HHS Public Access

Author manuscript

J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2024 July 02.

Published in final edited form as:

J Thorac Cardiovasc Surg. 2023 July ; 166(1): 141–152.e1. doi:10.1016/j.jtcvs.2021.08.061.

Mitral regurgitation severity at left ventricular assist device implantation is associated with distinct myocardial transcriptomic signatures

Neal M. Duggal, MD[a], **Ienglam Lei, PhD**[b], **Xiaoting Wu, PhD**[b], **Keith D. Aaronson, MD**[c], **Francis D. Pagani, MD, PhD**[b], **Hugo Y.-K. Lam, PhD**[d], **Paul C. Tang, MD, PhD**[b], **Michigan Congestive Heart Failure Investigators**, **Jonathan W. Haft, MD**[b], **Matthew A. Romano, MD**[b], **Steven F. Bolling, MD**[b], **Ashraf Abou El Ela, MD**[b], **Allison Janda, MD**[a], **Gorav Ailawadi, MD, MBA**[b], **David Nordsletten**[b]

[a]Department of Anesthesiology, Department of Internal Medicine, University of Michigan Frankel Cardiovascular Center, Ann Arbor, Mich

[b]Department of Cardiac Surgery, Department of Internal Medicine, University of Michigan Frankel Cardiovascular Center, Ann Arbor, Mich

[c]Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan Frankel Cardiovascular Center, Ann Arbor, Mich

[d]HypaHub, Inc, San Jose, Calif.

Abstract

Objectives: We examined for differences in pre–left ventricular assist device (LVAD) implantation myocardial transcriptome signatures among patients with different degrees of mitral regurgitation (MR).

Methods: Between January 2018 and October 2019, we collected left ventricular (LV) cores during durable LVAD implantation (n = 72). A retrospective chart review was performed. Total RNA was isolated from LV cores and used to construct cDNA sequence libraries. The libraries were sequenced with the NovaSeq system, and data were quantified using Kallisto. Gene Set Enrichment Analysis (GSEA) and Gene Ontology analyses were performed, with a false discovery rate <0.05 considered significant.

Results: Comparing patients with preoperative mild or less MR (n = 30) and those with moderate-severe MR (n = 42), the moderate-severe MR group weighted less (P = .004) and had more tricuspid valve repairs (P = .043), without differences in demographics or comorbidities. We then compared both groups with a group of human donor hearts without heart failure (n = 8). Compared with the donor hearts, there were 3985 differentially expressed genes (DEGs) for mild or less MR and 4587 DEGs for moderate-severe MR. Specifically altered genes included 448 DEGs for specific for mild or less MR and 1050 DEGs for moderate-severe MR. On GSEA, common regulated genes showed increased immune gene expression and reduced expression of

Address for reprints: Paul C. Tang, MD, PhD, University of Michigan Frankel Cardiovascular Center, 5158 Cardiovascular Center, SPC 5864, 1500 E Medical Center Dr, Ann Arbor, MI 48109-5864 (tangpaul@med.umich.edu).
Drs Duggal and Lei contributed equally to this work and should be considered co–first authors.

contraction and energetic genes. Of the 1050 genes specific for moderate-severe MR, there were additional up-regulated genes related to inflammation and reduced expression of genes related to cellular proliferation.

Conclusions: Patients undergoing durable LVAD implantation with moderate-severe MR had increased activation of genes related to inflammation and reduction of cellular proliferation genes. This may have important implications for myocardial recovery.

Keywords

heart failure; mitral regurgitation; left ventricular assist device; transcriptomics; outcomes

Moderate-severe mitral regurgitation (MR) occurs in 32% to 42% of patients undergoing left ventricular assist device (LVAD) implantation.[1,2] Left ventricular (LV) unloading with an LVAD support changes in LV volume and pressure reduction that contribute to spontaneous improvement of MR in selected patients.[3,4] Surgical intervention for significant MR associated with continuous-flow LVAD therapy remains controversial, however.[5] Chronic functional MR in the setting of heart failure is marked by LV remodeling and dilatation, leading to papillary muscle displacement and mitral leaflet retraction with regurgitation.[6] More severe MR associated with LVAD support is known to be associated with a lower likelihood of myocardial recovery.[7] Conversely, greater resolution of MR after LVAD is associated with partial or complete myocardial recovery.[7,8]

Although traditional assessment of MR focuses mainly on imaging and hemodynamics, myocardial biology likely has an important bearing on MR resolution and myocardial recovery. Kawase and colleagues[9] demonstrated that MR is associated with a significant reduction in sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a) expression, worsened LV function, and increased ventricular dimensions. Systemic inflammation also may play a role in heart failure–related complications in the setting of MR. In patients with severe MR undergoing Mitraclip procedures, the elevated expression of circulating inflammatory markers (eg, high-sensitivity C-reactive protein, interleukin [IL]-6, matrix metalloproteinases [eg, MMP2, MMP9]) have been associated with postprocedure mortality.[10] It is also well recognized that inflammatory mediators, such as IL-6, tumor necrosis factor α, and myeloperoxidase, are increased in both acute and chronic heart failure[11]; however, the contribution of valvular pathology to myocardial inflammation in the setting of durable LVAD support remains unclear.

In the present study, we aimed to examine the impact of MR severity on transcriptomic expression in patients with advanced heart failure undergoing LVAD implantation. We hypothesized that the myocardial transcriptome will reveal pathways that differentiate MR severity and can identify potential biomarkers of MR resolution after LVAD implantation.

METHODS

Patients and Follow-up

This study was approved by the University of Michigan Institutional Review Board with a waiver of informed consent (IRB#HUM00132895, approved December 7, 2020; IRB#HUM00131275, approved August 6, 2020).

We conducted a retrospective review of 72 patients who underwent durable continuous-flow LVAD implantation between January 11, 2018, and October 25, 2019. We excluded 9 patients who underwent temporary mechanical circulatory support (extracorporeal membrane oxygenation, n = 3; temporary percutaneous LVAD, n = 6), because temporary support and its complications may be proinflammatory and influence myocardial biology (eg, inflammatory response to pumps, plastic tubing, and extracorporeal oxygenation). LV control tissues were obtained from 8 donor hearts not used for clinical transplantation with an LV ejection fraction ≥45%. Apical LV myocardial specimens obtained as a part of the LVAD implantation procedure and from donor hearts were snap-frozen immediately after removal and then stored at −80°C for subsequent analysis.

