Effects of a Dobutamine-induced Increase in Splanchnic Blood Flow on Hepatic Metabolic Activity in Patients with Septic Shock

Helmut Reinelt, M.D.,* Peter Radermacher, M.D.,† Günther Fischer,‡ Wolfgang Geisser, M.D.,§
Ulrich Wachter,‖ Heidemarie Wiedeck, M.D.,# Michael Georgieff, M.D.,** Josef Vogt, Ph.D.††

Background: Septic shock leads to increased splanchnic blood flow (Qspl) and oxygen consumption (VO₂spl). The increased Qspl, however, may not match the splanchnic oxygen demand, resulting in hepatic dysfunction. This concept of ongoing tissue hypoxia that can be relieved by increasing splanchnic oxygen delivery (DO₂spl), however, was challenged because most of the elevated VO₂spl was attributed to increased hepatic glucose production (HGP) resulting from increased substrate delivery. Therefore the authors tested the hypothesis that a dobutamine-induced increase in Qspl and DO₂spl leads to increased VO₂spl associated with accelerated HGP in patients with septic shock.

Methods: Twelve patients with hyperdynamic septic shock in whom blood pressure had been stabilized (mean arterial pressure ≥ 70 mmHg) with volume resuscitation and norepinephrine received dobutamine to obtain a 20% increase in cardiac index (CI). Qspl, DO₂spl, and VO₂spl were assessed using the steady-state indocyanine green clearance technique with correction for hepatic dye extraction, and HGP was determined from the plasma appearance rate of stable, non–radioactive-labeled glucose using a primed-constant infusion approach.

Results: Although the increase in CI resulted in a similar increase in Qspl (from 0.91 ± 0.21 to 1.21 ± 0.34 $l \cdot min^{-1} \cdot m^2$;

$P < 0.001$) producing a parallel increase of DO₂spl (from 141 ± 33 to 182 ± 44 $ml \cdot min^{-1} \cdot m^2$; $P < 0.001$), there was no effect on VO₂spl (73 ± 16 and 82 ± 21 $ml \cdot min^{-1} \cdot m^2$, respectively). Hepatic glucose production decreased from 5.1 ± 1.6 to 3.6 ± 0.9 $mg \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$).

Conclusions: In the patients with septic shock in whom blood pressure had been stabilized with volume resuscitation and norepinephrine, no delivery-dependency of VO₂spl could be detected. Oxygen consumption was not related to the accelerated HGP either, and thus the concept that HGP dominates VO₂spl must be questioned in well-resuscitated patients with septic shock. (Key words: Drug effects: dobutamine; norepinephrine. Septic shock: hepatic glucose production; hepatic metabolism; oxygen transport and uptake; splanchnic blood flow.)

SEPSIS leads to increased splanchnic blood flow and oxygen consumption.[1-3] The increased splanchnic blood flow, however, may not be sufficient to meet the splanchnic oxygen demand,[4,5] and, in fact, impaired splanchnic lactate clearance and hepatic glucose output were found in burned patients in whom bacteremia developed despite enhanced splanchnic oxygen transport.[1] This concept of an ongoing tissue hypoxia in the splanchnic region that can be relieved by increasing splanchnic oxygen delivery, however, was challenged recently in resuscitated patients with sepsis[6]: Most of the elevated splanchnic oxygen uptake was attributed to increased hepatic glucose formation[7] resulting from increased substrate delivery.[1,8,9]

Septic shock is associated with hypotension despite adequate fluid resuscitation,[10] and treatment with norepinephrine may restore splanchnic blood flow.[5] The individual response to norepinephrine, however, is unpredictable,[5] and, moreover, norepinephrine may produce marked and selective constriction of the splanchnic capillary bed, potentially impairing the oxygenation of the splanchnic organs.[11,12]

Therefore we tested the hypothesis that a dobutamine-induced increase in splanchnic blood flow leads to increased regional oxygen uptake affiliated with accel-

* Staff Anesthetist.

† Professor of Anesthesiology.

‡ Medical Student.

