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Consequences of aortic insufficiency during long-term axial continuous-flow left ventricular assist device support

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BACKGROUND: Although left ventricular assist device (LVAD) management strategies are undertaken to reduce the development of aortic insufficiency (AI), the effect of AI on patient morbidity and mortality is not known.

METHODS: Patients undergoing HeartMate II (Thoratec, Pleasanton, CA) implant were prospectively monitored with serial echocardiograms. Kaplan-Meier methods and log-rank testing were used to estimate and compare mortality and freedom from moderate or worser right ventricular hypokinesis (RVHK), moderate or worse mitral regurgitation (MR), and hemolysis according to AI severity. Mixed modelling was used to examine for correlates of AI development in the pre-operative and post-operative setting and to investigate the effect of AI on post-operative MR and RVHK.

RESULTS: There were 930 echocardiograms completed in 166 patients. During 291 person-years of follow-up, mild-moderate or worse AI developed in 70 (0.38 persons per year [PPY]), moderate or worse AI in 36 (0.17 PPY), moderate-severe AI in 11 (0.039 PPY), and severe AI in 2 (0.0069 PPY). Overall 2-year survival and 2-year survival after onset of moderate or worse AI was 87% ± 6.2% and 65% ± 11%, respectively, compared with 76% ± 5.1% and 76% ± 5.1%, respectively, in those with less AI ($p = 0.57$). Patients with moderate AI were not more likely to develop MR, hemolysis events, or worsening RVHK, but patients with pre-existing RVHK appeared to be less tolerant of AI. Three of 35 deaths were directly attributed to AI. No reoperations were performed solely for AI.

CONCLUSIONS: AI is common after LVAD implant but did not affect survival in this cohort. Except in those with significant RV dysfunction, this calls into question need for echocardiogram-guided device settings to ensure aortic valve opening.

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The development of aortic insufficiency (AI) during continuous-flow (CF) axial-flow (AF) left ventricular assist device (CFAF-LVAD) support has been well documented. Previous studies have demonstrated that 25% to 52% of patients on LVAD support will develop AI by 1 year, and this incidence is greater in those supported with CF vs pulsatile-flow devices as well as in those without physiologic opening of the aortic valve and larger aortic sinus dimensions at follow-up.[1–4] The large variability in the reported cumulative incidence of AI development may due to the definition of what is considered hemodynamically significant AI (more than mild vs more than mild-moderate

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vs more than moderate) and the duration of follow-up after VAD implant. To date, the effect of AI on clinical outcomes is not known. The aims of this study were to:

1. better characterize AI development and progression during long-term LVAD support;
2. determine the burden of reoperation for hemodynamically significant AI;
3. determine whether AI affects right ventricular (RV) function, mitral regurgitation (MR), or hemolysis during CFAF-LVAD support; and
4. determine the effect of AI on survival.

Methods

Patients enrolled in the University of Michigan Mechanical Circulatory Support registry who underwent CF-LVAD implant with a HeartMate II (Thoratec Corp, Pleasanton, CA) between 2000 and 2011 were evaluated.

Echocardiograms were reviewed by a single reader at baseline ($\leq$3 months before LVAD implant), at 3, 6, 12, 18, 24 months after implant, and then yearly thereafter until death, transplant, or device explant for recovery. The American Association of Echocardiography guidelines and State of the Art Recommendations were used for measurements.[5,6] Parameters included left ventricular (LV) internal dimensions at end-diastole (LViDd) and end-systole (LViDs), LV volumes in end-diastole (LVDV) and end-systole (LVSV), MR, and severity of AI.

AI was graded per jet width/LV outflow tract diameter and vena contracta guidelines[5] and assigned an interval scale value of none (0), trivial (0.5), mild (1), mild-moderate (1.5), moderate (2.0), moderate to severe (2.5), and severe (3.0). The frequency of aortic valve (AV) opening was graded as fully open (3 of 3 beats), intermittent/partially open (at least 1 of 3 beats), and closed (0 of 3 beats).