RNA Isolation and RNA-seq Library Construction

Total RNA was isolated from tissues using a hybrid Trizol and Qiagen column protocol with on-column DNAse I digestion. Only total RNA with an RNA integrity number >8 was used for RNA-seq library preparation. Total RNA (1 μg) was used for the construction of sequence libraries using the NEBNext Ultra RNA II library preparation kit (E7770; New England Biolabs, Ipswich, Mass). In brief, the rRNA was removed from the total RNA using NEBNext rRNA depletion kit (E6310; New England Biolabs) according to the manufacturer's protocol. The rRNA-depleted RNA was mixed with NEBNext First-Strand synthesis buffer (New England Biolabs), followed by incubation at 94°C for 15 minutes for fragmentation to ~200 bp. The fragmented and primed RNA was then used for first-strand and second-strand cDNA synthesis. The cDNA was subjected to end-repair dA tailing and adaptor ligation. A final amplification of the cDNA library was performed using dual-index sequencing primers (E7600; New England Biolabs). The RNA libraries were then sequenced with the NovaSeq system (Illumina, San Diego, Calif) in 50-bp paired-end mode. On average, 40 million reads were obtained for each sample.

RNA-seq Analysis

RNA-seq data were quantified using Kallisto version 0.43.0 (Pachter Lab, California Institute of Technology, Pasadena, Calif) with default parameters using the Grch38 Human Genome Reference Consortium. Expressed transcripts were defined as genes if the summed transcripts per million reads were >10 in all conditions. Differentially expressed genes (DEGs) were analyzed using the DESeq2 package (PMID: 25516281) in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and defined as a fold change >2 with adjusted P<.05. Adjusted P values were corrected with the Benjamini–Hochberg method (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/p.adjust.html). Gene Set Enrichment Analysis (GSEA) analyses was performed using GSEA 4.0.3 with 1000 gene set permutations. Gene sets with FDR <0.10 was considered significantly enriched compared

with reference. Post-LVAD DEGs (fold change >2 and adjusted P <.05) between the mild or less MR and moderate-severe MR groups were analyzed using the DESeq2 package. MR severity–specific DEGs were used for GO enrichment using the Panther classification system (http://www.pantherdb.org/). Links to Online Data Supplements 1-6 for RNA-seq data can be accessed at https://figshare.com/s/94380468d4d7ea792b97.

Statistical Methods for Clinical Outcomes

Pearson's χ^2 test or Fisher's exact test was used to analyze categorical variables. Independent continuous variables were compared using the Kruskal–Wallis rank-sum test or Student's t test. Kaplan–Meier survival analysis with log-rank test statistics was used to analyze survival data. All statistics were performed using SPSS version 24 (IBM, Armonk, NY).

RESULTS

Study Population Characteristics and Survival

There were no differences in age, sex, comorbidities, etiology of heart failure, redo sternotomy status, or concomitant procedures between patients with mild or less MR and those with moderate-severe MR (P >.05) (Table 1). For the total study population, the average age was 54.12 ± 13.53 years with a 76.4% male preponderance (55 of 72). The etiology of heart failure included ischemic (37.5%) and nonischemic (62.5%) causes. The moderate-severe MR group had more frequent tricuspid valve repair (42.9% vs 20.0%; P = .043) and right ventricular assist device implants (11.9% vs 0.0%; P = .050) and a higher rate of preoperative moderate-severe tricuspid regurgitation (57.1% vs 42.9%; P = .023) (Table 2). However, other pre-LVAD echocardiographic and hemodynamic parameters were comparable (Table 2). The effective mean regurgitant orifice area for the moderate-severe MR group was 0.34 ± 0.10 cm^2.

The mean duration of clinical follow-up for the study population was 1.15 ± 0.73 years, with a median follow-up of 1.16 years (interquartile range, 1.21 years). There was no difference in the mean duration of follow-up between the mild or less MR group and moderate-severe MR groups (1.17 ± 0.72 years vs 1.139 ± 0.74 years; P = .842). All patients with pre-LVAD moderate-severe MR (n = 42) had annular dilatation and leaflet restriction (Carpentier class IIIb) as the mechanism. There was no difference in survival between the 2 groups (P = .679) with composite 1- and 2-year survival of 95.4% and 82.3%, respectively (Figure E1). Heart donors had an average age of 51.1 ± 11.9 years, with comorbidities comparable to those of LVAD recipients (Table 3). Research donor hearts were not used for transplantation owing to the following diagnoses: advanced donor age (n = 4), history of coronary artery disease (n = 3), low normal LVEF (n = 5), left ventricular hypertrophy (n = 2), diabetes type I (n = 1), and history of dialysis (n = 1).

The LV Myocardium Showed Specific Gene Transcript Expression Differences Between Patients With Pre-LVAD Moderate-Severe MR and Those With Mild or Less MR

To examinewhether MR severity influenced gene expression in patients with heart failure undergoing LVAD implantation, we performed global RNA-seq on LV tissue samples.

We compared the gene expression changes between patients with mild or less MR and nonfailing donor hearts as well as between patients with moderate-severe MR and donor hearts. There were 3985 DEGs between mild MR and donor heart samples and 4587 DEGs between severe MR and donor heart samples. Among these DEGs (Figure 1, A), 3537 genes were commonly differentially expressed in both low- and higher-severity MR phenotypes relative to donor hearts (Online Data Supplement 1). There also were 448 mild or less MR-specific DEGs (Online Data Supplement 2) and 1050 moderate-severe MR-specific DEGs (Online Data Supplement 3). GSEA on the 3537 common regulated genes in the 2 MR groups showed that gene sets related to cardiac contraction, cardiac conduction, and mitochondrial respiration and oxidation were significantly down-regulated in patients with end-stage heart failure compared with relatively normal donor hearts. Conversely, expression of transcripts related to innate and adaptive immune responses, phagocytosis, and the complement pathway were significantly up-regulated in advanced heart failure (Figure 1, B).

Box-and-whiskers dot plots of transcript fold inductions shows that for moderate-severe MR-specific genes that were down- or up-regulated, the same genes in the mild or less MR group showed a trend toward down-regulation, although this was not statistically significant compared with donor hearts. The same general directional trend can be appreciated for mild or less MR-specific genes that were down-and up-regulated. This suggests that the magnitude of expression of specific genes in the LV myocardium likely varies in a continuous spectrum and is related to MR severity (Figure 2).

Notable up-regulated gene expression specifically in those with pre-LVAD moderate-severe MR (1050 genes; Online Data Supplement 4) included pathways related to immune response (*CXCL9*, 4.8-fold increase; *IRAK3*, 1.7-fold increase; *IRF6*, 1.8-fold decrease; *IRF8*, 2.00-fold increase; *S100A8*, 2.5-fold increase; *S100B*, 2.5-fold increase; *PTX3*, 4.6-fold increase), reactive oxygen species (ROS; *MPO*, 2.1-fold increase; *NOX4*, 2.2-fold increase), cardiac remodeling (*MMP1*, 10.1-fold increase), and cell death (*MLKL*, 1.7-fold increase; *PARP8*, 1.7-fold increase).

