

## Effect of Dobutamine on Splanchnic Carbohydrate Metabolism and Amino Acid Balance after Cardiac Surgery

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**Background:** As a predominant  $\beta$ -adrenergic agonist, dobutamine may modify blood flow distribution and increase metabolic demands. The authors investigated the effect of a dobutamine-induced increase in cardiac output on splanchnic and femoral blood flow and metabolism in patients after cardiac surgery.

**Methods:** Seventeen stable patients were randomized to receive dobutamine or placebo ( $n = 8$  per group, one dropout). After baseline measurement for systemic, splanchnic, and femoral blood flow (by dye dilution); oxygen consumption; gastric mucosal pressure of carbon dioxide ( $P_{CO_2}$ ); total and splanchnic glucose production (by stable isotope tracer dilution); and regional lactate and amino acid balance, patients received either dobutamine, at a dosage ( $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) sufficient to increase cardiac index by at least 25%, or placebo. A second set of measurements was performed 60 min after the start of dobutamine or placebo infusion.

**Results:** Dobutamine increased cardiac index ( $3.0 \pm 0.6$  to  $4.4 \pm 1.0 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , mean  $\pm$  SD;  $P < 0.05$ ), splanchnic blood flow (from  $0.8 \pm 0.2$  to  $1.0 \pm 0.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $P < 0.05$ ), femoral blood flow (from  $0.2 \pm 0.1$  to  $0.3 \pm 0.1 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $P < 0.05$ ), and the arterial-gastric mucosal  $P_{CO_2}$  gap (from  $11.4 \pm 9.5$  to  $11.9 \pm 8.0 \text{ mmHg}$ ;  $P < 0.05$ ). Dobutamine increased systemic oxygen consumption (from  $132 \pm 14$  to  $146 \pm 13 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $P < 0.05$ ) but not splanchnic or femoral

oxygen consumption. Splanchnic glucose production and lactate and amino acid balance did not change.

**Conclusion:** After coronary artery bypass surgery, dobutamine increased systemic and regional blood flow and decreased systemic and regional oxygen extraction. Dobutamine did not affect splanchnic glucose production or lactate or amino acid balance. This suggests that dobutamine increases splanchnic blood flow without a concomitant increase in hepatosplanchnic metabolism. (Key words: Coronary artery bypass; metabolism; splanchnic circulation; drug effects.)

DOBUTAMINE is used frequently to support myocardial function after cardiac surgery. In addition to improving systemic hemodynamics, adrenergic drugs may alter the distribution of regional and local blood flow<sup>1,2</sup> and increase the hepatosplanchnic metabolic activity.<sup>3,4</sup> Specifically,  $\beta$ -adrenergic agonists increase splanchnic glucose production, which is an energy-consuming process. As a predominantly  $\beta$ -adrenergic agonist, dobutamine is likely to also increase hepatosplanchnic metabolic activity. Because splanchnic perfusion may be compromised after cardiac surgery (e.g., in postoperative low cardiac output), an increase in splanchnic metabolic demand may be harmful if it is not accompanied by an appropriate increase in blood flow or if blood flow is maldistributed. Increased splanchnic metabolic activity also may contribute to the persistence of gastric mucosal acidosis despite dobutamine-induced increase in splanchnic blood flow in patients after cardiac surgery. Severe splanchnic hypoperfusion with clinically relevant gastrointestinal complications after cardiac surgery obviously is rare. Nevertheless, postoperative cardiac surgical patients provide a relevant model for the evaluation of the metabolic and circulatory effects of commonly used vasoactive drugs.

We hypothesized that dobutamine increases the hepatosplanchnic metabolism after cardiac surgery. To test this hypothesis, we measured in a randomized, controlled study the effects of dobutamine on hepatosplanchnic blood flow, oxygen consumption, glucose

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**Table 1. Patient Characteristics**

	Dobutamine	Placebo
Number of patients	8	8
Age (yr)	58 ± 6	60 ± 3
Sex (male/female)	7/1	8/0
Height (cm)	173 ± 7	171 ± 6
Body weight (kg)	92 ± 13	78 ± 8
BSA (m <sup>2</sup> )	2.05 ± 0.18	1.89 ± 0.11
NYHA	3 ± 0	3 ± 1
Number of distal anastomoses	5 ± 2	5 ± 1
Perfusion time (min)	144 ± 71	125 ± 52
Aortic cross-clamp time (min)	101 ± 24	107 ± 28

Values are mean ± SD.

BSA = body surface area; NYHA = severity of heart failure according to the New York Heart Association.

metabolism, and lactate and amino acid balance in patients after cardiac surgery.

