Natural history and clinical effect of aortic valve regurgitation after left ventricular assist device implantation

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Objectives: Aortic valve regurgitation reduces left ventricular assist device mechanical efficiency. Evidence has also suggested that left ventricular assist device implantation can induce or exacerbate aortic valve regurgitation. However, this has not been compared with aortic valve regurgitation progression in a nonsurgical end-stage heart failure population. Furthermore, its clinical effect is unclear. We sought to characterize the development and progression of aortic valve regurgitation in left ventricular assist device recipients and to identify its clinical effect.

Methods: A review of all consecutive patients who received an intracorporeal left ventricular assist device at Duke University Medical Center from January 2004 to January 2011 was conducted. Cases of previous or concomitant aortic valve surgery were excluded. Data from the remaining implants (n = 184) and a control group of contemporaneous nonsurgical patients with end-stage heart failure (n = 132) were analyzed. Serial transthoracic echocardiography was used to characterize aortic valve regurgitation as a function of time.

Results: Left ventricular assist device implantation was associated with worsening aortic valve regurgitation, defined as an increase in aortic valve regurgitation grade, relative to the nonsurgical patients with end-stage heart failure ($P < .0001$). The recipients of continuous flow left ventricular assist devices were more likely than recipients of pulsatile left ventricular assist devices to develop worsening aortic valve regurgitation ($P = .0348$). Moderate or severe aortic valve regurgitation developed in 21 left ventricular assist device recipients; this was unrelated to the type of device implanted (continuous vs pulsatile; $P = .754$) or aortic valve regurgitation grade before left ventricular assist device implantation ($P = .42$). Five patients developed severe aortic valve regurgitation; all of whom underwent aortic valve procedures.

Conclusions: Native aortic valve regurgitation developed and/or progressed after left ventricular assist device implantation, with this effect being more pronounced in continuous flow left ventricular assist device recipients. However, the preoperative aortic valve regurgitation grade failed to correlate with the development of substantial aortic valve regurgitation after left ventricular assist device implantation. After left ventricular assist device implantation, aortic valve regurgitation had a small, but discernible, clinical effect, with some patients developing severe aortic valve regurgitation and requiring aortic valve procedures. These data have implications for the long-term management of left ventricular assist device recipients, in particular as the durability of implantable continuous flow left ventricular assist device therapy improves. (J Thorac Cardiovasc Surg 2013;145:1373-9)

End-stage heart failure (ESHF) refractory to maximal pharmacologic therapies is an increasingly prevalent problem in the United States and worldwide. ESHF treatment is largely surgical and generally by cardiac transplantation (CT) and implantation of left ventricular (LV) assist devices (LVADs), as either bridging or destination therapy. Because of the limitations in the donor organ supply, a small fraction of all patients with ESHF undergo CT. Thus, with the current technology level, chronic implantable LVAD therapy likely represents the most widely applicable ESHF treatment strategy. Consistent with this, in the United States, the annual number of LVAD implants is approaching the annual number of CTs.[1]

Despite its obvious benefits, LVAD therapy has several limitations. Of these, progression of aortic valve (AV) regurgitation (AR) might substantially effect the physiology and clinical outcomes of LVAD recipients. It is widely recognized that substantial AR recognized at LVAD implantation should be addressed surgically to prevent the loss of LVAD mechanical efficiency that AR would otherwise cause.[2,3] AR results in a requirement for an excessive total left-sided output to maintain the constancy of a normal net antegrade left-sided output, with the difference between the 2 equaling the regurgitant flow rate. In the LVAD

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Disclosures: Authors have nothing to disclose with regard to commercial support.

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Received for publication Aug 13, 2012; revisions received Nov 2, 2012; accepted for publication Nov 28, 2012; available ahead of print Jan 10, 2013.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.11.066

Abbreviations and Acronyms

AR = aortic valve regurgitation
AVR = AV replacement
AV = aortic valve
cfLVAD = continuous flow LVAD
CT = cardiac transplantation
ESHF = end-stage heart failure
HF = heart failure
LV = left ventricular
LVAD = left ventricular assist device
LVIDd = LV diastolic dimensions
NS-ESHF = nonsurgical ESHF
pfLVAD = pulsatile flow LVAD
TTE = transthoracic echocardiography

recipient, this generally results in greater device work and flow rate for the systemic output to be normal.

