Clinical Update in Liver Transplantation

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There has been considerable recent progress liver transplantation (LTX). The postreperfusion syndrome has clearly defined and typically responds to vasopressin in and/or methylene blue when refractory to catecholamine therapy. Diastolic dysfunction and cirrhotic cardiomyopathy are prevalent and important in LTX recipients. The high cardiovascular risk and the increasing medical complexity of the current liver transplant recipient have stimulated the publication of guidelines for cardiovascular assessment before LTX. Cardiac surgery is increasingly more successful in patients with cirrhosis, including simultaneous heart-liver transplantation. Cardiopulmonary bypass in LTX is indicated for hemodynamic rescue and, at some centers, serves as the hemodynamic platform for liver implantation. Although acute renal injury is common after LTX, early diagnosis is now possible with novel biomarkers. Earlier detection of postoperative renal dysfunction may prompt intervention for renal recovery. The metabolic milieu in LTX remains critical. Regular insulin therapy may be more effective than infrequent large bolus therapy for potassium homeostasis. Careful titration of insulin therapy may improve freedom from severe hyperglycemia to decrease morbidity. Since the organization of dedicated anesthesia care teams for LTX improves perioperative outcome, this aspect of perioperative care is receiving systematic attention to optimize safety and quality. The specialty of LTX is likely to continue to flourish even more, given these pervasive advances.

A recent Chinese single-center trial (n = 330; 2005-2009) evaluated the incidence and risk factors for postreperfusion syndrome after LTX according to the standard definition already discussed. Extensive perioperative analysis revealed that this syndrome had an incidence of 17% and that it correlated significantly with perioperative mortality and renal dysfunction. Analysis of preoperative echocardiographic data demonstrated that left ventricular diastolic dysfunction was significantly associated with postreperfusion syndrome. Multivariate analysis isolated 2 independent predictors for this clinically significant syndrome: a prolonged cold ischemia time and left ventricular diastolic dysfunction. This study highlights the clinical importance of diastolic dysfunction in the cardiomyopathy associated with end-stage liver disease. Diastolic dysfunction is a common finding in LTX recipients with an incidence that varies from 16% to 45%, depending in part on the type of pretransplant liver disease.

EXPERT REVIEW

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A single-center North American study \((n = 107; 2001-2009)\) also identified diastolic dysfunction as an independent predictor of heart failure after LTX \((\text{odds ratio } 3.4; 95\%\ CI 1.2-9.4; p = 0.017).^{16} \) In this analysis, heart failure after LTX was defined by a composite of clinical signs and symptoms, radiographic evidence of pulmonary edema, and echocardiographic demonstration of left ventricular dysfunction \((\text{ejection fraction less than } 50\%).\) Diastolic dysfunction was defined as an early mitral inflow velocity/mitral annular velocity ratio greater than 10, a measure that has been validated in multiple clinical settings.\(^11\) According to these definitions, the incidence of heart failure was 24\% after LTX: the incidence of diastolic dysfunction in this cohort was 39\% as compared to 11\% in the control group.\(^10\) This important set of studies has advanced our understanding of cirrhotic cardiomyopathy, a syndrome that is often part of the postreperfusion syndrome and that is only diagnosed during phases of clinical decompensation such as may be experienced during LTX.\(^12\)–\(^13\)

The postreperfusion syndrome may at times be so acute and severe that it precipitates intraoperative cardiac arrest. A recent single-center series \((n = 1581; 1997-2011)\) documented an incidence of 1\% for cardiac arrest associated with the postreperfusion syndrome.\(^14\) The rapid institution of systemic anticoagulation and cardiopulmonary bypass for hemodynamic support frequently facilitated myocardial recovery, resulting in a 14\% intraoperative mortality rate. The investigators also concluded that the rapid institution of cardiopulmonary bypass in this scenario not only maintains cerebral perfusion but also allows restoration of the metabolic milieu.\(^14\) The data from this large series support the central role of cardiopulmonary bypass in the perioperative management algorithm for cardiac arrest associated with the postreperfusion syndrome in LTX.\(^14\) Future trials should explore the development of a risk model for heart failure and cardiac arrest after LTX, including echocardiographic parameters such as diastolic dysfunction and related biomarkers such as natriuretic peptide.\(^15\)