§ Resident in Anesthesiology.

‖ Chemist, Experimental Anesthesiology.

Assistant Professor of Anesthesiology.

** Professor and Chairman of Anesthesiology.

†† Assistant Professor of Experimental Anesthesiology.

erated hepatic glucose production in patients with septic shock in whom blood pressure had been stabilized with volume resuscitation and norepinephrine.

Methods

The study protocol was approved by the local ethics committee, and informed consent was obtained from next of kin of the patients.

Patients

Twelve patients with septic shock due to necrotizing pancreatitis were included in the study. Septic shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine's Consensus Conference, and patients were eligible for the study if they fulfilled the following criteria[10]: core temperature > 38.5°C or <35.5°C, leukocyte count > 12,000/μl or <4,000/μl or >10% immature forms, presence of perfusion abnormalities such as oliguria (urine output < 500 ml/die $\cdot$ 1.73 m^2) or an increased lactate concentration. All patients had hyperdynamic (cardiac index $\geq$ 4 l $\cdot$ min^{-1} $\cdot$ m^2) septic shock, and despite adequate volume resuscitation (pulmonary artery occluded pressure, 19 $\pm$ 1 mmHg) all required norepinephrine (0.21 $\pm$ 0.08 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) to maintain mean arterial pressure at 70 mmHg or more.

The patients were sedated with a continuous infusion of fentanyl combined with midazolam and were paralyzed with vecuronium. Their lungs were mechanically ventilated (inspired oxygen fraction [$F_{I_{O_2}}$] $\leq$ 0.5 to ensure validity of calorimetric measurement of oxygen uptake) in the pressure-controlled/inverse-ratio mode (EVITA 2; Dräger, Lübeck, Germany) combined with a positive end-expiratory pressure of 10 cm H$_2$O. Acute renal failure with a creatinine concentration greater than 170 μmol/l was present in all patients. Patients requiring continuous hemodiafiltration were excluded because of the potential loss of isotope tracer over the filtration membrane. Liver dysfunction defined by bilirubin values greater than 60 μmol/l and/or aspartate aminotransferase/alanine aminotransferase/γ-glutamyl-cyclotransferase values more than three times normal levels were present in seven patients; disseminated intravascular coagulation defined as a platelet count less than 100,000/μl or decreased more than 50% and partial thromboplastin time more than 60 s without therapeutic heparinization or thromboplastin time (Quick) less than 50% of a reference value was present in eight

patients. Because all patients had failure of two or more organ systems, the expected mortality rate was 50–95%.[13-15]

Measurements of Hemodynamics and Oxygen Kinetics

Routine clinical monitoring of the patients included a thermodilution pulmonary artery catheter (93A 754 7 Fr; Baxter Healthcare, Irvine, CA) and an arterial cannula. Mean systemic arterial pressure, right atrial pressure, mean pulmonary arterial pressure, and pulmonary artery occluded pressure were measured using standard disposable pressure transducers (Medex MX 80; Medex Inc., Hillard, OH) together with a lead II/V5 electrocardiograph to determine the heart rate. The zero reference for the supine position was the midaxilla. Cardiac output was determined by thermodilution (Explorer; Baxter Healthcare), the data reported being the mean cardiac index (CI) after four or five injections of 10 ml ice-cold saline randomly spread over the respiratory cycle.[16] Arterial and mixed-venous blood samples were analyzed for partial pressure of oxygen (P$_{O_2}$) and carbon dioxide (P$_{CO_2}$), pH (Stat 5; NOVA Biomedical, Waltham, MA), and total hemoglobin and hemoglobin oxygen saturation values (IL 482 CO-Oximeter; Instrumentation Laboratories, Lexington, MA). Systemic oxygen delivery (DO$_2$sys) was calculated using the standard formula.

Global oxygen uptake (VO$_2$tot) was continuously measured directly from the respiratory gases and recorded minute by minute using a Deltatrac Metabolic Monitor (Datex, Finland). Body temperature did not vary by more than 0.3°C of the baseline value.

