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Mechanisms of hypertension during and after orthotopic liver transplantation in children

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The aim of this study was to assess the hormonal alterations that may mediate the systemic hypertension that develops in patients during the perioperative period of orthotopic liver transplantation. We studied nine pediatric patients without previous hypertension or renal disease during six time points, starting before transplantation and ending at 48 hours after surgery. Hypertension developed in all patients in association with central venous pressures <10 mm Hg. Free water clearance was negative in all nine patients. Vasopressin levels increased intraoperatively but fell as hypertension developed. Atrial natriuretic factor levels increased as systemic blood pressure rose. A high level of plasma renin activity was observed in four patients with renal insufficiency. In six patients, postoperative 24-hour urinary norepinephrine excretion was within the normal age-adjusted range. These findings suggest that the combination of cyclosporine, corticosteroids, and, in some patients, an elevated plasma renin activity prevents the kidney from responding to the acute volume and salt overload with an appropriate diuresis and natriuresis, thus leading to systemic hypertension. The treatment of hypertension after liver transplantation may include salt restriction, diuretics, and, in those patients with a low creatinine excretion index, angiotensin converting enzyme inhibitors. (J Pediatr 1989;115:372-9)

Systemic hypertension complicates the intraoperative and postoperative course of more than 80% of children undergoing orthotopic liver transplantation.[1-4] This hypertension typically develops after hepatic artery anastomosis, is sustained for months, and often is severe, leading to increased morbidity.[3] The attempt to control such hypertension has had unpredictable results and has had only limited success despite the use of antihypertensive agents.[1-4] Severe hypertension has been reported to occur during pediatric orthotopic liver transplantation before cyclosporine was used as part of the immunosuppressive regimen,[7] but because of the nearly 30-fold increase in the risk of hypertension with the use of cyclosporine, as compared with other immunosuppressive agents,[8] attention has focused on the effects of this agent in altering salt and water balance and in increasing vascular tone, thereby producing hypertension. The mechanisms responsible for the development of hypertension in patients treated with

ANF	Atrial natriuretic factor
AVP	Arginine vasopressin
MAP	Mean arterial pressure
PRA	Plasma renin activity

See commentary, p. 410.

Submitted for publication Nov. 14, 1988; accepted March 8, 1989.

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cyclosporine remain poorly understood[9,10] despite several studies examining the role of the renin-angiotensin-aldosterone system,[11-13] prostaglandin excretion,[14] and the sympathetic nervous system.[15]

The purpose of this study was to determine how the physiologic mechanisms that normally maintain blood pressure and tissue perfusion respond to the immediate stresses of liver transplantation, and how these responses relate to the development of hypertension. Such understanding may result in more rational and effective treatment of postoperative hypertension.

METHODS

Nine consecutive patients aged 2 to 16 years were studied prospectively during and after primary orthotopic liver transplantation. The study was approved by the hospital's human rights committee and appropriate consent was obtained. The preoperative diagnoses were biliary atresia (three patients), non-A, non-B hepatitis, cirrhosis after treatment of hepatoblastoma, choledochal cyst, sclerosing cholangitis, α_1-antitrypsin deficiency, and type IV glycogen storage disease. The mean arterial pressure was calculated as one third of the pulse pressure plus the diastolic pressure. No patient had preoperative hypertension or hypotension (defined as a calculated MAP >90th or <10th percentile for age),[16] renal dysfunction (abnormal blood urea nitrogen and serum creatinine values for age), or heart disease (abnormal chest radiograph and abnormal findings on physical examination). A baseline blood pressure was obtained with a sphygmomanometer before arrival of each patient in the operating room.

The perioperative period was divided into six periods for the purpose of blood sampling and postoperative collection of urine: induction of anesthesia, the anhepatic phase, reperfusion after revascularization of the donor liver, arrival in the intensive care unit, 24 hours postoperatively, and 48 hours postoperatively.

