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Dopamine, dopexamine and dobutamine in liver transplant recipients: a comparison of their effects on hemodynamics, oxygen transport and hepatic venous oxygen saturation

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Abstract The purpose of this study was to determine the effects of vasoactive treatment with dopamine (DO), dopexamine (DX), and dobutamine (DOB) on hemodynamics, oxygen transport and hepatic venous oxygen saturation ($SvhO_2$) after orthotopic liver transplantation (OLT). A pulmonary artery catheter was inserted into the right hepatic vein of 17 OLT patients. Timed infusion of DO, DX, and DOB was performed at the following rates: DO at 4 and 8 μg/kg per minute, DX at 4 and 8 μg/kg per minute, and DOB at 5 and 10 μg/kg per minute. Hemodynamics, oxygen transport variables, and $SvhO_2$ were assessed. Each catecholamine induced a significant increase in cardiac index, oxygen delivery, and $SvhO_2$. Mean arterial pressure was increased during DO and DOB, but significantly reduced during DX. Each inotrope increased oxygen delivery in parallel with $SvhO_2$, suggesting a corresponding increase in hepatic oxygen supply. Therefore, it appears that each vasoactive drug may be utilized in OLT patients to provide oxygen delivery without impairment of splanchnic oxygenation.

Key words Liver transplantation · Catecholamines · Hepatic venous oxygenation

Introduction

Postoperative management of patients receiving an orthotopic liver transplant (OLT) remains difficult because of the complex interaction between different causes of early graft dysfunction, such as ischemic damage, acute rejection, drug toxicity and infection [6]. Moreover, interventions of postoperative critical care including therapy with vasoactive drugs, may impair liver graft function. Thus, it is important to monitor regional blood flow response to vasoactive treatment in the postoperative course after OLT [10].

Monitoring hepatic venous oxygen saturation ($SvhO_2$) provides on-line information about the hepatic-splanchnic oxygen supply-demand ratio [11]. Alterations in $SvhO_2$ levels indicate that at least one of the constituents of the hepatic-splanchnic oxygen delivery system has been altered. Therefore, estimation of $SvhO_2$ as an index of splanchnic oxygenation appears to be of clinical relevance in the transplanted liver.

In the early postoperative course following OLT, maintenance of an adequate oxygen delivery to the liver graft is crucial, and the administration of low-dose dopamine has been recommended in order to increase hepatic perfusion [7]. We hypothesized that increasing systemic oxygen delivery in liver transplant recipients might improve splanchnic oxygenation. Using the previously established method of hepatic venous catheterization in liver transplant recipients [13], we tested this hypothesis by administering dopamine (DO) and dopexamine (DX), inotropes with dopaminergic properties, and dobutamine (DOB), a potent β_1-agonist, and determining their effects on hemodynamics, oxygen transport, mixed venous oxygen saturation (SvO_2), and $SvhO_2$ in patients following OLT.

Materials and methods

In accordance with the ethical standards laid down in the Helsinki Declaration, and after approval of the Institutional Review Board, informed consent was obtained from each patient who participated in this study. We studied 17 consecutive patients (12 male, 5 female), aged 31–63 years, within 8 h of receiving an OLT.

Liver transplantation

In all cases, the operation was performed following standard techniques. The grafts were preserved with University of Wisconsin (UW) solution, intraoperative bypass was used in all cases, and all vascular anastomoses were completed before reperfusion of the graft. Ischemia times ranged from 4 to 20 h, with a median of 12 h. Biliary anastomosis was performed as side-to-side choledochocholedochostomy with a T tube in all patients.

Postoperative procedure

Postoperatively, following routine procedures of our institution, patients were sedated with methohexital and fentanyl and were submitted to volume-controlled mechanical ventilation (Puritan Benett 7200, Carlsbad, CA, USA). Fraction of inspiratory oxygen (FIO_2) was 0.3–0.5 to obtain a arterial oxygen tension (PaO_2) of 80–100 torr (10.6–13.3 kPa), respiratory rate was 12–18/min, and minute volume 7.0–12.2 l/min in order to achieve a arterial carbon dioxide tension ($PaCO_2$) of 35–40 torr (4.6–5.3 kPa). Arterial pH was 7.45 ± 0.06 and hemoglobin remained constant at 10.2 ± 0.9 g/dl throughout the study. In all patients, mechanical ventilation was performed using positive end-expiratory pressure (PEEP) of 5 cm H_2O.

