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Significance of Residual Mitral Regurgitation After Continuous Flow Left Ventricular Assist Device Implantation

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ABSTRACT

OBJECTIVES This study hypothesized that the presence of residual mitral regurgitation (MR) post-continuous flow (CF) left ventricular assist device (LVAD) implantation based on quantitative assessment would be negatively associated with right ventricular (RV) size and function and clinical outcomes.

BACKGROUND MR is associated with elevated left atrial pressure, secondary pulmonary hypertension and RV dysfunction. Implantation of a LVAD leads to mechanical unloading of the left ventricle and generally improves MR. The clinical significance of residual MR in patients supported with CF LVADs is uncertain. Most studies evaluating the presence of MR in LVAD patients have utilized predominantly qualitative assessments of MR.

METHODS We retrospectively identified patients implanted with CF LVADs at our institution from 2007 to 2013 who had a pre-operative transthoracic echocardiogram (TTE) within 3 months of LVAD implant and who had a post-operative TTE at least 1 month post-LVAD. MR was assessed quantitatively using the ratio of MR color jet area (CJA)/left atrial area (LAA) in apical views. We also compared quantitative RV metrics, hospitalizations, and mortality in patients with and without significant residual MR (defined as MR CJA/LAA >0.2) on post-implantation TTE.

RESULTS Sixty-nine patients were included in this study. Post-LVAD implantation, 55 patients (80%) had mild or less MR (mean MR CJA/LAA 0.08) but 14 (20%) had significant residual MR (mean MR CJA/LAA 0.34). Patients with residual MR had significantly larger RV size (right ventricular end diastolic dimension 49 mm vs. 45 mm; $p = 0.04$) and worse RV function (tricuspid annular plane systolic excursion 10 mm vs. 12 mm; $p = 0.02$; and right ventricular fractional area change 29% vs. 34%; $p = 0.02$). Post-implantation pulmonary artery pressures were higher in patients with residual MR (pulmonary artery systolic 43 mm Hg vs. 35 mm Hg; $p = 0.05$). In patients with residual MR there was slightly greater posterior displacement of the mitral coaptation point on pre-operative TTE (28 mm vs. 26 mm; $p = 0.16$) but this difference was not significant. Time from LVAD implantation to first hospitalization was shorter in patients with residual MR (62 days vs. 103 days; $p = 0.05$) as was time from LVAD implantation to death (80 days vs. 421 days; $p = 0.03$).

CONCLUSIONS Significant residual MR post-LVAD implantation assessed by a quantitative measure is associated with persistent pulmonary hypertension, worse RV function, and significantly shorter time to hospitalization and death. MR post-LVAD implantation may serve as a surrogate for adverse outcomes post-LVAD implantation.
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ABBREVIATIONS AND ACRONYMS

CF = continuous flow

CJA = color jet area

LAA = left atrial area

LV = left ventricular

LVAD = left ventricular assist device

LVEDD = left ventricular end-diastolic dimension

MR = mitral regurgitation

PA = pulmonary artery

PCW = pulmonary capillary wedge

RV = right ventricular/ventricle

RVEDD = right ventricular end-diastolic dimension

RVFAC = right ventricular fractional area change

TAPSE = tricuspid annular plane systolic excursion

TTE = transthoracic echocardiogram

Mitral regurgitation (MR) is associated with elevated left atrial pressure and left ventricular end diastolic pressure, secondary pulmonary hypertension and right ventricular (RV) dysfunction (1,2). Patients with dilated or ischemic cardiomyopathy often have functional MR secondary to left ventricular (LV) dilation, apical tethering of the mitral valve leaflets, and chordal shortening (3,4). Implantation of a left ventricular assist device (LVAD) leads to mechanical unloading of the LV, can induce LV reverse remodeling, and generally improves MR (5,6). The clinical significance of residual MR in patients supported with continuous flow (CF) LVADs remains uncertain and mitral repair at the time of LVAD implantation is not commonly used. Prior studies have suggested that the presence of residual MR after LVAD implantation might be predicted by posterior displacement of mitral leaflet coaptation on pre-operative echocardiograms (7). However, most studies evaluating the presence of MR in LVAD patients have utilized predominantly qualitative assessments of MR (5,6,8). We hypothesized that the presence of residual MR post-CF LVAD implantation based on quantitative assessment would be negatively associated with post-implantation hemodynamics, RV geometry and function, and clinical outcomes.

