Transplantation*

Evidence for Early Postoperative Myocardial Depression

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Objective: To describe the hemodynamic and oxygen transport patterns in survivors and nonsurvivors following liver transplantation (LT) and to assess their relationship to organ failure and mortality.

Design: Retrospective cohort.

Setting: Surgical ICU in a tertiary care university teaching hospital.

Patients: Consecutive series of 113 adults undergoing LT between 1984 and 1992. Patients were excluded if they died intraoperatively (n=2), required retransplantation (n=8), or their records were incomplete (n=7).

Measurements and main results: Preoperative severity of illness was assessed by the acute physiology and chronic health evaluation (APACHE) II scoring system. Hemodynamic and oxygen transport variables were recorded immediately preoperatively and sequentially every 12 h during the first 2 postoperative days. Organ failures (pulmonary, renal, cardiovascular, hepatic, and central nervous system) were assessed for patients in the postoperative period. Patients were grouped as survivors (n=52) or nonsurvivors (n=14) with a mortality rate of 15%. Preoperative APACHE II scores were significantly lower in survivors compared with nonsurvivors (7±0 vs 11±2; p=0.029). Both preoperatively and postoperatively, survivors sustained a relatively higher mean arterial pressure, stroke volume index, left ventricular stroke work index, cardiac index, and oxygen delivery as compared with nonsurvivors (p<0.01). The postoperative decline in systemic blood flow that was seen in both groups was particularly prominent in nonsurvivors during the first 12 h following LT (p<0.03). Nonsurvivors sustained an approximately fivefold increase in the rate of organ failure (p<0.0001); all patients (n=6) with 4 or more organ failures died.

Conclusion: Nonsurvivors of LT have less cardiac reserve pretransplant; postoperatively, they demonstrate early myocardial depression and subsequently lower levels of cardiac index and oxygen delivery. Patients who develop these hemodynamic patterns are more prone to organ failure and death.

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Key words: cardiac output; hemodynamics; liver transplantation; multiple organ failure; oxygen delivery

Liver transplantation (LT) in the United States is an increasingly common and extraordinarily costly procedure.1,2 Patients who undergo LT represent a unique group of high-risk surgical patients, all of whom suffer from advanced liver disease preoperatively.2,3 Pretransplant hepatic failure is characterized by a hyperdynamic circulation (high cardiac output, low systemic vascular resistance) and tissue hypoxia,4-6 yet little is known about the hemodynamic patterns of this patient population following transplantation. High blood lactate concentrations consistent with tissue hypoxia during transplantation have been observed; unfortunately, outcome data were not reported.7 Occult tissue hypoxia, when unrelieved, is thought to be a contributing cause of multiple organ failure.8-10 In support of this hypothesis, recent reports suggest that maximizing systemic oxygen delivery in patients with septic shock11,12 or in high-risk surgical patients13-15 can improve survival and attenuate organ failure.15,16 Limited reports17,18 have described the postoperative hemodynamic profile of LT patients who have an uncomplicated postoperative course. The hemodynamic response following LT and its related impact on outcome previously have not been reported.

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APACHE=acute physiology and chronic health evaluation; CI=cardiac index; DO2=system oxygen delivery; LT=liver transplantation; LVSWI=left ventricular stroke work index; MAP=mean arterial pressure; PAWP=pulmonary artery wedge pressure; SVI=stroke volume index
The purpose of this study was to describe the hemodynamic profiles of patients undergoing LT and to determine their relationship to outcome. Our data suggest that nonsurvivors experience early postoperative myocardial depression which is associated with a lower cardiac index (CI), systemic oxygen delivery (DO₂), and mean arterial pressure as compared with survivors. Nonsurvivors sustained five times as frequent organ failure as did survivors. Each sequential organ failure conferred a sixfold increase in the risk of death.

**MATERIALS AND METHODS**

**Study Design**

We reviewed the medical records of all adults (>18 years of age) undergoing LT between the period of January 1984 to May 1992 at the New England Medical Center in Boston. Approval for this study was granted by the Institutional Review Board.

**Study Population**

One hundred thirteen adults underwent LT at the New England Medical Center during the study period. Seventeen patients were excluded from the study; the medical records of seven patients were incomplete, two patients died intraoperatively, and eight others required retransplantation. Review of the available data of the 7 patients with incomplete records showed that these patients were not significantly different (age, preoperative criteria, outcome) from the 96 patients studied. The final study group included 96 patients. They ranged in age from 18 to 67 years and included 60 men and 36 women.