Routine clinical monitoring of our patients included thermodilution via a pulmonary artery catheter (7.5 Fr, Baxter, Irvine, CA, USA) and an arterial line. Another fiber optic pulmonary artery catheter (7.5 Fr, Baxter) was inserted over an 8.5 Fr sheath (Baxter) *via* the right internal jugular vein into the right hepatic vein using fluoroscopic guidance. Correct placement of the intravascular devices was checked by appropriate pressure traces and confirmed by chest roentgenography. The hepatic venous catheter was kept in place for postoperative $SvhO_2$-monitoring and removed after 72 h. Any complications associated with the device were recorded. Electrocardiographic readings were recorded continuously during the study in all patients.

Measurements

Central venous pressure (CVP), mean arterial pressure (MAP), mean pulmonary artery pressure (PAP), and pulmonary artery wedge pressure (PCWP) were assessed using a disposable transducer (Baxter) and a monitoring system (Hewlett-Packard, Böblingen, Germany). Measurements were taken in the supine position with a zero reference level at the midaxilla, vascular pressures were the average taken at end-expiration from three successive respiratory cycles. Cardiac output (CO) was determined following standard thermodilution techniques (Baxter) and expressed as the mean of four measurements using injections of saline (10 ml at 1–5 °C) arbitrarily performed during different phases of the respiratory cycle. Blood-gas analyses were performed using standard blood-gas electrodes (ABL 520, Radiometer, Copenhagen, Denmark), and spectrophotometry (OSM 3 Hemoximeter, Radiometer) was done to obtain total hemoglobin concentration, SvO_2, and $SvhO_2$.

The following calculations were made. Body surface area (BSA) was calculated from measurements of height and weight by standard nomograms. Cardiac index was calculated as cardiac output ÷ BSA. Arterial and mixed venous oxygen content (ml/dl) were calculated as: (Hb × 1.34 × % O_2-Saturation) + (PO_2 × 0.0031), where Hb denotes hemoglobin. Arteriovenous oxygen content difference ($AvDO_2$) was calculated as arterial oxygen content – mixed venous oxygen content. Arterial oxygen delivery index (DO_2), expressed in ml/min per m^2, was equivalent to cardiac index × arterial oxygen content × 10 and oxygen uptake index (VO_2), expressed in ml/min per m^2, was equivalent to cardiac index × (arterial oxygen content – mixed venous oxygen content) × 10.

Study protocol

Eight hours postoperatively, after hemodynamics arterial blood gases and temperature had become stable, baseline values of hemodynamics, DO_2, VO_2, and $SvhO_2$ were obtained. Dopamine (DO), dopexamine (DX), and dobutamine (DOB) were infused at the following rates: DO at 4 and 8 μg/kg per minute, DX at 4 and 8 μg/kg per minute, and DOB at 5 and 10 μg/kg per minute. Each step in each sequence lasted 35 min, and each step was followed by baseline therapy for 35 min. Measurements were performed at the end of each period, when hemodynamic function was stable. To exclude the effects of sequential administration of catecholamines, the sequence of administration was randomized.

Statistical analysis

Results are expressed as mean ± SD, treatment effects are reported as mean value during baseline and the values during the infusion of catecholamines. Statistical analysis was performed using Friedman's two-way ANOVA. Differences within the treatment groups were analyzed using a Kruskal-Wallis one-way ANOVA. Stepwise multiple regression analysis was performed. All tests of significance were two-tailed. *P* values are given as the calculated values, and *P* values of 0.05 or less were considered to be significant.

Results

The demographic information about the 17 patients were studied and their baseline values of CI, SvO_2 and $SvhO_2$ are summarized in Table 1. At a mean follow-up time of 399 days, 15 out of 17 patients were alive with their liver graft. During the baseline condition, $SvhO_2$ values showed a considerable interindividual variability (58 %–87 %, median 75 %). Individual values of $SvhO_2$ during baseline and during vasoactive treatment are given in Fig. 1.

MAP was significantly increased by DO and DOB but decreased by DX at both dosages. PCWP was significantly increased by DO as well as by DX, whereas DOB had no effect.