Patients With Moderate-Severe MR Expressed Additional Immune Response Transcripts and Fewer Cell Proliferation–Related Genes in the LV Myocardium

To sub-phenotype specific gene profiles, we performed hierarchical clustering of these genes. The samples segregated into 3 large clusters characterized by donor hearts, moderate-severe MR, and mild or less MR (Figure 3, A). Examination of moderate-severe MR-specific DEGs (Figure 1, A) using GSEA showed that additional complement activation and immune response genes were further enriched in moderate-severe MR myocardial sample genes, whereas expression of gene-related cellular proliferation and structure (eg, cytoskeleton, actin) were significantly reduced (Figure 3, B). We did not identify any significant GSEA gene sets expressed in the mild or less MR-specific DEGs. Thus, GSEA evaluation suggests greater expression of immune transcripts and less expression of transcripts related to cellular proliferation and structure in the myocardium of pre-LVAD patients with moderate-severe MR compared with those with lesser degrees of MR. A direct comparison of mild or less MR and moderate-severe MR samples showed

9 DEGs (fold change >2; FDR <0.05; adjusted $P < .05$) and are listed in Online Data Supplement 4. Among patients with pre-LVAD moderate-severe MR, there were 193 DEGs comparing ischemic with nonischemic MR (Online Data Supplement 5), and GSEA showed more inflammatory pathways upregulations in the non-ischemic group when compared to ischemic cardiomyopathies (Figure E2).

Correlation of RNA-seq Data With MR Resolution at 8 Months Post-LVAD

At 1 year after LVAD implantation in the pre-LVAD moderate-severe MR group (n = 42), there were 36 patients with residual mild or less MR and 6 patients remained with moderate-severe MR. There was no difference in mean echocardiographic follow-up between patients with residual mild or less MR and those with moderate-severe MR (0.67 ± 0.46 years vs 0.83 ± 0.35 years; $P = .420$). There also was no difference in LV diameter between the 2 residual MR groups in either diastole (67.16 ± 14.10 mm vs 76.67 ± 15.04 mm; $P = .143$) or systole (62.41 ± 15.09 mm vs 70.83 ± 19.85 mm; $P = .239$). A total of 188 DEGs were compared between patients with residual mild or less MR and those with moderate-severe MR following LVAD implantation. Specific DEGs of note that were up-regulated in the residual moderate-severe MR group were related to immune responses (*CD22*, 5.1-fold increase; *FUT9*, 3.1-fold increase), ROS (*NOX5*, 3.3-fold increase; *XDH*, 3.8-fold increase), heart failure mediators (*ARG1*, 5.0-fold increase; *FABP4*, 3.2-foldx increase; *NANOG*, 2.7-fold increase), cardiac remodeling (*MMP25*, 4.0-fold increase; *PCSK5*, 4.8-fold increase), and ion channels (*CASR*, 2.7-fold increase, *NEDD4*, 2.1-fold increase). Other DEGs are listed in Online Data Supplement 6.

GO enrichment of post-LVAD transcripts reflecting MR severity compared with donor hearts showed that common up-regulated genes that are representative of heart failure were related to immune responses and down-regulated genes were related to cardiac contraction. Interestingly, patients with MR resolution after LVAD implantation had greater expression of innate and adaptive immunity transcripts, whereas patients with significant residual MR had increased expression of cell–cell adhesion and synaptic transmission genes (Table 4).

DISCUSSION

LVAD implantation is a critical component in the arsenal of modern therapy for advanced heart failure[12]; however, the diversity of myocardial biology underlying the clinical manifestations has received little attention in the clinical realm. Previous predictive models for LVAD outcomes, such as right heart failure and myocardial recovery, were focused mainly on clinical parameters, imaging, and hemodynamics.[13,14] The underlying myocardial biology associated with MR has been explored in a limited number of studies. We now use transcriptomics as an unsupervised approach to investigating relevant signaling pathways from the perspective of global gene expression relative to MR severity rather than focusing on specific genes of interest conceived a priori.

Our mild or less MR and moderate-severe MR groups had comparable demographics and comorbidities. The increased rate of tricuspid valve repair in the moderate-severe MR group likely reflects greater afterload from MR applied to the right ventricle, leading to more severe tricuspid regurgitation necessitating repair. Besides these valvular pathologies in

the moderate-severe MR group, the were no other significant differences. This paucity of differences in clinical features other than atrioventricular valve regurgitation is the setting in which our subsequent transcriptomic analysis is undertaken. Although this small study population showed no difference in survival between the 2 groups, previous studies of outcomes with larger study populations showed that significant residual MR was associated with more right ventricular failure and poorer survival, particularly in the destination therapy population.[15–18]

End-stage heart failure itself is associated with greater inflammatory transcript responses (eg, complement activation, innate and adaptive immune responses) coupled with reduced expression of mediators in contractile and energetic/oxidative processes. Indeed, heart failure is known to be associated with increased inflammation.[19] Heart failure patients with a “cardioinflammatory” phenotype have been shown to respond selectively to anti-inflammatory therapies, such as canakinumab, used in the CANTOS trial.[20] Our present study demonstrates that increased MR severity is associated with greater immune transcriptomic responses (eg, complement and innate/adaptive immune responses) in the myocardium. Furthermore, gene expression in structural and proliferative pathways were decreased. Stainback and colleagues[21] also showed that MR is associated with increased expression of inflammatory mediators (eg, CXCL9, CLEC10A, immune cell infiltration) within the mitral leaflets.[21] Consistent with these findings, patients with degenerative MR had greater myocardial fluorine 18–labeled fluorodeoxyglucose uptake, consistent with myocardial inflammation. This inflammation is also present in those with normal LV function and dimensions.[22] Therefore, myocardial inflammation and injury can contribute to worsening of existing MR.[22–24]