A range of treatment strategies, including AV repair using various techniques,[4] AV replacement (AVR) with biologic prostheses,[5] AV closure, or left ventricular outflow tract patching,[6,7] and percutaneous transcatheter techniques,[8,9] have been successfully implemented. In addition, it is now increasingly appreciated that LVAD therapy can cause AV damage as a function of time,[10,11] resulting in de novo and/or progressive AR, which, in turn, could adversely affect the mechanical efficiency of the LVAD. Two recent studies[12,13] have echocardiographically characterized the development and progression of post-LVAD implantation AR. These 2 studies suggested that patients with a continuous flow LVAD (cfLVAD) had more rapid progression of AR relative to patients supported with pulsatile flow LVADs (pfLVAD). In addition, greater pump speeds and larger aortic root dimensions were associated with greater progression of AR. In addition, a recent study has reviewed a large series of LVAD recipients who required either concomitant or delayed AV procedures because of AR, with 8 patients having undergone post-LVAD implantation AV procedures at concomitant LVAD exchange.[6] However, the echocardiographic and invasive hemodynamic characteristics of AR in these patients were not reported, and whether AR was a predominant contributor to heart failure (HF) in these patients is not clear. Therefore, we sought to characterize the development and progression of post-LVAD implantation AR relative to a nonsurgical HF control group and to examine its clinical effect.

METHODS

Patients and Surgical Procedures

The study groups were composed of patients treated at Duke University Medical Center from January 2004 to January 2011. The LVAD recipient group (n = 184) included pfLVAD (n = 36) and cfLVAD (n = 148) recipients. Patients in the pfLVAD group underwent implantation of the Thoratec HeartMate XVE device (n = 33; Thoratec, Pleasanton, Calif) or the Novacor LVAD (n = 3; Novacor, Oakland, Calif). Patients in the cfLVAD group underwent implantation with the Thoratec HeartMate II (n = 139), HeartWare HVAD (n = 6), or Ventracor VentrAssist (n = 3) device. In patients treated with more than 1 LVAD, the attribution of AR was made to the device in place when AR progressed. Patients who underwent concomitant or previous AV surgery were excluded from the study. The nonsurgical ESHF (NS-ESHF) group (n = 132) included contemporaneous patients who did not undergo LVAD implantation. The NS-ESHF group all underwent evaluation at the advanced HF clinic at Duke University Medical Center from 2005 to 2010. The diagnostic evaluation to assess ESHF included transthoracic echocardiography (TTE), right-sided cardiac catheterization, and cardiopulmonary exercise testing. In both LVAD and NS-ESHF groups, the patients who underwent CT were censored at CT.

Assessment of AR

Serial TTE assessments were performed in both patient groups. Baseline studies were performed before LVAD implantation. Postimplantation assessments were performed as clinically indicated, rather than at scheduled intervals. AR was graded using standard American Society of Echocardiography criteria[14] translated into a specific grade: none or trivial (grade 0), mild (grade 1), moderate (grade 2), moderate-to-severe (grade 3), and severe (grade 4). Progression was defined as an increase in AR grade of 1 grade or more. Our protocol for determining LVAD speed settings during the study period was to achieve optimal LV unloading, with characteristic TTE findings of normal LV dimensions, neutral septal position, and typically persistent AV closure. Greater pump speeds that resulted in leftward septal distortion and LV collapse were avoided. This strategy was consistent with the study by Amin and colleagues,[15] who first demonstrated that septal distortion and LV collapse occurred at even greater cfLVAD speeds than those required to induce persistent AV closure.