Splanchnic blood flow (Qspl) was assessed according to the Fick principle using the steady-state dye infusion technique described by Uusaro et al.[17] The hepatic vein was cannulated via the right internal jugular vein under fluoroscopy using an angiography catheter (7-Fr Multipurpose A-1; Cordis, Roden, The Netherlands), and the correct position of the catheter was verified using a small amount of contrast dye. Indocyanine green (or ICG; Cardiogreen; Beckton-Dickinson Microbiology Systems, Cockeysville, MD) was dissolved in sterile water (2.25 mg/ml) and continuously infused (0.45 mg/min) for 45 min at each data point. Blood was sampled for the measurement of arterial and hepatic venous ICG concentrations after 35, 40, and 45 min of infusion. The blood samples were centrifuged, and ICG concentrations were determined spectrophotometrically using a wavelength of 805 nm. The blood concentrations were derived from a calibration curve, and the coefficient

of variation (SD/mean) of the ICG analysis was 8.7% (n = 12). Qspl was then calculated as

Splanchnic blood flow [l/min]

$$= \frac{\text{Dye-infusion rate [l/min]} \cdot \text{Dye-ICG-concentration [mg/l]}}{(\text{arterial} - \text{hepatic venous}) \cdot \text{ICG-concentration [mg/l]} \cdot (1\text{-hematocrit})}.$$

The mean hepatic ICG extraction ratio ([arterial ICG concentration − hepatic venous ICG concentration]/arterial ICG concentration) was 30% ± 15% (mean ± SD). Splanchnic oxygen transport (DO_2spl) and uptake (VO_2spl) were calculated as splanchnic blood flow times arterial oxygen content and arterial minus the hepatic venous oxygen content difference, respectively.

The hepatic glucose production rate (HGP) was determined as described previously.[18] Briefly, stable, nonradioactive isotope-labeled [6,6-^{2}H$_2$]-glucose (Cambridge Isotope Laboratories, Woburn, MA) was dissolved in physiologic saline (50 mg/ml) and continuously infused for 120 min (0.05 mg·kg^{-1}·min^{-1}) after a priming dose of 4 mg/kg. The glucose rate of appearance (Ra) was derived from the arterial plasma isotope enrichment (atom percentage excess, or APE) according to the formula

$$\text{Ra} = \text{F/APE}_{pl},$$

where APE_{pl} is the isotope enrichment in the plasma and F is the infusion rate of the labeled glucose.[19] The atom percentage excess used to compute the Ra were the corresponding mean of three atom percentage excesses measured in triplicate blood samples obtained within 10 min of each other. The isotope concentrations were determined by gas chromatography–mass spectrometry (GC 5890, MS 5971; Hewlett Packard, Palo Alto, CA) in the selected-ion monitoring mode using electron impact ionization after derivatization of glucose to 1,5-penta-acetate. The HGP rate was subsequently calculated as the difference between Ra and the infusion rate of unlabeled glucose.[19,20]

Protocol

Fluid therapy, ventilator strategy, and intravenous drugs including the norepinephrine dosage were kept constant throughout the study. After 120 min had elapsed during stable hemodynamic and respiratory gas exchange conditions during isotope infusion, a baseline set of data was obtained. Then continuous intravenous dobutamine was started, and the dosage was incrementally increased until a 20% increase in CI was achieved.

Table 1. Global and Splanchnic Hemodynamics and Oxygen Saturations before (Baseline) and during Dobutamine Infusion (Dobutamine) in the Patients Studied

	Baseline	Dobutamine
Heart rate (1/min)	96 ± 15	110 ± 17*
Mean arterial pressure (mmHg)	75 ± 5	74 ± 6
Mean pulmonary artery pressure (mmHg)	31 ± 3	30 ± 3
Right atrial pressure (mmHg)	16 ± 2	16 ± 3
Pulmonary artery occluded pressure (mmHg)	19 ± 1	17 ± 2
Cardiac index (l·min^{-1}·m^2)	4.3 ± 0.3	5.1 ± 0.4*
Splanchnic blood flow index (l·min^{-1}·m^2)	0.91 ± 0.21	1.21 ± 0.34*
Arterial O_2 saturation (%)	94 ± 2	94 ± 2
Mixed-venous O_2 saturation (%)	71 ± 2	75 ± 2*
Hepatic venous O_2 saturation (%)	45 ± 8	52 ± 7*

All values are mean ± standard deviation; n = 12.

