

## Effect of Intraoperative Low-dose Dopamine on Renal Function in Liver Transplant Recipients

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Patients undergoing orthotopic liver transplantation frequently receive dopamine infusions to preserve renal function. To test the benefit of such infusions on renal function, 48 nonanuric patients presenting for OLT were entered into a randomized double-blind protocol. After exclusion of 1 patient for intraoperative nephrectomy, 22 patients received dopamine at a rate of  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  during surgery and the first postoperative 48 h, and a control group of 25 patients received saline. Venovenous bypass was used in 45 of 47 patients. During the hepatic vascular anastomoses, the donor liver was flushed with cold saline. In 7 patients, the flush contained mannitol (50 g) as part of a surgical protocol to investigate its role as a potential free radical scavenger. Initially, it appeared that there was an increase in urine output during the neohepatic phase in those patients receiving dopamine versus controls ( $4.20 \pm 3.3$  vs  $2.10 \pm 1.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , respectively). Upon further statistical analysis, this increase was associated with inclusion of mannitol in the liver flush of 5 patients in the dopamine group. After excluding all patients receiving flush containing mannitol, there was no significant difference in urine output during the neohepatic phase between the dopamine group and controls ( $2.94 \pm 0.45$  and  $2.10 \pm 0.28 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , respectively). The glomerular filtration rates at 1 month after surgery were similar and decreased approximately 40% in each group. Although a beneficial effect of dopamine in all situations cannot be ruled out the authors conclude that routine perioperative use of dopamine is of little value in nonanuric patients presenting for orthotopic liver transplantation. (Key words: Kidney failure: acute; chronic. Immune system: cyclosporines. Transplantation: hepatic. Sympathetic nervous system, catecholamines: dopamine.)

LIVER TRANSPLANT recipients are at high risk for developing postoperative renal dysfunction. Reported decreases in glomerular filtration rate (GFR) range from 40 to 60%,<sup>1,2</sup> and the need for postoperative dialysis after orthotopic liver transplantation (OLT) is associated with a high mortality.<sup>3,4</sup> Factors that can be implicated in the

development of renal insufficiency include preexisting renal dysfunction, acute changes in intraoperative hemodynamics, and pharmacologic agents influencing renal function. The potential for massive hemorrhage with subsequent vasoconstriction is of particular concern, as is the need for clamping of the inferior vena cava, with or without venovenous bypass (VVB). Clamping of the vena cava can result in an increase in caval and renal vein pressures and thus decrease renal perfusion pressure (mean arterial pressure minus renal vein pressure).<sup>5,6</sup> Another major concern is renal dysfunction secondary to cyclosporine nephrotoxicity, believed to be related to its effect on prostaglandins and/or to an increase in efferent renal sympathetic nerve activity.<sup>7-11</sup>

Two reports<sup>12,13</sup> have suggested that dopamine may ameliorate the renal dysfunction associated with parenchymal liver disease and OLT, possibly through renal vasodilation. Dopamine has been shown to increase urine output in patients with oliguric renal failure<sup>14</sup> and in those with hepatorenal syndrome.<sup>15</sup> The purpose of this study was to evaluate prospectively the value of routine perioperative dopamine administration on renal function in patients undergoing OLT.

### Materials and Methods

After receiving approval for this study from the Baylor University Medical Center Institutional Review Board, informed consent was obtained from 48 patients who were presenting for liver transplantation and who were not anuric preoperatively. These 48 patients were divided in randomized double-blind fashion into two groups: one group ( $n = 22$ ) received dopamine at a rate of  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  during surgery and the first postoperative 48 h, and the other group ( $n = 25$ ) received saline. One patient was excluded from the study because of an intraoperative nephrectomy.

OLT typically is divided into three phases. The preanhepatic phase begins with surgery, includes ligation of the hepatic artery, and concludes upon clamping of the portal vein, which marks the beginning of the anhepatic phase. The anhepatic phase is terminated with unclamping of the portal vein and reperfusion of the graft liver. The

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TABLE 1. Demographics

	Dopamine	Placebo	P
Age (yr)	37.9 ± 2.2	44.1 ± 2.5	NS
Weight (kg)	66.9 ± 12.1	76.6 ± 16.9	NS
Preoperative GFR (ml · min <sup>-1</sup> )*	97.8 ± 7.2	84.9 ± 7.4	NS
Preoperative creatinine (mg · dl <sup>-1</sup> )*	1.3 ± 0.2	1.0 ± 0.1	NS
Preoperative SUN (mg · dl <sup>-1</sup> )*	19.4 ± 3.7	14.0 ± 1.7	NS
Intraoperative diuretic use (number of patients)	8/22 (36%)	9/25 (36%)	NS
Intraoperative aminoglycoside use (number of patients)	2/22 (9%)	1/25 (4%)	NS
Surgery time (h)	9.9 ± 0.4	10.9 ± 0.4	NS
Cy A (mg · kg <sup>-1</sup> )†	17.4 ± 10.2	18.7 ± 6.5	NS

GFR = glomerular filtration rate; SUN = serum urea nitrogen; NS = nonsignificant; Cy A = cyclosporine.