Data Collection and Statistical Analysis

The institutional review board approved the study, and individual patient consent was waived. Data were collected in a post hoc fashion from a review of the clinically generated patient care documentation. Data were analyzed using R, version 2.15.0 GUI 1.51 Leopard build 64-bit (6148; R Foundation for Statistical Computing, Vienna, Austria).[16] Continuous covariates are reported as the median and interquartile range. Categorical variables are reported as proportions. Continuous covariates were compared using the Wilcoxon rank sum test or Kruskal-Wallis test, as appropriate. Categorical covariates were compared using the Fisher exact test or chi-square test, as appropriate. Survival and failure curves were generated using the Kaplan-Meier method.[16,17] The survival and failure curves were compared using the log-rank test.

RESULTS

Patient Characteristics

The characteristics of the NS-ESHF and LVAD recipient groups are listed in Table 1. The LVAD recipients had more severe LV systolic dysfunction, as assessed by the LV ejection fraction. In addition, a greater percentage of LVAD recipients had an ischemic/postmyocardial infarction etiology relative to the NS-ESHF group. Finally, the LVAD recipients were older than their NS-ESHF counterparts. The median duration of LVAD support, total LVAD patient years for the cfLVAD and pfLVAD groups, median interval to echocardiographic follow-up for all 3 groups, and total echocardiographic follow-up in patient years for both groups are also listed in Table 1. As anticipated, the duration of support and the interval to the follow-up echocardiogram were

TABLE 1. Patient characteristics

Characteristic	NS-ESHF (n = 132)	LVAD (n = 184)	cfLVAD (n = 148)	pfLVAD (n = 36)	*P* value: NS-ESHF vs LVAD	*P* value: NS-ESHF vs cfLVAD and pfLVAD
Age (y)						
Median	52	58	59	52	<.0001	.0002
Interquartile range	40-60	46-68	46-68	48-61		
Gender (n)					.6046	.0028
Male	95	138	103	35		
Female	37	46	45	1		
Etiology (n)					<.0001	.001
Ischemic/post-MI	34	69	54	15		
Idiopathic	56	52	46	6		
Valvular	1	4	3	1		
Congenital	1	1	1	0		
Mixed ischemic/post-MI	21	21	17	4		
Mixed, nonischemic	19	37	27	10		
LVEF (%)						
Median	20	10	10	10	<.0001	<.0001
Interquartile range	15-30	10-20	10-20	10-22.5		
LVAD duration (d)						
Median		308	371	83.5		
Interquartile range		56-722	89-796	42-252		
Total (pt-y)		231.2	208.1	23.1		
Interval to echocardiographic follow-up (d)						
Median	843	220	243	68.5		
Interquartile range	272-1912	21-314	18-364	31-157		
Total follow-up (pt-y)	483.9	111.1	98.5	12.6		

NS-ESHF, Nonsurgical end-stage heart failure; *LVAD*, left ventricular assist device; *cfLVAD*, continuous flow LVAD; *pfLVAD*, pulsatile flow LVAD; *MI*, myocardial infarction; *LVEF*, left ventricular ejection fraction.

considerably longer for the cfLVAD than for the pfLVAD group. The medical therapy control group had longer follow-up relative to the combined LVAD group.

Development and Progression of Post-LVAD Implantation AR

Serial TTE was used to assess the development and progression of AR (defined as an increase in AR grade of 1 or more, which would thus include new-onset AR) in the LVAD and NS-ESHF groups. LVAD implantation was associated with an increased rate of the development and progression of AR relative to the nonsurgical controls ($P < .0001$; Figure 1, *A*). The control group displayed virtually no AR progression during the follow-up period. AR progression was more rapid after cfLVAD implantation than after pfLVAD implantation ($P = .0348$; Figure 1, *B*).