* Significant difference ($P < 0.001$) *versus* baseline.

The dobutamine infusion rate was adjusted to a maximum increase in heart rate of 20%. After another 2 h had elapsed during stable conditions, a second set of data was obtained. To minimize changes in oxygen delivery and oxygen uptake unrelated to the study protocol, none of the patients was turned or otherwise manipulated during the observation period. To limit interference with routine therapy and nursing, we did not collect a third set of data after dobutamine.

Statistical Analysis

All values recorded are means ± standard deviation. Differences between baseline values and those during dobutamine infusion were tested using a Wilcoxon rank sign test for paired samples, and probability values less than 0.05 were regarded as significant.

Results

Table 1 summarizes the global and splanchnic hemodynamic response to the dobutamine infusion. Dobutamine significantly ($P < 0.001$) increased the CI in all patients, mainly due to a significant ($P < 0.001$) increase in heart rate. There was no change in systemic or pulmonary vascular pressures. The increased CI was
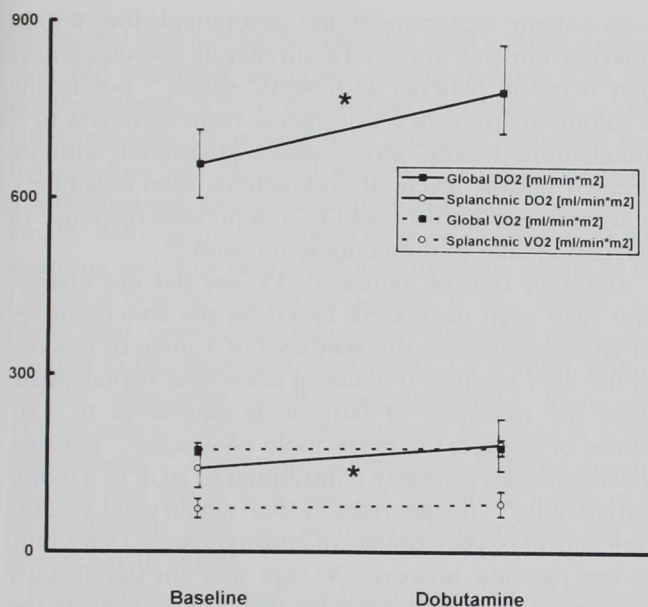
Fig. 1. Global (solid lines) and splanchnic (dotted lines) oxygen delivery (DO₂, closed squares) and uptake (VO₂, open circles) before (baseline) and during dobutamine infusion. All values are means ± SD, n = 12; *Significant difference ($P < 0.001$).

associated with a similarly significant ($P < 0.001$) increase in Qspl, with the contribution of regional to global flow remaining unaltered (22% ± 5% and 23% ± 6% before and during dobutamine infusion, respectively). Because pulmonary gas exchange was not influenced by the catecholamine administration, the increased CI and Qspl resulted in a parallel significant increase of DO₂sys (from 656 ± 58 ml · min⁻¹ · m² to 780 ± 70 ml · min⁻¹ · m²; $P < 0.001$) and DO₂spl (from 141 ± 33 ml · min⁻¹ · m² to 182 ± 44 ml · min⁻¹ · m²; $P < 0.001$; fig. 1). Neither VO₂tot (173 ± 10 ml · min⁻¹ · m² and 177 ± 13 ml · min⁻¹ · m², respectively) nor VO₂spl (73 ± 16 ml · min⁻¹ · m² and 82 ± 21 ml · min⁻¹ · m², respectively), however, changed during dobutamine infusion (fig. 1), and consequently hepatic and mixed venous oxygen saturation significantly ($P < 0.001$; table 1) increased.

