow, which counterbalanced the decreased PaO_2, resulting in increased oxygen delivery. Surprisingly, this effect was not accompanied by a

Table 4 Metabolic response to iloprost (*RGR* renal glucose release) Data are median/25/75 percentiles

	Baseline	Iloprost	Baseline
Lactate balance (μmol·kg·min)	12/4–13	13/2–14	11/5–13
Pyruvate balance (μmol·kg·min)	0.2/–0.2–0.6	–0.1/–0.6–0.6	–0.3/–0.7–0.2
RGR (μmol·kg·min)	19.2/7.9–30.6	12.9/7.8–23.1*	14.5/9.5–22.6
Splanchnic glucose uptake (μmol·kg·min)	3.7/0.0–8.5	3.5/0.1–7.4	2.7/0.4–7.2
Splanchnic glucose release (μmol·kg·min)	9.0/1.0–12.7	10.2/1.6–14.7	7.2/1.5–11.3
Hepatic venous lactate/pyruvate[a]	14/13–24	14/12–26	12/12–18
Hepatic venous β-OH-butyrate/acetoacetate	0.21/0.13–0.59	0.22/0.08–0.45	0.22/0.05–0.34
Alanine balance (μmol·kg·min)	4.3/3.2–5.6	4.8/3.5–5.6	4.3/2.7–5.5
Glutamine balance (μmol·kg·min)	–0.4/–0.2–1.0	–0.5/–1.4–0.2	–0.4/–0.8–0.2
Glucose (mg/dl)	146/116–200	142/116–191	143/113–192
Arterial lactate (mmol/l)	1.8/1.5–2.1	1.8/1.4–2.1	1.8/1.6–2.1
Arterial pyruvate (mmol/l)[a]	0.09/0.05–0.10	0.07/0.04–0.11	0.09/0.07–0.16
Plasma noradrenaline (pg/ml)	3130/2549–4493	3104/2901–5031	3177/2543–5567
Plasma adrenaline (pg/ml)	15/15–39	24/15–77	15/15–47

* indicates significance ($p < 0.05$; difference to baseline)
[a] indicates $n = 10$

fall in blood pressure such as is usually observed during the infusion of prostacyclin. The effects of prostacyclin and iloprost are mediated through cyclic AMP [26] and, hence, an intrinsic inotropic and chronotropic effect of iloprost may at least partly explain this observation. This rationale is underscored by the data of Kieler-Jensen et al., who compared i.v. prostacyclin with sodium-nitroprusside in patients after cardiac surgery [27]: these authors reported both increased stroke volume and heart rate associated with an improved myocardial pressure-volume relationship. Finally, the unchanged plasma catecholamine levels may also support the notion of an intrinsic inotropic effect of iloprost in our patients.

The fractional contribution of Qspl to cardiac index was not altered during iloprost infusion, even though it increased in 8 of 11 patients. These changes and the number of patients were too small, however, to reach statistical significance and probably lack clinical significance. Nevertheless, our findings are in accordance with studies infusing iloprost in porcine endotoxic shock: pretreatment with iloprost led to a preferential increase in superior mesenteric artery blood flow [14] and, together with dextran or hydroxyethyl starch, iloprost particularly increased hepatic arterial blood flow [15, 28]. It could be argued that our findings on the tonometric PCO_2 gradient contradict this conclusion: infusing iloprost did not significantly change the gastric mucosal-arterial PCO_2 gradient, which is in contrast to previous data from our group in patients with septic shock [24]. It is noteworthy that Lehmann et al. recently also reported unchanged pHi values in patients with septic shock despite improved ICG dye removal in the liver [16]. Moreover, most of the patients in our present study had baseline PCO_2 gradients within the normal range, which made a substantial iloprost-induced decrease of this gradient unlikely.