We hypothesized that clinically important AR would be at least moderate in severity. Thus, we assessed the development of moderate or worse AR over time in the LVAD and NS-ESHF groups. Freedom from moderate or greater AR decreased over time in the LVAD group (Figure 2, *A*). This result was statistically significant ($P < .0001$). However, no difference was found in the freedom from moderate or greater AR between the cfLVAD and pfLVAD subgroups ($P = .754$; Figure 2, *B*). Also, freedom from moderate AR was unrelated to the preimplantation AR grade ($P = .42$; Table 2). This finding might have been a consequence of an institutional preference for treating moderate or greater AR identified at LVAD implantation with a concomitant AV procedure (see the "Discussion" section). Finally, patient survival divided by the development of moderate or greater AR is shown in Figure 3. This statistically equivalent survival might have resulted from the smaller number of patients with progression to severe AR who underwent successful surgical reoperation to correct the AR. Furthermore, the overall small number of patients in the moderate and severe AR group also limited the power of the survival analysis.

Patients With Moderate or Worse AR

Within the LVAD group, 21 patients (19 cfLVAD and 2 pfLVAD) developed moderate or greater AR during the study period. Of these 21 patients, 16 had moderate AR and 5 developed severe AR (see the next section). Patients with moderate or greater AR, however, demonstrated effective mechanical unloading, with LV diastolic dimensions (LVIDd) that were within the normal range (mean LVIDd before LVAD, 6.9 ± 1.0 cm vs mean LVIDd after LVAD, 5.3 ± 1.2 cm; $P < .0001$). One patient with moderate AR

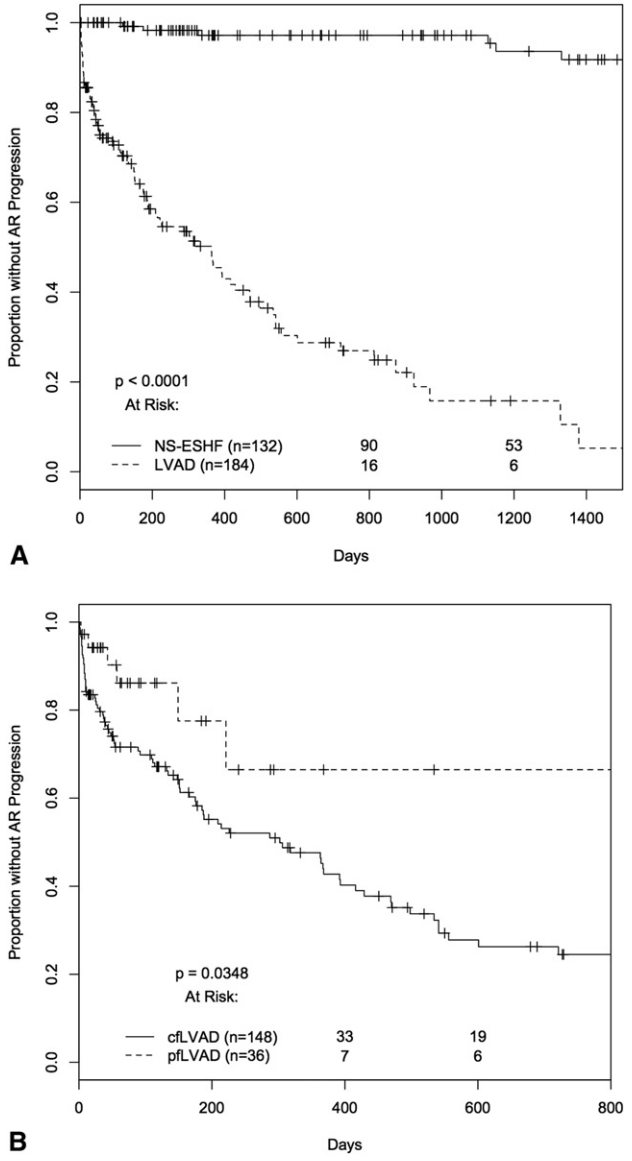

FIGURE 1. A, Freedom from progression of aortic valve regurgitation *(AR)* in nonsurgical patients with end-stage heart failure *(NS-ESHF)* versus all left ventricular assist device *(LVAD)* recipients. B, Freedom from progression of AR for pulsatile flow *(pfLVAD)* versus continuous flow *(cfLVAD)* LVAD recipients.