RV function was graded as normal function or as mild, moderate, or severe systolic dysfunction based on visual estimates. Tissue Doppler to measure systolic annular motion of the tricuspid annulus was not available. LVAD speed (rpm), LVAD flows (liters/min), and pulsatility index (PI), and systolic blood pressures were tallied at the time of all echocardiograms.

Our institutional protocol is to surgically intervene on valves exhibiting moderate or worse AI on intraoperative transesophageal echocardiogram. LVAD speeds are adjusted intraoperatively and immediately before discharge for optimal LV offloading, such that there is no more than mild mitral insufficiency and an LViDd ideally of $<$60 mm but no evidence of septal shift to impair RV function. On outpatient follow-up, LVAD speed changes are made for evidence of left-sided heart failure (e.g., increased diuretic needs, increased renal function) and/or wedge pressures $>$18 mm Hg on outpatient heart catheterization with concomitant evidence of poor LV offloading on echocardiography. Speed optimization is also performed in asymptomatic patients with moderate MR or a severely dilated LV (LViDd $>$ 70 mm). Patients and device flows are monitored 20 minutes after speed adjustments, and orthostatic vitals are obtained. Echocardiogram measures are repeated 5 minutes and 1 month after speed adjustment. It is not institutional protocol to adjust CF-LVAD speeds to ensure intermittent AV opening, even in the setting of AI.

Hemolysis and pump thrombosis

Hemolysis markers are obtained monthly after LVAD implant. Peak serum lactate dehydrogenase (LDH) values beginning 30 days after implant and the occurrence of pump thrombosis (confirmed on explant) were tallied for each patient.

Outcomes

The primary aim of this analysis was to determine the level of AI that leads to a clinically significant difference in outcomes. The primary outcome of interest was overall survival based on AI severity. Secondary outcomes of interest included (1) survival after the onset of AI, (2) development of moderate or worse mitral regurgitation, (3) development of moderate or worse RV dysfunction, (4) occurrence of pump thrombosis or hemolysis, and (3) need for reoperation primarily for AI.

Statistical analysis

SPSS 20 software (IBM, Armonk, NY) and SAS software (SAS Institute, Cary, NC) were used for data analysis. Continuous variables were evaluated for normality and then compared with Student's *t*-test or the Mann-Whitney test, respectively, as appropriate. Categoric variables were compared with chi-square (for $>$2 comparisons) or Fisher's exact testing.

Mixed-model linear regression with random-effects modeling was used to evaluate the effect of baseline characteristics on the development of AI after LVAD implant. The slope represents the change in AI severity per day of LVAD support for the presence or absence of the categoric variable or per unit measure of a continuous variable. For serial measures obtained after LVAD implant, mixed modeling for repeated measures (using maximum likelihood and unstructured symmetry) was used. Time was treated as a continuous variable, and β represents the change in the degree of AI for each unit change in post-operative variable.

The cohort was then grouped by AI severity (mild to moderate or worse, moderate or worse, moderate to severe or worse, and severe or worse). Because few patients had AI that was moderate to severe or worse, these patients were condensed into the moderate or worse AI category. Overall cohort survival, survival based on AI severity, survival after the onset of mild-moderate or worse and moderate or worse AI, survival free of transplant, and survival free of at least moderate MR and at least moderate RV failure in those with and without moderate or worse AI was estimated using Kaplan-Meier methods. Log-rank testing and Breslow-Day testing were performed for group comparisons. Cox hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to compare risk. Patients were censored at the time of transplant, reoperation with valve intervention, or explant for recovery.

Results

CFAF-LVAD implant was performed in 166 patients. Baseline characteristics of the cohort are reported in Table 1. One patient had had a bioprosthetic AV replacement (AVR) 2 years before LVAD implant, and 1 had had a prior mechanical AVR. An intraoperative AV intervention was required in 12 patients. The mechanical AVR was excised and the AV annulus closed with a patch. The remaining 11 patients had a bioprosthetic AVR ($n = 2$) or AV repair using the modified Park stitch technique ($n = 9$) due to the presence of moderate or worse AI on intraoperative transesophageal echocardiogram.[7] The bioprosthetic AVR antedating LVAD demonstrated no intraoperative AI and was left in place at the time of LVAD implant.