General anesthesia was induced with atropine and fentanyl, and neuromuscular relaxation was obtained with pancuronium. Anesthesia was maintained during surgery by nitrous oxide, oxygen, isoflurane, and morphine. Neuromuscular blockade was maintained with pancuronium or atracurium. After induction of general anesthesia, an arterial catheter, a central venous catheter, and a urinary catheter were inserted for routine monitoring throughout the study.

At the beginning of each of the six periods, an arterial blood sample was drawn for determination of serum osmolarity and of arginine vasopressin, atrial natriuretic factor, blood urea nitrogen, creatinine, and sodium concentrations. Plasma renin activity was determined on arrival of the patient in the intensive care unit, and at 24 hours and 48 hours postoperatively. Plasma cyclosporine concentration was determined at 24 and 48 hours postoperatively. During the postoperative 0 to 24-hour and 24 to 48-hour periods, urine was collected for determination of sodium and creatinine concentrations and osmolarity. During the first 24 hours postoperatively, urine was collected (in 6N hydrochloric acid) from six of the patients for determination of norepinephrine excretion.

Sodium, creatinine, and blood urea nitrogen concentrations and osmolarity were measured by standard laboratory techniques. Plasma renin activity was measured by radioimmunoassay of generated angiotensin I. Cyclosporine, ANF, and AVP were measured by radioimmunoassay. Urinay norepinephrine was assayed by high-performance liquid chromatography.

Postoperative hypertension or hypotension was defined as a calculated MAP greater than the 90th or less than the 10th percentile for age.[3,4,6,16] A normal ANF concentration was 25 to 77 pg/ml. Vasopressin concentrations were interpreted in terms of serum osmolarity[17]: if the serum was hypotonic, an AVP concentration <1 pg/ml was considered normal; if the serum was normotonic or hypertonic, any AVP value >2 pg/ml was abnormal; and a concentration of >6 pg/ml at any time represented a nonphysiologic stimulation of AVP. A concentration of >2.0 ng/ml/hr was considered abnormal. Our laboratory does not report a normal range for urinary nonepinephrine concentration for pediatric patients; previously published age-adjusted norepinephrine values were used for comparison.[18-20]

The patient's weight was recorded preoperatively, on the patient's arrival in the intensive care unit, and at 24 and 48 hours postoperatively. During each period the central venous pressure was continuously monitored and fluid therapy was adjusted to maintain a central venous pressure of 4 to 10 mm Hg. There was continuous monitoring of mean, systolic, and diastolic arterial blood pressures. Hypertension was treated with antihypertensive agents (nitroprusside, hydralazine, labetalol, captopril, or nifedipine) or diuretics (furosemide) if the hypertension was sustained for more than 15 minutes despite appropriate analgesia. Two patients had been treated with furosemide preoperatively as part of the management of ascites. However, once anesthesia was induced, none of the patients received antihypertensive agents or diuretics before the onset of hypertension. Hypotension with a central pressure of <4 mm Hg and tachycardia was treated with colloid or, if the hematocrit was <25%, with packed erythrocytes. Methylprednisolone, 20 to 30 mg/kg, and cyclosporine, 2 to 3 mg/kg, were administered intravenously immediately after the donor liver was revascularized. Postoperatively, methylprednisolone was given on the