Baseline total EGP was approximately 2–3 times higher than the normal value. Since glucogenolysis probably did not contribute to glucose formation [1], the increased EGP reflects a markedly enhanced rate of gluconeogenesis, which is in good agreement with previous findings in patients with sepsis or septic shock reported by other investigators [1] as well as by our own group [4, 7, 19]. It should be noted, however, that, in contrast to the previous study by Scheeren et al. [25], who had reported unchanged EGP during i.v. prostacyclin, iloprost significantly decreased EGP in the present investigation. This discrepancy probably results from the pronounced difference in the patients' metabolic statuses: EGP was 3 times higher in the present study than in the study by Scheeren et al. [25], which may be explained by major differences in patient management. First, all patients in the study by Scheeren et al. received a continuous infusion of insulin, which is known to suppress EGP [29]. Second, the patients in our present investigation required continuous i.v. norepinephrine to maintain arterial blood pressure. Catecholamines per se increase endogenous glucose production due to their β-adrenoreceptor agonist properties [30], both in volunteers [31] and patients [32]. Hence, the differences in therapies may have altered the metabolic response to iloprost infusion.

It is noteworthy that renal glucose release (RGR) accounted for about 50–60% of overall EGP. At first glance this finding is in sharp contrast to literature data reporting an only minor renal contribution to overall EGP [22]. These results, however, are largely based on net balance experiments, which cannot discriminate between regional glucose uptake and release. Our findings confirm data reported by Stumvoll et al. [22] using similar isotope approaches. In fact, these authors demonstrated that RGR may account for approximately one-half of total EGP during stress states. Since iloprost sig-

nificantly reduced RGR, theoretically we cannot rule out the possibility that renal function worsened as we did not measure urine output and creatinine clearance. In fact, experimental data have related a decrease in RGR to a compromised renal metabolism [33, 34, 35]. These data, however, were obtained in rodent endotoxin models associated with reduced kidney blood flow [34] or from experiments using an in situ autonomously perfused organ preparation [35]. This may not be true when cardiac output is preserved. In fact, iloprost only deteriorated glomerular filtration in canine rapid right ventricular pacing-induced heart failure associated with low cardiac output, while it increased renal plasma flow without affecting glomerular filtration when cardiac output was well maintained [33].

Infusing iloprost significantly increased VO_2sys and VO_2spl in 9 of 11 patients. This finding is of particular importance since VO_2sys was determined using indirect calorimetry and, thereby, mathematical coupling of shared variables was avoided [36]. A thermogenic effect of iloprost such as that described by Nagai et al. [37] for prostaglandin E_2 may have assumed importance in this context. Dahn et al. [38], however, recently showed that EGP is particularly sensitive to thermogenic effects and, therefore, given the decreased EGP, it is unlikely that an intrinsic thermogenic effect contributed to the increased VO_2sys. Moreover, the significantly reduced EGP makes it tempting to speculate that the increased VO_2sys reflects reduced oxygen requirements for this metabolic pathway together with a shift of oxygen utilization away from carbohydrate de novo synthesis in favor of other energy-demanding processes. Iloprost infusion reduced EGP by about one-third while splanchnic glucose release remained unchanged, suggesting that the decreased EGP was primarily due to decreased RGR. Based on the stoichiometry of gluconeogenesis, the synthesis of 1 mol of glucose requires 6 mol of ATP or, in other words, the reduced RGR decreased the energy demands of the kidneys by about 3 mmol ATP/min. It should be stressed that this putative shift in oxygen utilization apparently was not accompanied by compromised hepato-splanchnic metabolic performance.

In former studies, deteriorated hepatic metabolic capacity was always accompanied by markedly reduced uptake rates of the glucose precursors [3, 7]. Furthermore, unchanged hepatic venous lactate/pyruvate and ketone body ratios suggest uninfluenced regional cytosolic and mitochondrial redox state [39]. We found both unchanged glucose precursor uptake rates as well as unchanged hepatic venous ketone body and lactate/pyruvate ratios, in other words a well-maintained energy balance [40]. Finally, the decreased respiratory quotient (RQ) further underscores a shifting of oxygen utilization to other metabolic pathways: Frayn et al. [41] demonstrated that the overall RQ of gluconeogenesis from amino acids (e.g. alanine) is 0.13. Reducing the rate of gluconeogenesis should theoretically result in both reduced VO_2 and increased RQ. By contrast, iloprost increased VO_2 while RQ even decreased.

In summary, infusing the stable prostacyclin analogue iloprost in patients with septic shock increased hepato-splanchnic blood flow and oxygen availability and shifted oxygen utilization from the energy-requiring de novo gluconeogenesis to other oxygen-demanding metabolic pathways without impairing the metabolic capacity of the hepato-splanchnic region.

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