The Perioperative Management of Patients Undergoing Combined Heart-Liver Transplantation

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Background. Combined heart-liver transplantation (CHLT) is an uncommonly performed procedure for patients with coexisting cardiac and liver disease. Methods. A retrospective review was performed of patients undergoing CHLT at our institution from 1999 to 2013. Information related to preoperative organ function, intraoperative management, surgical approach, transfusions, postoperative findings, and 30-day mortality was reviewed. Results. Twenty-seven CHLT were performed, with 4 of the 27 including simultaneous kidney transplantation. Familial amyloidosis was the indication for 21 CHLTs (78%), and 12 of these explanted livers were used for domino transplantations. Nineteen patients (70%) were receiving inotropic infusions at the time of organ availability. Median preoperative model for end-stage liver disease score was 12. Liver transplantation immediately preceded cardiac transplantation in 2 of the 27 cases because of the presence of high titer donor-specific antibodies and the potential of the liver to lead to a reduction in the antibody titer. Venovenous bypass was used in 14 operations (52%) which were performed with the caval interposition approach to liver transplantation, cardiopulmonary bypass during liver transplantation in two cases (7%), and no bypass in 11 operations (41%) performed with caval sparing (piggyback) surgical technique. Postoperatively, median duration of mechanical ventilation, intensive care unit stay, and hospital stay until discharge were 1 day, 5.5 days, and 15 days, respectively. Transfusions in the first 48 hr after CHLT were not substantial in most patients. One patient died within 30 days of CHLT. Conclusion. Combined heart-liver transplantation is a life-saving operation that is performed with relatively low mortality and can be successfully performed in select patients with congenital or acquired cardiac disease.

RESULTS

Twenty-seven patients underwent CHLT, with 4 of the 27 patients undergoing simultaneous kidney transplantation. Mean age at time of transplantation was 53.8±9.7 years (median, 57 years; range, 29–66 years), and 16 of the 27 patients (59%) were men. Preoperative findings are listed in Table 1. A wide variety of echocardiographic findings were present preoperatively (Table 2). No patient had undergone prior heart or liver transplantation. One patient had received dialysis within 1 week before CHLT.
Seven patients received preoperative transfusions within 24 hr of CHLT. Preoperative transfusions consisted of fresh frozen plasma (range, 1–3 units) given for reversal of warfarin anticoagulation (four patients), for plasma exchange and warfarin anticoagulation reversal (2 patients), or for plasma exchange without preoperative warfarin use (one patient). Three patients underwent preoperative plasma exchange for donor-specific antibodies.

Details related to intraoperative management are listed in Table 3. Vascular access consisted of radial and femoral arterial lines and a 9 Fr introducer with a pulmonary artery catheter placed in the internal jugular vein in all cases. Additionally, all cases used an additional 8.5 Fr quad lumen central line, 8.5 Fr single lumen cannula inserted into an internal jugular vein, and 1–2 8.5 Fr peripheral venous catheters in the antecubital fossae. Transesophageal echocardiograms were performed in all patients. No patient required an intraaortic balloon pump intraoperatively.

Intraoperative anesthetic management consisted of a team-based approach with separate cardiac and liver transplantation anesthesia teams involved during transplantation of respective organs. After induction of anesthesia and endotracheal intubation, anesthesia was maintained with isoflurane in air or oxygen. Neuromuscular blockade was maintained with cisatracurium, vecuronium, or pancuronium. Inotropic and vasoactive infusions present 10 min after cardiopulmonary bypass (CPB) separation after cardiac transplantation and 10 min after liver graft recirculation are listed in Table 4. Ten minutes after CPB separation after cardiac transplantation, two patients were receiving inhaled nitric oxide and two inhaled alprostadil.

Ten minutes after liver graft recirculation, seven patients were receiving inhaled nitric oxide and two inhaled alprostadil.
TABLE 3.
Intraoperative management of patients undergoing combined heart-liver transplantation