SEE PAGE 89

METHODS

PATIENT SELECTION. All patients implanted with durable CF LVADs at our institution between 2007 and 2013 were retrospectively identified. Patients were included in the study if they had a pre-operative transthoracic echocardiogram (TTE) within the 3 months before LVAD implantation and a second echocardiogram at least 1 month post-operatively, with interpretable color flow imaging of the mitral valve. Patients with concomitant RV assist device implantation were excluded. Demographic, clinical, and laboratory variables, as well as invasive hemodynamic data, when available, were recorded. In addition, post-operative clinical outcomes were identified including post-implantation hospitalization, transplantation, and survival. The study was part of a protocol (RC-5842) approved by the Institutional Review Board at our institution.

ECHOCARDIOGRAPHY. Pre-operative and post-operative echocardiograms were quantitatively analyzed offline by a single research echocardiographer blinded to patient outcomes using digital analysis software (Syngo Dynamics, Siemens Medical, Malvern, Pennsylvania). MR was assessed quantitatively using the ratio of regurgitant color jet area (CJA)/left atrial area (LAA) in apical views (**Figure 1A to 1C**). Significant residual MR was defined as at least moderate MR with a mean MR CJA/LAA >0.2 on post-implantation TTE (9-11). RV dimensions were measured from standard apical 4 chamber views. RV function was assessed quantitatively using both tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RVFAC) according to American Society of Echocardiography Guidelines (12). Apical and posterior displacement of mitral valve leaflets were measured according to previously reported methods (7).

STATISTICAL ANALYSIS. Clinical, demographic, echocardiographic, and LVAD parameters were compared in the cohort with moderate or greater MR on post-LVAD echocardiogram versus the cohort who did not have significant post-operative MR on quantitative assessment. In addition, time to first post-LVAD hospitalization, time to death, and time to cardiac transplantation was assessed in each cohort. Differences in categorical variables were assessed using Fisher's exact test and in continuous variables using 2-tailed Student *t* tests.

RESULTS

Flow of patients through the study is illustrated in **Figure 2**. A total of 157 patients were implanted with durable CF LVADs at our institution during the study period. Of these, 7 were excluded due to concomitant RV assist device implantation, 14 were excluded due to absence of a pre-operative TTE, and 67 were excluded due to absence of post-implantation TTE after the 1 month post-implantation window or inadequate color flow imaging of the mitral valve on post-implantation TTE. The 69 remaining patients (mean age, 61 ± 11 years) comprised the final analysis

Actelion; is a speaker for United Therapeutics, Actelion, and Bayer Pharmaceuticals; and is a consultant for United Therapeutics, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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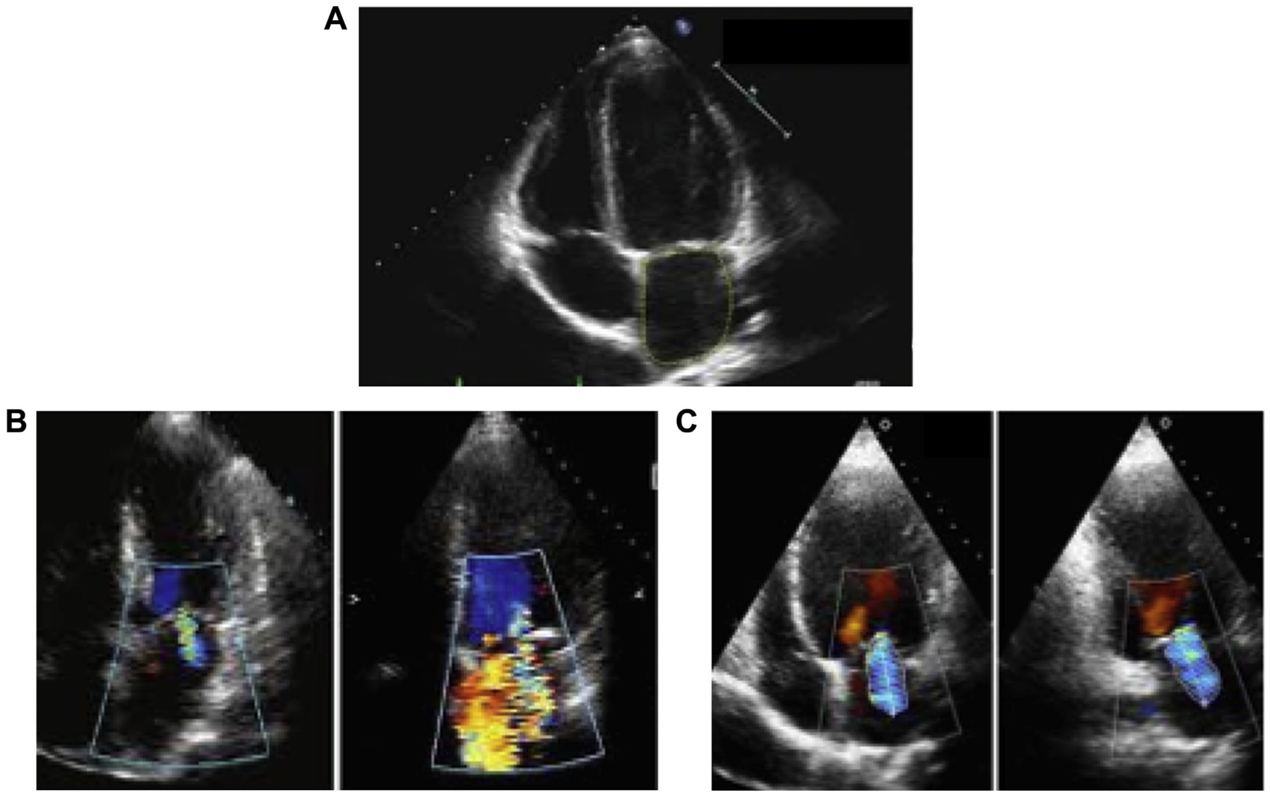
FIGURE 1 Measurement of Left Atrial and Mitral Regurgitant Color Jet Area Post-LVAD Implantation