## Materials and Methods

In a prospective, randomized study, 17 patients after coronary artery bypass grafting were studied after approval by the ethics committee of the Kuopio University Hospital and after a written informed consent from the patient was obtained. The study was conducted according to the principles established in the Helsinki Declaration. In one patient, the study was discontinued because of reoperation for hemostasis, and an additional patient was subsequently randomized (n = 16 completed). The patient characteristics are listed in table 1.

Before induction of anesthesia, catheters for routine invasive hemodynamic monitoring were inserted during local anesthesia. These included an arterial catheter and a pulmonary arterial catheter with an introducer *via* the internal jugular vein. A second introducer was inserted after induction of anesthesia *via* the jugular vein to facilitate the postoperative insertion of the hepatic venous catheter. This introducer was used perioperatively for infusion.

Standard anesthesia was induced with 20 μg/kg fentanyl, 0.07 mg/kg midazolam, and neuromuscular blocking drugs, a mixture of 0.125 mg/kg alcuronium and 0.15 mg/kg pancuronium. Anesthesia was maintained with a continuous infusion of 0.07 μg · kg<sup>-1</sup> · min<sup>-1</sup> fentanyl, 0.5 μg · kg<sup>-1</sup> · min<sup>-1</sup> midazolam, and 1.1 μg · kg<sup>-1</sup> · min<sup>-1</sup> alcuronium and supplemented with thiopentone and halothane. Cardiopulmonary bypass with nonpulsatile flow rates of 2–2.5 l · min<sup>-1</sup> · m<sup>-2</sup> was used. Systemic hypothermia (28–30°C), topical myocardial hypother-

mia, and hyperkalemic cardioplegia were used. Patients were weaned from cardiopulmonary bypass at a rectal temperature of more than 34°C.

After transfer to the intensive care unit, all patients underwent mechanical ventilation (according to the clinical routine) using controlled mechanical ventilation, an inspired oxygen fraction of 0.4, and a positive end-expiratory pressure of 5 cm H<sub>2</sub>O. Appropriate sedation was confirmed by continuous monitoring at the bedside. All patients were sedated to the same end point: nonresponsiveness to audible stimuli and routine monitoring procedures. The residual anesthesia was supplemented with thiopentone and oxycodone chloride, if needed. If shivering occurred, vecuronium was used. Immediately after admission to the intensive care unit, 16-gauge polyurethane catheters were inserted in a femoral artery and the ipsilateral femoral vein. The previously inserted right jugular vein introducer was used to insert a 7-French courmand catheter in a right hepatic vein during portable fluoroscopy. The correct placement of the catheter tip, in a nonwedged position at least 5 cm within the vein, was verified using a small amount of contrast dye.

After the patients became stable, with special concern for body temperature and intravascular volume, the study protocol was begun (fig. 1). Each experiment lasted for 220 min. After the baseline measurement between 90 and 110 min after the start of the primed continuous tracer infusion, either dobutamine or placebo were infused. The dosage of dobutamine was increased in steps of 2 μg · kg<sup>-1</sup> · min<sup>-1</sup> to attain an initial increase in cardiac index of 25% above the control measurement. The second measurement during placebo or dobutamine administration was performed between 200 and 220 min after the start of the tracer infusion. At the time of baseline measurement, pulmonary arterial blood temperature (mean ± SD) was 38.1 ± 0.6°C in the placebo group and 38.4 ± 0.6°C in the dobutamine group; during the second measurement it was 38.2 ± 0.7°C in the placebo group and 38.4°C in the dobutamine group. The primed continuous tracer infusion was started 5.5 ± 1.7 h after the end of the operation in the placebo group and 4.9 ± 1.5 h in the dobutamine group. The amounts of crystalloids, colloids, and blood with which the patients were infused is shown in table 2.

The rate of glucose production was measured using [6,6]-D<sub>2</sub>-glucose (Cambridge Isotope Laboratories, Boston, MA). At t = 0 min, a primed continuous infusion of [6,6]-D<sub>2</sub>-glucose was commenced (4.0 mg/kg + 0.05 mg · kg<sup>-1</sup> · min<sup>-1</sup>). At t = 90, 100, 110, 200, 210, and