| Order of operation | 25 (93%) heart transplantation before liver transplantation |
|--------------------|-----------------------------------------------------------|
| Use of bypass for liver transplantation | 2 (7%) liver transplantation before heart transplantation |
| Caval interposition or sparing technique used for liver transplantation | 11 (41%) none |
| Antifibrinolytic use | 14 (52%) venovenous bypass |
| | 2 (7%) cardiopulmonary bypass |
| | 14 (52%) caval interposition |
| | 13 (48%) caval sparing (piggyback) |
| | 6 (22%) none |
| | 8 (30%) aminocaproic acid |
| | 8 (30%) aprotinin |
| | 5 (18%) tranexamic acid |
| Duration of operation<sup>a</sup>, min | Mean, 760±125; median, 754; range, 545-1124 |
| Donor heart ischemic time, min | Mean, 141±57; median, 142; range, 58-257 |
| Donor liver ischemic time, min | Mean, 390±104; median, 413; range, 151-536 |
| Cardiopulmonary bypass duration, min | Mean, 134±40; median, 122; range, 82-244 |
| Anhepatic period duration, min | Mean, 62±11; median, 61; range, 45-82 |
| Red blood cell transfusion, units | Mean, 7.7±5.8; median, 6.0; range, 1-26 |
| Autologous cell salvage use, L | Mean, 2.0±1.2; median, 1.8; range, 0.5-6.8 |
| Fresh frozen plasma transfusion, units | Mean, 7.7±4.9; median, 7.0; range, 0-23 |
| Platelet transfusion (apheresis units) | Mean, 2.5±2.1; median, 2.0; range, 0-8 |
| Cryoprecipitate transfusion (number of pooled units administered) | Mean, 1.7±1.9; median, 1.0; range, 0-6 |

<sup>a</sup> Venovenous bypass consisted of a double-limb (femoral and portal vein) inflow with a dedicated internal jugular outflow cannula.

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Twelve explanted livers from patients with familial amyloidosis undergoing CHLT were used for domino liver transplantations. The liver transplantation portions of these 12 CHLTs were performed using the caval interposition technique and venovenous bypass (VVB). Two additional patients (one familial amyloidosis and one idiopathy cardiomyopathy with congestive hepatopathy) underwent CHLT using the caval interposition liver transplantation approach and VVB. The livers were not used for domino transplantation because of advanced fibrosis. Eleven patients underwent CHLT using the piggyback (caval sparing) liver transplantation technique without VVB. In two patients, CPB was used during transplantation of both the heart and liver (both using piggyback liver transplantation techniques). One case, previously reported in detail, involved liver transplantation before cardiac transplantation to protect the cardiac graft from high titer donor-specific antibodies. Cardiopulmonary bypass was initiated during the anhepatic phase before hepatic reperfusion to facilitate reduction in hepatic venous pressure for the liver graft. The second case involved a donor who sustained a cardiac arrest during organ retrieval because of hemorrhagic shock and was placed on CPB in an attempt to improve cardiac function. Cardiac transplantation followed by liver transplantation was performed in the recipient also using CPB to minimize any hemodynamic disturbances to the organ grafts during transplantation, given the donor instability.

In two patients, the liver graft was transplanted before the cardiac graft. One case was previously reported. The second patient was a 41-year-old female with apical variant hypertrophic cardiomyopathy, congestive hepatopathy, and high titers of preformed donor-specific anti–human leukocyte antigen (HLA) antibodies. Preoperative plasma exchange was performed. After sternotomy and exposure of the recipient’s heart, the liver graft was transplanted first to protect the cardiac graft from donor-specific antibodies. Cardiopulmonary bypass was available at the time of hepatic reperfusion if hemodynamic instability arose; however, hepatic reperfusion was tolerated by the recipient’s native heart without the need for CPB or VVB.

Postoperative management details are listed in Table 5. All patients were transferred to the intensive care unit (ICU) intubated, mechanically ventilated, and sedated. No patient required a tracheostomy. Five patients required dialysis postoperatively, none of whom were receiving dialysis preoperatively. No differences in perioperative outcomes were observed in patients with preoperative severe right ventricular dysfunction compared to normal right ventricular function. One death occurred within 30 days of CHLT, involving a 58-year-old female undergoing CHLT for familial amyloidosis (preoperative model for end-stage liver disease [MELD] score 6, left ventricular ejection fraction 53%, restrictive diastolic function, and normal right ventricular size and function) who suffered two intraoperative cardiac arrests during reperfusion of the liver and abdominal closure. After cardiac transplantation, liver transplantation was performed using caval interposition surgical approach and VVB without heparinization (activated clotting time 130 sec before VVB), as was our practice at that time. After hepatic graft recirculation and discontinuation of VVB, severe bleeding was encountered (hemoglobin nadir, 4.1 g/dL), followed by diffuse intravascular thrombosis including a left atrial thrombus that was subsequently noted on transesophageal echocardiography. Cardiopulmonary bypass was reintiated, and the left atrial thrombus removed. Because of subsequent right ventricular failure, a right ventricular assist device was placed. Right ventricular assist device support was changed intraoperatively to venoarterial extracorporal membrane oxygenation that was
TABLE 4.
Intraoperative inotropic and vasoactive infusions in patients undergoing combined heart-liver transplantation