Heart rate was significantly increased by DX and DOB. Within the treatment groups, values for heart rate during DX at 8 μg/kg per minute were higher than those for DO and DOB at the higher dosage ($P < 0.05$).

Table 1 Patient characteristics ($n = 17$) and baseline values of cardiac index (CI), mixed venous oxygen saturation (SvO_2), and hepatic venous oxygen saturation ($SvhO_2$). (*autoimmune hep* autoimmune hepatitis, *HCV* hepatitis C cirrhosis, *HCC/HCV* hepatocellular carcinoma in HCV, *alc-tox* alcoholic cirrhosis, *HBV* hepatitis B cirrhosis, *PBC* primary biliary cirrhosis)

Patient number	Sex	Age (years)	Diagnosis	CI (L/min per m^2)	SvO_2 (%)	$SvhO_2$ (%)	Outcome
1	m	31	autoimmune hep	3.9	74	72	survived
2	m	56	HCV	4.1	83	67	survived
3	m	63	HCC/HCV	4.4	74	78	survived
4	m	32	autoimmune hep	6.1	85	68	survived
5	m	44	HBV	4.4	76	71	died
6	f	51	alc-tox	6.7	88	84	survived
7	m	41	HCC/HCV	4.9	82	75	survived
8	m	49	HBV	5.9	76	58	survived
9	m	40	HCV	5.8	82	78	died
10	m	39	alc-tox	6.4	83	87	survived
11	f	60	PBC	5.4	85	76	survived
12	m	42	HCV	4.9	79	72	survived
13	f	56	PBC	4.6	84	79	survived
14	m	54	PBC	5.6	83	70	survived
15	m	56	HCV	7.7	83	82	survived
16	m	50	alc-tox	5.8	83	73	survived
17	f	41	alc-tox	3.6	81	80	survived

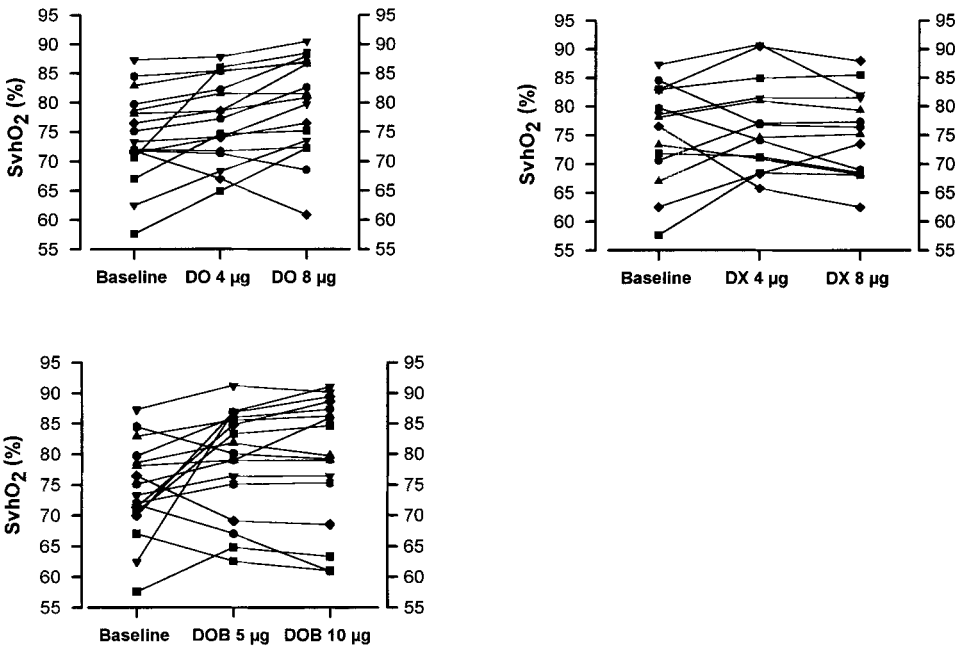

Fig. 1 Individual values of hepatic venous oxygen saturation ($SvhO_2$) during baseline and during the different dosages of dopamine (*DO*), dopexamine (*DX*), and dobutamine (*DOB*) infusion

Each catecholamine produced a significant increase in CI at both dosage. Comparing treatment groups, DX at 8 µg/kg per minute had the strongest effect on CI ($P < 0.05$; Table 2).