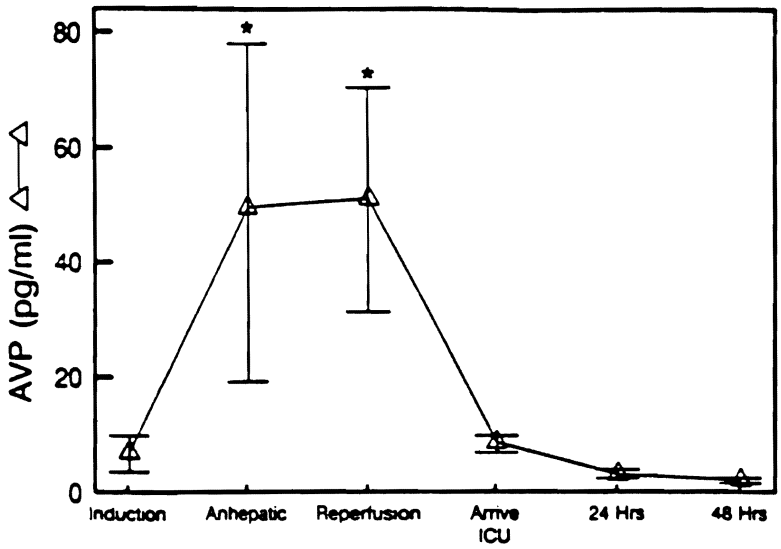

Fig. 1. Changes in plasma AVP concentration during operative (induction, anhepatic, and reperfusion) and postoperative (arrival in intensive care unit, at 24 hours, and at 48 hours) time points of study. *p <0.05.

first day in a dose of 2 mg/kg and on the second day in a divided dose of 1 mg/kg. Postoperatively, cyclosporine dosage was adjusted to maintain plasma trough concentrations of 500 to 700 ng/ml.

Renal function was evaluated by (1) the 24-hour determination of creatinine excretion index (calculated as the 24-hour collected urinary creatinine divided by the weight, and expressed as milligrams of creatinine per kilogram per day)[21]; (2) 24-hour creatinine clearance (calculated as follows: [Urinary creatinine/Serum creatinine] × [Urine volume/Total minutes of the collection] corrected to 1.73 m^2); (3) fractional excretion of sodium; (4) osmolar clearance (calculated as follows: [Urine osmolarity/Plasma osmolarity] × [Urine volume/Unit time]); (5) free water clearance (calculated as follows: [Urine volume/Unit time] − Osmolar clearance); (6) serum creatinine concentration; and (7) blood urea nitrogen concentration. The creatinine excretion index has been used as an aid in identifying renal insufficiency (low glomerular filtration rate) in patients with cirrhosis who have normal serum creatinine values.[21,22]

Statistical analysis was performed with the use of nonparametric tests.[23,24] The Friedman statistic was used to determine differences in group means over multiple periods, and the differences in group means between periods were analyzed by the Wilcoxon signed-rank sum test. Correlation between variables was established with the Spearman rank correlation coefficient. The relationship of PRA and the creatinine excretion index was analyzed by the Fisher Exact Test. Values are represented as mean +/− SEM. Significance was defined as p <0.05.

RESULTS

Hypertension developed in all nine patients but in only seven during the study period. In all patients, hypertension developed while the central venous pressure was <10 mm Hg. The onset of hypertension occurred after donor liver reperfusion in three patients and within 12 hours postoperatively in four patients. Two patients experienced severe hemorrhage and hypotension postoperatively, and only after reoperation to control bleeding did hypertension develop (after the 48-hour postoperative period). In all patients, hypertension was sustained after onset and was treated with multiple antihypertensive agents in combination with diuretics.

All patients maintained a negative water clearance throughout the postoperative period. The serum creatinine concentrations postoperatively ranged from 0.1 to 1.2 mg/dl (10 to 110 μmol/L). The fractional excretion of sodium ranged from 0.2% to 2.0% in the postoperative period. There were no correlations among change in central venous pressure, weight change, osmolar clearance, free water clearance, creatinine excretion index, or creatinine clearance.

There was a significant and nonphysiologic increase in AVP during the anhepatic and donor reperfusion periods (the periods of massive fluid shifts and blood loss)[25] and then a return to normal with the onset of hypertension (Fig. 1). This rise of AVP was not related to any change in serum osmolarity or central venous pressure. During the postoperative periods, AVP concentration changed appropriately with changes in serum and urine osmolarity.[17]

The mean plasma concentration of ANF (Fig. 2) was normal at induction of anesthesia and decreased during