**Study Protocol**

Vital signs, hemodynamic data, and pertinent laboratory values were obtained from the medical records. One set of data was obtained in the preoperative period just prior to surgery. Two sets of postoperative data, 7 AM and 7 PM, were recorded for each of the first 2 days of stay in the surgical ICU. Postoperative use of hemodialysis or continuous arteriovenous hemofiltration/dialysis, the duration of intubation, the use of vasopressors, the date of discharge from the surgical ICU, the disposition and date of hospital discharge, the date and cause of death, and hospital charges (including pretransplant hospital stay) were recorded. Causes of death were recorded as: (1) multiple organ failure, (2) cerebral hemorrhage, (3) cardiovascular failure, or (4) sepsis. These data were obtained from review of each nonsurvivor's death summary.

Patients were defined as survivors if they left the hospital alive or as nonsurvivors if they died during their hospital stay. Postoperative organ failures were determined for each patient. These could occur at any time during the hospitalization and included the following: (1) central nervous system failure, (2) renal failure, (3) pulmonary failure, (4) cardiovascular failure, and (5) hepatic failure. Definitions for organ failure were chosen and are listed in Table 1. Multiple organ failure was defined as the failure of two or more organ systems. The following outcomes were determined for each group: (1) ICU length of stay (ICU discharge date/death minus transplant date) and (2) the hospital length of stay (hospital discharge date/death minus transplant date). Severity of illness preoperatively was assessed according to the criteria of the acute physiology and chronic health evaluation (APACHE) II scoring system. Information on hospital charges (from admission date to discharge/death date) was provided by New England Medical Center.

**Measurements**

All patients underwent peripheral and pulmonary artery (Swan-Ganz catheter, American Edwards) catheterization with continuous arterial and pulmonary artery pressure monitoring. All pressures were recorded with the patient in the supine position using strain-gauge transducers, with zero references at the midchest level and calibrated to a known mercury standard. Thermodilution cardiac output was taken as the average of three measurements using 10 mL of 5% dextrose in water injected at room temperature. A sample of arterial blood was drawn for measurement of all laboratory values (arterial blood gas levels, hemoglobin value, total bilirubin level, prothrombin time, aspartate aminotransferase). Measured hemodynamic variables included blood pressure, heart rate, pulmonary artery pressure, central venous pressure, pulmonary artery wedge pressure (PAWP) and cardiac output. Calculated variables included mean arterial pressure (MAP), CI, stroke volume index (SVI), arterial oxygen saturation, arterial oxygen content, and DO₂. These calculations were performed as:

- Body surface area=\[\text{Height} \times \text{Weight} / 3,600\]^\frac{0.73}{3};
- Mean arterial pressure (MAP)=\left(\frac{\text{systolic BP} + (2 \times \text{diastolic BP})}{3}\right);
- CI=\left(\frac{\text{cardiac output}}{\text{body surface area}}\right) \times 1,000;
- Left ventricular stroke work index (LVSWI)=\left(\frac{\text{MAP} - \text{PAWP}}{\text{SVI}}\right) \times 0.036;
- Systemic vascular resistance index=\left(\frac{\text{MAP} - \text{CI}}{\text{SVI}}\right);
- Arterial oxygen saturation=\left(100 - \frac{[23,400/\text{PaO₂}^3 + 150 \text{PaO₂}^3]}{100}\right)^{21}.
- Arterial oxygen content=\left(\frac{\text{Arterial oxygen saturation} \times \text{hemoglobin} \times 1.34}{10}\right) + (\text{PaO₂} - 0.003); and
- DO₂=\left(\frac{\text{CI} \times \text{arterial oxygen content}}{10}\right).

Blood lactate and mixed venous blood gas values were not routinely drawn or available during the study period; oxygen consumption and extraction could not be calculated. Available hemodynamic measurements taken at 7 AM and 7 PM from each of the first two postoperative days were studied. The average of these four measurements was calculated as a mean postoperative value.

**Statistical Analysis**

The APACHE scores, number and type of organ failure, and preoperative and postoperative hemodynamic parameters were
examined for significance between survivors and nonsurvivors. Data were analyzed by the Mann-Whitney test for APACHE II scores and cost; repeated measures analyses of variance were performed to evaluate the hemodynamic data; logistic regression was used for relating organ failure to survival and linear regression for relating organ failure to hemodynamics. Differences were considered statistically significant at a probability value of less than 0.05. All data are reported as numbers, mean±SE, or medians (range).