Specifically changed genes in the myocardial transcriptomic profiles of patients with pre-LVAD moderate-severe MR are mainly in the inflammatory pathways. This is in addition to genes expressed in common with and distinct from those with mild or less MR. The increased myocardial expression of chemokines CXCL9 will recruit lymphocytes and macrophages that expressed its cognate receptor CXCR3.[25,26] CXCL9 is known to be elevated in the plasma and myocardium of patients with heart failure.[25] This is accompanied by increased expression of Toll-like receptor innate immune signaling components, such as IRAK3 and IRF8, via MyD88-dependent signaling.[27,28] Conversely, there is decreased expression of IRF6, a negative regulator of innate immunity.[29] Pre-LVAD moderate-severe MR also showed increased expression of S100A8 and S100B, Toll-like receptor ligands or “alarmins” expressed during cardiac injury.[30] Increase expression of myeloperoxidase produced by neutrophils and macrophages also add to increased oxidative stress, and endothelial dysfunction.[31] Greater MR was associated with necroptotic and pyroptotic cell death, as demonstrated by increased MLKL transcript expression. MLKL protein expression also is associated with ROS production, which impairs cardiac contraction,[32] and reportedly has a greater impact on right ventricular failure.[33] The specific expression of other genes in moderate-severe MR, such as *NOX4*, *PARRP8*, *PTX3*, and *MMP1*, contribute to extracellular matrix and ventricular remodeling,[34] mitochondrial-associated ROS production in cardiomyocytes,[35] apoptosis,[36] and NFκB inflammatory pathway activation.[37]

Given the known improvement in MR following LVAD implantation,[2,38] we examined the expression of myocardial transcripts based on pre-LVAD moderate-severe MR (n = 42) resolution at approximately 8 months after LVAD implantation. The majority (n = 36) showed improvement in MR to mild or less, whereas only 6 patients had residual moderate-severe MR. In a direct comparison of the 2 groups, we identified 188 DEGs between individuals who did or did not have improvement in their MR after LVAD implantation. Here we highlight selected DEGs that represent transcriptomic biomarkers for nonresolution of preoperative moderate-severe MR after LVAD implantation. Immune-related DEGs, including B cell marker CD22, is impactful, because B cells and their antibodies have important roles in the pathogenesis of cardiomyopathy by activating pathways that contribute to cardiac fibrosis, contractile dysfunction, cell death, and inflammation.[39,40] Increased *FUT9* expression indicates increased leukocyte adhesion and recruitment to the cardiac vasculature associated with MR.[41] Furthermore, the increased expression of ion channels (eg, *CASR*, *NEDD4*) in the myocardium can activate proapoptotic mitochondrial pathways and promote fibrosis,[42] and the decreased expression of voltage-gated sodium channel Nav1.5 may impair electrical conduction.[43] These can contribute to a pro-arrhythmogenic phenotype and promote heart failure.[43] Increased expression of MMP25 and its convertase PCSK5 also are known to occur in dilated cardiomyopathies.[44–46] Increased expression of ROS sources (eg, *NOX5*, *XDH*) in cardiomyocytes and vasculature likely contributes to cardiac remodeling and dysfunction.[47–50] Other biomarkers (eg, *NANOG*, *ARG1*, *FABP4*) also have been associated with systolic dysfunction, altered energy utilization, and dilated cardiomyopathies.[51–53]

Interestingly, patients with pre-LVAD moderate-severe MR expressing more inflammatory transcripts based on GO analysis had a greater likelihood of MR resolution. A paucity of myocardial inflammation in patients with pre-LVAD moderate-severe MR potentially may indicate a “burnt-out” phenotype with a nonviable and noncontractile LV wall with reduced compliance. This may lead to persistent mitral annular dilatation and noncoaptation of the leaflets despite LVAD decompression. This is consistent with clinical findings by our group and others that larger LV dimensions, which likely signals a more advanced stage of heart failure, is associated with significant residual MR after LVAD implantation.[54,55]

In addition to hemodynamic considerations, increased myocardial inflammation and elaboration of factors that may promote maladaptive ventricular remodeling can explain in part the lower likelihood of myocardial recovery with LVAD support in severe MR.[7] Although immune mediators such as IL-6 and tumor necrosis factor α are known to negatively impact cardiac function in myocarditis,[56,57] the impact of lower levels of inflammation in the setting of preoperative and/or residual post-LVAD moderate-severe MR remains unclear. Current pharmacologic regimens used to promote myocardial recovery in the setting of LVAD have anti-inflammatory effects. These include mineralocorticoid receptor antagonists,[58] beta-blockers,[59] and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[60] It is important to note that correction of the mechanical aspects of MR with valve repair or replacement is very important as well. This can restore ventricular geometry and lead to a 34% to 42% improvement in LV ejection fraction.[61] Recently there have been reports of improved right ventricular function, less readmissions, and improved survival with reestablishment of mitral competence at the time

of LVAD implantation[2,16,62]; however, severe MR resolves without intervention in 62% to 80% of patients, and so identifying those likely to have residual moderate-severe MR using molecular markers (eg, inflammation) may avoid unnecessary mitral surgery with its inherent risks.[2,16]

Future therapies to improve LVAD outcomes (eg, myocardial recovery) with valvular lesions may include several treatment goals, including alleviation of wall stress, correction of valve lesion to improve hemodynamics, and pharmacologic molecular therapies that inhibit inflammation, increase cellular survival/proliferation, and promote myocardial energy production through the activation of adaptive metabolic pathways. Thus, the underlying cardiac biology is highly heterogenous in end-stage heart failure. This should be addressed in our prognostic and therapeutic strategies when undergoing durable mechanical support. This study provides evidence that biological markers can correlate with anatomic and functional cardiac pathology. In particular, a search for circulating biomarkers can greatly facilitate a personalized approach to surgical heart failure therapy.

Study limitations include the retrospective single-center design with inherent biases. The limited size of the study population means that there are possible confounders (eg, MR and heart failure etiology) that might not be adjusted for. Furthermore, smaller differences in clinical outcomes (eg, survival, postoperative complications), echocardiographic findings, and gene expression data might not be appreciated. In particular, the low number of cases of post-LVAD moderate-severe MR (n = 6) limited the evaluation of post-LVAD data. Furthermore, there likely are protein expression differences and post-translational modifications of protein products that were not explored in this study that would be expected to impact cardiac responses to mitral valve pathologies in the mechanically supported heart. As we accumulate more human myocardial specimens in our biobank, we anticipate greater granularity in future studies from our institutional patient population, as well as the possibility of pooling data from multiple institutions. A graphical abstract summary of our study is shown in Figure 4, and a brief overview is provided in Video 1.

CONCLUSIONS

Significant transcriptomic heterogeneity occurs in heart failure requiring LVAD support. Greater severity of preoperative MR is associated with increased inflammatory gene expression coupled with decrease expression of gene pathways related to cellular proliferation and structure. DEGs associated with both preoperative (eg, *CXCL9*, *IRAK3*) and postoperative (eg, *CD22*, *NEDD4*, *NOX5*, *PCSK5*) moderate-severe MR have been identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest Statement

We acknowledge the administrative and database support provided by Stacy Haverstick, BS, MHA, Alondra Dorsey, BS, Jeremy Wolverton, BBA, MSI, and Sandra Marshall for the submission of this manuscript. We also thank the Gift of Life Michigan Organ Procurement Organization for their invaluable support.