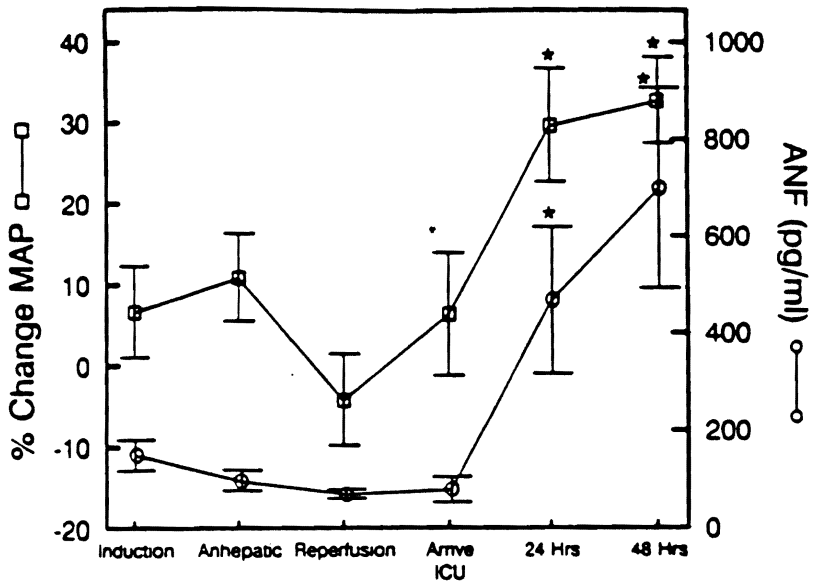

Fig. 2. Changes in ANF concentration and percent change from preoperative baseline MAP during operative (induction, anhepatic, and reperfusion) and postoperative (arrival in intensive care unit, at 24 hours, and at 48 hours) time points of study. *p <0.05.

those periods of massive blood loss and fluid shifts associated with the rise in plasma AVP concentration, but then increased significantly (p <0.05) postoperatively with the onset of hypertension. This increase occurred during a period of relative fluid homeostasis and after the administration of corticosteroids and cyclosporine. There was no significant correlation between ANF and postoperative renal function (urine output, creatinine excretion index, creatinine clearance, blood urea nitrogen level, fractional excretion of sodium, osmolar clearance, free water clearance) or fluid balance.

At the same time that the MAP was rising significantly and hypertension developed, the plasma concentration of AVP decreased (Fig. 1) and the plasma concentration of ANF increased (Fig. 2). There was a significant (p <0.03) correlation between the increase in MAP from baseline and the increase in ANF over time.

In those patients with marginal renal function (creatinine excretion index <12 mg[1060 μmol]/kg/day),[28] the PRA was significantly elevated (p <0.003). None of the patients with a normal creatinine excretion index had an elevated PRA (Fig. 3).

In the six patients in whom urinary norepinephrine excretion was measured, there was no significant elevation (range 20 to 75 μg/24 hr) in comparison with the published normal age-adjusted range of norepinephrine excretion.[18-20] There was no relationship between excretion of norepinephrine and the volume status, renal function, severity of hypertension, or persistent hemorrhage.

The mean plasma cyclosporine concentration 24 hours postoperatively was 695 ng/ml (range 253 to 1027 ng/ml). The mean plasma cyclosporine concentration 48 hours postoperatively was 855 ng/ml (range 525 to 1135 ng/ml). There was no correlation between the cyclosporine concentration and the severity of hypertension, renal function, or fluid status.

DISCUSSION

The underlying hemodynamic abnormalities of severe hepatic dysfunction frequently include a high cardiac index and low systemic vascular resistance. Despite the low systemic vascular resistance, blood flow and oxygen delivery to actively respiring tissues, such as the kidneys, are low, probably because arteriovenous shunting produces organ hypoperfusion.[27,28] This profound vasodilation results in simultaneous total body fluid overload but a marginal circulatory volume. Restoration and maintenance of this decreased "effective circulatory volume" result from the interaction of vasoregulatory hormones and substances that regulate renal handling of salt and fluid.[29-31] Included in this regulation are the renin-angiotensin-aldosterone system, the sympathetic nervous system, AVP, ANF, and prostaglandins.[29,32-35]