Both DO_2 and VO_2 were increased by each inotrope ($P < 0.05$). The higher dosage of DO and DX induced a further increase in oxygen delivery compared to infusion at 4 µg/kg per minute ($P < 0.05$). $SvhO_2$ values were increased during infusion with each catecholamine. The mean difference between SvO_2 and $SvhO_2$ was 7 % ± 7 % at baseline and did not change significantly during treatment. $AvDO_2$ was significantly decreased by all of the drugs. Comparing the effects of each inotrope on $AvDO_2$, DX had the most powerful effect ($P < 0.01$; Table 3).

Figure 2 gives boxplots (10th , 50th, and 90th percentiles) of $SvhO_2$ during baseline and during vasoactive treatment. Figure 3 depicts the percentage change of DO_2 and the corresponding change in $SvhO_2$ during all study conditions.

Table 2 Hemodynamics during baseline and during vasoactive treatment. Values represent mean ± SD (*HR* heart rate, *CI* cardiac index, *CVP* central venous pressure, *MAP* mean arterial pressure, *PAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure)

	Variable [mean ± SD]					
	HR (min^{1})	CI (L/min per m^2)	CVP (mm Hg)	MAP (mm Hg)	PAP (mm Hg)	PCWP (mm Hg)
Baseline	100 ± 13	5.3 ± 1	9 ± 3	78 ± 9	21 ± 3	11 ± 3
Dopamine						
4 μg/kg per min	103 ± 22	6.2 ± 1.6*	10 ± 4	88 ± 13*	24 ± 5*	13 ± 5*
8 μg/kg per min	103 ± 22	6.6 ± 1.7*	11 ± 4	99 ± 13*, **	26 ± 6*	15 ± 7*
Dopexamine						
4 μg/kg per min	118 ± 7*	7.6 ± 1*	9 ± 3	68 ± 12*	22 ± 4	13 ± 3*
8 μg/kg per min	128 ± 7*, **	8.4 ± 1*, **	8 ± 3*	65 ± 13*	22 ± 4	14 ± 4*
Dobutamine						
5 μg/kg per min	108 ± 18*	6.6 ± 1.3*	9 ± 4	83 ± 11*	21 ± 5	12 ± 4
10 μg/kg per min	115 ± 22*, **	7.0 ± 1.6*,**	9 ± 4	88 ± 17*	22 ± 5	12 ± 6

* $P < 0.05$ compared to baseline
** $P < 0.05$ compared to the lower dosage of the catecholamine

Table 3 Oxygenation variables during baseline and during vasoactive treatment (SvO_2 mixed venous oxygen saturation, $SvhO_2$ hepatic venous oxygen saturation, SvO_2-$SvhO_2$ difference between mixed venous oxygen saturation and hepatic venous oxygen saturation, $AvDO_2$ arterial venous oxygen content difference, DO_2 systemic oxygen delivery index, VO_2 oxygen uptake inded)

	Variable (mean ± SD)					
	SvO_2 (%)	$SvhO_2$ (%)	[SvO_2–$SvhO_2$ (%)]	$AvDO_2$ (ml)	DO_2 (ml/min per m^2)	VO_2 (ml/min per m^2)
Baseline	81 ± 4	74 ± 8	7 ± 7	2.8 ± 0.6	789 ± 139	146 ± 22
Dopamine						
4 μg/kg per min	83 ± 4*	77 ± 7*	5 ± 5	2.6 ± 0.6*	947 ± 241	157 ± 25*
8 μg/kg per min	84 ± 4*	80 ± 7	3 ± 5	2.5 ± 0.6*	1037 ± 273*, **	159 ± 25*
Dopexamine						
4 μg/kg per min	86 ± 2*	78 ± 9*	8 ± 7	2.0 ± 0.3*	1149 ± 162*	153 ± 22*
8 μg/kg per min	86 ± 2*	76 ± 8*	10 ± 7	2.0 ± 0.3*	1246 ± 213*, **	164 ± 26*
Dobutamine						
5 μg/kg per min	84 ± 4*	79 ± 9*	5 ± 7	2.4 ± 0.6*	989 ± 202*	155 ± 31*
10 μg/kg per min	84 ± 4*	79 ± 10*	5 ± 8	2.4 ± 0.6*	1063 ± 238*	162 ± 28*

* $P < 0.05$ compared to baseline
** $P < 0.05$ compared to the lower dosage of the catecholamine

Stepwise multiple regression analysis of the relationship between $SvhO_2$ and the components of the systemic oxygen transport showed measurement of CI ($r = 0.76$, $P < 0.05$) and SvO_2 ($r = 0.52$, $P < 0.05$) as the most important determinants of $SvhO_2$ during catecholamine infusion.

