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The Effect of Dobutamine on Hepatic Blood Flow and Oxygen Supply–Uptake Ratio during Enflurane Nitrous Oxide Anesthesia in Humans Undergoing Liver Resection

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Liver surgery is often accompanied by hepatic hypoperfusion and hypoxia, and it is controversial whether catecholamines increase hepatic blood flow and oxygen supply. The effects of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine on hepatic circulation and oxygen balance were examined in patients anesthetized with enflurane, nitrous oxide, and oxygen for liver surgery. Dobutamine did not cause a significant increase in hepatic arterial blood flow. However, total hepatic blood flow and portal venous blood flow were increased, resulting in an increase in hepatic oxygen delivery ($H\dot{D}_{O_2}$). The increase in $H\dot{D}_{O_2}$ was not associated with an improvement of hepatic oxygen supply–uptake ratio, since hepatic oxygen uptake ($H\dot{V}_{O_2}$) also increased. After hepatectomy, the increases in portal venous blood flow and $H\dot{D}_{O_2}$ were not accompanied by an increase in $H\dot{V}_{O_2}$. The stimulation of hepatocellular oxygen metabolism by dobutamine and depressed responsiveness of adrenoceptors on hepatocytes in which metabolism was already augmented are the likely explanation for the different reactions before and after hepatectomy. (Key Words: Liver: blood flow; oxygen transport; oxygen uptake. Surgery: hepatic. Sympathetic nervous system, catecholamines: dobutamine.)

LIVER SURGERY may be accompanied by impaired hepatic perfusion and oxygen balance in the peri- and postoperative periods. Such hypoperfusion may in turn be related to postoperative liver failure.[1–4] Consequently, various pharmacologic agents have been used in an attempt to protect the liver from perioperative ischemia and/or to improve impaired metabolism after ischemia.[5] The vasoactive drugs used to increase systemic oxygen delivery do not necessarily improve the oxygenation of the splanchnic organs.[6,7] The α-adrenergic properties of norepinephrine, epinephrine, and dopamine produce marked and selective constriction of the splanchnic precapillary and postcapillary vessels and consequent reduction in arterial inflow.[6,7] Furthermore, dopamine reportedly increases hepatic oxygen uptake ($H\dot{V}_{O_2}$) in a dose-dependent fashion, such that it is doubtful whether dopamine can improve the hepatic oxygen supply–uptake relationship.[8] Dobutamine has a less potent α-adrenergic effect than dopamine and has a mild β_2 effect[9] by which the hepatic arterioles may be dilated, leading to an increase in hepatic oxygen delivery ($H\dot{D}_{O_2}$). A recent animal study showed that dobutamine increased hepatic arterial blood flow (HABF) and improved the hepatic oxygen supply–uptake relationship.[10] Therefore, this study was conducted in a series of patients undergoing hepatectomy to examine 1) whether dobutamine can increase HABF and/or portal venous blood flow (PBF) and 2) whether it can improve the hepatic oxygen supply–uptake relationship.

Materials and Methods

Anesthesia and Surgical Procedure

After obtaining institutional approval and informed consent, we studied 14 consecutive adult patients (nine men and five women) undergoing elective hepatic lobectomy for hepatocellular carcinoma. Their average age, height, and weight were 57 yr (range 72–38 yr), 160 cm (range 171–141 cm), and 54 kg (range 73–44 kg), respectively (table 1). All patients preoperatively had normal cardiac and respiratory function, serum electrolytes, and urinalysis. Liver function studies were all within normal limits. Abdominal angiography, including selective hepatic venography, was performed to evaluate the liver tumor.

Patients received 0.5 mg atropine sulfate and 50 mg hydroxyzine hydrochloride intramuscularly as premedication. Fiberoptic flow directed catheters (Opticath model P7110-EH, Oximetrix, Mountain View, CA) were inserted through the right internal jugular vein into the pulmonary artery and the hepatic vein under fluoroscopic guidance. Preoperative roentgenogram of selective hepatic venography was used to confirm proper placement of the catheter into the hepatic vein. The details of this procedure have been described elsewhere.[3,4] Both catheters were used for continuous monitoring of mixed venous and hepatic venous oxygen saturations and pulmonary arterial, central venous, and hepatic venous pressures and for intermittent measurement of pulmonary artery wedge pressure and cardiac output. Mixed venous and

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TABLE 1. Patient Population Characteristics and Operative Variables