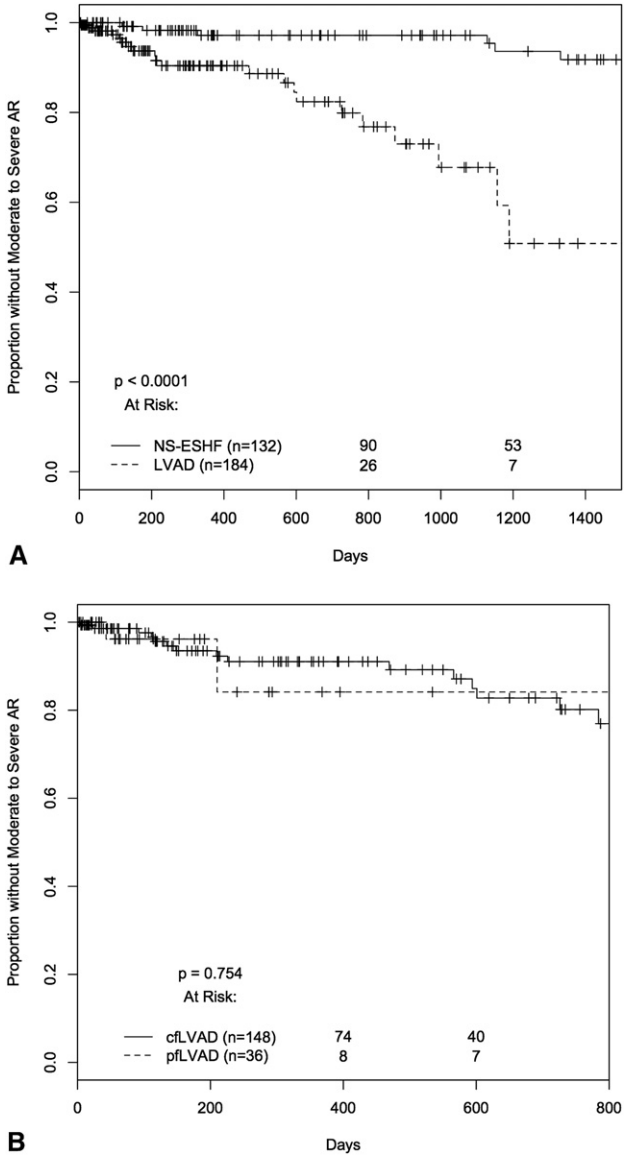

FIGURE 2. A, Freedom from moderate or severe aortic valve regurgitation *(AR)* in nonsurgical patients with end-stage heart failure *(NS-ESHF)* versus all left ventricular assist device *(LVAD)* recipients. B, Freedom from moderate to severe AR for pulsatile flow *(pfLVAD)* versus continuous flow *(cfLVAD)* LVAD recipients.

and pfLVAD dysfunction underwent CT. However, no other patients with moderate AR developed clinical HF or were deemed to require AV surgery.

Severe AR

Five cfLVAD patients developed severe AR. All five had recurrent HF symptoms, and, after a thorough evaluation, all five underwent AV procedures. One patient underwent AV repair with concomitant LVAD exchange because of suspected intradevice thrombus. This patient was later successfully bridged to CT. At the last follow-up examination, she was alive and well. A second patient underwent percutaneous AV closure using an Amplatzer occluder device; however, the device migrated retrograde into the LV cavity and threatened to occlude apical LVAD inflow. That patient underwent an emergent attempted AV repair that failed intraoperatively with residual AR, requiring AVR with a 19-mm St Jude Biocor Supra valve (St Jude Medical, St Paul, Minn). At the last follow-up visit, he was alive and well, continuing with LVAD support. A third patient was directly bridged to CT and was also doing well approximately 4 years after CT. A fourth patient developed severe AR less