Discussion

The significance of oxygen transport as a major function of the circulatory system and as a predictor of outcome in various disease states has been emphasized previously [4, 24]. The maintenance of a DO_2 of more than 600 ml/min per m^2 has been suggested for critically ill patients, but appropriate values for oxygen delivery are difficult to define after OLT. There is clinical evidence, however, that hemodynamic function and, thus, DO_2 are impaired immediately after OLT [26] and that therapy with catecholamines might be inevitable in order to maintain oxygen delivery. Yet, the potential hazard of vasoactive treatment in the liver transplant recipient is an impairment of the hepatic-splanchnic oxygen supply-demand ratio. Clinical data presented by Ruokonen and colleagues [22] demonstrated significant alterations in $SvhO_2$ during vasoactive treatment with DO, norepinehrine, and DOB in critically ill patients.

Continuous monitoring of $SvhO_2$ supplies real time information about the hepatic oxygen supply-demand ratio [11]. It could, therefore, provide an early warning prior to attainment of flow limiting oxygen transport states and ranges of hepatic venous desoxygenation associated with anaerobic metabolism in the transplanted liver. Under normal conditions, oxygen uptake in the

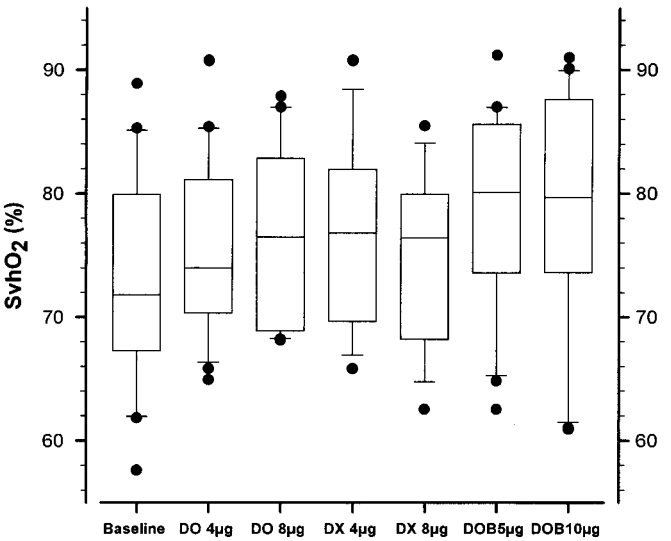

Fig. 2 Boxplot (10th, 50th, and 90th percentiles) of values of hepatic venous oxygen saturation ($SvhO_2$) during baseline and during the different dosages of dopamine (DO), dopexamine (DX), and dobutamine (DOB) infusion

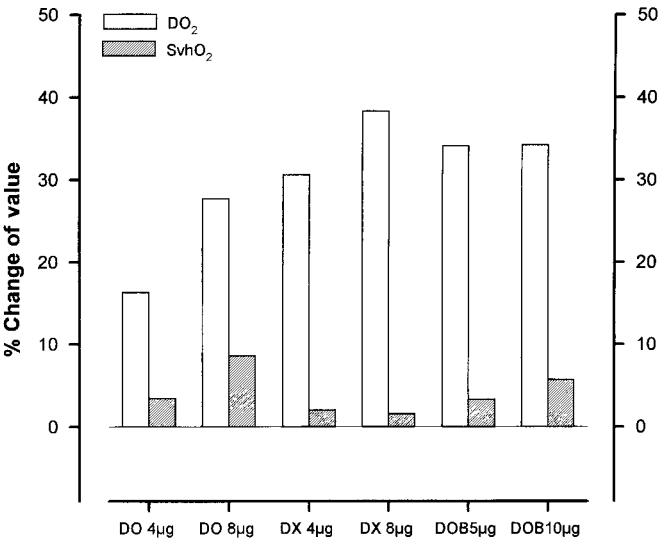

Fig. 3 Median percentage change in oxygen delivery index (DO_2) and the corresponding change in hepatic venous oxygen saturation ($SvhO_2$) during the different infusion rates of dopamine (DO), dopexamine (DX), and dobutamine (DOB)