Case Number	Age (yr)	Sex	Height (cm)	Weight (kg)	BSA (m^2)	Operation	R Weight (g)	EBL (ml)	Hx t (min)	Operating t (min)
1	61	M	157	50	1.48	RL	510	860	46	317
2	60	M	171	56	1.65	LL	480	1,683	60	255
3	54	M	166	73	1.81	SP	150	1,800	115	490
4	42	M	165	47	1.50	LL	650	3,680	128	457
5	48	M	166	57	1.63	RL	880	2,334	120	453
6	68	M	167	46	1.49	RL	650	1,800	118	510
7	57	F	155	48	1.44	LL	450	285	55	275
8	59	F	150	46	1.37	RL	580	800	110	470
9	63	M	168	49	1.54	CBS	260	3,100	80	420
10	72	F	147	54	1.46	CBS	400	2,500	160	540
11	54	F	148	44	1.34	SP	96	2,500	140	415
12	60	M	160	66	1.69	RL	3,000*	571	45	457
13	38	F	158	49	1.47	RPS	150	863	85	325
14	60	M	169	65	1.75	SP	200	960	50	300
Mean	57		160	54	1.54		420	1,695	94	403

BSA = body surface area; R weight = the weight of the resected liver mass; EBL = estimated blood loss; Hx t = hepatectomy time; Operating t = total operating time; M = male; F = female; RL = right lobectomy; LL = left lobectomy; SP = subsegmental or partial resection; CBS = central bisegmentectomy; RPS = right posterior segmentectomy; mean = the mean values.

The mean value of the weight of the resected liver mass was calculated by excluding the weight of the giant liver tumor in case 12.
* The weight including the giant liver tumor.

hepatic venous oxygen saturations were calibrated by measuring hemoglobin oxygen saturation of venous blood samples with a Co-oximeter (OSM-3, Radiometer, Copenhagen, Denmark). Systolic, diastolic, and mean arterial pressures were monitored continuously *via* an arterial catheter inserted in the radial artery.

Anesthetic induction and tracheal intubation were accomplished with 5 mg/kg thiamylal sodium and 0.1 mg/kg vecuronium bromide intravenously. Anesthesia was maintained with 67% nitrous oxide and oxygen with enflurane. Anesthetic management was supervised by the same anesthesiologist in all cases. When vessels and bile ducts in the hepatic hilus were exposed, the tip of a 4-Fr polyvinyl catheter was inserted into the portal vein through the superior mesenteric vein for measurement of portal venous pressure and for blood sampling. Hepatectomy was performed by one of two chief surgeons in our institute. The relevant factors related to hepatectomy are listed in table 1.

STUDY PROTOCOL

The first series of measurements (control-I) was performed when vessels and bile ducts in the hepatic hilus were exposed. During this period, inspiratory concentration of enflurane was adjusted to maintain a mean arterial pressure of 80–90 mmHg. Then the end-expired concentration of enflurane (1–2%), which was verified by an anesthetic gas monitor (Capnomac, Datex Inc., Tewksbury, MA), was maintained at a constant level during the first series of measurements. The ventilatory setting was also adjusted to maintain Pa_{CO_2} between 35 and 40 mmHg while expired carbon dioxide concentration was continuously monitored. Measured variables included heart rate; mean arterial, pulmonary arterial, pulmonary artery wedge, central venous, portal venous, and hepatic venous pressures; and cardiac output, HABF, and PBF. Hepatic venous pressure was measured *via* the hepatic venous catheter. Cardiac output was measured with the thermodilution method. An ultrasonic flowmeter (Transonic Systems Inc, New York, NY) was used for measurement of HABF and PBF. Blood samples were taken simultaneously through the radial arterial, hepatic venous, pulmonary arterial, and portal venous catheters for measurements of blood gas tensions, oxygen contents, and hemoglobin concentration using a blood gas analyzer and Co-oximeter (ABL III and OSM-3, Radiometer, Copenhagen, Denmark). Simultaneously, blood samples were taken through the radial arterial catheter for measurements of blood concentrations of ketone bodies and through the hepatic venous catheter for measurements of blood concentrations of pyruvate and lactate. Then an intravenous administration of dobutamine was initiated at 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Ten to twelve minutes were allowed for the stabilization of hemodynamics, and the second series of measurements (dobutamine-I) were performed in the same manner as control-I. After the completion of the second series of measurements, dobutamine administration was stopped and hepatectomy was commenced. After completion of hepatectomy, the third and the fourth series of measurements were performed using the same methods as those used for the first and the second measurements. The third series of measurements (control-II) served as control values after hepatectomy. Subsequently, a second intravenous administration of dobutamine was

initiated at 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After confirming steady-state hemodynamic parameters for 10–12 min, the fourth series of measurements (dobutamine-II) was performed.