RESULTS

Clinical Characteristics and Utilization of Resources

The mortality rate following LT was 15% (n=14). The most common cause of death was multiple organ failure (n=5; 36%) followed by cerebral hemorrhage (n=4), cardiovascular failure (n=3), and sepsis (n=2). The clinical characteristics comparing survivors and nonsurvivors of LT are shown in Table 2. A higher preoperative severity of illness, as assessed by the APACHE II scoring system, was significantly related to a poor outcome. Moreover, nonsurvivors required a longer median hospital length of stay and incurred greater median hospital charges (Mann-Whitney test).

Hemodynamic Parameters

Table 3 compares the preoperative and postoperative hemodynamic profiles of survivors and nonsurvivors. Preoperatively, both groups demonstrated an elevated CI as typically seen with advanced liver disease. In both the preoperative and postoperative periods, survivors demonstrated significant hemodynamic increases in MAP, SVI, CI, LVSWI, and DO2 as compared with values of nonsurvivors (p<0.01). The CI in nonsurvivors was decreased even though nonsurvivors had a higher mean heart rate than survivors (99±5 vs 85±2 beats per minute; p<0.01).

Survivors and nonsurvivors showed significant hemodynamic changes between the preoperative and postoperative periods (Table 3). For both survivors and nonsurvivors, SVI, CI, and DO2 declined postoperatively from baseline preoperative values.

We also investigated postoperative hemodynamic trends between survivors and nonsurvivors over each time point (Fig 1). The decrease in LVSWI, CI, and DO2 in nonsurvivors was most marked during the first 12 postoperative hours (for all tests, p<0.03). This decline in cardiac function and oxygen transport

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**Table 2—Clinical Characteristics and Resource Variables in Survivors and Nonsurvivors of Orthotopic Liver Transplantation**

<table>
<thead>
<tr>
<th>Parameters*</th>
<th>Survivors (n=82)</th>
<th>Nonsurvivors (n=14)</th>
<th>Probability Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45±1</td>
<td>47±3</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td>6 (2-24)</td>
<td>10 (2-23)</td>
<td>0.029</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>27 (14-183)</td>
<td>13 (1-86)</td>
<td>0.193</td>
</tr>
<tr>
<td>Hospital charges</td>
<td>$135,432</td>
<td>$191,997</td>
<td>0.002</td>
</tr>
<tr>
<td>(n=82)</td>
<td>($55,816-$666,752)</td>
<td>($117,920-$827-831)</td>
<td></td>
</tr>
</tbody>
</table>

*Parameters are reported as numbers (sex), means±SE (age), or median (range [APACHE II, ICU and hospital length of stay, hospital charges]).
†APACHE II preoperative score.

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**Table 3—Comparison of Hemodynamic Parameters Between Survivors and Nonsurvivors of Orthotopic Liver Transplantation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Differences†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors</td>
<td>Nonsurvivors</td>
<td>Survivors</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>85±1</td>
<td>78±5</td>
<td>100±1</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>89±2</td>
<td>80±5</td>
<td>85±2</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>13±1</td>
<td>15±2</td>
<td>15±0.4</td>
</tr>
<tr>
<td>SVI, mL/beat·m²</td>
<td>61±2</td>
<td>54±7</td>
<td>52±2</td>
</tr>
<tr>
<td>CI, L/min·m²</td>
<td>5.3±0.2</td>
<td>4.2±0.5</td>
<td>4.5±0.1</td>
</tr>
<tr>
<td>LVSWI, g·m/m²</td>
<td>58±2</td>
<td>49±8</td>
<td>60±2</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne·s/cm²·m²</td>
<td>1,460±69</td>
<td>1,799±287</td>
<td>1,998±62</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.5±1.2</td>
<td>9.6±1.1</td>
<td>11.5±1.4</td>
</tr>
<tr>
<td>DO2, mL/min·m²</td>
<td>736±30</td>
<td>552±88</td>
<td>637±18</td>
</tr>
</tbody>
</table>

*Parameters are reported as means±SE.
†Postoperative values are averages of four standard readings on the first two postoperative days.
†A—survivors vs nonsurvivors, p<0.01. B—preoperative versus postoperative, p<0.01.
in nonsurvivors was then followed by a general recovery over the following 36 h.