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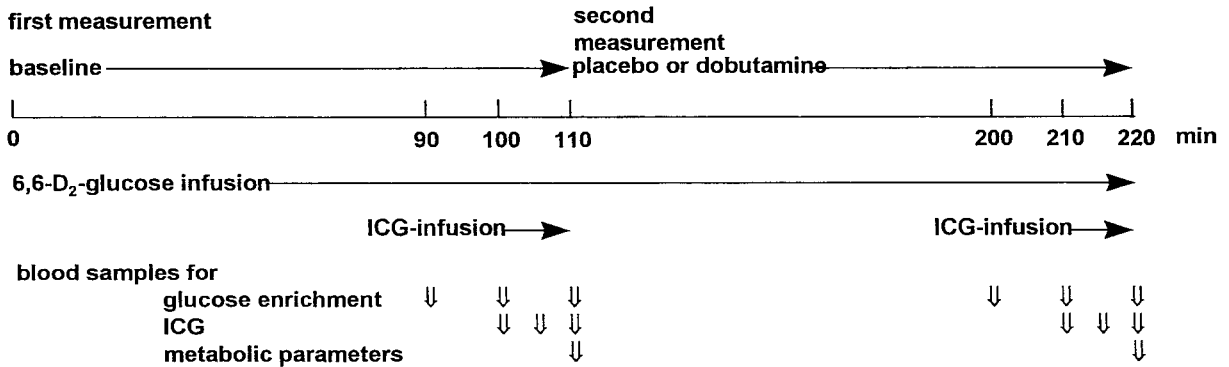


Fig. 1. The time course of the study protocol is shown. Arrow = blood sampling.

220 min blood samples (10 ml each) were taken to determine the isotopic enrichment. The isotopic enrichment of glucose was determined by gas chromatography-mass spectrometry (Hewlett Packard GC 5890, MS 5971, Munich, Germany) in the selected ion monitoring mode using electron-impact ionization as described previously.<sup>4</sup> The coefficient of variation is less than 10% for enrichments of more than 1%, with a difference between measured and expected enrichment of less than 7% of the expected value. The atom percentage excess used in the calculation was the corresponding mean of the three atom percentage excesses determined at t = 90, 100, and 110, and at t = 200, 210, and 220, respectively. Because the atom percentage excesses did not change within the 20-min period of blood, the rate of appearance was calculated for steady state conditions.<sup>5</sup> Because the patients received small amounts of intravenous glucose, the calculated rate of glucose production minus the glucose infusion rate was taken as the endogenous glucose production. The splanchnic rate of glucose production and rate of disappearance were calculated as described by Fong *et al.*<sup>6</sup>

$$Ra_{spl} = Q_{spl} * C_{hv} * \left(1 - \frac{E_{hv}}{E_{art}}\right) \quad (1)$$

$$Rd_{spl} = Q_{spl} * C_{art} * \left(1 - \frac{C_{hv} * E_{hv}}{C_{art} * E_{art}}\right) \quad (2)$$

Table 2. Amount of Crystalloids (Saline and Ringer's Solution), Colloids (Hydroxyethylstarch and Fresh Frozen Plasma), and Packed Red Cells

	Placebo	Dobutamine
Crystalloids	2,500 ± 900	3,200 ± 900
Colloids	900 ± 400	1,300 ± 400
Packed red cells	900 ± 200	1,200 ± 500

Values are mean ± SD.

$Q_{spl}$  is splanchnic blood flow, C is glucose concentration, E is glucose enrichment, and art and hv indicate arterial and hepatic venous values, respectively.

For determination of the metabolic parameters, 10-ml blood samples were placed in chilled test tubes containing heparin. Glucose was determined photometrically using the hexokinase reaction. Lactate was measured enzymatically (Boehringer Mannheim GmbH, Mannheim, Germany). The amino acids were separated using high-performance liquid chromatography using a lithium buffer, ion-exchange chromatography, and ninhydrin for detection (Chromacron 500, Kontron, Eiching, Germany). The intraassay coefficient of variation was 1-9%, and the difference between the measured and expected value of the concentration was 2.3% or less.

Splanchnic and leg blood flow were measured using a primed continuous indocyanine green (ICG) infusion and hepatic and femoral venous and femoral arterial catheterization.<sup>7</sup> A bolus of ICG was followed by a continuous infusion from t = 80 to t = 110 min and from t = 190 to t = 220 min (12 mg followed by 1.1 mg/min).

$$Q_{spl} = IR_{ICG} * \frac{C_1}{(C_{art} - C_{hv}) * (1 - Hcr)} \quad (3)$$

where  $IR_{ICG}$  is the infusion rate of ICG,  $C_1$  is the ICG infusate concentration,  $C_{art}$  and  $C_{hv}$  are the arterial and hepatic venous ICG plasma concentrations, and Hcr is hematocrit.

$$Q_{fem} = \frac{IR_{ICG} * (C_1 - C_{fem})}{(C_{fem} - C_{art}) * (1 - Hcr)} \quad (4)$$

where  $C_{fem}$  is the femoral venous ICG concentration. Blood samples for ICG concentration determination were taken at t = 100, 105, and 110 min and at t = 210, 215, and 220 min. Plasma ICG concentration was mea-

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sured spectrophotometrically using a wavelength of 805 nm. The coefficients of variation for the femoral and splanchnic blood flow and the splanchnic ICG extraction were  $3.7 \pm 2.5\%$ ,  $3.4 \pm 2.3\%$  and  $1.1 \pm 0.5\%$ , respectively. Cardiac output was measured by both thermodilution (mean of three measurements) and the Fick principle, and the mean value was used for analysis. Arterial blood pressure, pulmonary artery blood pressure, and pulmonary capillary wedge pressure were measured at end-expiration using the midaxillary line as the zero reference.