The surgical maneuvers were interrupted entirely during the measurements. End-expired enflurane concentrations during measurement times were 1.5 ± 0.1% before hepatectomy and 1.3 ± 0.1% after hepatectomy, respectively. Lactated Ringer's solution was infused at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$, and no other vasoactive agents were administered during the study periods. Estimated blood loss was replaced by blood transfusion to maintain blood hemoglobin concentration at 9–10 $g \cdot dl^{-1}$ during hepatectomy as well as throughout the surgery.

Biochemical Assays

For the assay of ketone bodies, 5 ml blood was drawn into a heparinized syringe and mixed with 5 ml ice-cold 10% (weight/volume) perchloric acid. The suspension was centrifuged at 10,000 × g for 15 min at 0–4° C. The supernatant was adjusted to a *p*H of 6.0 with cold 69% (weight/volume) potassium carbonate and recentrifuged at 10,000 × g for 5 min at 0–4° C. The final supernatant was used to determine the ketone body concentration. Acetoacetate and β-hydroxybutyrate levels were measured spectrophotometrically by the methods of Mellanby and Williamson[11] and Williamson and Mellanby,[12] respectively. The coefficient of variation was less than 3.0% for the ketone body concentration and less than 2.8% for acetoacetate and β-hydroxybutyrate. The ratio of acetoacetate to β-hydroxybutyrate concentrations in the hepatic venous blood was represented as arterial blood ketone body ratio. For the assay of lactate and pyruvate, 2 ml blood was taken from the hepatic vein and immediately mixed with 80 μl fluoride/EDTA solution (Boehringer Mannheim Co., Germany). It was centrifuged at 10,000 × g for 5 min, and the supernatant was obtained for the enzymic reaction of lactate dehydrogenase. Lactate and pyruvate concentrations were measured spectrophotometrically by the methods of Noll[13] and Czok and Lamprecht,[14] respectively. The coefficient of variation for both values was less than 1.3%. The ratio of lactate to pyruvate concentrations in the hepatic venous plasma was denoted the lactate–pyruvate ratio.

Calculations

Systemic and hepatic circulation and oxygen supply–uptake variables were calculated by the following formulas:

$$SVR = \frac{MAP - CVP}{CI} \times 80 \ (dyn \cdot s \cdot cm^{-5} \cdot m^2)$$

$$PVR = \frac{MPAP - PAWP}{CI} \times 80 \ (dyn \cdot s \cdot cm^{-5} \cdot m^2)$$

$$HAVR = \frac{MAP - HVP}{HABF \times 0.001} \times 80 \ (dyn \cdot s \cdot cm^{-5} \cdot m^2)$$

$$PoVR = \frac{PVP - HVP}{PBF \times 0.001} \times 80 \ (dyn \cdot s \cdot cm^{-5} \cdot m^2)$$

$$S\dot{D}_{O_2} = CI \times Ca_{O_2} \times 10 \ (ml\ O_2 \cdot min^{-1} \cdot m^{-2})$$

$$S\dot{V}_{O_2} = S\dot{D}_{O_2} - CI \times Cv_{O_2} \times 10 \ (ml\ O_2 \cdot min^{-1} \cdot m^{-2})$$

$$H\dot{D}_{O_2} = HABF \times Ca_{O_2} \times 0.01 + PBF \times Cpv_{O_2} \times 0.01 \ (ml\ O_2 \cdot min^{-1} \cdot m^{-2})$$

$$H\dot{V}_{O_2} = H\dot{D}_{O_2} - (HABF + PBF) \times Chv_{O_2} \times 0.01 \ (ml\ O_2 \cdot min^{-1} \cdot m^{-2})$$

$$Prep\ \dot{D}_{O_2} = PBF \times Ca_{O_2} \times 0.01 \ (ml\ O_2 \cdot min^{-1} \cdot m^{-2})$$

$$Prep\ \dot{V}_{O_2} = Prep\ \dot{D}_{O_2} - PBF \times Cpv_{O_2} \times 0.01 \ (ml\ O_2 \cdot min^{-1} \cdot m^{-2})$$

where SVR, PVR, HAVR, and PoVR = systemic, pulmonary, hepatic arterial, and portal venous vascular resistances, respectively; $S\dot{D}_{O_2}$ and $S\dot{V}_{O_2}$ = systemic oxygen delivery and uptake, respectively; Prep $\dot{D}_{O_2}$ and Prep $\dot{V}_{O_2}$ = preportal oxygen delivery and uptake, respectively; CI = cardiac index (liters per minute per square meter); Ca_{O_2}, Cv_{O_2}, Cpv_{O_2}, and Chv_{O_2} are oxygen contents in arterial, mixed venous, portal venous, and hepatic venous blood, respectively (milliliters oxygen per deciliter).