The HGP showed a similarly homogenous response in all patients (fig. 2): Despite the unchanged VO₂spl, increasing Qspl and DO₂spl resulted in a significant decrease of HGP from 5.1 ± 1.6 mg · kg⁻¹ · min⁻¹ to 3.6 ± 0.9 mg · kg⁻¹ · min⁻¹ ($P < 0.001$).

Discussion

The objective of this study was to determine whether increasing Qspl leads to increased VO₂spl affiliated with

accelerated HGP in patients with septic shock in whom blood pressure had been stabilized with volume resuscitation and norepinephrine. Qspl was increased by infusing dobutamine, and HGP was assessed using a primed-continuous infusion of stable, nonradioactively isotope-labeled glucose during steady-state conditions.

We used the stable isotope approach to assess HGP for several reasons. First, calculating regional substrate flux parameters according to the Fick principle[1,2,6,7] crucially depends on accurate flow measurements. Furthermore, this approach is particularly sensitive to measurement errors when the arteriohepatic venous concentration difference is small compared with the absolute blood level (such as for glucose). In addition, while the Fick principle can only yield glucose net balances rather than uptake or release rates, the Ra of [6,6-²H₂]-glucose represents HGP because the 6-label of the glucose molecule does not recycle.[19,20] Finally, the derivation of HGP from the Ra of [6,6-²H₂]-glucose avoids mathematical coupling of shared variables when both VO₂spl and
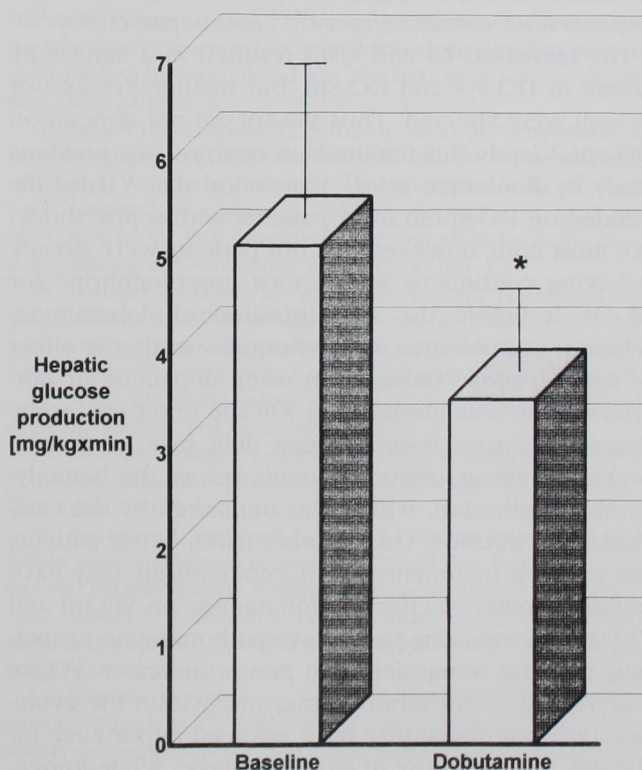

Fig. 2. Hepatic glucose production rate before (baseline) and during dobutamine infusion. Values are means ± SD, n = 12, for baseline and dobutamine infusion. *Significant difference ($P < 0.001$).

HGP are calculated as the product of flow times arteriohepatic venous content differences.[7]

In our patients, baseline Qspl was 0.91 ± 0.21 $l \cdot min^{-1} \cdot m^2$, accounting for $22\% \pm 5\%$ of CI. Infusing dobutamine produced a marked increase in CI and Qspl, and the ratio between regional and total flow remained unchanged. This Qspl and the fractional contribution to CI are less than that reported by others in patients after injury or with sepsis,[2-4,6,7] necrotizing pancreatitis,[17] or septic shock.[5] A more severe illness in our patients leading to redistribution of blood flow at the expense of the splanchnic bed may have accounted for this discrepancy because in all but one of the previous reports shock was not present, and septic shock was probably less pronounced in the patients studied by Ruokonen *et al.*[5]: In our patients, higher filling pressures (pulmonary artery occluded pressure, 19 ± 1 mmHg *vs.* 10 ± 3 mmHg) and norepinephrine administration were necessary to achieve comparable mean arterial pressure and cardiac output. The parallel increase of Qspl and CI confirms the nonpreferential effect of dobutamine in the splanchnic bed compared with other vascular regions, as previously described in patients after cardiac surgery[21,22] and hepatectomy.[23]