The liver transplant recipient undergoes massive perioperative shifts in fluids and hemodynamics. The usual operative course is characterized by the turnover of between 0.6 and 25 blood volumes.[35,36] Although patients rarely evidence gross hypervolemia or hypovolemia at completion of surgery, the precise intravascular blood volume in the immediate recovery period is not known. In

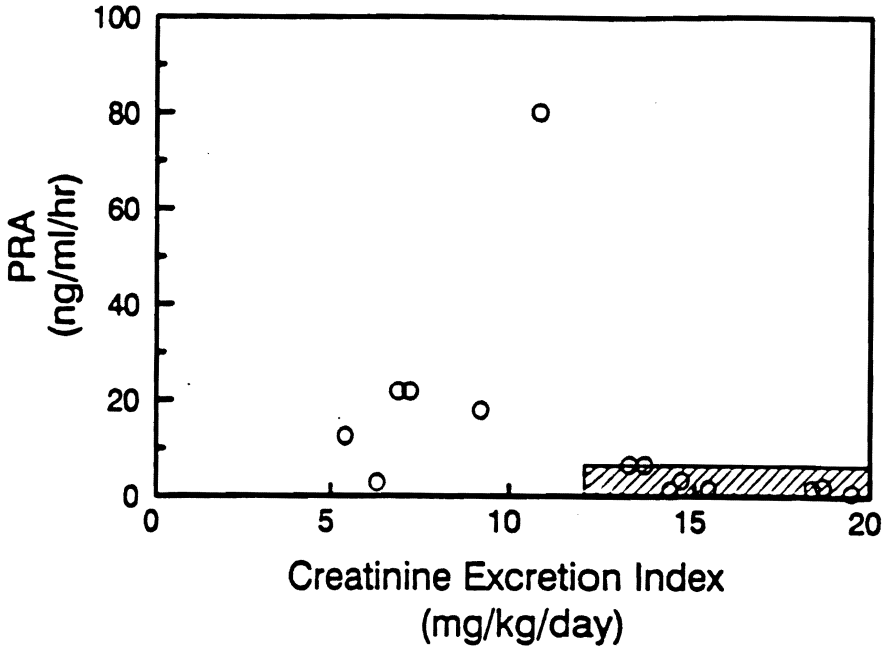

Fig. 3. PRA value in relation to measured creatinine excretion index in patients during two postoperative periods: 0 to 24 hours, and 24 to 48 hours. *Shaded area* represents normal range.
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addition, it is not currently known how effective the newly transplanted liver metabolizes endogenous vasoactive substances.[28, 29] Indeed, the physiologic adaptations to chronic liver failure will be markedly altered by the posttransplant circulatory environment.[37, 38]

Vasopressin is released in response to dehydration, salt administration, hypotension, and surgical stress.[39-42] Atrial distension, not increased atrial pressure, and acute but not chronic salt loading lead to increased circulating ANF.[43, 44] Certain anesthetic agents and high doses of narcotics also stimulate ANF release,[45] but neither the type of anesthetic agents, the doses of narcotic administered, nor any of the diuretics, antihypertensive drugs, nor immunosuppressive agents administered to the study patients have been shown to raise the plasma ANF concentration.[46-54]

The release of AVP and of ANF are inversely related, with no inhibiting interaction.[55] We have demonstrated this relationship in these patients. During the intraoperative phase, the plasma AVP concentration increased in response to stress and hemorrhage but then decreased as the intravascular volume became more stable. The ANF concentration decreased in response to decreased intravascular volume but then increased when the patients had a significant rise in blood pressure from their preoperative baseline and became hypertensive.

We did not determine cardiac output or blood volume, but the postoperative increase in ANF concentration and decrease in AVP concentration suggest that these patients' blood volume or salt load, or both, had acutely increased despite an unchanged central venous pressure.[30] Patients with cirrhosis already have a positive sodium balance.[56] In addition, corticosteroid administration increases salt retention in these patients. Large doses of methlyprednisolone exert a significant mineralocorticoid effect, wich is further compounded by decreased hepatic blood flow.[57] The high salt content of administered blood products further increases the circulatory load in these patients.