All results were expressed as means ± SEM. Data were analyzed using repeated-measures analysis of variance. The Student-Newman-Keuls test was used to make pairwise mean comparisons. Data points with P values < 0.05 were considered statistically significant.

Results

Dobutamine infusion was associated with significant increases in mean arterial pressure, heart rate, and CI; however, no changes occurred in pulmonary arterial, pulmonary artery wedge, central venous, portal venous, and hepatic venous pressures either before or after hepatectomy (tables 2 and 3). CI increased and systemic vascular resistance decreased significantly after hepatectomy (table 2). PBF was significantly increased, whereas HABF was not changed by dobutamine either before or after hepatectomy. There were no differences in hepatic arterial vascular resistance, venous vascular resistance, and the ratio of HABF to PBF between any measurement times. The ratio of total hepatic blood flow (THBF) to CI was not changed by dobutamine, but it was significantly decreased after hepatectomy (table 3).

There were no significant changes in Pa_{O_2} or Pa_{CO_2} or in arterial, mixed venous, portal venous, and hepatic ve-

TABLE 2. Hemodynamic Variables in Systemic Circulation With or Without Dobutamine Administration

	Control-I	DOB-I	Control-II	DOB-II
HR	84 ± 3	94 ± 5*	94 ± 3	103 ± 4*†
MAP	88 ± 2	96 ± 4*	82 ± 2	93 ± 3†
MPAP	14 ± 1	15 ± 1	16 ± 1	17 ± 2
PAWP	8 ± 1	7 ± 2	8 ± 1	8 ± 1
CVP	5 ± 1	5 ± 1	5 ± 1	5 ± 1
CI	3.5 ± 0.3	4.3 ± 0.3*	4.1 ± 0.4*	4.7 ± 0.4*†
SVR	2,088 ± 208	1,814 ± 581	1,621 ± 139*	1,634 ± 154*
PVR	154 ± 18	151 ± 14	158 ± 21	168 ± 18

Means ± SEM. n = 14.

Control-I = without dobutamine before hepatectomy; DOB-I = with 3 $\mu g \cdot kg^{-1}$ min^{-1} dobutamine before hepatectomy; Control-II = without dobutamine after hepatectomy; DOB-II = 3 $\mu g \cdot kg^{-1}$ min^{-1} of dobutamine after hepatectomy; HR = heart rate in beats · min^{-1}; MAP, MPAP, PAWP, and CVP = mean arterial, mean pulmonary arterial, pulmonary artery wedge, and central venous pressures, respectively (mmHg); CI = cardiac index ($l \cdot min^{-1} \cdot m^{-2}$); SVR and PVR = systemic and pulmonary vascular resistances, respectively (dyn $s \cdot cm^{-5} \cdot m^2$).

* $P < 0.05$ *versus* Control-I.

† $P < 0.05$ *versus* Control-II.

nous oxygen contents by dobutamine infusion. However, arterial and mixed venous oxygen contents and blood hemoglobin concentration decreased significantly after hepatectomy (table 4). Dobutamine infusion was associated with significantly increased $H\dot{D}_{O_2}$ and $H\dot{V}_{O_2}$ before hepatectomy, and only $H\dot{D}_{O_2}$ increased significantly after hepatectomy. These variables were significantly lower at control-II than control-I. Hepatic oxygen extraction as measured by the ratio of $H\dot{V}_{O_2}$ to $H\dot{D}_{O_2}$ was maintained between 0.19 and 0.23 without significant differences between any measurement times. Preportal oxygen delivery was significantly increased by dobutamine, whereas preportal oxygen uptake and preportal oxygen extraction showed no significant changes. Systemic oxygen delivery and uptake increased with dobutamine both before and after hepatectomy, without changes in systemic oxygen extraction (table 5). Dobutamine infusion was not associated with significant changes in the ratios of THBF to CI, $H\dot{D}_{O_2}$ to systemic oxygen delivery, and $H\dot{V}_{O_2}$ to systemic oxygen uptake. The ratio of THBF to CI, $H\dot{D}_{O_2}$, and $H\dot{V}_{O_2}$ significantly decreased after hepatectomy. Dobutamine infusion was not associated with significant changes in blood concentrations of lactate, pyruvate, and ketone bodies. However, blood concentrations of lactate, pyruvate, and the lactate–pyruvate ratio increased significantly after hepatectomy (table 6).