Gastric tonometry (Tonomitor; Tonometrics, Worcester, MA) was performed using saline and a stabilization period of 60 min. The correct location of the gastric tonometer was confirmed by radiography. The saline pressure of carbon dioxide ( $P_{CO_2}$ ) was always measured using the same clinical blood gas analyzer (ABL-520; Radiometer, Copenhagen, Denmark) immediately after sampling.<sup>8-10</sup> We previously demonstrated that the within-subject variability of gastric  $P_{CO_2}$  in healthy subjects is  $7 \pm 4\%$ . Whole-body oxygen consumption was measured from the expired gases by indirect calorimetry using a previously validated device (Deltatrac; Datex/Instrumentarium, Helsinki, Finland).<sup>11</sup> In the study condition, the relative error of the oxygen consumption is less than 5%. The within-subject coefficient of variation for the measurements of oxygen consumption was  $1.6 \pm 1.5\%$ . Splanchnic and leg oxygen consumption were measured using the Fick principle, based on arterial-venous oxygen content differences (sampled at  $t = 100, 105,$  and  $110$  min and at  $t = 210, 215,$  and  $220$  min) and the measured blood flow.

#### Statistical Analysis

The Statistical Analysis Software (SAS; SAS Institute, Carey, NC) and SPSS (SPSS Inc., Chicago, IL) statistic programs were used for statistical evaluation. Data are presented as the mean  $\pm$  SD. Two-way analysis of variance (independent variable treatment and time, the latter for repeated measurements) was used. The model for the analysis of variance was adjusted for the fact that the treatment with placebo or dobutamine was administered only during the second measurement period. Thus, the time  $\times$  treatment interaction with  $P < 0.05$  was regarded as a dobutamine effect. This is referred to in the Results section as the *drug effect*. In case of missing data, the observation was omitted in the statistical treatment of the missing variable and the derived variables, and the actual number of observations was given in the results.

## Results

Two of the 16 patients in whom the study protocol was completed underwent reoperation for hemostasis after completion of the study protocol. Fourteen patients were discharged from the intensive care unit the day after the operation, the remaining two patients were discharged 2 and 3 days after coronary artery bypass graft surgery.

The infusion rate of dobutamine to attain an initial increase in cardiac output was  $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in all patients. Hemodynamic and oxygen-related data are shown in table 3. The ICG extraction was high in all patients, with a slight decrease caused by dobutamine. The pulmonary arterial occlusion pressure decreased similarly in both. At the time of data sampling, dobutamine increased cardiac output, splanchnic blood flow, and femoral blood flow by 47, 25, and 50%, respectively; in the placebo group the corresponding values were unchanged from baseline. The percentage of femoral blood flow of cardiac output during dobutamine was preserved; the percentage of splanchnic blood flow of cardiac output decreased from 27 to 23% ( $P = 0.007$ ). During dobutamine infusion, systemic oxygen consumption increased by 10%, and splanchnic and femoral oxygen consumption did not change compared with the placebo group. The relations between cardiac index and splanchnic and femoral blood flow are shown in figure 2. In both groups, the respiratory exchange ratio did not change. The systemic, splanchnic, and femoral oxygen extraction rates decreased during dobutamine infusion. Although there was no statistically significant difference in gastric mucosal pH between placebo and dobutamine, the changes in  $P_{CO_2}$  gap were different: The  $P_{CO_2}$  gap decreased slightly in the placebo group and either increased or remained unchanged during the dobutamine infusion ( $P = 0.025$ ; table 3; fig. 2).