Whether the change in the plasma concentration of ANF is physiologically significant could not be determined, but there was no significant decrease in blood pressure, increase in fractional excretion of sodium, or increase in free water clearance associated with the rise in ANF levels.

The elevated PRA at a time of fluid overload or salt overload, or both, indicates that some of the patients may have been in a hyperreninemic state. Although diuretic and antihypertensive agents can elevate PRA, the elevated PRA in our patients was demonstrated before these agents were administered. A low creatinine excretion index (<12 mg/kg/day),[26] and thus a low glomerular filtration rate, may serve as a marker for an elevated PRA. The creatinine excretion index may give a better indication of impaired glomerular function than calculated creatinine clearance gives.[21] An impaired liver may not be able to convert muscle creatine to creatinine optimally. In addition, patients in a poor nutritional state may not have significant

creatine stores. Both of these factors could result in a low serum creatinine concentration, which would also falsely elevate the calculated creatinine clearance.[21, 58]

The effect of cyclosporine on the early hemodynamic status of liver transplant recipients is not entirely clear. Postoperative hypertension can occur in pediatric patients after liver transplantation if they are not treated with cyclosporine.[7] Hypertension develops in many patients who receive cyclosporine either for transplantation or for immunosuppression without transplantation.[9, 11, 59] However, despite the use of similar or higher doses of cyclosporine,[57, 58] the hypertension that develops in patients receiving cyclosporine as part of their non-liver-transplantation immunosuppression is less acute and less severe than the hypertension that initially occurs after liver transplantation.[9, 11]

In our pateints the cyclosporine plasma concentrations were therapeutic after the initial dose. A cyclosporine infusion can acutely cause renal vasoconstriction mediated by the sympathetic nervous system[60-62] and can also lead to sodium and water retention.[12, 63] This renal vascular effect of cyclosporine could partially account for the inadequate natriuretic and diuretic response to the elevated ANF concentrations after liver transplantation. The chronic hypertension that develops in patients receiving cyclosporine is attenuated by salt restriction.[64]

The urinary norepinephrine excretion, rather than the plasma norepinephrine concentration, was chosen as a marker of sympathetic tone in the immediate 24-hour postoperative period. The plasma norepinephrine concentration does not consistently reflect sympathetic activity in human beings because of a wide range and variability in plasma concentrations[65] and may be less reflective of norepinephrine turnover than urinary norepinephrine excretion.[66, 67] The urinary norepinephrine excretion values obtained could reflect a significant stimulation of the sympathetic nervous system by either cyclosporine or stress, but there are few published normal values of age-specific urinary catecholamine excretion and no previously published reference values for pediatric patients who have undergone liver transplantation.[18-20]

The data from our study indicate that the perioperative course of liver transplantation is characterized by massive fluid shifts, which result in a transition from a central hyperdynamic state of normal or low blood pressure, with marginal organ perfusion, to a state of volume overload and acute severe systemic hypertension. The physiologic mechanisms regulating AVP and ANF release attempt to effect a normal adjustment to intravascular hypervolemia and acute salt overload. The kidney, however, cannot compensate with an appropriate diuresis or natriuresis, for a variety of reasons, such as a high PRA in patients with impaired renal function and the effects of cyclosporine and steroids. The hypertension that develops in patients after liver transplantation appears to be multifactorial and may involve a relative salt and volume overload in conjunction with absence of a diuretic or natriuretic response by the kidney to these loads. Although many of the hormonal changes and renal responses observed may reflect our specific perioperative management, we recommend that the treatment of the acute hypertension that develops after pediatric orthotopic liver transplantation include restricted salt intake, the use of diuretics, and, in those patients with a decreased creatinine excretion index, the use of angiotensin converting enzyme inhibitors.

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