(A) Measurement of left atrial area in apical 4 chamber view. **(B)** Example of mild residual mitral regurgitation (MR) **(left)** and severe residual MR **(right).** **(C)** Measurement of MR regurgitant color jet area in apical 4 and 2 chamber views.

cohort. The vast majority of patients (n = 63, 91%) had the Heartmate II (Thoratec Corporation, Pleasanton, California) CF device. Baseline demographic and clinical information of the entire cohort and the cohorts with and without significant post-operative MR are demonstrated in Table 1. Patients were mostly men (80%), with LVAD implantation as bridge to transplantation in the majority (65%) of patients. Roughly one-half of patients (51%) had an ischemic etiology of heart failure.

Pre-implantation echocardiographic parameters of the overall cohort are shown in Table 2 and those in patients with and without significant residual post-operative MR are shown in Table 3. On pre-implantation TTE, the vast majority of patients (77%) had moderate or greater MR by quantitative assessment: mean MR CJA/LAA was 0.42 among patients with significant pre-operative MR versus mean MR CJA/LAA 0.09 in patients with no pre-operative MR.

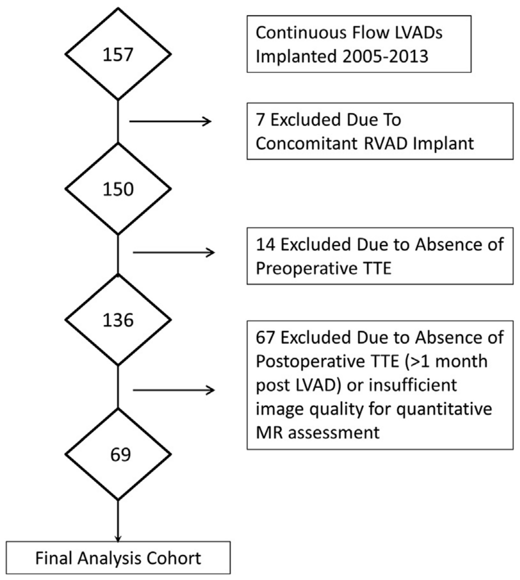
Mitral annular diameter was larger (37 mm vs. 41 mm; p = 0.04) in patients with significant pre-operative MR versus those without significant pre-operative MR and baseline posterior displacement of mitral leaflet coaptation was greater (27 mm vs. 23 mm; p = 0.001) in those with significant pre-operative MR compared with those without.

RV size was also significantly larger in those with significant baseline mitral regurgitation (right ventricular end-diastolic dimension [RVEDD] 50 mm vs. 42 mm; p = 0.003) although there was no significant difference in baseline LV dimensions between patients with and without significant pre-operative MR.