### VASOPLEGIA DURING LIVER TRANSPLANTATION: FOCUS ON VASOPRESSIN AND METHYLENE BLUE

The generalized systemic vasodilation associated with end-stage liver disease may be associated with vasopressin deficiency. A recent trial assessed endogenous vasopressin levels in patients with end-stage liver disease and hemodynamic response to exogenous vasopressin administration during LTX.\(^16\) This study is important because it suggests that, much like the case of septic shock, vasodilation in advanced liver disease is associated with relative vasopressin deficiency.\(^16\)–\(^17\)

This prospective, randomized, single-center observational study analyzed baseline vasopressin levels in 28 patients undergoing LTX as compared to 8 controls without liver disease undergoing comparable major surgery. Patients undergoing LTX had significantly lower baseline vasopressin levels \((p = 0.0015)\) that were significantly associated with lower mean arterial blood pressure \((p = 0.0013).^{16}\) Vasopressin therapy in this setting significantly raised systemic vascular resistance and mean arterial pressure \((p = 0.028).^{16}\)

Given that vasopressin deficiency is common during LTX, it is hardly surprising that vasopressin administration is an option for hemodynamic rescue in catecholamine-refractory vasoplegia during LTX, especially if associated with severe postreperfusion syndrome.\(^18\)–\(^19\) Furthermore, if this vasoplegia precipitates left ventricular outflow tract obstruction with associated mitral regurgitation, vasopressin therapy can facilitate pharmacologic reversal of this adverse hemodynamic scenario.\(^20\)–\(^22\) The renal outcome benefits of perioperative therapy with the vasopressin analogue, terlipressin, were recently highlighted in an open-label single-center prospective randomized trial.\(^23\)–\(^24\) The main finding of this trial was that perioperative terlipressin in LTX significantly improved postoperative renal function with no adverse effects on hepatopulmonic function.\(^23\) Further trials are required to confirm this encouraging finding.

The vasoplegia associated with the postreperfusion syndrome in LTX may not only be refractory to catecholamine therapy but also to intervention with vasopressin.\(^25\) Methylene blue is an established rescue agent in perioperative vasoplegia refractory to vasopressin and catecholamine therapy, including LTX.\(^25\)–\(^27\) This hemodynamic rescue is clinically important because the postreperfusion syndrome during LTX has been associated with adverse graft function. Since nitric oxide may play a role in the development of vasoplegia in LTX, the clinical utility of methylene blue make physiologic sense since it inhibits inducible nitric oxide synthetase to restore systemic vascular tone.\(^25\)–\(^27\)

A recent single-center retrospective observational trial \((n = 715; 2003-2008)\) evaluated the outcome effects of methylene blue therapy as a bolus prior to graft reperfusion in LTX.\(^28\) After propensity score matching, exposure to prophylactic methylene blue had no significant effect on hemodynamic profiles, graft function, and graft survival.\(^28\) In contrast, an earlier randomized trial \((n = 36)\) demonstrated that prophylactic methylene blue prior to graft reperfusion significantly raised systemic mean arterial pressure \((p = 0.035),\) cardiac index \((p = 0.04)\) with significant reduction in inotrope requirement \((p = 0.02)\) and serum lactate \((p = 0.03).^{29}\) This study also demonstrated that these beneficial effects of methylene blue were associated with inhibition of guanylate cyclase, an enzyme whose activation is significantly associated with the postreperfusion syndrome in LTX.\(^30\) Further randomized trials are required to explore the outcome effects of methylene blue in LTX. Nevertheless, methylene blue remains a clinically useful agent for hemodynamic rescue during LTX when catecholamine and vasopressin therapy are ineffective.