Discussion

METHODOLOGY AND HEMODYNAMICS

The limitations associated with human investigation imposed a limitation to this study in that only a single dose of dobutamine could be investigated. The dose was

TABLE 3. Hemodynamic Variables in Hepatic Circulation With or Without Dobutamine Administration

	Control-I	DOB-I	Control-II	DOB-II
PVP	12 ± 1	12 ± 1	13 ± 1	13 ± 1
HVP	7 ± 1	6 ± 1	7 ± 1	7 ± 1
HABF	147 ± 21	171 ± 26	124 ± 17	146 ± 20
PBF	428 ± 32	556 ± 43*	386 ± 28	445 ± 30†
THBF	574 ± 36	753 ± 49*	511 ± 37	591 ± 42
HABF/PBF	0.39 ± 0.07	0.35 ± 0.07	0.34 ± 0.04	0.33 ± 0.04
HABF/CI	0.05 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.03 ± 0.00‡
PBF/CI	0.13 ± 0.01	0.13 ± 0.01	0.10 ± 0.01‡	0.11 ± 0.01‡
THBF/CI	0.18 ± 0.02	0.18 ± 0.01	0.14 ± 0.01‡	0.14 ± 0.02‡
HAVR	53,510 ± 6,920	53,070 ± 8,010	62,540 ± 9,550	57,270 ± 6,820
PoVR	897 ± 140	777 ± 159	920 ± 197	858 ± 209

Means ± SEM. n = 14.

Control-I = without dobutamine before hepatectomy; DOB-I = with 3 $\mu g \cdot kg^{-1}$ min^{-1} of dobutamine before hepatectomy; Control-II = without dobutamine after hepatectomy; DOB-II = 3 $\mu g \cdot kg^{-1}$ min dobutamine after hepatectomy; PVP and HVP = portal venous and hepatic venous pressures, respectively (mmHg); HABF, PBF, and THBF = hepatic arterial, portal venous, and total hepatic blood flows, respectively ($ml \cdot min^{-1} \cdot m^{-2}$); HABF/PBF = the ratio of hepatic arterial to portal venous blood flow; HABF/CI = hepatic arterial blood flow fraction in cardiac index; PBF/CI = portal venous blood flow fraction in cardiac index; THBF/CI = total hepatic blood flow fraction in cardiac index; HAVR and PoVR = hepatic arterial vascular resistance and portal venous vascular resistances, respectively (dyn $s \cdot cm^{-5} \cdot m^2$).

* $P < 0.01$ *versus* Control-I.

† $P < 0.01$ *versus* Control-II.

‡ $P < 0.05$ *versus* Control-I.

TABLE 4. Endoexpiratory Enflurane Concentration, Blood Hemoglobin Concentration, and Blood Oxygen Variables With or Without Dobutamine Administration

	Control-I	DOB-I	Control-II	DOB-II
Enflurane %	1.5 ± 0.1	1.5 ± 0.1	1.3 ± 0,1*	1.3 ± 0.1*
Hb	11.1 ± 0.5	11.4 ± 0.5	9.7 ± 0.2*	10.1 ± 0.2*
Pa_{O_2}	158 ± 7	162 ± 6	174 ± 7	178 ± 6
Pa_{CO_2}	36 ± 1	37 ± 1	36 ± 2	36 ± 2
Ca_{O_2}	15.3 ± 0.6	15.6 ± 0.6	13.5 ± 0.4*	14.0 ± 0.3*
Cv_{O_2}	12.9 ± 0.5	13.4 ± 0.6	11.6 ± 0.3*	12.0 ± 0.3
Spv_{O_2}	87.2 ± 1.9	89.4 ± 1.5	88.5 ± 1.5	89.3 ± 1.8
Cpv_{O_2}	13.2 ± 0.7	13.9 ± 0.6	11.7 ± 0.4	12.4 ± 0.4
Shv_{O_2}	72.3 ± 3.7	74.9 ± 4.8	71.0 ± 4.4	75.9 ± 5.3
Chv_{O_2}	11.3 ± 0.6	12.0 ± 0.8	9.9 ± 0.7	10.8 ± 0.7

Means ± SEM. n = 14.