\* Within 24 h preoperatively.

† During the first 72 h postoperatively.

neohepatic phase lasts from reperfusion until the end of surgery.

Anesthesia was induced with ketamine (1–2 mg · kg<sup>-1</sup>) or thiopental (3–5 mg · kg<sup>-1</sup>) with approximately 70% of patients in each group receiving ketamine. Maintenance of anesthesia consisted of 0.5–1.0% isoflurane in an air/oxygen mixture and was supplemented by intravenous diazepam or midazolam, and sufentanil. Pancuronium was administered for muscle relaxation. Monitoring included arterial, pulmonary artery, and central venous pressures; urine and serum osmolalities; thromboelastography; coagulation profiles; and laboratory analysis of electrolytes. VVB was used in 45 of 47 patients; one patient in each group had surgery without bypass because of technical difficulties. All patients received mannitol in a dose of 0.5 g · kg<sup>-1</sup> during the procedure for two reasons: to serve as a free radical scavenger and to ensure uniformity in management.

Crystalloid was administered to maintain filling pressures at a level providing urine output of at least 0.5 ml · kg<sup>-1</sup> · h<sup>-1</sup>. When urine output decreased to less than this amount, crystalloid was administered at an increased rate until either urine output improved or filling pressures increased to a pulmonary artery occlusion pressure of greater than 16 mmHg. At this point, if urine output had still not improved, then a loop diuretic (furosemide 20–100 mg or bumetanide 1.25–2.5 mg) was administered. Blood was transfused to maintain a hematocrit of 25–30%. Sodium bicarbonate, calcium chloride, and potassium chloride were given to maintain laboratory values within therapeutic limits.

Heart rate was sampled every 5 s and averaged over 5-min intervals throughout the procedure. Mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure, cardiac index, systemic vascular resistance, free water clearance, serum osmolality, and urine osmolality were determined during each phase of the procedure. Urine output was measured at 30-min intervals during surgery. Hepatic blood flow, oxygen production, and carbon dioxide production were calculated for the

native and graft liver in each patient. Prothrombin time, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvate transaminase were obtained within 24 h preoperatively and at 48 h postoperatively. GFRs were determined by iothalamate I-125 injection (Glofil, Iso-tex, Inc., Diagnostics, Friendswood, TX) within 1 month before transplantation and again approximately 1 month after transplantation. Serum creatinine and serum urea nitrogen determinations were made within 24 h preoperatively and on each of the first 7 postoperative days.

During the hepatic vascular anastomoses, the donor liver was flushed with cold saline. The flush was administered *via* the portal vein and the effluent collected *via* a suction catheter in the infrahepatic vena cava. In 7 patients (5 in the dopamine group and 2 in the placebo group) the flush contained mannitol (50 g) as part of a surgical protocol to investigate its role as a potential free radical scavenger.

Data were analyzed using analysis of variance and Student's *t* test. Statistical significance was set at *P* < 0.05. Data are presented as the mean ± the standard error of the mean.

## Results

There were no significant differences between the two groups in age or weight; preoperative laboratory studies (GFR, creatinine, and serum urea nitrogen); diagnosis; duration of surgery; or exposure to intraoperative loop

TABLE 2. Intraoperative Fluid and Blood Product Administration

	Dopamine	Placebo	P
Crystalloid (ml · kg <sup>-1</sup> · h <sup>-1</sup> )	6.6 ± 3.1	6.8 ± 2.9	NS
Packed red blood cells (units)	7.9 ± 1.8	7.8 ± 1.3	NS
Salvaged blood (units)	3.3 ± 2.2	4.0 ± 1.1	NS
Fresh frozen plasma (units)	12.9 ± 4.1	11.6 ± 2.1	NS
Cryoprecipitate (units)	13.9 ± 6.1	18.2 ± 3.8	NS
Platelets (units)	9.1 ± 3.1	12.8 ± 3.5	NS

NS = nonsignificant.