### LIVER TRANSPLANTATION AND CONCOMITANT CARDIAC SURGERY

Cardiac surgery in the setting of end-stage liver disease typically is higher risk for perioperative liver failure due to multiple processes such as hypoperfusion, ischemia-reperfusion injury, cardiopulmonary bypass, and the systemic inflammatory response.\(^31\) In the setting of severe liver dysfunction as reflected by the Child-Turcotte-Pugh class or the Model for End-Stage Liver Disease score, LTX combined with the required cardiac surgical procedure is proving to be an increasingly prevalent strategy, given the prohibitive risk of liver failure in this setting without LTX.\(^31\)
RENAI DYSFUNCTION AFTER LIVER TRANSPLANTATION

Although common, the reported incidence of acute kidney injury following LTX varies significantly, depending on the criteria chosen to define the syndrome.\(^{41-42}\) Renal dysfunction continues to be a research priority because it is both common and independently predicts adverse clinical outcomes both in the short- and long-term after LTX.\(^{43}\) Traditional markers of renal function in the perioperative period such as urine output and serum creatinine are confounded by clinical issues such as lack of specificity and sensitivity.\(^{44}\) Given these considerations, novel biomarkers for detection of renal injury such as neutrophil gelatinase-associated lipocalin (NGAL) have attracted considerable interest due to superior diagnostic sensitivity and specificity in LTX.\(^{45-46}\) This release of NGAL in the urine within hours after renal injury may allow the rapid detection of clinically important renal dysfunction to allow early institution of perioperative intervention.

This possibility has recently been explored further in clinical studies. In a single university center study (n = 92), urinary NGAL levels were evaluated at regular intervals after LTX.\(^ {47}\) Trial exclusion criteria included preoperative renal dysfunction, including patients requiring renal replacement therapy. The investigators chose to represent NGAL levels as urinary NGAL/urine creatinine ratios to control for variations in urinary concentration. Acute kidney injury in this trial was defined by the accepted risk, injury, failure, loss, endstage kidney disease (RIFLE) criteria.\(^ {48}\)

The incidence of acute kidney injury was 40.2%, as defined by RIFLE criteria.\(^ {47}\) The urinary NGAL/urine creatinine ratio significantly predicted the development of acute kidney injury at both 3 hours (area under the curve 0.800; 95% CI 0.732-0.869; p<0.0001) and 18 hours after graft reperfusion (area under the curve 0.636; 95% CI 0.551-0.720; p<0.005).\(^ {47}\) In this trial, serum creatinine only distinguished significantly the subgroup with acute kidney injury by 48 hours after graft reperfusion, a clinically significant delay as compared with the discriminatory power of NGAL.

This study corroborates previous evidence that renal dysfunction is a common complication following LTX. It is among the first, however, to demonstrate that a novel urine biomarker, NGAL, predicts postoperative renal dysfunction both accurately and early after LTX. Perhaps more importantly, the earlier detection of renal injury by NGAL may allow for interventions to mitigate the severity of renal damage. For example, postoperative immunosuppression regimens may be tailored to eliminate nephrotoxins such as calcineurin inhibitors. Earlier identification may augment future understanding of the pathogenesis of renal dysfunction after LTX and thus aid in the development of future renal protective strategies and interventions.\(^ {43-44}\) Future investigations in this area will likely have more power as multicenter clinical trial registries, and consortia have now emerged in hepatology and LTX: these collaborative efforts have renal outcomes and protection as a research priority.\(^ {49-50}\)

