Impact of Postoperative Liver Dysfunction on Survival After Left Ventricular Assist Device Implantation

Kaustav Majumder, MBBS, John R. Spratt, MD, MA, Christopher T. Holley, MD, Samit S. Roy, MSPH, Rebecca J. Cogswell, MD, Kenneth Liao, MD, and Ranjit John, MD

Department of Surgery, University of Minnesota, Minneapolis, Minnesota; Cardiovascular Division, Department of Medicine, University of Minnesota, Minneapolis, Minnesota; and Division of Cardiothoracic Surgery, Department of Surgery, University of Minnesota, Minneapolis, Minnesota

Background. **Liver dysfunction in left ventricular assist device (LVAD) recipients is common both before and after implantation. Postoperative liver dysfunction (PLD) develops in some LVAD recipients without preoperative liver dysfunction. The aim of this study was to assess clinical outcomes in such patients.**

Methods. **Records of all patients undergoing implantation of a HeartMate II (HM II, St. Jude Medical, Inc, Minneapolis, MN) LVAD at a single center at the University of Minnesota from January 2005 through June 2014 were analyzed. PLD was defined by hypertransaminasemia or hyperbilirubinemia, or both, during the hospitalization for LVAD implantation.**

Results. **During the study period, 284 patients underwent HM II implantation. Excluded from analysis were 14 recipients with preoperative liver dysfunction. In the final cohort (n = 270), there were no major difference in preoperative characteristics among those patients with versus without PLD. PLD developed in 129 (47.8%) recipients: 16 (12.4%) had isolated hypertransaminasemia (group I), 76 (58.9%) had isolated hyperbilirubinemia (group II), and 37 (28.7%) had combined hypertransaminasemia and hyperbilirubinemia (group III). Group III LVAD recipients had significantly greater rates of 30-day, 90-day, and 1-year mortality, along with significantly higher transfusion requirements and higher rates of renal replacement therapy, prolonged ventilation, and vasopressor use. Moreover, their mortality risk was significantly higher than that of PLD-free LVAD recipients (hazard ratio, 4.6; 95% confidence interval, 2.1 to 10.1; $p < 0.001$).**

Conclusions. **Isolated hyperbilirubinemia is common after LVAD implantation. In this study, it was not associated with an increase in early or midterm postoperative mortality. However, postoperative combined transaminasemia and hyperbilirubinemia was associated with a significant increase in early and midterm morbidity and mortality. Further research into the pathogenesis of post-LVAD PLD is necessary.**

(Ann Thorac Surg 2017;104:1556–63)

Heart failure is a significant public health concern [1]. Left ventricular assist devices (LVADs) have become important components of heart failure management, both as a bridge to transplantation (BTT) and as destination therapy (DT), and they are associated with improved quality of life [2–4].

Continuous-flow LVADs (CF-LVADs), such as the HeartMate II (HM II, St. Jude Medical, Inc, Minneapolis, MN) and HeartWare HVAD (HeartWare, Framingham, MA), have greater durability and a more favorable complication profile than earlier pulsatile-flow devices [4]. However, device-related complications, including stroke, gastrointestinal bleeding, infection, and end-organ dysfunction, remain common [5].

Postoperative liver dysfunction (PLD) is associated with increased in-hospital mortality rates after cardiac surgical procedures, including LVAD implantation [6–15]. Heart failure–related liver dysfunction has been attributed to hepatocellular ischemia resulting from poor antegrade perfusion and to passive venous congestion secondary to right ventricular dysfunction [16, 17]. PLD after LVAD implantation has been attributed to perioperative hemodynamic changes and preexisting liver dysfunction [18]. The negative postoperative effects of preoperative liver dysfunction in LVAD recipients have been reported, but the impact of isolated PLD is poorly characterized [5, 14, 18–23]. The aims of this study were use a large, single-center cohort to characterize the incidence and forms of PLD and to determine the relationship of PLD with major morbidity and mortality after LVAD

Accepted for publication April 18, 2017.

Presented at the Thirty-fifth Annual Meeting of the International Society for Heart and Lung Transplantation, Nice, France, April 15, 2015.

Address correspondence to Dr John, Division of Cardiothoracic Surgery, Department of Surgery, University of Minnesota Medical School, Mayo Mail Code 207, 420 Delaware St SE, Minneapolis, MN 55455; email: johnx008@umn.edu.