Control-I = without dobutamine before hepatectomy; DOB-I = with 3 $\mu g \cdot kg^{-1}$ min^{-1} dobutamine before hepatectomy; Control-I = without dobutamine after hepatectomy; DOB-II = 3 $\mu g \cdot kg^{-1}$ min^{-1} of dobutamine after hepatectomy; Enflurane %, end-expired enflurane concentration (%); Hb = arterial blood hemoglobin concentration ($g \cdot dl^{-1}$); Pa_{O_2} and Pa_{CO_2} = arterial oxygen and carbon dioxide pressures, respectively (mmHg); Ca_{O_2}, Cv_{O_2}, Cpv_{O_2}, and Chv_{O_2} = arterial, mixed venous, portal venous, and hepatic venous oxygen contents, respectively ($ml \cdot dl^{-1}$); Spv_{O_2} and Shv_{O_2} = portal and hepatic venous oxygen saturations, respectively (%).

* $P < 0.05$ *versus* Control-I.

limited to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, because even such a small dose was conceivably sufficient to affect hepatic and systemic circulation without causing excessive hypertension and tachycardia.[9] The measurement times of dobutamine-I and dobutamine-II were predetermined to permit a maximal effect of intravenous dobutamine, since the mean plasma half-life of dobutamine is 2 min.[9] In addition, dobutamine is metabolized or eliminated within 10–12 min after cessation of its administration.[9,15] Therefore, we assumed no residual effect of dobutamine at control-II because more than 40 min always was required for hepatectomy to be accomplished.

Lower than normal values of PBF and THBF[16] at control-I could be explained in part by the presence of enflurane anesthesia. A recent animal study demonstrated that enflurane causes a dose-dependent decrease in PBF and THBF.[17] The increase in PBF by dobutamine in this study might be a passive response to the increased CI when the unchanged ratio of PBF to CI from control-I to dobutamine-I and control-II to dobutamine-II, respectively, was taken into consideration. This phenomenon agrees with the concept that portal vascular bed lacks an intrinsic pressure–flow autoregulatory mechanism.[18] The result of constant portal venous pressure also might support the concept that portal venous pressure instead of PBF is a principally regulated variable in portal vasculature.[18,19] These results suggest that dobutamine could ameliorate the decrease in PBF that may have been caused by enflurane. An unexpectedly small increase in HABF and the absence of change in hepatic arterial vascular resistance imply that dobutamine could not dilate hepatic arterioles enough through its β_2-receptor agonistic effect. There may be some hepatic arterial vasoconstricting effect through a hepatic arterial buffer response[20,21] and/or a pressure–flow autoregulatory mechanism[19] to counteract the β_2-receptor agonistic effect of dobutamine.

The increased THBF by dobutamine should be linked to an increase in $H\dot{D}_{O_2}$. However, the increase in $H\dot{D}_{O_2}$ was relatively small because of the significant increase in PBF rather than in HABF. The increase in $H\dot{D}_{O_2}$ was accompanied by an increase in $H\dot{V}_{O_2}$ before hepatectomy,

TABLE 5. Oxygen Delivery and Uptake Variables in Systemic and Hepatic Circulations With or Without Dobutamine Administration

	Control-I	DOB-I	Control-II	DOB-II
$S\dot{D}_{O_2}$	533.6 ± 46.5	667.2 ± 52.1*	549.8 ± 41.4	662.8 ± 61.1†‡
$S\dot{V}_{O_2}$	78.5 ± 5.4	90.9 ± 6.5†	74.1 ± 6.2	87.5 ± 7.1‡
$S\dot{V}_{O_2}/S\dot{D}_{O_2}$	0.15 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.14 ± 0.01
$H\dot{D}_{O_2}$	78.0 ± 5.1	104.4 ± 7.8*	62.5 ± 5.4†	78.1 ± 6.3‡
$H\dot{V}_{O_2}$	16.4 ± 3.4	21.8 ± 3.5†	13.0 ± 2.2†	13.4 ± 2.5†
$H\dot{V}_{O_2}/H\dot{D}_{O_2}$	0.21 ± 0.04	0.23 ± 0.06	0.23 ± 0.05	0.19 ± 0.04
$H\dot{V}_{O_2}/S\dot{V}_{O_2}$	0.19 ± 0.04	0.20 ± 0.05	0.16 ± 0.02	0.14 ± 0.02
$H\dot{D}_{O_2}/S\dot{D}_{O_2}$	0.16 ± 0.02	0.16 ± 0.01	0.12 ± 0.01†	0.12 ± 0.01†
Prep $\dot{D}_{O_2}$	65.0 ± 5.2	87.8 ± 8.4*	52.7 ± 4.3	62.6 ± 4.9
Prep $\dot{V}_{O_2}$	9.2 ± 1.5	9.2 ± 1.4	7.3 ± 1.2	6.9 ± 0.9
Prep $\dot{V}_{O_2}$/Prep $\dot{D}_{O_2}$	0.12 ± 0.02	0.11 ± 0.02	0.14 ± 0.02	0.12 ± 0.02

Means ± SEM. n = 14.