Prediction of Survival by Hemodynamic Parameters

For each of the hemodynamic variables, the midpoint of the means for survivors and nonsurvivors was used as a cutpoint (similar to discriminant function analysis); the sensitivity and predictive values were calculated. By this analysis, there was no sensitive hemodynamic determinant of nonsurvival. Heart rate had the highest predictive value for death, at 30%. Predictive values for death by LVSWI, CI, and DO2 were 21, 22, and 21%, respectively.

Organ Failure and Death Following Liver Transplantation

The numbers of organ failures per patient between survivors and nonsurvivors were compared. There were a total of 54 organ failures among 82 survivors as compared with 45 organ failures among just 14 nonsurvivors. Nonsurvivors sustained a fivefold greater incidence of organ failures. Logistic regression showed outcome (survival or death) to be significantly associated with the number of organ failures (p<0.0001). The analysis gives an estimated odds ratio of 5.78 (95% confidence interval: 2.43 to 13.79) suggesting an approximate sixfold increase of risk of death for each additional organ failure. All six patients with four or more organ failures died.

We investigated the relationship between total organ failure and hemodynamic variables; only postoperative stroke volume was significantly correlated with the number of organ failures, and this correlation was minimal (r²=0.05; p=0.027).

Discussion

Critically ill patients with lower levels of DO2 may have a propensity toward organ failure and a higher mortality rate. Shoemaker and colleagues, Fleming et al., Shoemaker et al., Bishop et al., and Shoemaker et al. have promoted the idea that high-risk surgical patients may accrue intraoperative and postoperative tissue oxygen debts that must be repaid with supranormal levels of DO2 by methods of aggressive hemodynamic resuscitation. Observational studies in general surgical and in hemorrhagic trauma populations have identified the association between survival and higher levels of CI and DO2. Prospective, randomized, controlled trials performed by the same investigators using predetermined goal-directed levels of CI (≥4.5 L min⁻¹ m⁻²) and DO2 (≥600 mL/min m⁻²) as therapeutic endpoints have demonstrated less organ failure and improved survival. The notion that high-risk surgical patients should receive supranormal resuscitation to meet theoretical perioperative tissue oxygen deficits has not yet been fully embraced by the critical care community. Validation of this potentially important idea will most likely occur only after other investigators reproduce the same findings independently at other study sites.

We studied the early hemodynamic patterns of 96 adults following LT, a costly and resource-intensive high-risk surgical procedure. Survivors were characterized by higher levels of MAP, SVI, LVSWI, CI, and DO2 when compared with nonsurvivors in both the preoperative and postoperative periods; the de-
crease in cardiac function seen in nonsurvivors was most marked during the first 12 postoperative hours (Fig 1). The relative reduction in systemic blood flow following transplantation was chiefly attributable to a decrease in ventricular function, as reflected by decreases in stroke output and work. The fall in CI in nonsurvivors might have been more remarkable had nonsurvivors not manifested a significant and compensatory increase in heart rate. These findings indicate that nonsurvivors of LT experience early postoperative cardiac failure relative to survivors. Shoemaker and colleagues, recently made the same observation in their recently reported hemodynamic study of 708 consecutive high-risk surgical patients (exclusive of LT).

There may be several explanations for the reduced cardiac performance seen in this series of nonsurvivors. Although the postoperative mean PAWP of 14 ± 2 mm Hg seen among nonsurvivors may represent an inadequate preload, there was no significant difference in PAWP between survivors and nonsurvivors. Therefore, inadequate preload, by itself, is unlikely to fully explain the decrease seen in ventricular function. An excessive afterload would impair cardiac flow; however, systemic vascular resistance index was not elevated and did not differ between groups. Depression of intrinsic myocardial contractility would be one plausible explanation for the reduced LVSWI and CI in nonsurvivors. Moreover, CI was reduced in nonsurvivors as compared with survivors, both preoperatively and postoperatively, suggesting that nonsurvivors may have had less pretransplant cardiac reserve. The hemodynamic observations made in this study will need to be validated by more advanced and reliable measurements of ventricular function, e.g., ejection fraction, before conclusions can be drawn about cardiac performance following LT.

How else can the postoperative reduction in ventricular function among LT patients be explained? Recent studies have suggested that in LT an inflammatory response develops which is accompanied by the release of circulating mediators, such as endotoxin and tumor necrosis factor, both of which have been implicated as independent myocardial depressants during critical illness. Intraoperative manipulation of the visera and its vascular supply during LT may facilitate the release of endotoxin and initiation of the cytokine cascade. Alternatively, reperfusion of the ischemic donor organ has been shown to increase serum concentrations of tumor necrosis factor during LT. Early postoperative myocardial depression in patients undergoing LT may be multifactorial, with independent factors having an additive effect; patients with less cardiac reserve pretransplant may be more susceptible to cardiac failure in the face of cytokine release after LT.