The increased CI and Qspl resulted in a similar increase in DO_2sys and DO_2spl, but neither VO_2tot nor VO_2spl were affected. Thus VO_2spl did not depend on DO_2spl. Clearly this finding is in contrast to a previous study by Ruokonen *et al.*[5] that found that VO_2spl depended on DO_2spl in most patients with septic shock. We must note, however, that our patients were already receiving continuous intravenous norepinephrine for 24–36 h before the administration of dobutamine, whereas in Ruokonen and colleagues' study the effect of hemodynamic stabilization using dopamine or norepinephrine was investigated. On the one hand, some degree of covert tissue oxygen debt may have been present in those authors' patients before the hemodynamic stabilization, which was unmasked by the catecholamine infusion. On the other hand, in our patients the ongoing treatment with norepinephrine may have blunted a putative effect of dobutamine on VO_2tot and VO_2spl because, due to its β-sympathomimetic properties, infusing norepinephrine *per se* increases VO_2tot and VO_2spl.[24] Furthermore, the time within the evolution of septic shock may have assumed importance for the different response in oxygen uptake: While Ruokonen *et al.* studied patients immediately after the diagnosis of hyperdynamic septic shock, our patients were studied at least 24 h after hemodynamic stabilization

with volume replacement and norepinephrine. Within this time interval, impaired β-adrenergic responsiveness may occur in patients with septic shock,[25] potentially resulting in attenuated calorigenic responsiveness to β stimulation. Finally, stress states associated with increased plasma levels of endogenous catecholamines, glucagon, and cortisol lead to a depressed response of oxygen uptake to dobutamine infusion.[26]

Although DO_2spl increased, VO_2spl did not change and HGP even decreased. Based on the stoichiometry of gluconeogenesis, the synthesis of 1 mole of glucose in the liver requires 6 moles of adenosine triphosphate from the oxidation of fatty acids equivalent to 1.07 moles of oxygen for every mole of glucose.[7] Because glycogenolysis probably contributed to HGP to a minor extent only,[7,27] the decrease in HGP would yield a reduction in liver oxygen uptake of approximately 15 ml/min. In our patients, however, VO_2spl was not significantly influenced. We must consider that VO_2spl reflects the oxygen uptake of the whole splanchnic region, whereas HGP as derived from the Ra of $[6,6-^2H_2]$-glucose is an organ-specific mirror of hepatic metabolic activity alone.[19,20] Furthermore, we can only speculate on a putative thermogenic effect of dobutamine on the other splanchnic organs or a shift to other oxygen-consuming metabolic pathways within the liver due to hepatocellular heterogeneity.[28] No matter the reason of the unchanged VO_2spl, however, our results clearly show that in our well-resuscitated patients with septic shock, splanchnic oxygen requirements and thus VO_2spl were not determined by enhanced HGP. In addition, accelerated HGP was not directly related to DO_2spl or, in other words, precursor supply.