Control-I = without dobutamine before hepatectomy; DOB-I = with 3 $\mu g \cdot kg^{-1}$ min^{-1} dobutamine before hepatectomy; Control-II = without dobutamine after hepatectomy; DOB-II = 3 $\mu g \cdot kg^{-1}$ min^{-1} of dobutamine after hepatectomy; SD_{O_2} and SV_{O_2} = systemic oxygen delivery and uptake, respectively (ml $O_2 \cdot min^{-1} \cdot m^{-2}$); $S\dot{V}_{O_2}/S\dot{D}_{O_2}$ = systemic oxygen extraction; $H\dot{D}_{O_2}$ and $H\dot{V}_{O_2}$ = hepatic oxygen delivery and uptake, respectively, (ml O_2 $min^{-1} \cdot m^{-2}$); $H\dot{V}_{O_2}/H\dot{D}_{O_2}$ = hepatic oxygen extraction; $H\dot{V}_{O_2}/S\dot{V}_{O_2}$ = the ratio of hepatic to systemic oxygen uptake; $H\dot{D}_{O_2}/S\dot{D}_{O_2}$ = the ratio of hepatic to systemic oxygen delivery; Prep $\dot{D}_{O_2}$ and Prep $\dot{V}_{O_2}$ = preportal oxygen delivery and uptake, respectively (ml $O_2 \cdot min^{-1} \cdot m^{-2}$); Prep $\dot{V}_{O_2}$/Prep $\dot{D}_{O_2}$ = preportal oxygen extraction.

* $P < 0.01$ *versus* Control-I.

† $P < 0.05$ *versus* Control-I.

‡ $P < 0.05$ *versus* Control-II.

TABLE 6. Blood Lactate, Pyruvate, and Ketone Body Concentrations With or Without Dobutamine

	Control-I	DOB-I	Control-II	DOB-II
L	18.3 ± 3.0	17.8 ± 2.5	36.5 ± 8.7*	38.1 ± 3.1†
P	1.9 ± 0.4	1.8 ± 0.4	2.7 ± 0.4†	2.5 ± 0.3†
L/P	11.2 ± 1.2	12.0 ± 1.6	15.0 ± 1.2*	17.6 ± 2.8†
TK	74.2 ± 9.9	82.4 ± 12.1	61.4 ± 6.0	58.0 ± 5.2
AA	32.8 ± 5.8	35.8 ± 6.7	31.4 ± 4.8	36.1 ± 5.3
β-HBA	41.3 ± 5.6	46.8 ± 7.6	30.0 ± 4.2	31.1 ± 7.5
AKBR	0.92 ± 0.17	1.10 ± 0.31	1.51 ± 0.43	1.75 ± 0.39

Means ± SEM. n = 14.

Control-I = without dobutamine before hepatectomy; DOB-I = with $3\ \mu g \cdot kg^{-1} min^{-1}$ dobutamine before hepatectomy; Control-II = without dobutamine after hepatectomy; DOB-II = $3\ \mu g \cdot kg^{-1} min^{-1}$ dobutamine after hepatectomy; L = hepatic venous blood concentration of lactate (mg/dl); P = hepatic venous blood concentration of pyruvate (mg/dl); L/P = lactate–pyruvate ratio; TK = arterial blood concentration of total ketone bodies (μM); AA = arterial blood concentration of acetoacetate (μM); β-HBA = arterial blood concentration of β-hydroxybutyrate (μM); AKBR = arterial blood ketone body ratio.

* $P < 0.01$ *versus* Control-I.

† $P < 0.05$ *versus* Control-I.

but not after hepatectomy. This point was so characteristic in this study that it is worthy of detailed discussion.