The mean duration from LVAD implantation to post-operative TTE was 120 ± 83 days. Post-LVAD implantation, most patients (n = 55, 80%) now had mild or less MR (mean MR CJA/LAA 0.08); however, 14 (20%) had significant residual MR (mean MR CJA/LAA 0.64) as shown in Table 2. Twelve of 14 patients (86%) who had significant residual MR had at least

JACC: HEART FAILURE VOL. 5, NO. 2, 2017
FEBRUARY 2017:81–8

FIGURE 2 **Flow of Patients Through the Study**



moderate MR detected by quantitative analysis on their pre-operative echocardiograms.

Post-LVAD implantation clinical and LVAD parameters in the patients with and without residual MR are shown in **Table 4**. Mean arterial pressure at the time of post-implantation TTE was similar in both cohorts (84 mm Hg vs. 83 mm Hg; p = 0.66). The mean set speed of the Heartmate II LVAD was similar in patients with and without residual MR (8,707 rpm vs. 8,832 rpm; p = 0.26). Moreover, set speed indexed for body surface area was also similar on both groups (4,422 rpm/m^2 vs. 4,538 rpm/m^2; p = 0.54) as was the ratio of set speed to pre-operative LV end-diastolic dimension (LVEDD) (120 rpm/mm vs. 132 rpm/mm; p = 0.19). There was no significant difference in other device parameters such as pulse index (5.2 vs. 5.6; p = 0.13) or pump power (5.4 W vs. 5.7 W; p = 0.16) between patients with and without residual MR. There was no significant difference in the use of traditional heart failure disease modifying medications as well as phosphodiesterase type 5 inhibitors in the patients with and without residual MR (**Table 4**).

In terms of post-operative echocardiographic parameters, patients with significant residual MR had larger left ventricular dimensions (LVEDD 67 ml vs. 61 mm; p = 0.04) and left atrial diameter (48 mm vs. 43 mm; p = 0.05) (**Table 2**). However, there was no difference in the mean change in LVEDD post-LVAD implantation in patients with and without residual MR (-8 mm vs. -8 mm; p = 0.98). In addition, the ratio of aortic valve opening to heart rate was very similar between patients with and without residual MR (0.32 vs. 0.35; p = 0.83).

Patients with residual MR had significantly larger post-operative RV dimensions (RVEDD 49 mm vs. 45 mm; p = 0.04) and worse RV function by both quantitative metrics (TAPSE 10 mm vs. 12 mm; p = 0.02 and RVFAC 29% vs. 34%; p = 0.02) as shown in **Table 2**. In patients with significant MR, there was a negative correlation between quantitative MR (CJA/LAA) and RVFAC (R = -0.35) as well as a positive correlation between quantitative MR (CJA/LAA) and RVEDD (R = 0.46). In contrast, in patients without significant MR, there was a modest positive correlation between quantitative MR (CJA/LAA) and RVFAC (R = 0.26) and no significant association between quantitative MR (CJA/LAA) and RVEDD (R = 0.06).

In those patients with significant post-operative residual MR, there was more posterior displacement of the mitral coaptation point on their pre-operative echocardiogram (28 mm vs. 26 mm; p = 0.16) but this difference was not statistically significant and there was no difference in pre-operative mitral annular diameter (41 mm vs. 40 mm; p = 0.33).

Invasive hemodynamic assessment was available post-LVAD implantation in 54 of 69 patients (78%), separated from the post-operative TTE by an average of 37 days. Hemodynamic variables are illustrated in **Table 5**. Patients with residual MR had significantly higher pulmonary artery (PA) systolic pressure (43 mm Hg vs. 35 mm Hg; p = 0.05), PA diastolic pressure (21 mm Hg vs. 15 mm Hg; p = 0.007)

TABLE 1 **Pre-Implantation Clinical and Demographic Characteristics of the Entire Study Cohort and Patients With and Without Significant Post-Operative MR**

	All Patients	Residual MR	No Residual MR	p Value
Total patients	69	14 (20)	55 (80)	
Age, yrs	61 ± 11	61 ± 14	60 ± 11	0.81
Male	55 (80)	12 (86)	43 (78)	0.73
Ischemic cardiomyopathy	35 (52)	5 (36)	30 (55)	0.24
Bridge-to-transplant LVAD	45 (65)	10 (71)	35 (64)	0.76
History of prior cardiac surgery	15 (22)	5 (36)	10 (18)	0.17
Obesity	20 (30)	3 (21)	17 (31)	0.74
Hypertension	55 (80)	10 (71)	45 (81)	0.46
Diabetes mellitus	31 (45)	4 (29)	27 (49)	0.23
Dyslipidemia	47 (68)	10 (71)	37 (67)	0.99
Atrial fibrillation	30 (43)	4 (29)	26 (47)	0.24
Obstructive sleep apnea	12 (17)	2 (14)	10 (18)	0.99
COPD	16 (23)	0 (0)	16 (29)	0.03
Peripheral arterial disease	14 (20)	5 (36)	9 (16)	0.14
Chronic kidney disease	26 (38)	6 (43)	20 (36)	0.76

Values are N, n (%), or mean ± SD.