Dr Janda is funded by a US National Institutes of Health T32 Grant (National Institute of General Medical Sciences Grant T32GM103730) and has received research support paid to the University of Michigan from Becton, Dickinson and Company. All other authors reported no conflicts of interest.

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Abbreviations and Acronyms

DEG	differentially expressed genes
ECMO	extracorporeal membrane oxygenation
IL	interleukin
LV	left ventricular
LVAD	left ventricular assist device
MR	mitral regurgitation

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PERSPECTIVE

End-stage heart failure is associated with significant myocardial transcriptomic heterogeneity. Greater severity of mitral regurgitation (MR) before left ventricular assist device (LVAD) implantation correlates with greater expression of inflammatory transcripts with reduced expression of genes related to cellular proliferation and oxygen utilization. This may have implications for LVAD outcomes, such as myocardial recovery, heart failure, and MR resolution.

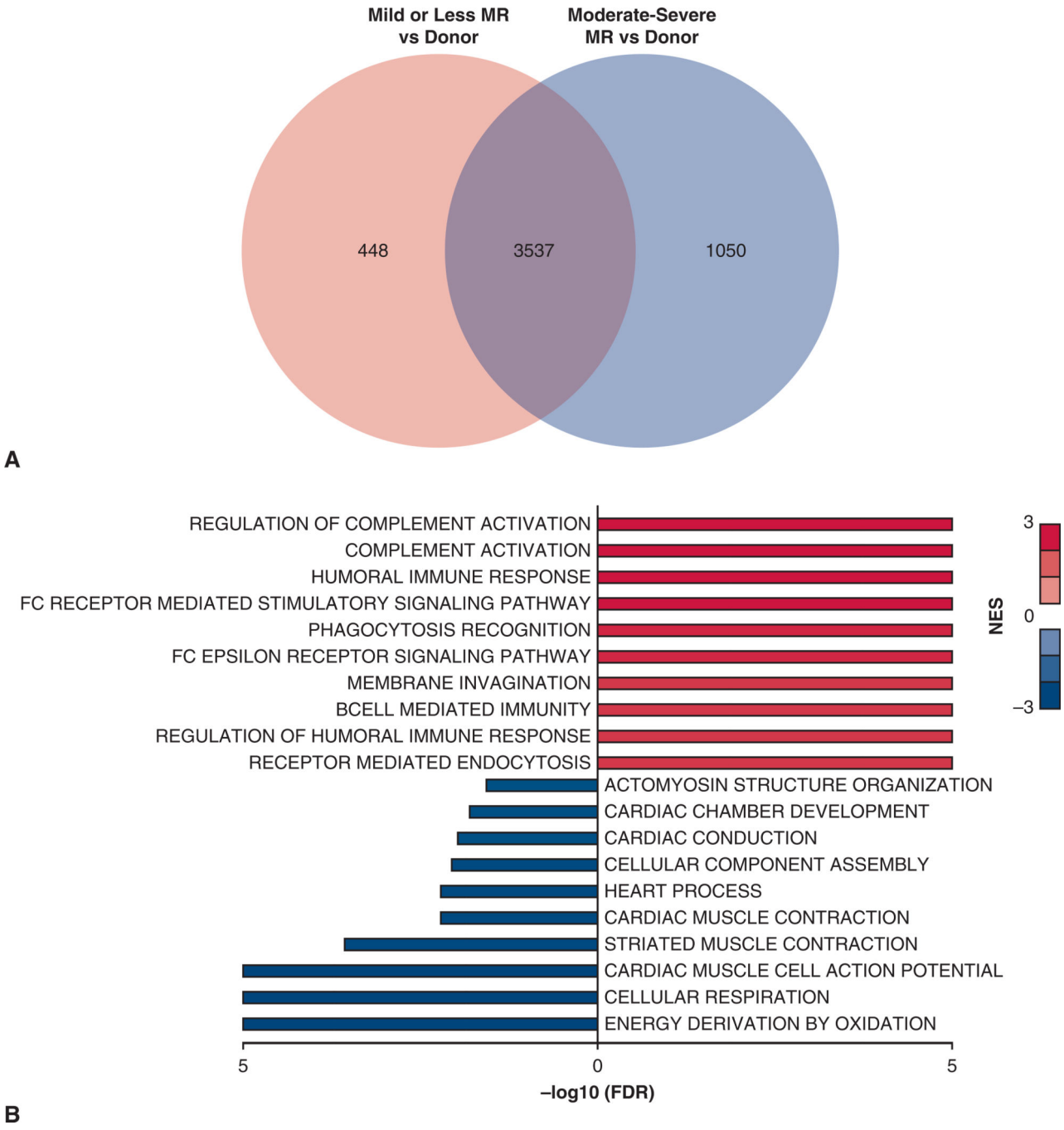


FIGURE 1.

Inflammatory gene up-regulation and down-regulation of metabolic genes occur in failing hearts. A, Number of differentially expressed genes (log2 fold change >1; false discovery rate <0.05) compared between donor hearts versus respective mild or less mitral regurgitation (*MR*) and moderate-severe MR left ventricular assist device samples. B, Gene set enrichment analysis using common altered genes.