The variables related to glucose metabolism and lactate and amino acid balance are given in table 4. Dobutamine did not change any of the variables related to glucose metabolism. The arterial and femoral venous plasma glucose concentrations were similar; the hepatic venous glucose concentration was consistently higher than the arterial glucose concentration. There was a decrease in endogenous glucose production rate and an increase in the arterial plasma glucose concentration over time that was similar in both groups ( $P < 0.001$  and  $P = 0.006$ , time effect, respectively). Splanchnic glucose production accounted for 66 and 75% of the total glucose production rate in the two baseline periods. The calcu-

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**Table 3. Hemodynamic and Oxygen-related Variables**

	Placebo Group		Dobutamine Group		P Value	
	Baseline	Second Measurement	Baseline	Second Measurement	Time Effect	Drug Effect
Heart rate (beats/min)	82 ± 15	81 ± 15	84 ± 16	107 ± 10		
Mean arterial pressure (mmHg)	69 ± 12	69 ± 11	71 ± 7	70 ± 6		
Pulmonary capillary wedge pressure (mmHg)	8 ± 3	8 ± 1	7 ± 2	7 ± 3		
Cardiac index (l · min <sup>-1</sup> · m <sup>-2</sup> )	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.6	4.4 ± 1.0	0.003	0.003
Oxygen consumption (ml · min <sup>-1</sup> · m <sup>-2</sup> )	131 ± 12	135 ± 9	132 ± 14	146 ± 13	<0.001	0.031
Systemic oxygen extraction ratio	0.26 ± 0.03	0.26 ± 0.04	0.29 ± 0.07	0.21 ± 0.05	<0.001	<0.001
Respiratory quotient	0.83 ± 0.04	0.80 ± 0.04	0.82 ± 0.02	0.79 ± 0.02		
Splanchnic blood flow (l · min <sup>-1</sup> · m <sup>-2</sup> )	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	1.0 ± 0.2	0.003	0.002
Splanchnic blood flow (as % of cardiac output)	25 ± 7	26 ± 7	26 ± 9	22 ± 7	0.016	0.007
Splanchnic oxygen consumption (ml · min <sup>-1</sup> · m <sup>-2</sup> )	46 ± 4	45 ± 13	49 ± 12	49 ± 6		
Splanchnic oxygen extraction ratio	0.40 ± 0.13	0.39 ± 0.13	0.43 ± 0.11	0.33 ± 0.08	0.008	0.035
Femoral blood flow (l · min <sup>-1</sup> · m <sup>-2</sup> )	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	<0.001	<0.001
Femoral blood flow (as % of cardiac output)	8 ± 1	7 ± 1	8 ± 2	7 ± 1		
Femoral oxygen consumption (ml · min <sup>-1</sup> · m <sup>-2</sup> )	10 ± 2	10 ± 2	11 ± 3	11 ± 2		
Femoral oxygen extraction ratio	0.26 ± 0.07	0.25 ± 0.05	0.35 ± 0.15	0.24 ± 0.10	<0.001	<0.001
Gastric mucosal pH	7.29 ± 0.09	7.29 ± 0.08	7.26 ± 0.06	7.22 ± 0.08		
Gastric mucosal P <sub>CO<sub>2</sub></sub> gap (kPa)	1.68 ± 0.78	1.36 ± 0.73	1.52 ± 1.26	1.59 ± 1.07		0.025
Gastric mucosal P <sub>CO<sub>2</sub></sub> gap (mmHg)	12.6 ± 5.9	10.2 ± 5.5	11.4 ± 9.5	11.9 ± 8.0		0.025
Splanchnic ICG extraction (%)	87 ± 5	87 ± 7	87 ± 6	80 ± 4	<0.001	0.001

Values are mean ± SD. Statistical significance is given for the time or drug effect, two-way analysis of variance for repeated measurements. The data set is complete (n = 8 in each group and period). Blood pressure and heart rate were not tested for significance.

lated values for splanchnic glucose disposal were not different from zero. Dobutamine did not change the concentration or balance of lactate. The net femoral release of lactate was 12–17% of the net splanchnic lactate uptake. The femoral venous plasma concentration of total amino acids was consistently higher compared with the arterial concentration, which was higher than the hepatic venous concentration (data not shown). Although there were differences in the plasma amino acid concentrations caused by dobutamine, there were no changes in the interorgan amino acid balance. The net amino acid uptake in the splanchnic region was four to five times the net femoral release.

There was no correlation between the splanchnic oxygen consumption and endogenous glucose production. There were weak correlations between splanchnic glucose production and the P<sub>CO<sub>2</sub></sub> gap ( $r^2 = 0.12$ ), splanchnic lactate balance ( $r^2 = 0.19$ ), and splanchnic oxygen consumption ( $r^2 = 0.23$ ; fig. 2). Splanchnic oxygen consumption and splanchnic lactate balance also were correlated ( $r^2 = 0.51$ ; fig. 2). The data were analyzed for the effect of mathematical coupling as proposed by Stratton *et al.*<sup>12</sup> The changes in the slope of the regression were less than 10% and the decrease in the *t* value for the slope was less than 5%.