COPD = chronic obstructive pulmonary disease; LVAD = left ventricular assist device; MR = mitral regurgitation.

and PA mean pressure (26 mm Hg vs. 23 mm Hg; p = 0.03). There were nonsignificant trends towards higher pulmonary capillary wedge (PCW) pressure (17 mm Hg vs. 13 mm Hg; p = 0.08) and right atrial pressure (13 mm Hg vs. 9 mm Hg; p = 0.09) in residual MR patients.

In patients with residual MR, 67% of patients were hospitalized at least once whereas 76% of patients without MR were hospitalized (p = 0.78). Those with significant residual MR had significantly less time between LVAD implantation and first hospitalization (mean time, 62 ± 34 days vs. 103 ± 112 days; p = 0.05). Etiology of first hospitalization is detailed in **Table 6**. Venous thromboembolism was more common in patients with residual MR (20% vs. 0%; p = 0.03) but there were no other significant differences in etiology of first hospitalization between groups.

Overall, 20% of patients in the cohort of patients with residual MR died over the course of follow up versus 24% of patients without residual MR. There was a significantly shorter time between LVAD implantation and death in those with significant residual MR (mean time, 80 ± 11 days vs. 421 ± 514 days; p = 0.03). Time to cardiac transplantation was not different between patients with and without residual MR (257 ± 129 days vs. 260 ± 161 days; p = 0.95).

TABLE 2 Echocardiographic Characteristics of the Entire Pre-Operative Cohort and Comparison of Post-Operative Echocardiographic Measures in Patients With and Without Residual MR

	Pre-Operative Overall Cohort (N = 69)	Residual MR (n = 14, 20%)	No Residual MR (n = 55, 80%)	p Value*
LVEDD, mm	71 ± 12	67 ± 8	61 ± 13	0.04
LVESD, mm	62 ± 14	62 ± 9	55 ± 14	0.03
LA diameter, mm	48 ± 8	48 ± 6	43 ± 9	0.05
LAA, apical views, cm^2				
4-chamber	27 ± 6	23 ± 5	22 ± 7	0.59
2-chamber	28 ± 6	24 ± 9	22 ± 8	0.35
3-chamber	25 ± 6	21 ± 9	21 ± 7	0.99
LAV, apical views, ml				
4-chamber	93 ± 37	75 ± 31	69 ± 31	0.05
2-chamber	100 ± 40	86 ± 39	72 ± 42	0.25
MR CJA, apical views, cm^2				
4-chamber	11.0 ± 7.4	8.5 ± 5.8	1.7 ± 2.0	0.001
2-chamber	9.0 ± 6.0	7.4 ± 4.1	1.4 ± 1.9	0.0001
3-chamber	9.0 ± 6.3	5.9 ± 4.3	1.2 ± 1.7	0.001
MR CJA/LAA				
4-chamber	0.38 ± 0.27	0.36 ± 0.17	0.07 ± 0.08	<0.001
2-chamber	0.30 ± 0.19	0.36 ± 0.19	0.05 ± 0.07	<0.001
3-chamber	0.33 ± 0.23	0.29 ± 0.28	0.03 ± 0.05	0.004
RVEDD, mm	48 ± 8	49 ± 6	45 ± 9	0.04
TAPSE, mm	14 ± 4	10 ± 2	12 ± 3	0.02
RVFAC, %	26 ± 12	29 ± 5	34 ± 9	0.02
TR jet, mm Hg	38 ± 13	26 ± 7	25 ± 10	0.79
PASP, mm Hg	51 ± 14	35 ± 9	34 ± 11	0.85
RVOT VTI, cm	12 ± 4	13 ± 4	16 ± 12	0.13
Mitral E:A	2.6 ± 1.4	2.38 ± 1.24	1.7 ± 0.9	0.09
Change in LVEDD post-LVAD (mm)		-8 ± 11	-8 ± 9	0.98
Aortic valve opening: heart rate ratio		0.32 ± 0.42	0.35 ± 0.40	0.83

Values are mean ± SD. *p value for significance testing between "residual MR" and "no residual MR" groups.