METABOLIC MANAGEMENT DURING LIVER TRANSPLANTATION

Hyperkalemia in LTX matters because it remains common and still independently predicts mortality after LTX.\(^ {51-52}\) An international multicenter study (n = 5942) demonstrated that hyperkalemia independently predicted mortality in the first year after adult LTX (hazard ratio 1.38; 95% CI 1.01-1.88).\(^ {51}\) Published predictors of hyperkalemia before reperfusion included high baseline serum potassium and red blood cell transfusion, while during reperfusion, hyperkalemic predictors also included prolonged warm ischemia time, lower intraoperative urine output, and exposure to venovenous bypass.\(^ {52}\)
A large single academic medical center study (n = 717; 2004-2007) demonstrated that regular divided doses of insulin, as compared to large bolus therapy, significantly lowered blood glucose and serum potassium levels during LTX.\textsuperscript{53} This study is important, as hyperkalemia is a common and potentially life-threatening complication during liver transplantation, particularly during the reperfusion phase. The incidence of hypoglycemia in this trial did not depend on the type of insulin regimen.

The regular insulin regimen in this trial facilitated better intraoperative glucose control in LTX which is frequently associated with disturbances in glucose homeostasis on a multifactorial basis.\textsuperscript{54-55} Recent trials have demonstrated that severe hyperglycemia (defined as serum glucose $>200$ mg/dL) during LTX is significantly associated with graft rejection (when blood glucose $<200$ mg/dL, odds ratio 0.055; 95% CI 0.0154-0.200; $p<0.001$), surgical site infection (odds ratio 2.25; 95% CI 1.26-4.03; $p = 0.006$), and mortality at i-year (21.9% v 8.8%; $p = 0.05$).\textsuperscript{56-58} In light of these adverse outcome associations after LTX due to hyperglycemia, recent recommendations suggest that modest glucose control would be reasonable in LTX (target blood glucose of $<150$ mg/dL).\textsuperscript{55}

Cardiovascular Risk after Liver Transplantation

Cardiovascular disease has emerged as a leading cause of mortality after LTX.\textsuperscript{59} It is likely that cardiovascular morbidity and mortality will continue to increase after LTX as clinical outcomes improve and increasing high risk patients are transplanted. A recent large, single-center trial (n = 773, with a mean age of 53.3 years: 1996-2008) evaluated the incidence and risk of cardiovascular events in the first 3 years after LTX.\textsuperscript{60} In this trial, patients who were deemed to be at excessive cardiovascular risk were excluded from LTX. Prohibitive cardiovascular risk factors during LTX evaluation included left ventricular dysfunction (defined as an ejection fraction $<45\%$), right ventricular dysfunction, severe pulmonary hypertension, significant structural valvular heart disease, uncorrectable coronary artery disease with inducible ischemia by stress testing, significant carotid disease, and diffuse peripheral atherosclerotic disease.\textsuperscript{60} The primary trial endpoint was the occurrence of post-transplant cardiovascular events such as acute coronary syndrome, stroke, heart failure, arrhythmia, and peripheral arterial disease.

The incidence of patients experiencing cardiovascular events was 10.7%. Multivariate analysis identified the following independent predictors for cardiovascular events after LTX: older age at transplantation (odds ratio 1.2; 95% CI 1.1-1.3; $p = 0.006$); male sex (odds ratio 2.0; 95% CI 1.2-3.3; $p = 0.01$); post-transplant diabetes (odds ratio 2.0; 95% CI 1.3-3.3; $p = 0.003$); post-transplant hypertension (odds ratio 1.8; 95% CI 1.1-3.0; $p = 0.02$); and mycophenolate mofetil exposure (odds ratio 2.0; 95% CI 1.3-3.2; $p = 0.003$).\textsuperscript{60}

In the early postoperative period, cardiac complications continue to be the leading cause of mortality.\textsuperscript{61} A recent single-center Canadian trial (n = 197; 2002-2007) identified the following independent factors for cardiac complications in the early postoperative period: adverse intraoperative cardiovascular events (odds ratio 5.89; 95% CI 1.82-19.14), history of cardiac disease (odds ratio 2.42; 95% CI 0.89-6.6), and high model for end-stage liver disease score (odds ratio 1.08; 95% CI 1.02-1.14).\textsuperscript{61} Although cardiac arrest after graft reperfusion only has a $1\%$ incidence, it frequently requires open cardiac massage.\textsuperscript{62-63} A recent large, single-center study (n = 1581: 1997-2011) demonstrated that early institution of cardiopulmonary bypass in this setting frequently was life-saving as it facilitated correction of electrolyte derangements, maintenance of systemic perfusion, and gradual myocardial recovery.\textsuperscript{14}