It could be argued that the decrease in HGP may reflect impaired hepatic metabolic performance. In fact, we recently showed that a positive-end expiratory pressure–induced decrease in CI resulted in a marked decrease in hepatic venous oxygen saturation as well as HGP in patients with septic shock,[29] particularly in those patients who subsequently died. It is noteworthy, however, that in that study HGP decreased to levels slightly greater than normal in the survivors and substantially less than that in those who died. On the contrary, in our present study, HGP was always greater than normal during dobutamine infusion. Furthermore, the positive-end expiratory pressure–induced decrease in CI presumably lead to decreased Qspl, such as demonstrated in critically ill patients by Bonnet *et al.*,[30] whereas dobutamine improved regional oxygen availability in our present investigation. In fact, restoring

global and regional hemodynamics with volume expansion and dopamine administration in patients with abdominal sepsis whose lungs were mechanically ventilated not only decreased HGP but also improved the hepatic first-pass effect of leucine,[31] a mirror of both gastrointestinal and hepatic perfusion and function.[20] Finally, a dobutamine-induced increase in arteriovenous shunting and thus decreased nutritive flow resulting in impaired hepatic metabolic activity is also rather unlikely: First, hepatic venous oxygen saturation increased parallel to the increased Qspl (table 1). Second, dobutamine combined with norepinephrine increased VO_2spl when replacing epinephrine in patients with septic shock.[32] And finally, dobutamine restored intestinal mucosal blood flow and pH to normal levels in a hyperdynamic porcine endotoxin shock model and in patients with sepsis.[33]

In summary, we tested the hypothesis that a dobutamine-induced increase in Qspl leads to increased VO_2spl affiliated with accelerated HGP in patients with septic shock in whom blood pressure had been stabilized with volume resuscitation and norepinephrine. Qspl was increased in parallel to CI, suggesting that dobutamine had no preferential effect on the splanchnic vascular bed. Although DO_2spl increased, VO_2spl did not change and HGP even decreased. Therefore we conclude that in our well-resuscitated patients with septic shock, splanchnic oxygen requirements and thus VO_2spl were not determined by enhanced HGP. Furthermore, in these patients HGP was not directly related to DO_2spl or, in other words, precursor supply.

References

1. Wilmore DW, Goodwin CW, Aulick LH, Powanda MC, Mason AD, Pruitt BA: Effect of injury and infection on visceral metabolism and circulation. Ann Surg 1980; 192:491-500

2. Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA: Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery 1987; 101:69-80

3. Dahn MS, Lange MP, Wilson RF, Jacobs LA, Mitchell RA: Hepatic blood flow and splanchnic oxygen consumption measurements in clinical sepsis. Surgery 1990; 107:295-301

4. Dahn MS, Wilson RF, Lange P, Stone A, Jacobs LA: Hepatic parenchymal oxygen tension following injury and sepsis. Arch Surg 1990; 125:441-3

5. Ruokonen E, Takala J, Kari A, Saxén H, Mertsola J, Hansen EJ: Regional blood flow and oxygen transport in septic shock. Crit Care Med 1993; 21:1296-1303

6. Steffes CP, Dahn MS, Lange MP: Oxygen transport-dependent splanchnic metabolism in the sepsis syndrome. Arch Surg 1994; 129:46-52

7. Dahn MS, Mitchell RA, Lange MP, Smith S, Jacobs LA: Hepatic metabolic response to injury and sepsis. Surgery 1995; 117:520-30

8. Wolfe RR, Durkot MJ, Allsop JR, Burke JF: Glucose metabolism in severely burned patients. Metabolism 1979; 28:1031-9

9. Tappy L, Cayeux MC, Schneiter P, Schindler C, Temler E, Jéquier E, Chioléro R: Effects of lactate on glucose metabolism in healthy subjects and in severely injured hyperglycemic patients. Am J Physiol 1995; 268:E630-5

10. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for innovative therapies in sepsis. Crit Care Med 1992; 20:864-74

11. Kvietys PR, Granger DN: Vasoactive agents and splanchnic oxygen uptake. Am J Physiol 1982; 243:G1-9

12. Banks RO, Gallavan RH, Zinner MJ, Bulkley GB, Harper SL, Granger DN, Jacobson ED: Vasoactive agents in the control of the mesenteric circulation. Fed Proc 1985; 44:2743-9

13. Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbrère JS: Multiple-organ failure: Generalized autodestructive inflammation? Arch Surg 1985; 120:1109-15

14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: Prognosis in acute organ-system failure. Ann Surg 1985; 202:685-93