TABLE 2. Characteristics of LVAD recipients

Characteristic	Moderate or worse AR (n = 21)	Less than moderate AR (n = 164)	*P* value
Age (y)			.848
Median	58	59	
Interquartile range	44-69	47-67	
Gender (n)			.0599
Male	12	126	
Female	9	38	
Etiology (n)			.8106
Ischemic/post-MI	7	62	
Idiopathic	6	46	
Valvular	1	3	
Congenital	0	1	
Mixed, ischemic/post-MI	2	20	
Mixed, nonischemic	5	32	
LVEF (%)			.8857
Median	10	10	
Interquartile range	10-25	10-20	
Preoperative AR grade (n)			.42
None	11	99	
Mild	8	37	
Moderate	2	19	

LVAD, Left ventricular assist device; *AR*, aortic valve regurgitation; *MI*, myocardial infarction; *LVEF*, left ventricular ejection fraction.

than 1 month after LVAD implantation and was admitted to the hospital with shock and multiorgan system dysfunction. She underwent urgent AVR with a 19-mm St Jude Biocor Supra valve, tricuspid valve repair with a 27-mm St Jude Tailor annuloplasty ring for severe tricuspid valve regurgitation, and concomitant LVAD exchange because of pump thrombus with hemolysis. She died approximately 1 month after surgery secondary to renal and hepatic failure. The fifth patient recently underwent AVR with a 19-mm St Jude Trifecta valve with concomitant LVAD exchange owing to an ascending driveline infection. At her last follow-up visit, she was recovering well.

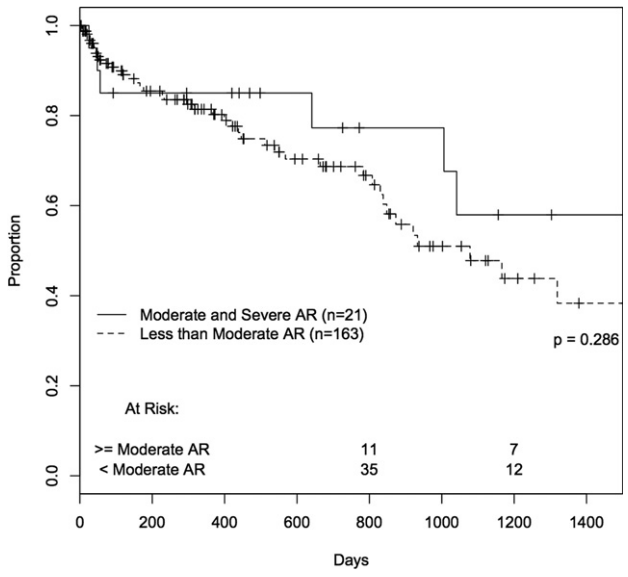

FIGURE 3. Survival over time for left ventricular assist device *(LVAD)* recipients with progression to either moderate or severe aortic valve regurgitation *(AR)* versus those with less than moderate AR.

DISCUSSION

Most patients with ESHF will not undergo CT. The reasons for this are, principally, the lack of adequate donor organ availability, and the relatively stringent recipient criteria that exclude patients with many common comorbidities or advanced age. Thus, mechanical circulatory support as long-term or "destination therapy" is the best treatment option for most patients with ESHF. With the increasing durability and longevity of cfLVADs, attention has focused on the management of long-term LVAD complications, including AR, right ventricular dysfunction, hemorrhagic and thromboembolic complications, and device-related infections.

The development and progression of AR in LVAD recipients is not well understood. Previous reports[11-13] have established significant associations between LVAD implantation and the development of AR; however, these studies did not include nonsurgical HF control groups. In the present report, we have demonstrated that LVAD therapy is associated with the development and progression of AR relative to the natural history of patients with ESHF not treated with implantable LVADs. Our use of a nonsurgical HF group allowed for a rigorous assessment of the contributions of LVADs to AR development and progression over time. Minimal AR progression was evident in the nonsurgical HF group.

It is challenging to predict the circumstances under which AR will occur after LVAD implantation. Our data did not identify an association between preoperative AR grade and the development of moderate or greater postoperative AR. Some patients with preoperative moderate or severe AR underwent concomitant AV procedures at LVAD implantation and were censored. Thus, a putative association between the preoperative AR grade and the development of moderate or greater AR might not have been identified owing to the exclusion of some patients with preoperative moderate or worse AR that might have progressed even further after LVAD implantation. Nonetheless, the lack of a demonstrable association between the preoperative and postoperative AR grades underscores the importance of serial AV surveillance after LVAD implantation.