Recent data has highlighted that pulmonary thromboembolism frequently presents with cardiac arrest in the postreperfusion period in LTX, even though its incidence is only about 4.0% (20 out of 495 total cases: 2004-2006).\textsuperscript{63} In this trial, the diagnosis of pulmonary thromboembolism was based on the following criteria: acute cor pulmonale, observation of thrombi in the pulmonary vasculature, and, echocardiographic detection of right heart pressure overload with or without identification of intracardiac clot.\textsuperscript{63}

The contemporary literature has thus focused on cardiovascular risk after LTX because it is common and determines post-transplant outcome both in the short- and long-term. Given the increasing age, higher medical acuity, and greater cardiovascular comorbidity in liver transplant candidates, it is hardly surprising that there has been a strong focus on comprehensive preoperative cardiovascular assessment in LTX, including guidelines from the American Heart Association.\textsuperscript{64-66} Further clinical trials will likely refine these guidelines even further, including the promising technology of preoperative coronary risk assessment with computed tomographic coronary arteriography.\textsuperscript{67}

ORGANIZATION OF ANESTHESIA CARE FOR LIVER TRANSPLANTATION

The organization of anesthetic care significantly affects patient outcomes after LTX.\textsuperscript{68} Despite this observation, sparse details have been published about the delivery of anesthetic care in different transplant centers. A recent multicenter trial by the Liver Transplant Anesthesia Consortium evaluated, by web-based survey, the organization of anesthetic teams for LTX at adult transplant centers across the United States.\textsuperscript{69} In this trial, the response rate was 71%. Participating centers were categorized as high-volume, medium-volume, or low-volume based on annual LTX frequency.

All programs had a dedicated transplant team, although the criteria for membership differed between centers. Large- and medium-volume centers relied on on-the-job training for team members, whereas low-volume centers relied on postgraduate training in cardiovascular or intensive care anesthesia.\textsuperscript{60} A call system was utilized to ensure constant availability for liver transplantation, although only 30% of centers employed the transplant team for subsequent emergent surgery within 72 hours of transplant. Liver transplant anesthesiologists participated in routine preoperative evaluation in 100%, 79%, and 86% of large, medium, and small-volume centers, respectively. A standard preoperative and intraoperative protocol was employed at the majority of centers. Involvement of the transplant anesthesia team in postoperative care was low across all centers. While 80% of programs reported regular attendance
at multidisciplinary morbidity and mortality conference, regular team meetings (including journal club and other educational activities) occurred in only 35% of centers.69 This study suggests that while the existence of a dedicated liver transplant anesthesia team is consistent across academic centers, significant variation persists in the criteria for team membership, involvement in postoperative care and quality assurance measures. Furthermore, LTX center volume was associated with trends in delivery of anesthetic care. This study is among the first to attempt to categorize the current organization of liver transplant anesthesia teams at academic centers across the United States. As with any survey, the potential exists for response bias. It is important to recognize that the results of this study were limited to adult academic centers, and may not be applicable to pediatric or private centers. The importance of organized dedicated anesthesia services for LTX has resulted in a call by the United Network for Organ Sharing for all programs to appoint a director of anesthesiology for LTX. Recent data from the Liver Transplant Anesthesia Consortium suggest that this quality metric has been adopted by all programs and that there was increasingly greater uniformity in the criteria for this directorship position.70

The organization of anesthetic care for LTX was also recently evaluated throughout Italy.71 This trial presents an analysis of survey data regarding the current perioperative practices for LTX at the 22 designated LTX centers in Italy.71 The response rate was 77.3%. Of those sites surveyed, 2 were classified as high-volume (>100/year), 5 as moderate-volume (50-100/year), and 10 as low-volume (<50/year) LTX centers.