15. Dhainaut JFA, Tenaillon A, Le Tulzo Y, Schlemmer B, Solet JP, Wolff M, Holzapfel L, Zeni F, Dreyfuss D, Mira JP, De Vathaire F, Guinot P: Platelet-activating factor receptor antagonist BN52021 in the treatment of severe sepsis: A randomized, double-blind, placebo-controlled, multicenter clinical trial. BN52021 Study Group. Crit Care Med 1994; 22:1720-8

16. Jansen JR, Schreuder JJ, Settels JJ, Kloek JJ, Versprille A: An adequate strategy for the thermodilution technique in patients during mechanical ventilation. Intensive Care Med 1990; 16:422-5

17. Uusaro A, Ruokonen E, Takala J: Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. Cardiovasc Res 1995; 30:106-12

18. Ensinger H, Träger K, Geisser W, Anhäupl T, Ahnefeld FW, Vogt J, Georgieff M: Glucose and urea production and leucine, ketoisocaproate and alanine fluxes at supraphysiological plasma adrenaline concentrations in volunteers. Intensive Care Med 1994; 20:113-8

19. Wolfe RR: Stable isotope approaches for study of energy substrate metabolism. Fed Proc 1982; 41:2692-7

20. Ensinger H, Vogt J, Träger K, Georgieff M, Radermacher P: Use of tracer techniques in intensive care research. Part II. Clin Intensive Care 1996; 7:30-3

21. Parviainen I, Ruokonen E, Takala J: Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. Br J Anaesth 1995; 74:277-82

22. Uusaro A, Ruokonen E, Takala J: Splanchnic oxygen transport after cardiac surgery: Evidence for inadequate tissue perfusion after stabilization of hemodynamics. Intensive Care Med 1996; 22:26-33

23. Kainuma M, Kimura N, Nonami T, Kurokawa T, Ito T, Nakashima K, Shimada Y: The effect of dobutamine on hepatic blood flow and oxygen supply-uptake ratio during enflurane nitrous oxide anesthesia in humans undergoing liver resection. ANESTHESIOLOGY 1992; 77:432-8

24. Bearn AG, Billing B, Sherlock S: The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. J Physiol 1951; 115:430-41

25. Silverman HJ, Penaranda R, Orens JB, Lee NH: Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: Association with myocardial hyporesponsiveness to catecholamines. Crit Care Med 1993; 21:31–9

26. Uusaro A, Hartikainen J, Parviainen M, Takala J: Metabolic stress modifies the thermogenic effect of dobutamine in man. Crit Care Med 1995; 23:674–80

27. Liaw KY: Effect of injury, sepsis, and parenteral nutrition on high-energy phosphates in human liver and muscle. J Parent Enteral Nutr 1985; 9:28–33

28. Gumucio JJ: Hepatocyte heterogeneity: The coming age from the description of a biological curiosity to a partial understanding of its physiological meaning and regulation. Hepatology 1989; 91:154–60

29. Träger K, Radermacher P, Georgieff M: PEEP and hepatic metabolic performance in septic shock. Intensive Care Med 1996; 22: 1274–5

30. Bonnet F, Richard C, Glaser P, Lafay M, Guesde R: Changes in hepatic flow induced by continuous positive pressure ventilation in critically ill patients. Crit Care Med 1982; 10:703–5

31. Bagley JS, Wan JM, Georgieff M, Forse RA, Blackburn GL: Cellular nutrition in support of early multiple organ failure. Chest 1991; 100:182S–8S

32. Meier-Hellmann A, Reinhart K: Influence of catecholamines on regional perfusion and tissue oxygenation in septic shock patients, Sepsis Current Perspectives in Pathophysiology and Therapy. Edited by Reinhart K, Eyrich K, Sprung C. Berlin, Springer, 1994, pp 274–91

33. Nevière R, Vallet B: β-Adrenergic drugs to improve gastrointestinal mucosal blood flow in sepsis, Yearbook of Intensive Care and Emergency Medicine. Edited by Vincent JL. Berlin, Springer, 1996, pp 333–41