| Inotropic infusions present 10 min after cardiopulmonary bypass (CPB) separation after cardiac transplantation |
|--------------------------------------------------------------------------------------------------|
| Epinephrine, isoproterenol, and milrinone                  | 9 |
| Epinephrine, isoproterenol, and dopamine                    | 4 |
| Epinephrine and isoproterenol                               | 4 |
| Dopamine and isoproterenol                                  | 3 |
| Isoproterenol                                               | 3 |
| Isoproterenol and milrinone                                 | 1 |
| Dopamine, isoproterenol, and milrinone                       | 1 |
| Dopamine                                                    | 1 |
| Milrinone                                                   | 1 |

| Drug infusions primarily altering afterload present 10 min after cardiopulmonary bypass (CPB) separation after cardiac transplantation |
|---------------------------------------------------------------------------------------------------------------------------|
| Nitroprusside                                                                                                               | 9 |
| Norepinephrine                                                                                                              | 3 |
| Vasopressin                                                                                                                  | 3 |
| Norepinephrine and vasopressin                                                                                              | 1 |
| None                                                                                                                         | 11 |

| Inotropic infusions present 10 min after liver graft recirculation                                                          |
|---------------------------------------------------------------------------------------------------------------------------|
| Epinephrine, isoproterenol, and milrinone                                                                              | 6 |
| Epinephrine, isoproterenol, and dopamine                                                                               | 4 |
| Epinephrine and isoproterenol                                                                                        | 4 |
| Isoproterenol                                                                                                              | 3 |
| Epinephrine                                                                                                               | 3 |
| Dopamine and isoproterenol                                                                                               | 2 |
| Dopamine, epinephrine, isoproterenol, and milrinone                                                                          | 1 |
| Dopamine, isoproterenol, and milrinone                                                                                  | 1 |
| Esmolol                                                                                                                     | 1 |
| Milrinone                                                                                                                  | 1 |
| None                                                                                                                        | 1 |

| Drug infusions primarily altering afterload present 10 min after liver graft recirculation |
|--------------------------------------------------------------------------------------------|
| Nitroprusside                                                                                | 8 |
| Vasopressin                                                                                  | 7 |
| Norepinephrine                                                                               | 1 |
| Phenylephrine                                                                                | 1 |
| None                                                                                         | 10 |

continued postoperatively. Because of lack of neurologic recovery, multiple severe strokes on brain imaging, and multiorgan failure, care was withdrawn on postoperative day 3. No other patient suffered 30-day or in-hospital mortality.

DISCUSSION

The main findings of this study are as follows: (1) most patients undergoing CHLT showed metabolic abnormalities, such as amyloid production and preserved hepatic function as evidenced by a median MELD score of 11, with preoperative coagulation abnormalities most commonly attributed to warfarin therapy; 2) the caval interposition liver transplantation technique with VVB was most often used for planned domino liver transplantsations; 3) most patients postoperatively did not receive substantial transfusions, require prolonged mechanical ventilation, or experience 30-day mortality; 4) CHLT was successfully performed in patients with congenital or hereditary cardiac disease.

Consistent with national data for CHLT, familial amyloidosis was the most common indication for transplantation (78% of cases) at our institution. Interestingly, four series focusing on perioperative management of CHLT reported that only 0% to 20% of their cases involved amyloidosis. Domino transplantation involves transplantation of the liver from a patient undergoing liver transplantation (or CHLT) for familial amyloidosis into another recipient (typically older than 60 years), with an expected lifespan shorter than the time required to develop symptoms from the production or deposition of amyloid by the transplanted liver. At our institution, domino liver transplantsations were performed under 12 of the 21 livers (57%) from familial amyloidosis patients undergoing CHLT. Other reasons for CHLT included congenital or hereditary cardiac disease (15% of cases) or idiopathic cardiomyopathy (7% of cases). Liver transplantation was performed in 78% of CHLT cases to correct the underlying metabolic abnormality of familial amyloidosis and for congestive hepatopathy in the remaining cases (22%). Excluding patients receiving warfarin preoperatively, all our patients showed a normal international normalized ratio (INR) at the time of organ availability except for one patient with an INRx of 1.4. Patients with familial amyloidosis presenting for CHLT showed a preserved hepatic function. In patients without familial amyloidosis presenting for CHLT, median MELD score was 9 (range, 7–19). Combined heart-liver transplantation patients, especially in the setting of familial amyloidosis, commonly present with preserved hepatic function, as less severe liver disease is associated with improved survival to CHLT. However, the cardiac function at time of organ availability is typically compromised, as evidenced by the 30% requiring inotropic support at time of organ availability and preoperative echocardiographic findings including compromised systolic and diastolic function.