TABLE 3. Intraoperative Hemodynamics

		Preanhepatic	Anhepatic	Neohepatic
HR (beats per min)	Dopamine	104.1 ± 2.7*	102.2 ± 2.8*	98.5 ± 2.5
	Placebo	92.5 ± 1.8	91.6 ± 2.1	93.4 ± 1.8
MAP (mmHg)	Dopamine	79.9 ± 11.6	80.8 ± 10.2	82.4 ± 16.3
	Placebo	79.0 ± 11.6	77.2 ± 10.6	74.2 ± 8.4
CVP (mmHg)	Dopamine	11.6 ± 3.4	11.5 ± 3.4	11.7 ± 2.6
	Placebo	10.6 ± 2.3	11.5 ± 2.0	10.3 ± 2.9
PAOP (mmHg)	Dopamine	10.2 ± 2.3	8.6 ± 3.0	11.1 ± 2.1
	Placebo	10.0 ± 2.3	8.7 ± 2.2	9.8 ± 2.6
CI (l · min <sup>-1</sup> · m <sup>-2</sup> )	Dopamine	5.8 ± 3.1	3.5 ± 1.9	6.0 ± 2.0
	Placebo	4.9 ± 1.4	2.8 ± 1.1	4.7 ± 1.4
SVR (dyne · cm · s <sup>-5</sup> )	Dopamine	695 ± 333	1118 ± 447	614 ± 227
	Placebo	748 ± 345	1192 ± 448	670 ± 192

HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; CI = cardiac index; SVP = systemic vascular resistance.  
\* P < 0.05.

diuretics, nephrotoxic antibiotics, or cyclosporine (table 1). There were no episodes of massive hemorrhage or sustained hypotension, and no dysrhythmias were detected. If a transitory decline in hemodynamics occurred after reperfusion of the graft liver, the patient usually was treated with small bolus doses of epinephrine, phenylephrine, ephedrine, and/or calcium chloride, but sustained support with vasopressors or inotropes was not required. There were no differences in drug therapy between the two groups.

Each group received equivalent amounts of intraoperative fluids and blood products (table 2). There was a significantly higher heart rate during the preanhepatic

and anhepatic phases of the procedure in patients receiving dopamine but no statistically significant difference in mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure, cardiac index, or systemic vascular resistance (table 3). No significant differences between groups were found in portal vein flow, hepatic artery flow, or hepatic oxygen consumption or carbon dioxide production in either the native or graft liver (table 4). There were no significant differences in free water clearance, serum osmolalities, or urine osmolalities (table 5).

Initially it appeared that there was an increase in urine output during the neohepatic phase in patients receiving dopamine (table 6). Upon further statistical analysis, this

TABLE 4. Intraoperative Liver Function and Blood Flow

		Native Liver	Donor Liver	P
PVF (ml · g <sup>-1</sup> · min <sup>-1</sup> )	Dopamine	104.3 ± 91.4	139.8 ± 83.3	NS
	Placebo	100.6 ± 81.1	150.8 ± 62.5	NS
HAF (ml · g <sup>-1</sup> · min <sup>-1</sup> )	Dopamine	35.3 ± 33.3	32.5 ± 10.7	NS
	Placebo	27.6 ± 17.6	31.9 ± 14.7	NS
O <sub>2</sub> consumption (ml · g <sup>-1</sup> · min <sup>-1</sup> )	Dopamine	1.3 ± 0.4	2.7 ± 3.3	NS
	Placebo	1.0 ± 0.6	3.3 ± 1.8	NS
CO <sub>2</sub> production (ml · g <sup>-1</sup> · min <sup>-1</sup> )	Dopamine	0.9 ± 3.2	1.8 ± 6.9	NS
	Placebo	3.2 ± 6.8	3.7 ± 7.7	NS

PVF = portal vein flow; HAF = hepatic artery flow; O<sub>2</sub> consumption = hepatic oxygen consumption; CO<sub>2</sub> production = hepatic carbon dioxide production; NS = nonsignificant.

TABLE 5. Free Water Clearances and Osmolalities

		Preanhepatic	Anhepatic	Neohepatic
FWC (ml · min <sup>-1</sup> )	Dopamine	-30.6 ± 76.0	-28.0 ± 38.8	-28.1 ± 33.9
	Placebo	-65.3 ± 55.2	-56.2 ± 32.6	-40.7 ± 40.5
Serum osmolality (mOsm · l <sup>-1</sup> )	Dopamine	284.5 ± 6.0	289.8 ± 6.3	301.1 ± 7.5
	Placebo	279.8 ± 10.9	287.0 ± 7.6	298.3 ± 8.4
Urine osmolality (mOsm · l <sup>-1</sup> )	Dopamine	393.6 ± 98.0	344.5 ± 61.7	338.4 ± 34.9
	Placebo	497.6 ± 126.3	462.7 ± 129.6	368.4 ± 56.9

FWC = free water clearance.