AR development or progression was more pronounced in the cfLVAD recipients, consistent with the findings from previous studies.[12,13] AR might progress more rapidly after cfLVAD implantation owing to the constant and more complete LV unloading, resulting in a persistently closed or minimally mobile native AV. The lack of normal cyclic AV motion might then result in leaflet fibrosis or

scarring, causing or exacerbating regurgitation. However, although AR assessed by imaging studies might appear worse after LVAD implantation, with greater regurgitant flow rates, the regurgitant fraction (the regurgitant flow rate, or regurgitant volume per unit time, divided by the total left-sided flow rate or cardiac output) might not be substantially changed early after LVAD implantation. The trans-AV regurgitant flow rate in the setting of a well-functioning LVAD is determined by the systemic mean (instead of diastolic in the native circulation) arterial pressure, the intracavitary LV pressure, and the impedance of the AV to retrograde flow. The regurgitant flow rate is causally dependent on the aorta–LV pressure difference. However, the aorta–LV pressure difference is a function dependent on the LVAD pump speed and impedance or afterload of the systemic circulation, for an assumed fixed left-sided preload. Thus, the regurgitant flow rate is generally proportional to the total LVAD output, although the nature of this relationship is affected by the systemic afterload.

The complex relationships between the LV and aortic pressure, systemic circuit impedance/resistance, trans-LVAD and transnative AV antegrade and retrograde flow challenge the accurate prediction of the effect of post-LVAD implantation AR. Our findings suggest that AR progresses as a function of time and is likely related to alterations in the trans-AV pressure gradient combined with a dysfunctional, minimally mobile, or immobile AV. New moderate or greater AR developed in 11.4% of the LVAD recipients in our cohort. However, all patients in that group maintained LV unloading, with a mean LVIDd well less than the current American College of Cardiology/American Heart Association guideline criteria for surgical AVR for AR.[18] Additionally, a comprehensive study from the University of Michigan[13] actually correlated AR with smaller LV chamber dimensions. If post-LVAD implantation AR was physiologically important, the LV chamber dimensions should not be reduced, because volume unloading of the left ventricle should be difficult to achieve.

The present study did not try to define the treatment strategies for LVAD patients who experience significant AR. It is possible that medical treatment and pump speed adjustments could alter the rate of AR development or progression. We acknowledge that most of our patients had pump speeds set to achieve LV unloading, with infrequent opening of the AV. Furthermore, significant pump speed alterations were not performed for patients who developed AR. The most consistent medical intervention was systemic blood pressure reduction for those patients who presented with new AR and hypertension. Significant differences in medical management and pump speed adjustment might alter AR progression and could lead to inconsistent findings among different centers.

Although we did find that patients with moderate or greater AR maintained LV volume unloading, 5 of these patients (2.7% of the total) developed severe AR and clinical HF, all of whom underwent AV procedures that were, ultimately, open reoperations. The 4 survivors had clinical improvement after these procedures. The nonsurviving patient was in extremis on hospital readmission. Thus, when severe AR does occur after LVAD implantation, we believe that reoperation can be undertaken safely and using an open approach. Although percutaneous strategies have been used to treat AR in LVAD recipients, it is unclear whether such approaches yield equivalent outcomes to reoperative surgery.

Finally, our data did not identify an association between moderate or greater AR and diminished survival outcomes. This was in part owing to the generally favorable outcomes for the 5 patients with severe AR who underwent reoperation. The need for major cardiac reoperation for these 5 patients represented significant added morbidity.

CONCLUSIONS

Post-LVAD implantation AR remains a challenging entity to understand, anticipate, and treat. More long-term studies are required to better determine the physiologic and clinical effect of AR in this rapidly expanding subpopulation of patients with ESHF.

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