tissues remains relatively stable when delivery is altered, due to adjustments in oxygen extraction for changes in oxygen delivery. However, if oxygen supply decreases below a critical value, oxygen uptake will decrease as well. In patients undergoing hepatic lobectomy, the incidence of postoperative liver failure was significantly correlated to the length of hepatic venous desoxygenation during the surgical procedure [12].

Nevertheless, there are, as yet, no data available relating the value of hepatic venous oxygen saturation with the functional state of the liver parenchyma in the patient receiving an OLT.

The purpose of this study was to determine the impact of increasing systemic oxygen delivery on regional (splanchnic) oxygen saturation by three different regimens of vasoactive treatment in human liver transplantation. The hemodynamic effects of dopamine (DO) are mediated by β_1- and α-adrenoceptors, as well as by the release of norepinephrine. In the dose range used in this study (4 and 8 µg/kg per minute), DO acts as a combined positive inotrope and vasopressor. DO has a rather unique capacity to stimulate postsynaptic DA_1-, and presynaptic DA_2-dopaminergic receptors and thereby augments renal blood flow. Furthermore, it has been shown that DO was effective in the treatment of impaired renal function in patients undergoing OLT [21]. Nevertheless, its α-adrenergic agonism and norepinephrine release may offset any dopaminergic-stimulated vasodilatation in the hepatic-splanchnic vasculature [14]. However, our data demonstrate that DO at both dosages, increased systemic oxygen delivery as well as $SvhO_2$, suggesting no impairment in splanchnic oxygen delivery. DO may behave as a vasoconstrictor even at doses well below 10 µg/kg per minute [8], perhaps due to impaired drug clearance in the critically ill patient [5]. In our series, the vasopressor properties of DO at 8 µg/kg per minute produced a significant increase in MAP.

Dopexamine hydrochloride (DX), a chemical analogue of DO with β_2 and DA_1/DA_2 properties, had been developed as a peripherally acting DO receptor agonist with afterload-reducing effects [25]. It is one-third as potent as DO in stimulating DA_1 receptors but 60 times as potent as β_2-adrenoceptor agonists. Compared with DO, DX is a weak β_1-agonist and does not induce α_1 adrenoceptor-stimulated vasoconstriction. Furthermore, mild positive inotropic effects may arise from β_2 adrenoceptor activity and norepinephrine uptake-1 blockade [25]. DX has a reported half-life of 7 min in adult humans [19]. Its pharmacokinetics during the anhepatic phase of OLT are fundamentally changed, due to loss of the metabolic function of the liver. After reperfusion of the graft, DX plasma levels were found to have rapidly dropped back down to preanhepatic levels [9].

In patients following OLT, DX has recently been reported to be as effective as DO in the prevention of postoperative renal dysfunction [8]. Lokhandwala et al. [15] demonstrated in a canine model of hemorrhagic shock that DX at 4 µg/kg per minute restored mesenteric blood flow to control levels after reinfusion of the animals. These beneficial effects of DX on hepatic-splanchnic hemodynamics were due to its ability to activate DA_1 as well as β_2-adrenoceptors located on the vasculature.

In a mongrel dog model, Biro and coworkers [2] reported that DX maintained hepatic arterial blood flow at 1.3 μg/kg per minute but impaired hepatic arterial flow at higher doses. However, due to the limitations of the radionuclide-labeled microsphere method used in this study, the effects of DX on portal venous blood flow remain unclear. Leier [14] described a reduction in hepatic-splanchnic vascular resistance and, thereby, augmentation of flow to this region at 0.91 μg/kg per minute of DX in patients with congestive heart failure. The increase in hepatic-splanchnic blood flow was proportional to the increase in cardiac output. At 2.27 μg/kg per minute, the DX-induced increase in hepatic-splanchnic blood flow was reduced by absolute measurement and was less in relation to the increase in cardiac output than at the lower dosage.