In 25 of the 27 cases (93%), the cardiac graft was transplanted before the liver graft. Two operations (7%) were performed by transplanting the liver graft before the cardiac graft. This was performed, as previously reported, to allow the transplanted liver to absorb or neutralize high titer donor-specific HLA antibodies present in both recipients. Although the exact mechanism of reduction of donor-specific antibody after CHLT transplantation is unknown, theories include: phagocytosis of antibodies by Kupffer cells, HLA antigen secretion, or dilution of antibody concentrations caused by bleeding or a large vascular bed. Reduction in donor-specific HLA antibodies has also been observed after isolated liver and combined liver-kidney transplantsations. Typically, cardiac transplantation precedes liver transplantation in patients undergoing CHLT given the decreased ischemic tolerance of the cardiac graft compared to the liver graft. When the liver is transplanted first, complex and careful planning is necessary to choreograph the donor and recipient procedures to minimize the cardiac ischemic time. Transplantation of the heart and liver grafts en bloc has been reported as well, but our institution has not used this operative approach.

Various techniques have been successfully reported involving use of CPB, VVB, or no bypass for the liver transplantation portion of CHLT operations. Fourteen patients (52%) at our institution underwent liver transplantation using a caval interposition technique with VVB. The remaining
13 operations were performed with a piggyback approach with no bypass required (11 patients) or full CPB (2 patients). By preserving the recipient’s vena cava, the piggyback technique may eliminate the need for VVB and can be safely performed in most liver transplantations. Despite known complications of VVB, in cases of anticipated domino transplantation or anatomy rendering the piggyback technique difficult, this technique may mitigate hemodynamic instability and reduce portal or retroperitoneal venous hypertension during caval and portal vein occlusion. Subsequent to the CHLT patient who died after experiencing bleeding and diffuse intravascular thrombosis after liver transplantation with VVB without heparinization, our practice has changed to now heparinize patients for VVB with a goal activated clotting time of 180 to 220 sec. Before this case, our practice did not use heparinization for VVB. However, given the preserved synthetic liver function in the most CHLT patients and the potentially hypercoagulable state after discontinuation of CPB and heparin reversal with protamine, we believe that some degree of heparinization with VVB is advisable. Cardiopulmonary bypass was used in two cases for transplantation of both the heart and liver, both involving aforementioned unique circumstances. We do not routinely use this technique given the coagulopathy and inflammatory response associated with prolonged CPB times. However, the practice at some other institutions involves routine use of CPB during transplantation of both organs in all CHLT operations. These authors conclude that the risks of CPB during liver transplantation are outweighed by the decreased hemodynamic and metabolic disturbances with hepatic reperfusion, thereby lessening stress on the cardiac graft.

Although various combinations of inotropic infusions were used after CPB separation after cardiac transplantation, these typically involve positive inotropic and chronotropic agents, such as epinephrine, isoproterenol, milrinone, and dopamine. Agents to alter systemic and pulmonary vascular resistance are added at the discretion of the anesthesiologist. After liver graft recirculation, the aforementioned inotropic support is typically continued with alteration in vasoactive infusions affecting systemic and pulmonary vascular resistance at the anesthesiologist’s discretion. Intraoperative transfusions are typically guided by point-of-care laboratory testing and a previously published goal-directed transfusion algorithm. Since the withdrawal of aprotinin from the United States 2007, antifibrinolytics currently used for CHLT procedures consist of aminocaproic acid or tranexamic acid. As evidenced by 78% of patients receiving an antifibrinolytic, our practice favors antifibrinolytic agent administration for CHLT unless a contraindication exists (e.g., history of deep vein thrombosis, pulmonary embolism). Intraoperative antifibrinolytic therapy currently consists of a loading dose before incision followed by an infusion of tranexamic acid or aminocaproic acid.