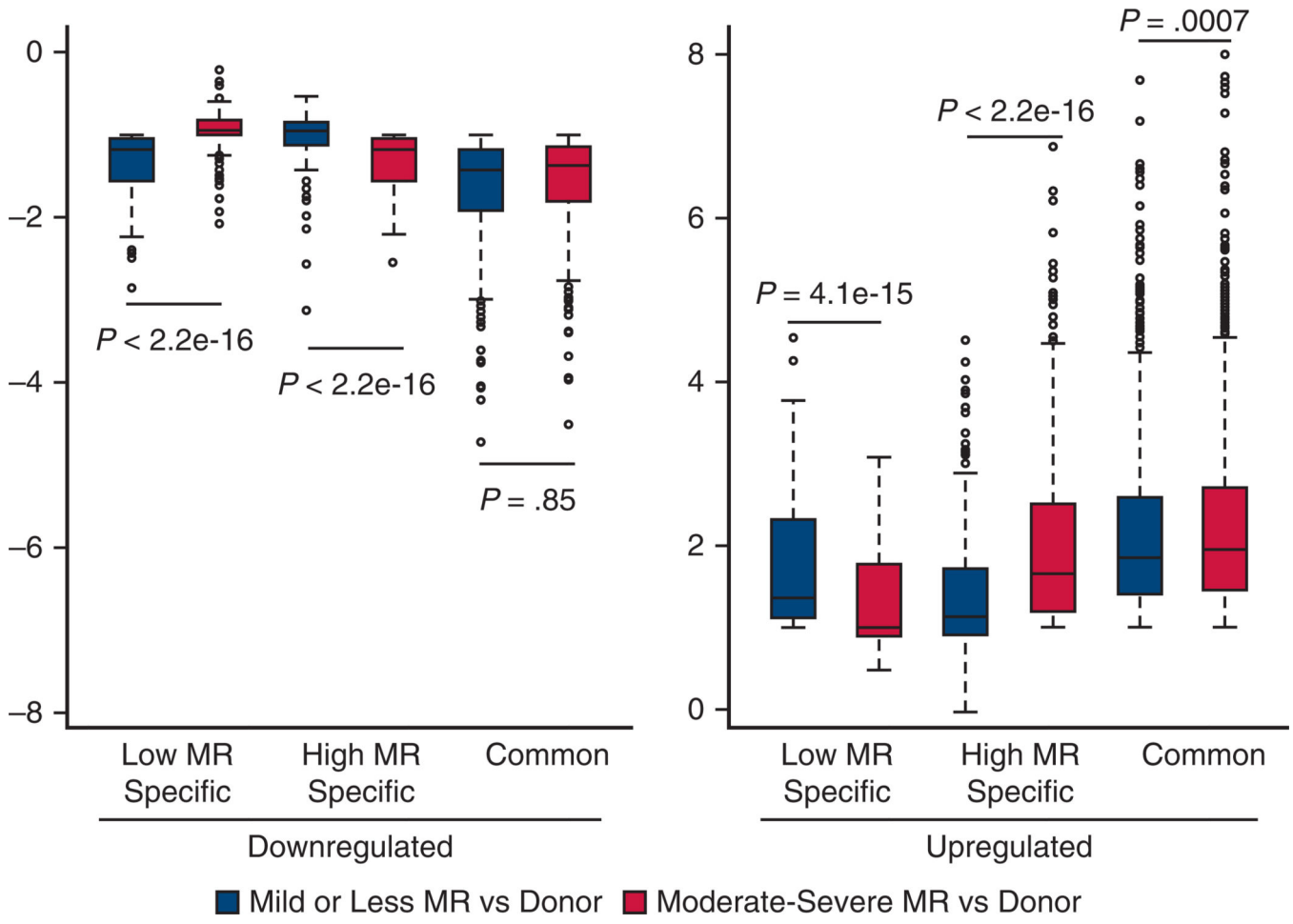


FIGURE 2.

Up- and down-regulated myocardial genes show a similar directional trend when comparing mitral regurgitation (*MR*) of differing severity, suggesting that progressive MR itself is associated with specific transcriptomic changes in the myocardium. The box-and-whisker dot plot shows log2 fold change using mild or less MR-specific, moderate-severe MR-specific, and common down-regulated and up-regulated genes. The *middle horizontal line* represents the median.

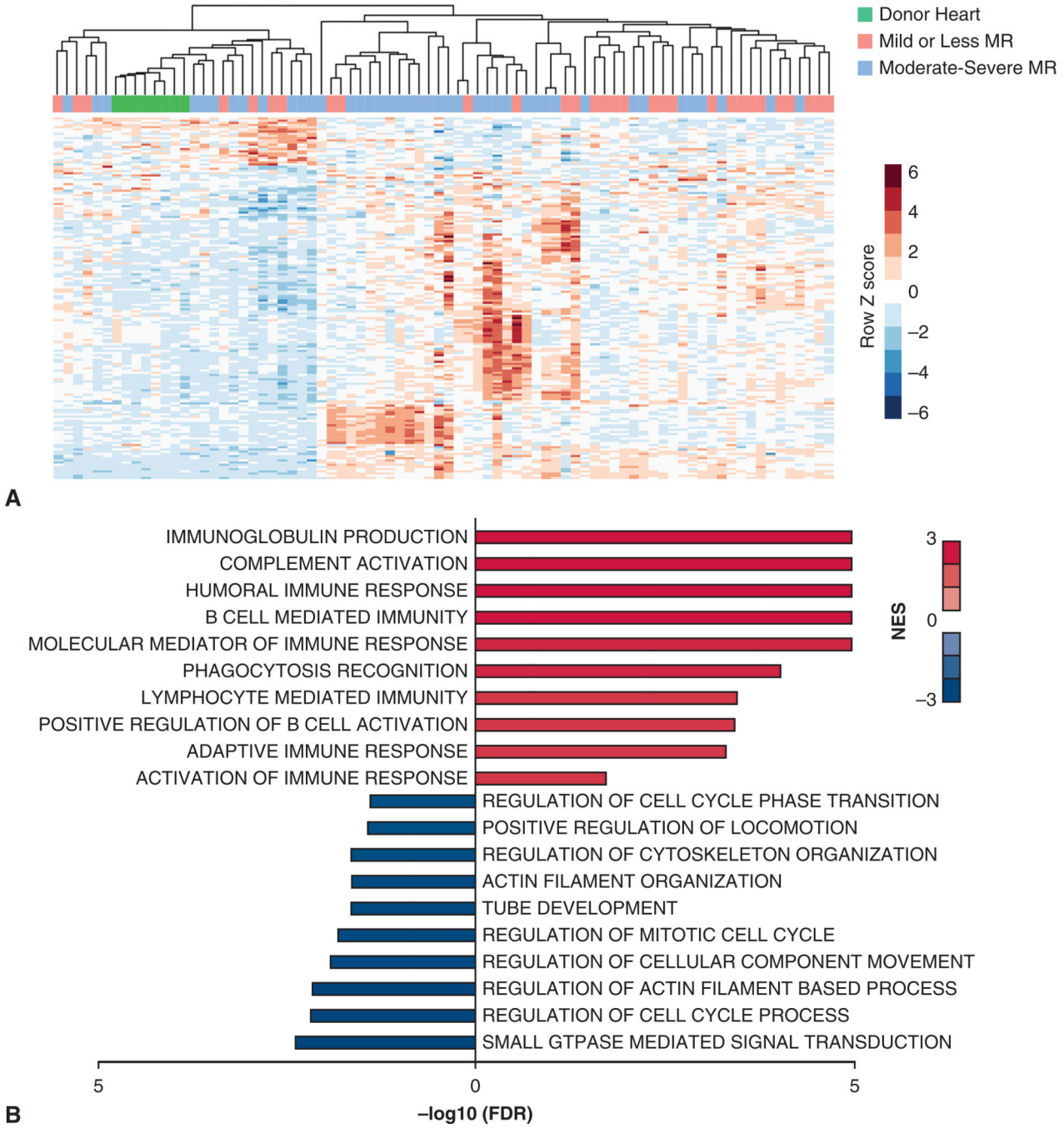


FIGURE 3.