CJA = color jet area; LA = left atrium; LAA = left atrial area; LAV = left atrial volume; LVEDD = left ventricular end diastolic dimension; LVESD = left ventricular end systolic dimension; PASP = pulmonary artery systolic pressure; RVEDD = right ventricular end diastolic dimension; RVFAC = right ventricular fractional area change; RVOT = right ventricular outflow tract; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; VTI = velocity time integral; other abbreviation as in **Table 1**.

DISCUSSION

Our study demonstrated that significant residual MR after CF LVAD implantation, based on quantitative echocardiographic analysis, was associated with larger RV dimensions and worse RV function by quantitative metrics. Additionally, patients with significant residual MR had higher PA pressures, as well as shorter time to hospitalization and death versus patients without residual MR. This study is the first, to our knowledge, to quantitatively assess the severity of MR post-LVAD implantation and its impact on right heart function and clinical outcomes. Indeed, although it may be intuitive that residual MR after LVAD implantation might be deleterious for short- and long-term outcomes, this has never been previously demonstrated in the era of CF LVADs.

Significant MR has been associated with adverse outcomes in patients with LV systolic dysfunction and mitral valve repair or replacement is recommended by present guidelines prior to the development of severe LV dilation or LV dysfunction (13). In patients with severe systolic heart failure and accompanying MR being evaluated for LVAD implantation, the impact of MR and its management at the time of LVAD surgery and in the post-VAD period is less clear (14,15). Because of the predominantly functional etiology of MR in most LVAD candidates, MR is expected to decrease with LV unloading such that consideration of concomitant mitral repair or replacement with LVAD is uncommon (5,6,8). However, more data is emerging on the clinical entity of MR in LVAD patients and a study by Kitada et al. (7) suggested that significant post-operative MR could be best predicted by posterior displacement of mitral coaptation point on pre-operative imaging. Prediction of post-operative MR with pre-operative imaging parameters could potentially provide clarity regarding concomitant MV repair at time of LVAD and enhance existing pre-operative risk assessment algorithms for post-LVAD implantation outcomes (16–18).

Our data is consistent with that of Kitada et al. (7) in that we also noted a nonsignificant trend towards

TABLE 3 Comparison of Pre-Operative Echocardiographic Measures in Patients With and Without Significant Post-Operative MR

	Residual MR (n = 14, 20%)	No Residual MR (n = 55, 80%)	p Value
Pre-operative MR CJA/LAA	0.39 ± 0.21	0.32 ± 0.20	0.28
Mitral annulus diameter, mm	41 ± 5	40 ± 7	0.32
Apical displacement, Da, mm	19 ± 4	18 ± 4	0.40
Posterior displacement, Dp, mm	28 ± 5	26 ± 4	0.16
Tethering proportion, Da:Dp	0.69 ± 0.21	0.70 ± 0.25	0.91
LVEDD, mm	75 ± 16	69 ± 11	0.22
LVESD, mm	66 ± 13	63 ± 12	0.40
LA diameter, mm	48 ± 6	48 ± 9	0.86
LAV 4-chamber, ml	97 ± 31	92 ± 38	0.59
LAV 2-chamber, ml	114 ± 35	96 ± 40	0.10
RVEDD, mm	50 ± 8	48 ± 8	0.29
TAPSE, mm	14 ± 5	14 ± 4	0.98
RVFAC, %	27 ± 9	25 ± 13	0.61
TR jet, mm Hg	36 ± 11	39 ± 14	0.50
PASP, mm Hg	50 ± 10	51 ± 14	0.81
RVOT VTI, cm	13 ± 5	12 ± 4	0.78
Mitral E:A ratio	2.5 ± 0.8	2.6 ± 1.5	0.78

Values are mean ± SD.
Abbreviations as in Tables 1 and 2.

greater posterior displacement of the mitral coaptation point on pre-operative imaging among those with residual MR versus those without. Given the small sample size of patients with significant residual MR in both of these studies, it is conceivable that differences in these very small study cohorts can explain the lack of a statistically significant association with posterior displacement of the mitral coaptation point in our study.