## Discussion

This is the first study of an adrenergic drug in cardiac surgery patients in which simultaneous regional blood flows, regional and interorgan glucose metabolism and net amino acid balance, and variables derived of gastric tonometry were determined. We found high splanchnic oxygen extraction rates, with maximum values exceeding 60%, low gastric pH<sub>i</sub>, and a high P<sub>CO<sub>2</sub></sub> gap, suggesting that the splanchnic perfusion was compromised in at least some patients. In these conditions, the potential adverse effects of dobutamine-induced increased splanchnic metabolic demand should have been apparent. The high splanchnic oxygen extraction at baseline was not related to increased splanchnic metabolism. Splanchnic oxygen consumption was only slightly higher than in healthy volunteers.<sup>13,14</sup> It was far less compared with patients with burns,<sup>13</sup> sepsis,<sup>15,16</sup> and septic shock.<sup>17,18</sup> Glucose production was not enhanced in contrast to burn patients<sup>13</sup> and septic patients.<sup>15,16,18</sup> However, the net femoral amino acid release and the net splanchnic lactate and amino acid uptake were increased, resembling a cortisol effect.<sup>19,20</sup>

The simultaneous determination of splanchnic and leg blood flow using a primed continuous infusion of ICG

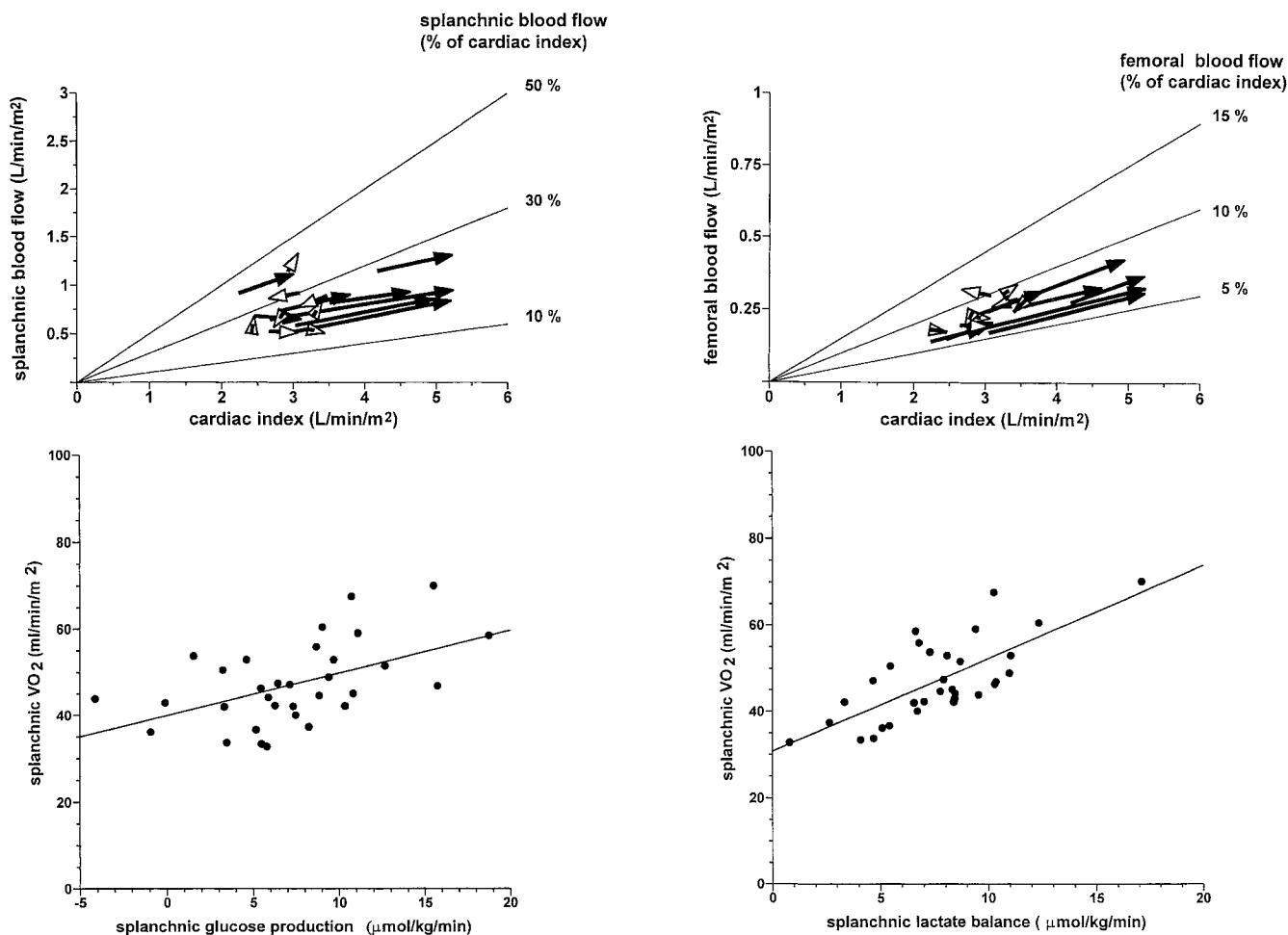


Fig. 2. (Top) Relation between cardiac index and splanchnic blood flow (left) and between cardiac index and femoral blood flow (right). Open arrows = placebo group; filled arrows = dobutamine group. (Bottom) Correlation between splanchnic glucose production and splanchnic oxygen consumption,  $r^2 = 0.23$  (left), and between splanchnic lactate balance and splanchnic oxygen consumption  $r^2 = 0.51$  (right). Because dobutamine did not affect splanchnic glucose production, lactate balance, or splanchnic oxygen consumption, the data were pooled.

was discussed recently.<sup>7</sup> In the current study, the splanchnic ICG extraction of 80–87% allowed a reliable estimation of splanchnic blood flow. The low coefficients of variation suggest a good reproducibility in the determination of the regional blood flows. This is a prerequisite for the derivation of regional metabolic effects by combining the stable isotope tracer approach with the measurement of regional blood flow. Equations for steady state kinetics were applied for the calculation of glucose production.<sup>5</sup> A slight increase in the glucose enrichment over time caused by a non-steady state of isotopic enrichment cannot be ruled out. However, an error introduced by a slow drift in enrichment should be identical in the placebo and in dobutamine groups, thus excluding a misinterpretation of our data. Despite the