Increased severity of mitral regurgitation (*MR*) is associated with increased expression of immune response genes and down-regulation of genes associated with cellular proliferation and structure. A, Heatmap of subtype specific differentially expressed genes (DEGs). B, Gene set enrichment analysis using moderate-severe MR-specific regulated genes.

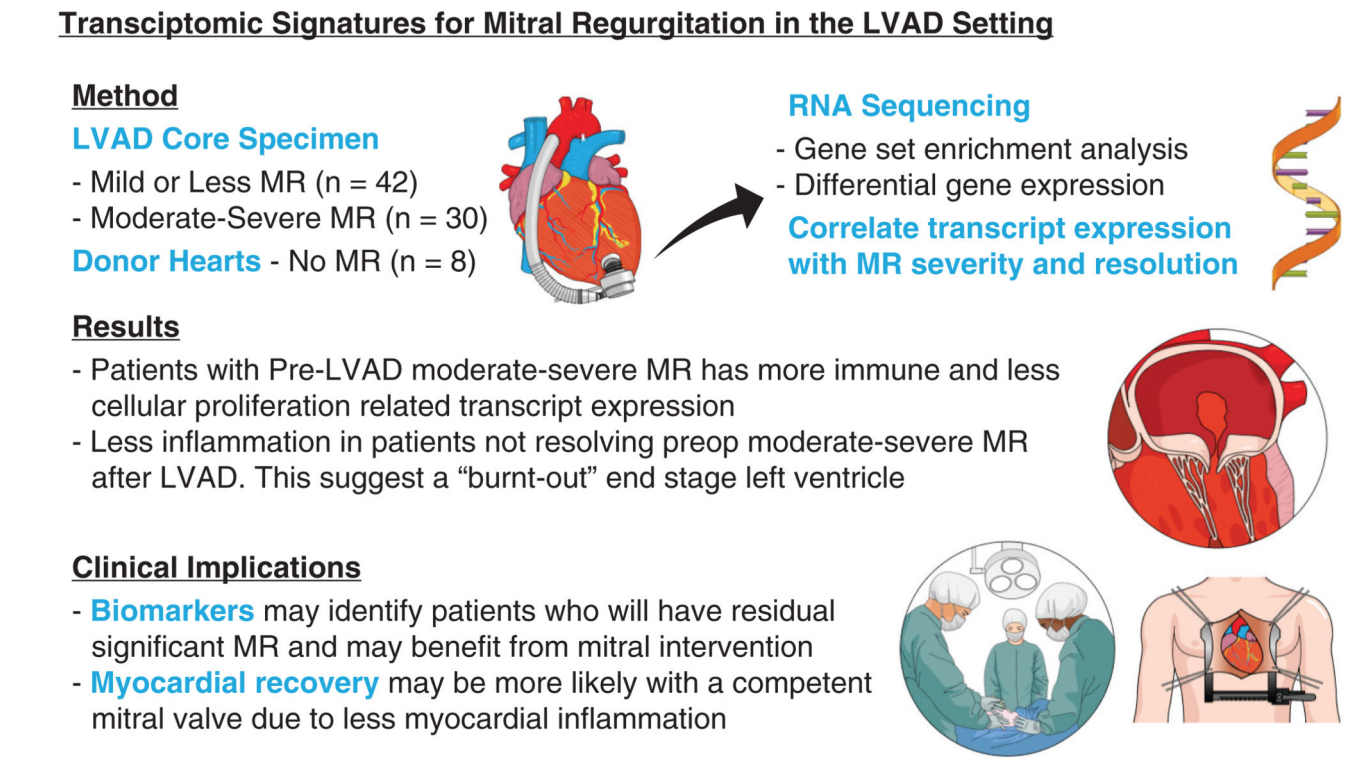
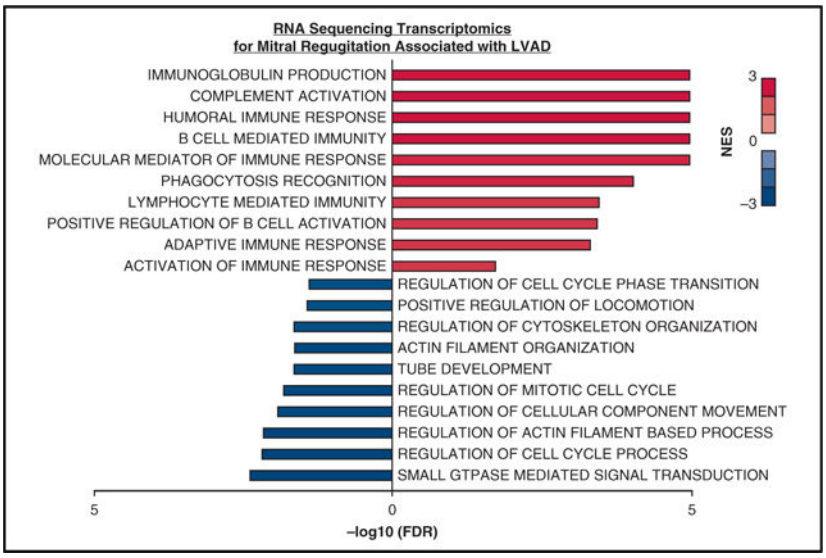


FIGURE 4.

Shown is the collection of a left ventricular core specimen for RNA sequencing and correlation of transcript expression with mitral regurgitation severity and resolution.



CENTRAL MESSAGE.

Mitral regurgitation is associated with specific transcriptomic signatures in patients undergoing left ventricular assist device implantation. This may have implications for myocardial recovery and performance of mitral interventions.

Significant mitral regurgitation increases immune transcripts and decreases structural gene expression.

TABLE 1.