TABLE 4 Post-Implantation Clinical Characteristics and LVAD Parameters of the Entire Study Cohort and Patients With and Without Significant Post-Operative MR

	All Patients	Residual MR	No Residual MR	p Value
BSA (m^2)	2.01 ± 0.28	1.99 ± 0.25	2.01 ± 0.29	0.86
Mean arterial pressure post LVAD (mm Hg)	83 ± 12	84 ± 11	83 ± 12	0.66
Heartmate II pump speed (rpm)	8,806 ± 305	8,707 ± 380	8,832 ± 281	0.28
Pump speed/BSA (rpm/m^2)	4,513 ± 648	4,422 ± 580	4,538 ± 669	0.54
Pump speed/pre-implantation LVEDD (rpm/mm)	129 ± 24	120 ± 29	132 ± 22	0.19
Pulse index	5.5 ± 0.8	5.2 ± 0.8	5.6 ± 0.7	0.13
Pump power (W)	5.7 ± 0.6	5.4 ± 0.7	5.7 ± 0.6	0.16
Pump flow (l)	4.9 ± 0.7	4.7 ± 0.7	5.0 ± 0.7	0.17
Beta blocker	45 (65)	7 (50)	38 (69)	0.22
ACE-I/ARB	46 (67)	7 (50)	39 (71)	0.20
Loop diuretics	60 (87)	14 (100)	46 (84)	0.19
Hydralazine	12 (17)	3 (21)	9 (16)	0.69
Aldosterone antagonist	16 (23)	2 (14)	14 (25)	0.49
PDE5 inhibitor	48 (70)	10 (71)	38 (69)	0.99
Hospitalized post-LVAD implantation	52 (75)	10 (71)	42 (76)	0.73
Death	16 (23)	3 (21)	13 (24)	0.99
Transplanted	32 (46)	7 (50)	25 (45)	0.78

Values are mean ± SD or n (%).
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BSA = body surface area; other abbreviations as in Tables 1 and 2.

An alternative hypothesis is that the residual MR in our study was simply driven by inadequate LV unloading despite durable mechanical support. Formal LVAD ramp studies were not commonly employed in our center until 2012 and very few patients in this study were managed based on RAMP protocols. This is certainly 1 potential mechanism of residual MR in our study and cannot be completely discounted, but is not supported by our data: we indexed LVAD speed to pre-implantation LVEDD and patient size as surrogates for individual patient-specific unloading and still found no significant differences in effective pump speed between the residual MR versus the no residual MR groups. The ratio of aortic valve opening to heart rate, another common metric of LV unloading was very similar between the 2 groups.

Although post-operative LVEDD was larger in patients with significant residual MR, it is difficult to distinguish whether this was related to inadequate LV unloading versus the effect of residual MR itself. Moreover, part of the reason for this difference was that pre-operative LVEDD was larger (although not meeting statistical significance) in patients with residual MR and notably, decrease in LVEDD after LVAD implantation was similar between groups with and without residual MR.

The Heartmate II pulsatility index was actually lower in patients with residual MR versus those without, the opposite of what one might typically expect if the speed was set too low for adequate LV unloading, and which might actually reflect the greater degree of RV dysfunction in these patients. Lastly, mean arterial pressure post-LVAD implantation as well as routine use of heart failure medications including phosphodiesterase type 5′ inhibitors was not different among patients with and without MR. In summary, save for the presence of residual MR, these 2 cohorts appeared relatively similar in terms of other echocardiographic parameters frequently assessed post-LVAD, as well as mean arterial pressure, medical therapy, and common LVAD parameters.

In terms of potential mechanisms wherein residual MR might lead to more adverse clinical events, it is possible that patients with significant residual MR are more prone to pulmonary venous congestion, secondary pulmonary hypertension and right heart failure, leading to more frequent hospitalization and ultimately death. This is confirmed by the post-implantation hemodynamic data, which showed significantly higher PA pressures in patients with

TABLE 5 Post-Operative Hemodynamics and Clinical Outcomes in Patients With and Without Residual Mitral Regurgitation

	Residual MR (n = 10)	No Residual MR (n = 44)	p Value
RA pressure (mm Hg)	13	9	0.09
PA systolic pressure (mm Hg)	43	35	0.05
PA diastolic pressure (mm Hg)	21	15	0.007
PA mean pressure (mm Hg)	26	23	0.03
PCW pressure (mm Hg)	17	13	0.08
Time from LVAD to first hospitalization, days	62 ± 34	103 ± 112	0.05
Time from LVAD to death	80 ± 11	421 ± 514	0.03
Time from LVAD to transplantation	257 ± 129	260 ± 160	0.95

Values are n or mean ± SD.
PA = pulmonary artery; PCW = pulmonary capillary wedge; RA = right atrial; other abbreviations as in Table 1.

residual MR, and a trend towards higher right atrial pressure consistent with worse RV function. Although wedge pressure was slightly higher in patients with MR, it was neither statistically significant nor likely clinically significantly different versus those without MR.