wide use of adrenergic agonists in critically ill patients, the interaction between metabolic and hemodynamic effects has received little attention. All adrenergic agonists with  $\beta$ -adrenoceptor activity increase whole-body oxygen consumption by 10–25%, usually in a dose-dependent fashion,<sup>21–29</sup> and increase splanchnic glucose turnover.<sup>3,30</sup> If the cardiovascular reserves are compromised, an increased metabolic demand may not be met by an increase in blood flow.<sup>31,32</sup>

Our results strongly suggest that, despite its predominantly  $\beta$ -adrenergic activity, dobutamine does not increase the splanchnic metabolic demands. The splanchnic oxygen consumption remained practically unchanged, and both the rate of total glucose appearance and the endogenous glucose production decreased over time in both groups.

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**Table 4. Glucose Metabolism and Amino Acid Balance**

	Placebo Group		Dobutamine Group		P Value (Time Effect)
	Baseline	Second Measurement	Baseline	Second Measurement	
Rate of total glucose appearance ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	13.9 $\pm$ 2.5	12.4 $\pm$ 2.5	14.5 $\pm$ 2.8	12.3 $\pm$ 1.8	<0.001
Endogenous glucose production ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	11.1 $\pm$ 2.5	9.6 $\pm$ 2.4	12.3 $\pm$ 2.7	9.4 $\pm$ 2.1	<0.001
Splanchnic glucose production ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	8.9 $\pm$ 3.9	7.5 $\pm$ 4.7	9.3 $\pm$ 4.5	6.4 $\pm$ 3.4	
Splanchnic glucose balance ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	-1 $\pm$ 5.0*	2.4 $\pm$ 3.4*	0.3 $\pm$ 6.0*	-0.5 $\pm$ 5.9*	
Arterial glucose concentration (mM)	7.6 $\pm$ 0.9	7.8 $\pm$ 0.8	7.1 $\pm$ 1.4	7.5 $\pm$ 1.3	0.006
Arterial lactate concentration (mM)	1.2 $\pm$ 0.6	1.2 $\pm$ 0.6	1.5 $\pm$ 0.9	1.4 $\pm$ 0.3	
Splanchnic lactate balance ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	7.8 $\pm$ 2.5	6.9 $\pm$ 4.8	7.1 $\pm$ 2.5	8.7 $\pm$ 2.6	
Femoral lactate balance ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	-1.3 $\pm$ 0.4	-0.9 $\pm$ 0.4	-1.0 $\pm$ 0.5	-1.0 $\pm$ 0.6	
Splanchnic amino acid balance ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	10.8 $\pm$ 3.7 (n = 5)	9.6 $\pm$ 1.8 (n = 6)	8.5 $\pm$ 2.4 (n = 7)	9.0 $\pm$ 2.1 (n = 6)	
Femoral amino acid balance ( $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	-1.2 $\pm$ 1.8* (n = 6)	-2.4 $\pm$ 0.7 (n = 6)	-1.9 $\pm$ 0.7 (n = 6)	-2.3 $\pm$ 0.8 (n = 6)	

Values are mean  $\pm$  SD. Statistical significance is given for the time effect, two-way analysis of variance for repeated measurements. No significant drug effects were observed. The data set is complete (n = 8) except for the amino acid data where the actual number of cases are given in parentheses as there were missing values due to failure in analysis.