TABLE 6. Intraoperative Urine Output

	Preanhepatic	Anhepatic	Neohepatic
Dopamine (n = 22)	2.4 ± 1.7	2.8 ± 3.1	4.2 ± 3.3*
Placebo (n = 25)	1.6 ± 1.1	1.5 ± 1.2	2.1 ± 1.3

Values are milliliter per kilogram per hour.

\*  $P < 0.05$ .

increase was found to be associated with inclusion of mannitol in the liver flush of five patients in the dopamine group. Urine output during the neohepatic phase of patients in the dopamine group who did not receive flush containing mannitol (n = 17) was  $2.94 \pm 0.45$  ml · kg<sup>-1</sup> · h<sup>-1</sup>, whereas that of patients receiving dopamine plus mannitol-containing flush (n = 5) was  $7.77 \pm 2.42$  ml · kg<sup>-1</sup> · h<sup>-1</sup> ( $P < 0.01$ ). After excluding all patients receiving additional mannitol *via* the liver flush from analysis, there was no significant difference in urine output between the two groups.

Preoperative and postoperative prothrombin time, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvate transaminase were similar (table 7). During the first 7 postoperative days there were no differences in serum creatinine or serum urea nitrogen (tables 8 and 9). No differences were identified either in the postoperative use of dialysis or in mortality. The GFRs 1 month postoperatively were similar and had decreased approximately 40% in each group (table 10).

### Discussion

We were unable to substantiate any beneficial effect of routine perioperative use of dopamine on renal function in nonanuric liver transplant recipients. No improvement was seen in the perioperative period, and no difference was noted in the long-term follow-up of GFR. Dopamine may not counteract the processes responsible for renal insufficiency in these patients, or the effects of dopamine may be clinically inconsequential relative to other factors affecting renal function.

Hemodynamics were closely monitored and remained relatively stable in these patients. Except for the higher heart rate in the dopamine group, consistent with the known chronotropic effects of dopamine, there were no differences in hemodynamics between the two groups. VVB, used in the vast majority of our patients, has previously been suggested to minimize alterations of renal function during OLT.<sup>16</sup> In contrast to the reports of Peachey *et al.*<sup>5</sup> and Estrin *et al.*,<sup>6</sup> a study by Gunning *et al.*<sup>17</sup> revealed preservation of renal perfusion pressure during the anhepatic phase with use of VVB. In addition, Gunning *et al.* demonstrated that the time course of the decrease in renal function suggested a minimal effect of perioperative events on renal function. If perioperative renal hemodynamics are well preserved and the decline in renal function is not primarily related to perioperative events, then use of dopamine during this period should not be expected to have a major effect.

GFR measured during the infusion of dopamine might have identified beneficial effects on renal function. In a study of six healthy volunteers, dopamine infusion restored renal plasma flow, GFR, and urinary volume, which had been decreased by cyclosporine administration.<sup>18</sup> After cessation of the dopamine infusion, however, the previously induced impairments in renal function reappeared. Acute effects of short-term interventions may not alter the ultimate outcome of continuing processes, such as chronic cyclosporine administration.

The diminution in renal impairment and morbidity associated with the use of dopamine that was demonstrated in a retrospective study by Polson *et al.*<sup>12</sup> was not confirmed by our data. This discrepancy may result from one or more of the following differences: the dose of dopamine used ( $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  by Polson *et al.* *vs.*  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in our study), the frequency of use of VVB in the two studies, aspects of clinical management (such as fluid management), study design (randomized *vs.* selected), and the overall higher incidence of postoperative renal impairment reported in Polson *et al.*'s study. A further consideration is the difference in the time frame of the creatinine clearance measurements: 24–48 h post-

TABLE 7. Pre- and Postoperative Hepatic Indices

		Preoperative*	Postoperative†	P
PT (s)	Dopamine	15.5 ± 3.9	14.3 ± 3.3	NS
	Placebo	15.0 ± 3.0	13.6 ± 1.7	NS
SGOT (mg · dl <sup>-1</sup> )	Dopamine	227.9 ± 228.7	744.6 ± 1204.6	NS
	Placebo	225.1 ± 531.6	465.1 ± 536.6	NS
SGPT (mg · dl <sup>-1</sup> )	Dopamine	150.6 ± 186.2	656.6 ± 844.8	NS
	Placebo	204.1 ± 443.2	477.0 ± 457.1	NS

PT = prothrombin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; NS = nonsignificant.