A previous single-center study showed that larger pre-operative left atrial size, an indirect surrogate of MR and LV filling pressures, was inversely associated with the risk of developing RV failure post-LVAD implantation presumably due to greater impact in decreasing left atrial pressures in these patients with the LVAD (19). However, in patients with significant residual MR post-LVAD, the ability to decongest the left atrium is diminished and thus more RV dysfunction and potentially RV failure may ensue and contribute to additional complications including renal congestion, coagulopathy (20), and overall "failure to thrive" on device support.

TABLE 6 Etiology of First Hospitalization Post-LAVD Implantation

	Residual MR (n = 10)	No Residual MR (n = 42)	p Value
Congestive heart failure (%)	1 (10)	6 (14)	0.99
GI bleeding (%)	1 (10)	13 (31)	0.25
Arrhythmia (%)	1 (10)	2 (5)	0.48
Infection (%)	2 (20)	12 (29)	0.71
Pump thrombosis (%)	2 (20)	1 (2)	0.09
Stroke or TIA (%)	1 (10)	3 (7)	0.98
Venous thromboembolism (%)	2 (20)	0 (0)	0.03
Miscellaneous (%)	0 (0)	5 (11)	0.57

Values are n (%).
GI = gastrointestinal; TIA = transient ischemic attack; other abbreviations as in Table 1.

In our relatively small cohort, there was, we suspect, an insufficient sample size to detect significant differences in etiology of first hospitalization between patients with and without post-operative MR. We did observe a higher incidence of venous thromboembolism as a reason for first hospitalization in patients with residual MR; we approach this finding with caution given the very small sample size, but we hypothesize that a patient with lower extremity swelling secondary to RV dysfunction/failure may also be more likely to be at risk for or be evaluated for deep venous thrombosis.

Regardless of mechanism, the presence of significant residual MR in this cohort had important prognostic significance both in terms of post-operative RV dimensions and function, invasive hemodynamics, and short-term clinical outcomes. Thus, the presence of residual MR could emerge as an important additional marker of adverse outcomes in LVAD patients. In addition, this may be 1 of the few post-implantation markers that may be associated with clinical outcomes, 1 that could be potentially modifiable at time of surgery with MV procedure and also in the post-VAD management period with speed optimization with RAMP testing along with aggressive blood pressure and volume control. Our study thus encourages further avenues of clinical research for the prediction and management of residual MR.

STUDY LIMITATIONS. Our study is a retrospective cohort analysis and as such, is subject to the same limitations as any retrospective, observational study. We were also limited in terms of the relatively small percentage of patients with significant residual MR. Several studies assessing post CF-LVAD echocardiographic parameters and clinical outcomes, however, contain a similar number of subjects. As with any retrospective study examining the differences in multiple parameters between 2 cohorts, there is a possibility that with multiple comparisons, differences can be detected by chance. However, in this instance there were multiple different measures of the right heart function by the same modality (RVEDD, TAPSE) as well as different modalities (post-operative invasive hemodynamics) as well as clinical outcomes that all point in the same physiologic direction making it far less likely that these are chance observations.

The assessment of MR was based on a semi-quantitative analysis using the ratio color flow Doppler jet area to LAA. Although this has been previously validated, it is limited in patients with eccentric MR that can be seen in some patients with functional MR (11). As the echocardiograms were obtained for clinical indications, we did not have uniform data assessing other quantitative metrics of MR such as vena contracta size or proximal isovelocity surface area (21). We were also limited in terms of the variable timing of echocardiograms pre-and post-operatively as again these echocardiograms were obtained for clinical indications. Finally, we had largely incomplete hemodynamic data before LVAD implantation and only a subset of patients had invasive hemodynamic data available at the time point >1 month post-LVAD implantation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Residual MR is currently not included in risk prediction algorithms for RV failure or post-LVAD morbidity or mortality. Residual MR, assessed by a simple semi-quantitative measure, after CF LVAD implantation is associated with worse RV geometry and function, pulmonary hemodynamics, and is an important predictor of short-term clinical outcomes.

TRANSLATIONAL OUTLOOK: Larger, prospective multicenter studies are required to confirm the link between residual MR, RV function, and clinical outcomes as well as to evaluate the impact of hemodynamic or echocardiographic optimization to minimize post-operative MR.

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