\* Substrate balance not different from zero.

Also, splanchnic amino acid balance remained unchanged. Although our methodology does not allow distinction between hepatic and intestinal metabolism, the observed splanchnic metabolic patterns almost certainly rule out a dobutamine-induced increase in the metabolic demand of the liver. The endogenous glucose appearance of 9–12  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in the current study is slightly lower compared with studies in postabsorptive volunteers from Wolfe *et al.*<sup>33</sup> and from our laboratory.<sup>4</sup> Glucose production and the femoral release and splanchnic uptake of lactate were not affected by dobutamine, suggesting that this adrenergic drug did not interfere with carbohydrate metabolism. The relation between total endogenous and splanchnic glucose production in the current investigation was similar to that of two recent studies.<sup>6,34</sup>

We previously showed that dobutamine and dopexamine worsen gastric mucosal acidosis after cardiac surgery, despite increased total hepatosplanchnic blood flow.<sup>35,36</sup> In the current study, the gastric mucosal  $\text{P}_{\text{CO}_2}$  gap was not normalized, despite the increase in total hepatosplanchnic blood flow. Because of the lack of dobutamine-induced changes in splanchnic metabolism, local metabolic changes are very unlikely to be the cause of the sustained increase of the mucosal  $\text{P}_{\text{CO}_2}$  gap. Dobutamine redistributed the whole-body blood flow because the fractional splanchnic blood flow decreased. Vasodilating adrenergic drugs may redistribute the blood flow locally and reduce the nutritive flow of the mu-

cosa,<sup>1,2</sup> which might contribute to the sustained high gastric mucosal  $\text{P}_{\text{CO}_2}$  gap. An additional explanatory factor is the Haldane effect: A dobutamine-induced increase in mucosal blood flow and hemoglobin saturation may result in a higher mucosal  $\text{P}_{\text{CO}_2}$ , despite decreased mucosal blood carbon dioxide content. In contrast to our results, dobutamine was found to increase gastric mucosal blood flow in sepsis and pHi in patients with sepsis<sup>37</sup> and septic shock.<sup>32,38</sup> Taken together, these results indicate that the relation among local perfusion, metabolism, and  $\text{P}_{\text{CO}_2}$  is complex, and conclusions regarding regional perfusion based on mucosal  $\text{P}_{\text{CO}_2}$  or other tonometry-derived variables alone may be misleading.

We previously showed that the effects of dobutamine on systemic oxygen consumption are attenuated after cardiac surgery and in healthy volunteers with simulated metabolic stress.<sup>35,39</sup> The 10% increase in systemic oxygen consumption in the current study is consistent with an attenuated thermogenic response. The interaction between endogenous catecholamines and dobutamine might lead to such an attenuation in oxygen consumption. Recently, dobutamine was shown to behave as a partial agonist at the  $\beta_2$ -adrenoceptor.<sup>40</sup> The antagonistic properties of a partial agonist become evident only at high concentrations of a full agonist. The endogenous catecholamine plasma concentration was not measured. However, we have no reason to assume that there was an exaggerated activity of the sympathetic nervous sys-

tem because heart rate, oxygen consumption, and glucose production were not elevated in our patients. Furthermore, the lack of an increase in glucose production by dobutamine was found in volunteers as well.<sup>41</sup> Taken together, these findings do not lead us to believe that high endogenous plasma catecholamine concentrations masked the actions of dobutamine. Increased hepatosplanchnic and skeletal muscle metabolic activity is supposed to contribute to the thermogenic response in healthy volunteers. We found no signs of either mechanism in the postoperative patients. It is possible that the sensitivity of our methods is not sufficient to detect small increases, especially if both the hepatosplanchnic bed and the skeletal muscle contribute. This explanation is unlikely because we used several independent methods to assess the hepatosplanchnic metabolic activity without any evidence of dobutamine-induced metabolic changes. If the increase in oxygen consumption was solely or predominantly caused by changes in the skeletal muscle, this still should have been detectable with our methodology as an increased leg oxygen consumption, as previously shown.<sup>35,42</sup>

In conclusion, we demonstrated that stable patients after coronary artery bypass surgery do not have an accelerated carbohydrate metabolism and have only a slight increase in net interorgan amino acid balance. After coronary artery bypass surgery, dobutamine increased systemic and regional blood flow and decreased systemic and regional oxygen extraction. Unexpectedly, dobutamine did not affect splanchnic glucose production or interorgan lactate or amino acid balance. This suggests that dobutamine improves splanchnic perfusion without a concomitant increase in hepatosplanchnic metabolism.

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