The postoperative courses of the most patients were relatively uneventful. Most patients did not require substantial transfusions in the first 48 hr after CHLT, with a median red blood cell transfusions of 2 units and median transfusion of platelets, fresh frozen plasma, and cryoprecipitate of 0 units. There were patients who remained significantly coagulopathic after CHLT and required more than 20 units of red blood cells and fresh-frozen plasma. Our median duration of mechanical ventilation, ICU stay, and hospital stay were relatively short at 1 day, 5.5 days, and 15 days, respectively, consistent with a recent series involving five CHLTs at a large academic center. However, as noted in this and other series, some patients will require prolonged mechanical ventilation, ICU stays, and hospital courses after CHLT. We credit the overall favorable postoperative courses and low 30-day mortality (1/27 patients) to the perioperative multidisciplinary approach to care received by CHLT patients at our institution.

Limitations of this study include all those inherit to a retrospective study, including charting inaccuracies or unclear reasons for management decision. By definition, only patients undergoing CHLT during a single operation were included, and cases of planned or unplanned sequential transplantation are not included. Immunosuppressive therapy, early and late graft function, rejection, and long-term outcomes were not included, as these have previously been reported. In conclusion, CHLT is a life-saving but uncommonly performed operation. Most patients have relatively preserved hepatic function preoperatively compared to the traditional liver transplantation patient. Cardiac function is typically significantly compromised. Although most commonly performed for familial amyloidosis, patients with acquired or congenital cardiac disease successfully underwent CHLT. A variety of operative and bypass techniques may be used successfully for completion of the liver transplantation portion of CHLT.

TABLE 5. Postoperative findings in patients undergoing combined heart-liver transplantation

| Procedure                                      | Mean ± SD   | Median | Range    |
|------------------------------------------------|-------------|--------|----------|
| Postoperative and bypass techniques may be used successfully for completion of the liver transplantation portion of CHLT. | | | |
operations. Overall, most patients experienced uneventful postoperative courses, and overall 30-day mortality was low.

MATERIALS AND METHODS

This study was approved by the Mayo Foundation Institutional Review Board. All patients had provided prior written consent for use of their records for research purposes. A database of liver transplantation patients was searched for those patients who underwent simultaneous heart transplantation from January 1, 1999, to June 1, 2013. Individual patient records were then reviewed by one of the authors (D.W.B.) to verify the patient had undergone CHLT in a single operation. Patients undergoing heart and liver transplantations in separate operations were excluded.

A standard data collection form was used. Demographic information (age at time of surgery and gender) was noted. Preoperative baseline information collected included cardiac and liver indications for transplantations, transplantations performed (CHLT, combined heart-liver-kidney transplantation), body mass index at time of surgery, transthoracic echocardiographic findings (left ventricular size, left ventricular ejection fraction, left ventricular diastolic function grade, right ventricular size, right ventricular function, right ventricular systolic pressure, cardiac valvular abnormalities—moderate in severity), presence of a left ventricular assist device at time of CHLT, cardiac rhythm on electrocardiogram, history of previous cardiac operation requiring sternotomy, history of prior upper abdominal operation, history of previous heart or liver transplantation, New York Heart Association functional classification, inpatient or outpatient at time of organ availability, presence and type of inotropic infusions at time of organ availability, presence of ascites, warfarin use at time of organ availability, if patient had received dialysis within 1 week of organ availability, laboratory values (platelet count, hemoglobin, creatinine, INR, total bilirubin), MELD score, transfusion within 1 day of transplantation, and plasma exchange.

Intraoperative findings collected included duration of anesthesia (as calculated from anesthesia start and end times), intravascular access (placed by anesthesia providers), transesophageal echocardiographic utilization, order of transplantation (heart before liver or liver before heart), CPB duration, anhepatic phase duration, surgical approach to liver transplantation (standard caval interposition or “piggy-back” caval sparing technique), bypass utilization for liver transplantation (none, VVB, CPB), donor heart ischemic time, donor liver ischemic time, vasoactive infusions present 10 min after CPB separation after cardiac transplantation, vasoactive infusions used 10 min after recirculation of the hepatic graft, intraaortic balloon pump use, antifibrinolytic use, autologous cell salvage (volume), red blood cell transfusion (unit), fresh frozen plasma transfusion (units), platelet transfusions (apheresis units), and cryoprecipitate transfusion (number of pooled units).

Each patient record was examined for the after postoperative findings: transfusion within 48 hr of surgery (red blood cells, fresh frozen plasma, platelets, and cryoprecipitate), number and type of subsequent procedures or operations performed during hospitalization, duration of mechanical ventilation, tracheostomy performed, requirement of dialysis, ICU length of stay, hospital length of stay, death within 30 days of transplantation, and death before hospital discharge.

Statistical analysis consisted of mean, standard deviation, median, and range determination for continuous variables and percent quantification for categorical variables.

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