Hepatic Oxygen Supply and Uptake before Hepatectomy

Concomitant increases in $H\dot{D}_{O_2}$ and $H\dot{V}_{O_2}$ before hepatectomy may represent at least two different possibilities. The first is that $H\dot{D}_{O_2}$ was less than the critical oxygen delivery and resulted in $H\dot{V}_{O_2}$ being $H\dot{D}_{O_2}$-dependent, suggesting a preexisting hepatic hypoxic state[22,23] in control-I. Unchanged hepatic oxygen extraction from control-I to dobutamine-I seems to support this possibility, because hepatic oxygen extraction should decrease if $H\dot{V}_{O_2}$ was independent of $H\dot{D}_{O_2}$. However, this possibility would necessitate an underlying oxygen deficit in the liver as indicated by an increased blood lactate concentration.[24] The lactate and pyruvate concentrations and the lactate–pyruvate ratio[25] were actually slightly higher, and the arterial blood ketone body ratio lower than normal.[26] However, these values are not sufficient to indicate hepatic hypoxia at control-I. Therefore, we could speculate on a second possibility, related to the fact that exogenous catecholamines can directly stimulate intracellular oxidative metabolism, thereby increasing tissue oxygen demand.[7,8,27,28] Although the exact mechanism is unknown, there is presumably an increase in oxygen metabolism, mediated by the activation of the cyclic adenosine monophosphate, alteration of active transport process at the membrane, and/or uncoupling oxidative phosphorylation at the mitochondria.[7] These could occur regardless of alterations in oxygen delivery. Furthermore, a larger dose of dobutamine would have caused a disproportionate increase in $H\dot{V}_{O_2}$, as reported in an animal study.[8] In this context, the second possibility is more likely to explain the increase $H\dot{V}_{O_2}$ by dobutamine before hepatectomy.

Hepatic Oxygen Supply and Uptake after Hepatectomy

Why was $H\dot{V}_{O_2}$ not increased by dobutamine after hepatectomy? First, we presumed that $H\dot{V}_{O_2}$ had already become independent of $H\dot{D}_{O_2}$ at control-II. The mean weight of the resected liver mass in our cases was 420 g, which was approximately 40% of the total liver weight. Accordingly, if $H\dot{V}_{O_2}$ at control-II was estimated from that value, it would approximate 10 $ml \cdot min^{-1} \cdot m^{-2}$, or 60% of the control-I value, which was 16.4 $ml \cdot min^{-1} \cdot m^{-2}$. However, the mean value of $H\dot{V}_{O_2}$ was actually increased to 13.0 $ml \cdot min^{-1} \cdot m^{-2}$ immediately after hepatectomy. A similar phenomenon was observed in an animal study.[10] Hepatocellular injury by hepatectomy could be followed by augmented intracellular oxygen metabolism, whether it is aerobic or anaerobic, associated with an acute inflammatory response triggering the abrupt release of interleukin-1 from Kupffer cells and the overwhelming production of acute-phase proteins in hepatocytes.[29,30] Thus, $H\dot{V}_{O_2}$ might already have increased enough to be independent of $H\dot{D}_{O_2}$ in the individual hepatocytes and could not be increased by dobutamine even when $H\dot{D}_{O_2}$ increased at dobutamine-II.[31] On the other hand, the pyruvate and lactate concentrations and the lactate–pyruvate ratio at control-II were abnormally large. These could reflect hepatic hypoxia, which might have given a response of oxygen uptake depending on oxygen supply.[24] However, there may have been an impairment of hepatocellular oxygen extraction,[23] causing unchanged $H\dot{V}_{O_2}$ despite an increased $H\dot{D}_{O_2}$ by dobutamine at dobutamine-II. Hepatocellular necrosis with cellular membranous disintegration caused by hepatectomy[32] should be associated with depressed responsiveness of adrenoceptors[33,34] on the hepatocytes. In addition, there may be less responsiveness of portal vascular beds to dobutamine. As a result, the increases in PBF and $H\dot{D}_{O_2}$ were too small to cause a significant increase in $H\dot{V}_{O_2}$ at dobutamine-II. Consequently, unchanged $H\dot{V}_{O_2}$ was presumably associated with depressed responsiveness of adrenoceptors on hepatocytes, where oxygen metabolism was already augmented after hepatectomy.

Intravenous administration of dobutamine at 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was associated with increases in PBF and $H\dot{D}_{O_2}$ before and after hepatectomy during enflurane, nitrous oxide, and oxygen anesthesia. $H\dot{V}_{O_2}$ was increased before hepatectomy, whereas it was unchanged after hepatectomy. The stimulation of hepatocellular oxygen me-

tabolism by dobutamine and the depressed responsiveness of adrenoceptors on hepatocytes with already augmented metabolism are likely explanations for the different reactions before and after hepatectomy.

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