Patient demographic and operative characteristics

Characteristic	Mild or less MR (N = 30)	Moderate-severe MR (N = 42)	*P* value
Age, y, mean ± SD	56.34 ± 12.22	52.53 ± 14.33	.242
Male sex, n (%)	26 (86.7)	29 (69.0)	.083
Weight, kg, mean ± SD	95.27 ± 20.68	79.91 ± 22.54	.004
Height, cm, mean ± SD	176.61 ± 10.60	173.98 ± 9.55	.276
Comorbidities, n (%)			
Hypertension	16 (53.3)	27 (64.3)	.350
Hyperlipidemia	16 (53.3)	16 (38.1)	.200
Diabetes	12 (40.0)	11 (26.2)	.215
Stroke	2 (6.7)	4 (9.5)	.665
Lung disease	2 (6.7)	3 (7.1)	.938
Atrial arrhythmia	10 (33.3)	15 (35.7)	.834
Ventricular arrhythmia	6 (20.0)	5 (11.9)	.347
Implantable cardioverter defibrillator, n (%)	22 (73.3)	31 (73.8)	.964
Serum creatinine level, mg/dL, mean ± SD	1.41 ± 0.40	1.49 ± 0.53	.468
Smoking history, n (%)	6 (20.0)	14 (33.3)	.213
Intra-aortic balloon pump, n (%)	4 (13.3)	3 (7.1)	.382
Etiology of heart failure, n (%)			
Ischemic cardiomyopathy	14 (46.7)	13 (31.0)	.175
Nonischemic cardiomyopathy	16 (53.3)	29 (69.0)	.175
Concomitant procedure, n (%)			
Redo sternotomy	7 (23.3)	7 (16.7)	.481
Aortic valve repair	3 (10.0)	2 (4.8)	.389
Aortic valve replacement	1 (3.3)	1 (2.4)	.808
Tricuspid valve repair	6 (20.0)	18 (42.9)	.043
Right ventricular assist device	0 (0.0)	5 (11.9)	.050

MR, Mitral regurgitation; *SD*, standard deviation.

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TABLE 2.

Preoperative echocardiography and cardiac catheterization findings

Parameter	Mild or less MR (N = 30)	Moderate-severe MR (N = 42)	*P* value
Echocardiography LVEF, %, mean ± SD	16.30 ± 5.69	15.17 ± 5.11	.380
Aortic insufficiency: moderate-severe, n (%)	1 (3.3)	0 (0.0)	.233
Tricuspid regurgitation: moderate-severe, n (%)	9 (30.0)	24 (57.1)	.023
Right ventricular dysfunction: moderate-severe, n (%)	17 (56.7)	23 (54.8)	.873
LV internal diameter Diastole, mm, mean ± SD	71.17 ± 11.47	74.74 ± 10.77	.181
Systole, mm, mean ± SD	65.23 ± 12.49	69.21 ± 11.06	.158
Left atrial diameter, mm, mean ± SD	51.40 ± 7.41	53.78 ± 8.80	.234
Cardiac catheterization Heart rate, bpm, mean ± SD	85.00 ± 17.62	92.69 ± 17.05	.067
Systolic blood pressure, mm Hg, mean ± SD	106.53 ± 20.15	102.71 ± 12.99	.332
Diastolic blood pressure, mm Hg, mean ± SD	68.90 ± 12.45	65.71 ± 10.45	.243
Mean blood pressure, mm Hg, mean ± SD	81.53 ± 14.68	79.07 ± 8.49	.372
Pulmonary artery systolic pressure, mm Hg, mean ± SD	47.93 ± 15.30	52.02 ± 13.11	.228
Pulmonary artery diastolic pressure, mm Hg, mean ± SD	27.13 ± 9.78	29.00 ± 7.93	.375
Pulmonary artery mean pressure, mm Hg, mean ± SD	34.53 ± 11.63	37.29 ± 9.48	.273
Pulmonary vascular resistance, Wood units, mean ± SD	3.21 ± 2.69	3.52 ± 1.82	.565
Cardiac output, L/min, mean ± SD	3.57 ± 0.81	3.37 ± 0.99	.361
Cardiac index, mean ± SD	1.72 ± 0.37	1.75 ± 0.47	.780
Pulmonary capillary wedge pressure, mm Hg, mean ± SD	24.23 ± 9.13	26.40 ± 8.83	.314
Right ventricular stroke work index, mean ± SD	496.15 ± 208.80	509.14 ± 210.20	.798
Right atrial pressure, mm Hg, mean ± SD	13.53 ± 13.27	12.14 ± 6.56	.559
Mixed venous oxygen saturation, %, mean ± SD	54.91 ± 7.18	51.75 ± 8.94	.115

MR, Mitral regurgitation; *LVEF*, left ventricular ejection fraction; *SD*, standard deviation; *LV*, left ventricular.

TABLE 3.

Characteristics of heart donors and LVAD recipients

Characteristic	Heart donors (N = 8)	LVAD recipients (N = 72)	*P* value
Age, y, mean ± SD	51.13 ± 11.91	54.12 ± 13.53	.551
Male sex, n (%)	6 (75.0)	55 (76.4)	.930
Height, cm, mean ± SD	176.10 ± 11.14	175.07 ± 10.02	.811
Weight, kg, mean ± SD	80.59 ± 15.91	86.31 ± 22.94	.522
Coronary artery disease, n (%)	3 (37.5)	11 (15.3)	.117
Hypertension, n (%)	4 (50.0)	43 (58.7)	.596
Diabetes, n (%)	2 (25.0)	23 (31.9)	.688
LVEF, %, mean ± SD	55.00 ± 9.64	15.64 ± 5.35	<.001
Creatinine, mg/dL, mean ± SD	2.27 ± 1.99	1.46 ± 0.48	.362
Total bilirubin, mg/dL, mean ± SD	1.00 ± 0.75	1.47 ± 1.73	.511
White blood count, × 10^9/L, mean ± SD	11.37 ± 6.33	9.21 ± 3.75	.205
Hemoglobin, mg/dL, mean ± SD	10.27 ± 1.36	11.53 ± 1.93	.121

LVAD, Left ventricular assist device; *SD*, standard deviation; *LVEF*, left ventricular ejection fraction.

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TABLE 4.

Gene Ontology enrichment analysis preoperative myocardial transcripts based on post-LVAD implantation MR severity

Genes	GO biological process	Fold enrichment	FDR
Common up-regulated genes between mild or less and moderate-severe MR compared to donor	Leukocyte chemotaxis	3.93	3.84E-09
	Chemokine-mediated signaling pathway	5.18	1.31E-11
	Regulation of inflammatory response	1.87	2.55E-06
	Immune response	1.79	4.87E-15
	Collagen fibril organization	2.95	2.16E-05
Common down-regulated genes between mild or less and moderate-severe MR compared to donor	Regulation of heart contraction	4.46	7.32E-03
	Muscle contraction	4.11	2.97E-02
Moderate-severe MR-specific up-regulated genes compared to donor	Cell-cell adhesion via plasma-membrane adhesion molecules	2.84	6.26E-03
	Chemical synaptic transmission	2.37	5.28E-03
Mild or less MR-specific up-regulated genes compared to donor	Complement activation, classical pathway	15.51	1.75E-51
	Humoral immune response	6.65	2.05E-42
	Adaptive immune response	5.72	1.25E-54
	Phagocytosis	7.24	2.64E-41
	Endocytosis	5.12	1.40E-38

GO, Gene Ontology; *FDR*, false discovery rate; *MR*, mitral regurgitation.