\* Within 24 h before surgery.

† Forty-eight hours after surgery.

TABLE 8. Serum Creatinine

	Preoperative*	Postoperative Day			
		1	3	5	7
Dopamine	1.3 ± 0.2	1.5 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	1.4 ± 0.2
Placebo	1.0 ± 0.1	1.4 ± 0.1	1.7 ± 0.2	1.5 ± 0.2	1.4 ± 0.1

Values are milligrams per deciliter.

\* Within 24 h before surgery.

TABLE 9. Serum Urea Nitrogen

	Preoperative*	Postoperative Day			
		1	3	5	7
Dopamine	19.4 ± 3.7	31.7 ± 4.2	41.1 ± 5.2	39.1 ± 5.5	31.6 ± 5.3
Placebo	14.0 ± 1.7	23.7 ± 2.6	41.8 ± 4.8	38.8 ± 5.3	33.5 ± 4.5

Values are milligrams per deciliter.

\* Within 24 h prior to surgery.

operatively in Polson *et al.*'s study versus 1 month in our study. Measurements made during a dopamine infusion, as in Polson *et al.*'s study, may influence the results, whereas after 1 month of exposure to the nephrotoxic effects of cyclosporine, the two groups may become similar.

A single patient in each group required postoperative dialysis. One patient was believed to have developed thrombotic thrombocytopenic purpura with subsequent multisystem organ failure, including acute tubular necrosis requiring dialysis. The other patient also developed acute tubular necrosis postoperatively; echocardiography revealed a cardiomyopathy with markedly impaired systolic function, and renal hypoperfusion was believed to be the cause of his kidney dysfunction. These instances demonstrate that derangements in other organ systems can adversely affect renal function and that dopamine might not be expected to confer renal protection in these situations. The need for postoperative dialysis in our series compares favorably with the results of Busuttill *et al.*<sup>3</sup> Their survey revealed 39.5% of adult patients undergoing OLT required postoperative dialysis and that 35.3% of adult patients requiring dialysis died.

TABLE 10. Postoperative Comparison

	Dopamine	Placebo	P
Postoperative dialysis	1/22 (4.5%)	1/25 (4.0%)	NS
Mortality at 1 month	3/22 (14.0%)	2/25 (8.0%)	NS
Postoperative GFR (ml · min <sup>-1</sup> )	59.4 ± 6.0	57.6 ± 9.8	NS
Change in GFR*	-41.6%	-42.6%	NS

GFR = glomerular filtration rate; NS = nonsignificant.

\* Change in GFR from pre- to postoperative.

There was a dramatic increase in urine output in the neohepatic phase in patients who received flush containing mannitol. We have previously determined that 200–300 ml of administered volume usually remains within the graft liver (unpublished data). This is equivalent to approximately 12.5 g of mannitol, which can enter the circulation upon revascularization. This study was not designed to examine in detail various combinations of dopamine and mannitol; however, the concurrent use of dopamine and mannitol in this manner may have produced a synergistic effect similar to that described for dopamine and furosemide.<sup>19,20</sup>

The low incidence of acute renal failure observed in our study made it impossible to rule out dopamine as a potential prophylaxis for acute renal failure in all scenarios. There still may be situations (*e.g.*, hepatorenal syndrome or hemorrhage with sustained hypotension) in which dopamine in combinations with other agents would lead to a clinically desirable diuresis, or in which the temporary use of dopamine might prevent permanent sequelae to other transient but deleterious phenomena. These suppositions remain to be evaluated. Our results suggest, however, that the routine perioperative use of dopamine is of little value in OLT, consistent with the observation that intraoperative factors do not appear to contribute greatly to the decline in renal function associated with OLT using VVB.<sup>17</sup> The most likely cause of decreased renal function postoperatively is chronic exposure to cyclosporine. Currently, patients undergoing liver transplantation must receive chronic cyclosporine therapy, and therefore a more advantageous approach to preserving renal function might be further investigation of cyclosporine nephrotoxicity and development of long-term therapy to counteract this effect. Less nephrotoxic

immunosuppressive agents may prevent the decrease in renal function in patients undergoing OLT.

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