Drs Cogswell and John disclose a financial relationship with St Jude Medical and Medtronic.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2017.04.048

Abbreviations and Acronyms

BTT	= bridge to transplantation
CABG	= coronary artery bypass grafting
CF	= continuous-flow
HM II	= HeartMate II
INTERMACS	= Interagency Registry for Mechanically Assisted Circulatory Support
LVAD	= left ventricular assist device
MELD	= Model for End-stage Liver Disease
PLD	= postoperative liver dysfunction
POD	= postoperative day
RRT	= renal replacement therapy

implantation, specifically common postoperative complications, survival, and rates of cardiac transplantation.

Patients and Methods

In this retrospective study, all patients who underwent HM II implantation from January 1, 2005, through June 30, 2014 were identified in the University of Minnesota LVAD database. This analysis was approved by the local Institutional Review Board (IRB #1403M48521).

Patient Care, Device Management, and Anticoagulation

Patients received standard heart failure care, including antiarrhythmic therapy, before and after LVAD implantation. Pump speed is optimized to provide adequate cardiac output and optimal left ventricular decompression while maintaining a good pulsatility index greater than 3.5 to 4.0 and intermittent aortic valve opening. Anticoagulation consisted of oral aspirin and warfarin with a low-dose heparin bridge, usually starting on postoperative days (POD) 1 to 2.

Clinical Outcomes

Demographics, clinical characteristics, and outcomes data were evaluated in each of the HM II recipients in this cohort. Preoperative liver dysfunction and PLD were both defined as serum levels of aspartate transferase or alanine transferase greater than five times the upper limit of normal (normal range for aspartate transferase, 0 to 45 U/L; for alanine transferase, 0 to 50 U/L) or total serum bilirubin of 5 mg/dL or higher between LVAD implantation and hospital discharge. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria were used to define other postoperative complications [24]. Baseline characteristics, including documented cirrhosis, chronic hepatitis, and a history of heavy alcohol use (considered surrogates for subclinical liver disease), were assessed to determine risk factors for development of PLD. Survival data were evaluated in all recipients.

Statistical Analysis

For between-group comparisons, two-sample Student's t testing was used for normally distributed continuous variables, and the Wilcoxon rank-sum test was used for other continuous variables. For categorical variables, χ^2 testing was used. Univariable and multivariable logistic regression was used to determine predictors of PLD. Survival analysis was performed using the Kaplan-Meier method, and log-rank testing was used to compare and assess unadjusted all-cause mortality rates for PLD versus non-PLD recipients, as well as PLD subgroup analyses. For all analyses, Stata release 13 (StataCorp LP, College Station, TX) was used, and a two-tailed $p < 0.05$ was considered significant.

Results

Baseline Characteristics and Incidence of Postoperative Liver Dysfunction

During the 9.5-year study period, 284 patients underwent HM II implantation (547 person-years of total follow-up). Excluded from analysis were 14 HM II recipients with preoperative liver dysfunction. The baseline characteristics of the final cohort of 270 HM II recipients are shown in Table 1. The mean age at implantation was 57 ± 14 years, 219 (81.1%) of the patients were male, and 208 (77%) recipients were considered as having BTT therapy at implantation. Rates of potential subclinical liver disease did not differ between patients with PLD and those without it. Of the 270 HM II recipients, PLD developed in 129 (47.8%): 16 (12.4%) had isolated hypertransaminasemia (group I), 76 (58.9%) had isolated hyperbilirubinemia (group II), and 37 (28.7%) had combined hypertransaminasemia and hyperbilirubinemia (group III).

Preoperative Risk Factors and Postoperative Complications

Between patients with PLD and those without it, baseline demographic characteristics did not significantly differ in terms of age, sex, BTT versus destination therapy, comorbidities, past tobacco use, or prior interventions. Patients with group III PLD were more likely to have a lower preoperative serum albumin level ($p = 0.001$) and a lower INTERMACS profile ($p = 0.044$) (Table 1). Postoperatively, the need for renal replacement therapy (RRT), prolonged (>7 days) ventilation, prolonged vasopressor use, increased early (POD 0 to 1) and late (POD >2) transfusion requirements, and increased inpatient length of stay were all associated with PLD generally ($p < 0.001$ for all) and with group III PLD specifically (Tables 2 and 3).

Serum albumin was significantly associated with any PLD and group III PLD on univariate and multivariable logistic regression, and levels were higher in recipients with minor (group I or II) or no PLD (Table 4). Postoperatively, RRT, prolonged ventilation and vasopressor use, and increased transfusion requirements were significantly associated with PLD on univariate analysis, but only elevated early transfusion requirements proved significant on multivariate analysis (odds ratio, 1.10; 95% confidence interval, 1.03 to 1.17; $p = 0.004$). Examining