In our series of patients following OLT, a rather high dosage of DX induced significant systemic vasodilatation and augmented oxygen delivery and $SvhO_2$, suggesting an unimpaired splanchnic oxygenation. However, at the higher dosage, DX induced no further augmentation of $SvhO_2$. This observation does not rule out an attenuation of hepatic arterial blood flow in response to a reduction in vascular resistance. In a clinical study of ten patients undergoing OLT, Payen and colleagues [20] reported that the reciprocity of hepatic blood flow is not fully preserved during hepatic artery clamping in the denervated liver graft and that the reduction in hepatic arterial blood flow is not appropriately compensated by an increase in portal blood flow.

The significant increase in heart rate during infusion with DX at 8 μg/kg per minute that was observed in our study might partly have been due to β_1-mediated cardiac stimulation at this rather high dosage. Moreover, studies in anesthetized dogs using ganglion blockade demonstrated that cardiac stimulation produced by DX was diminished, indicating that it was partly by way of the baroreceptor reflex, i.e., secondary to vasodilatation [25].

Generalized arterial vasodilatation produced by DX might potentially limit the clinical usefulness of the drug, particularly in hypovolemic patients after major surgery [23]. In our series, vasopressor therapy, in addition to DX infusion, was not required, since adequate intravascular volume had been ascertained before the study was performed (Table 2).

Dobutamine (DOB) alters hemodynamics by a marked β_1-receptor agonism and weak β_2 and α-adrenergic effects. These actions appear as the cumulative effects of the two enantiomers (optical isomers) of a racemic mixture: the (−) isomer is a selective and potent α-agonist, while the (+) isomer is a potent β_1- and β_2-receptor agonist and a competitive α-blocking agent [16]. The overall action on the vasculature results from the sum of vasoconstrictive α and vasodilatory β_2-effects, but generally β_2 action predominates slightly over the α effects, producing some direct vasodilatation with DOB. In our 17 patients following OLT, MAP was significantly increased during infusion of DOB, even at the higher dosage, indicating appropriate intravascular filling.

In the study by Biro and co-workers [2] that was mentioned earlier, hepatic artery flow was well preserved during DOB infusion. At doses of 34 μ/kg per minute, arterial blood flow was almost doubled. In our series, DOB infusion at both dosages increased oxygen delivery in parallel with $SvhO_2$, thus implying an unimpaired splanchnic-hepatic oxygen supply.

In conclusion, we found that the effects of DO, DX and DOB on cardiac index and systemic oxygen delivery were very much alike in the 17 OLT patients studied. However, DX, at a rather high dosage, produced tachycardia and a marked systemic vasodilatation that could possibly limit its clinical usefulness in the liver transplant recipient.

Infusion of each inotrope increased oxygen uptake in our series. Given the problem of mathematical coupling of DO_2 and VO_2 [1], it is difficult to perceive whether our liver transplant recipients demonstrated supply-dependent oxygen uptake. The significant increase in systemic oxygen delivery induced by each catecholamine was associated with an increase in $SvhO_2$, indicating that the use of these inotropes does not result in an important decrease in splanchnic oxygen delivery. However, the parallel increase in DO_2 and $SvhO_2$ does not imply the existence of supply-dependent oxygen uptake of the graft [18]. Such an assumption must clearly be substantiated by direct experimental measurements.

The improvement in hepatic venous oxygenation achieved by sympathomimetic therapy makes an impairment of splanchnic-hepatic blood flow unlikely. This conception is supported by clinical data presented by Matsuda et.al. [17], where changes in $SvhO_2$ followed changes in oxygen delivery and hepatic perfusion pressure in patients with congestive heart failure. Multiple regression analysis of the relationship between $SvhO_2$ and the components of the systemic oxygen delivery system showed hepatic venous oxygen saturation to be a flow-dependent variable after liver grafting. This concept is supported by experimental [18] as well as clinical data [3] where hepatic blood flow, as a major factor determining the value of $SvhO_2$, was found to be a constant fraction of CI.

Further studies on larger groups of patients will be necessary to determine the impact of vasoactive treatment with DO, DX, and DOB on postoperative graft function and outcome in patients receiving an OLT.

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