Clinical practice during the perioperative period varied widely between different institutions. All centers reported a specific preoperative evaluation protocol prior to surgery, but differences existed between required preoperative testing and the participation of the anesthesia team in preoperative patient selection. While 94% of centers reported the utilization of a balanced anesthesia protocol, center-specific protocols for LTX existed in only 70.5% of participating sites with significant variability in the choices of invasive hemodynamic monitoring techniques, availability of point-of-care resources such as thromboelastography and rapid infusers, blood product utilization, and use of vasoactive medications.71 Procedure-specific training and ongoing education varied widely between centers.

Of note, all centers reporting lower preoperative involvement, fewer available intraoperative resources, and less LTX-specific education and training were characterized as moderate- or low-volume. Postoperatively, patients are typically admitted to general surgical intensive care units under the supervision of anesthesiologists, given the availability of a dedicated liver transplant specific intensive care unit at only the highest volume centers in Italy. An early tracheal extubation protocol was practiced at 52.9% of centers, although the definition of early tracheal extubation varied between centers.

This study demonstrates significant variation in perioperative care at different OLT transplant centers in Italy. Despite evidence to suggest that standardized care by a dedicated team improves outcomes in LTX, this study adds to the literature demonstrating that further standardization is required in the delivery and organization of anesthetic care in LTX.72-73 Further study is warranted to evaluate LTX outcomes at different centers in an attempt to define a standardized “best practice” perioperative approach for enhanced safety, quality and clinical outcome.

CONCLUSIONS

There has been considerable recent progress in the field of LTX. The postreperfusion syndrome has been more clearly defined and may respond to vasopressin and/or methylene blue when refractory to catecholamine therapy. The outcome importance of diastolic dysfunction and criothetic cardiomyopathy has also recently been highlighted. The high cardiovascular risk after LTX and the increasing medical complexity of the current liver transplant recipient have together stimulated the development of expert consensus and guidelines for systematic cardiovascular assessment before LTX. Cardiac surgery is increasingly more common in patients with significant liver disease and may also include simultaneous heart-liver transplantation. The role of cardiopulmonary bypass in LTX includes hemodynamic rescue and, at some centers, is the hemodynamic platform for liver implantation. Although acute renal injury is common and important after LTX, early diagnosis is now possible with novel biomarkers such as neutrophil gelatinase-associated lipocalin. Earlier detection of postoperative renal dysfunction may prompt time-sensitive intervention for renal rescue. The metabolic milieu in LTX remains critical. Hyperkalemia is common and may be life-threatening: regular insulin therapy may be more effective than infrequent large bolus therapy for potassium rescue. The metabolic milieu in LTX also includes hemodynamic rescue and, at some centers, is the hemodynamic platform for liver implantation. Although acute renal injury is common and important after LTX, early diagnosis is now possible with novel biomarkers such as neutrophil gelatinase-associated lipocalin. Earlier detection of postoperative renal dysfunction may prompt time-sensitive intervention for renal rescue. The metabolic milieu in LTX remains critical. Hyperkalemia is common and may be life-threatening: regular insulin therapy may be more effective than infrequent large bolus therapy for potassium rescue. Careful titration of insulin therapy may also better control serum glucose to avoid severe hyperglycemia which has been associated with adverse perioperative outcomes. The organization of anesthesia care teams for LTX improves perioperative outcome. Recent trials suggest that this aspect of perioperative care is receiving systematic attention to optimize safety and quality. The specialty of LTX is likely to grow and flourish even more, given these pervasive advances.

REFERENCES

54. Merritt WT: Metabolism and liver transplantation: review of perioperative issues. Liver Transpl 6 (suppl 1):S76-S84, 2000
70. Mandell MS, Pomfret EA, Steadman R, et al: Director of anesthesiology for liver transplantation: Existing practices and recommendations by the united network for organ sharing. Liver Transpl 2013, [Epub ahead of print]