Previous studies have linked relative reductions in DO2 with organ failure in nonsurvivors of high-risk surgery. We have now made this observation in patients following LT. Nonsurvivors of LT incur organ failure at a rate fivefold greater than that of survivors. Whereas 66% of survivors in this series experienced no single organ failure, 93% of nonsurvivors had at least two organ failures, i.e., multiple organ failure. Each additional organ failure conferred a sixfold higher predicted mortality; four or more organ failures yielded a 100% mortality rate (Fig 2). These findings are consistent with those of other studies examining the relationship between multiple organ failure and death in critically ill patients.

The only report to study organ failure in LT was that by Kamath et al in which 15 patients with primary graft failure were evaluated. All five of their patients with four or more organ failures died; these findings match the results in our study (Fig 2).

Nonsurvivors of LT were typified by relatively lower levels of CI and DO2, a hemodynamic pattern associated with greater organ failure. Such an association may simply represent an epiphenomenon rather than a true cause and effect relationship given that no clear correlation could be determined between DO2 or other nonsurvivor hemodynamic variables, and death or organ failure in this study. Whether acute postoperative reductions in DO2 cause organ failure in high-risk surgical patients will only be answered through prospective testing of large number of patients with carefully defined endpoints and close inspection of the temporal relationship between changes in systemic blood flow and the development of organ failure.

The APACHE II scores as a predictor of postoperative mortality and hospital cost previously have been shown to correlate in critically ill patients. In

![Figure 2. The relationship between organ failure and mortality (p<0.0001). Mortality was 100% for 4 or more organ failures.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21706/)
the present study, preoperative APACHE II scores were associated with a higher incidence of postoperative organ failure, a greater hospital charge, and a greater mortality. These data support the findings of Baliga et al. who found that patients with preoperative extrahepatic organ failure sustain a worse outcome after LT. These authors advocated transplantation earlier in the course of advanced liver disease.

There are several potential limitations to this study. First would be its retrospective design over an 8-year study period. It is possible that other variables, such as advances in immunosuppressive therapy, could have influenced outcome differences between groups. However, this concern is lessened by the observation that deaths were equally distributed over the time period of this study. Another concern would be the relatively small sample size of nonsurvivors (n=14) and patients with four or more organ failures (n=6); conclusions regarding the latter subgroup may not be generalizable even though a statistically significant linear trend was observed between organ failure and mortality. The definitions for organ failure used in this study are at variance with the many different ones used in other studies. At present, no standard accepted definitions for individual organ failures exist; this lack of consensus is a weakness inherent in the field of multiple organ failure and makes it more difficult to compare results between studies.

The data from this study indicate that nonsurvivors of LT are characterized by lower preoperative CI and DO$_2$ and by early postoperative myocardial depression and consequently lower levels of systemic blood flow and DO$_2$. These early hemodynamic trends are followed by progressive organ failure, which is associated with increasing mortality, resource utilization, and hospital charges. These findings do not confirm a cause and effect relationship between DO$_2$ and outcome. Higher preoperative APACHE II scores and lower preoperative and postoperative CI/DO$_2$ ratios in nonsurvivors may be markers of intolerance to critical illness rather than determinants of outcome. Nevertheless, if additional prospective studies confirm an association between diminished DO$_2$ and a poor outcome in LT, then therapeutic trials of augmenting DO$_2$ to improve survival and attenuate organ failure could be indicated. Data obtained from similar investigations in this high-risk group will provide valuable assistance to critical care clinicians as they formulate strategies to provide cost-effective care for these desperately ill patients.

REFERENCES

8 Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s: Systemic inflammatory response and organ dysfunction. JAMA 1994; 271:226-33
14 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high risk surgical patients. JAMA 1993; 270:2699-2707
24 Hotchkiss RS, Karl IE. Re-evaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA 1992; 267:1505-10
35 Crump JM, Duncan DA, Wears R. Analysis of multiple organ system failure in trauma and nontrauma patients. Am Surg 1988; 547:702-08

Hemodynamic Correlates of Outcome in Orthotopic Liver Transplantation (Nasraway et al)

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