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Late right heart failure during support with continuous-flow left ventricular assist devices adversely affects post-transplant outcome

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survival

BACKGROUND: Right heart failure (RHF) is an unresolved issue during continuous-flow left ventricular assist device (LVAD) support. Little is known about post-transplant outcomes in patients complicated by late RHF during LVAD support.

METHODS: Between May 2004 and December 2013, 141 patients underwent cardiac transplantation after isolated LVAD bridging at our center. Late RHF was defined as heart failure requiring medical intervention >4 weeks after LVAD implantation.

RESULTS: The patients' mean age was 53 ± 13 years, 82% were men, and 36% had an ischemic etiology. The mean duration of LVAD support before transplantation was 0.75 years. Late RHF developed in 21 patients (15%) during LVAD support. Of these patients, 11 were supported with inotropic agents at the time of transplantation. Patients with RHF had higher creatinine (1.6 ± 0.88 mg/dL vs 1.3 ± 0.67 mg/dL, $p = 0.07$), higher blood urea nitrogen (32 ± 17 mg/dL vs 24 ± 10 mg/dL, $p = 0.0013$), higher total bilirubin (0.96 ± 0.46 mg/dL vs 0.78 ± 0.42 mg/dL, $p = 0.07$), and lower albumin (3.8 ± 0.60 g/dL vs 4.1 ± 0.46 g/dL, $p = 0.0019$) at the time of transplantation compared with patients who did not develop RHF. In-hospital mortality was significantly higher in patients with late RHF during LVAD support (29% vs 6.7%, $p = 0.002$). Overall post-transplant survival rates were 87% at 1 year, 83% at 3 years, and 77% at 5 years. The 5-year post-transplant survival was significantly worse in patients who developed late RHF during LVAD support compared with survival in patients who did not develop RHF (26% vs 87%, $p < 0.0001$).

CONCLUSIONS: Late RHF during LVAD support adversely affects post-transplant survival.

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The use of continuous-flow left ventricular assist devices (LVADs) has become standard care among patients with advanced heart failure.[1,2] The bridge to transplant (BTT) strategy is especially reasonable in patients listed for transplantation who are expected to have an extended waiting time because of blood type, a large body size, or a high degree of allosensitization. More recent evidence suggests that extended support with continuous-flow LVADs is associated with promising post-transplant outcomes.[3–5] However, successful bridging can be limited by the development of right heart failure (RHF) during waiting time. Approximately 20% of patients develop some form of RHF after continuous-flow LVAD placement, and RHF is associated with significantly high early and late mortality.[6,7] RHF adversely affects the BTT rate.

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In patients who develop severe RHF early after LVAD implantation, right ventricular assist device (RVAD) insertion is indicated to maintain adequate organ perfusion. A previous study suggested that the need for RVAD insertion was not associated with post-transplant mortality.[8] However, this option might be limited by the surgical complexity and a lack of available durable devices in patients who develop RHF late after LVAD implantation. The alternatives for BTT patients who develop late RHF include strengthening of heart failure therapies, including diuretics and the use of inotropes, until a donor heart becomes available. However, data regarding post-transplant outcomes in these patients are very limited. The aim of this study was to assess whether the development of late RHF during LVAD support adversely affected post-transplant survival.

Methods

Our institutional review board approved this study. We retrospectively reviewed our experiences with continuous-flow LVADs at Columbia University Medical Center between April 2004 and December 2013. During this period, an isolated continuous-flow LVAD was inserted as a BTT in 247 consecutive patients with advanced heart failure. Of these patients, 141 (57%) underwent cardiac transplantation, 40 (16%) died before transplantation, 58 (23%) remained listed for transplantation with ongoing LVAD support, and 8 (3.2%) were weaned from LVAD support. This study focused on the 141 patients who were successfully bridged at our center.

Definition of late RHF

Late RHF was defined as heart failure requiring medical intervention >4 weeks after LVAD implantation. More specifically, patients who required rehospitalization and medical treatment because of recurrent RHF or patients who required continuous inotropic support because of persistent RHF $>$ 4 weeks after implantation were included in the RHF group. Detection of RHF was based on clinical findings. Typical signs and symptoms of RHF included edema, weight gain, fatigue, ascites, and jugular venous distention. To rule out any device failure, the device was routinely interrogated during hospitalization. The hemolysis workup and echocardiography were routinely performed in all patients who developed recurrent heart failure symptoms. Any heart failure related to device failure or suspected device failure, such as device thrombosis, inflow and outflow obstruction, or drive-line fracture, was not considered as late RHF.

Device

Devices used as LVAD support included 120 HeartMate II (Thoratec, Pleasanton, CA), 7 VentrAssist (Ventracor Ltd, Chatswood, NSW, Australia), 6 DuraHeart (Terumo Heart, Ann Arbor, MI), 5 DeBakey (MicroMed Technology, Inc, Houston, TX), and 3 HeartWare HVAD (HeartWare International, Inc, Framingham, MA) devices.

Post-implant device management

After device implantation, all patients received a standardized medical regimen, including a neurohormonal antagonist, diuretics, and anti-arrhythmic agents, if needed. Anticoagulation therapy with aspirin and warfarin was implemented. Patients had follow-up evaluations at 1 week after the initial discharge and monthly thereafter, unless an issue necessitating more frequent visits arose.

Transplant procedures and postoperative immunosuppression

All patients underwent cardiac transplantation with bicaval anastomosis. All patients received standard therapy with calcineurin inhibitors, cyclosporine or tacrolimus, mycophenolate mofetil, and prednisone.

Post-transplant endomyocardial biopsy

Endomyocardial biopsies were performed on a regular basis. The degree of cellular rejection was graded according to the criteria of the International Society for Heart Transplantation grading criteria.[9] Antibody-mediated rejection was defined as histologic evidence of acute capillary injury and immunoglobulin and/or C4d deposition identified by immunofluorescence.

Post-transplant follow-up

After transplantation, patients were monitored by a cardiologist on a regular basis. The follow-up examinations were completed on May 30, 2014, and duration of follow-up ranged from 4 days to 8.3 years (median, 2.3 years; interquartile range, 0.97–3.8 years). Clinical follow-up was completed in 99% of patients.

Data collection

All clinical data were collected thorough a chart review of electronic medical records. For each patient, preoperative variables that might be correlated with survival were collected retrospectively for each procedure (i.e., LVAD implantation and transplantation). These included baseline demographics, medical histories, laboratory values, hemodynamic parameters, medications, and donor demographic data.

Intraoperative variables included concomitant procedures at the time of LVAD implantation and ischemic time, cardiopulmonary bypass time, blood product use, and nitric oxide use at the time of transplantation. Early post-transplant data included complications occurring between the operation and hospital discharge. Severe primary graft dysfunction (PGD) was defined as a need for mechanical circulatory support within 24 hours of completion of surgery.[10] Post-transplant hemodynamic parameters, including central venous pressure (CVP), mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, and pulmonary vascular resistance; left ventricular function on transthoracic echocardiogram; and endomyocardial biopsy data at 1 week and 1 year after transplantation were also analyzed to assess early and late graft function and the degree of rejection.

Statistical analysis

Data are expressed as frequencies and percentages for categorical variables. Continuous variables are expressed as mean $\pm$ standard deviation and were compared using two-sample t tests. Categorical variables were compared using the chi-square test. Kaplan-Meier curves were used to represent survival and were compared using a log-rank test. For all analyses, p-values <0.05 were considered statistically significant.