



Original Article

Effect of left ventricular geometric remodeling on restrictive filling pattern and survival in ischemic cardiomyopathy

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ABSTRACT

Background: To evaluate the effects of Left ventricular remodeling patterns in patients with left ventricular restrictive filling pattern (RFP; E/A>2) in ischemic cardiomyopathy (ICM) on prognosis.

Methods: Patient data was retrospectively analyzed over a period of 4.5 years to determine the effect of LV geometry by Echocardiographic parameter on survival and re-admission for heart failure. All patients with previous history of transmural myocardial infarction were studied and all were on guideline directed medical therapy. None underwent device therapy or surgery. The stored 2D Echocardiograms were studied. Left ventricular dimensions were noted, including the relative wall thickness (RWT). The patients were grouped based on RWT<0.34 and ≥ 0.34 and were compared for clinical outcomes of mortality and re-admissions for heart failure, over a period of 54 months.

Results: There were 102 ICM patients who had baseline RFP. We identified two sub-groups based on geometric phenotypes of left ventricular eccentric remodeling and dilated remodeling based on the relative wall thickness (RWT >0.34 or <0.34). The patients with preserved RWT had significantly more dilated ventricles (LVIDd and LVIDs), greater pulmonary artery systolic pressures (PASP), greater diastolic dysfunction (E/A) and less left ventricular ejection fraction (LVEF); $p < 0.001$. The number of deaths was higher in the reduced RWT patients, as were the number of re-admissions, although the time to survival and time to re-admission was not significant.

Conclusions: In this pilot study on ICM patients in advanced heart failure with baseline RFP, the presence of preserved RWT indicative of eccentric remodelling demonstrated a better clinical outcome.

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1. Introduction

Left ventricular (LV) restrictive filling pattern (RFP) is an index of severe diastolic dysfunction in patients with ischemic cardiomyopathy (ICM).^{1–3} It is a strong predictor of adverse clinical outcomes, independent of age and LVEjection fraction (LVEF).^{4–8} Therefore, RFP is a key parameter in the risk stratification of patients with ICM, reduced systolic function, and signs of congestive heart failure. The genesis of RFP is not fully understood, although some investigators have reported associations with infarct size, duration of ischemia, and myocardial viability.^{14,15} Once it develops, RFP persists even with optimal medical treatment (pharmacologic), implantable devices (cardiac resynchronization therapy), and

surgery that may achieve initial recovery of LV systolic function.^{7,9–13} In patients with ICM and baseline RFP a higher in-hospital mortality has been demonstrated after SVR compared with patients with a non-restrictive filling pattern.^{9–13} Fantini et al [23] have shown that in those ICM patients with RFP and preserved relative wall thickness (RWT) reflecting eccentric LV remodelling, the RFP reverted following surgical ventricular restoration (SVR) and these patients fared better than those with reduced RWT and RFP prior to SVR. The RFP in patients with reduced RWT did not revert following SVR.

There is a need for re-evaluation of this group of ICM patients with RFP and advanced heart failure for the presence of additional LV remodelling factors which define prognosis. We conducted a retrospective analysis of patients who presented with heart failure following myocardial infarction. Our aim was to assess for presence of additional factors of LV remodelling in patients with RFP which may influence prognosis in this sub-group of patients.

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2. Methods

This retrospective study was done from the database of heart failure patients referred to the Department of Cardiology. All patients had a previous history of transmural myocardial infarction. We enrolled patients with ICM who were in congestive cardiac failure, who demonstrated RFP on echocardiographic examination.

Exclusion criteria were atrial fibrillation or ventricular paced rhythm, left bundle branch block, any mitral or aortic valvulstenosis, previous valve repair or prosthetic valve implantation, moderate to severe mitral regurgitation, cardiogenic shock or a suboptimal echocardiographic examination. Only 102 patients with baseline RFP met all the criteria for inclusion in the present analysis. At 54 months, information on all patients was procured by telephone for clinical update (death and/or hospitalizations) or hospital outpatient visit. The study protocol was approved by the Institutional Review Board IEC No:171/2021. Informed consent waiver was obtained from the IEC.

The stored echocardiographic images were studied. All Echocardiographic examinations were done using a GE Vivid 7 machine (GE Healthcare, Wisconsin, Ill). The average of measurements of 3 cardiac cycles for each patient was recorded. Electrocardiographic monitoring was performed using limb electrodes. A standard 2-dimensional (2D) echocardiographic study was performed for assessment of LV wall thickness and dimensions according to the American Society of Echocardiography/European Association of Echocardiography recommendations.¹⁶ Diastolic and systolic LV internal diameters were measured from the parasternal long-axis view. Septal wall thickness and posterior wall thickness were measured in end-diastole. The relative wall thickness (RWT) was calculated as 2 times the posterior wall thickness divided by the LV diastolic diameter.

LV end-diastolic volume and end-systolic volume were measured from apical 4- and 2-chamber views applying the Simpson method and indexed for body surface area (EDVI and ESVI). LVEF was derived from LV volumes. Left atrial volume was calculated using the biplane area-length formula and indexed for body surface area.¹⁷ Systolic pulmonary artery pressure (sPAP) was calculated from the tricuspid regurgitation trace using continuous-wave Doppler.^{16,17}

Measures of early (E) and peak late (A) filling velocities, E/A ratio, and E-velocity deceleration time (DT) were measured on the pulsed-wave Doppler mitral-inflow profile.³ The tissue Doppler index was determined by placing the sample volume at the side of the medial (septal e') and lateral annulus (lateral e') from the apical 4-chamber view.³ We used an average of the septal and the lateral e' wave velocities (cm/sec) to calculate the ratio between mitral inflow E velocity and tissue Doppler index e' (E/e' ratio). Diastolic filling pattern was defined as restrictive with E/A ratio ≥ 2 .

3. Statistical methods

The data are summarized as mean \pm SD or n (%) depending on the nature of the data; continuous variables being characterized as mean \pm SD and categorical variables characterized as percentages. The data were compared between the RFP groups for preserved RWT and reduced RWT by independent sample *t*-test. The time to death and re-admission were compared between the groups using Kaplan Meier plots and Log-rank test. The echocardiographic measures were compared between baseline, 8, 14, 24 and 54 months follow up times using Repeated Measures Anova (RMANOVA). All statistical tests were considered significant at $p < 0.05$ level of significance and all analysis were performed in STATA software (version 16.0). A power analysis was not performed to

indicate if the statistics was reasonable as the sample size studied was small ($n = 102$).

4. Results

There were 102 patients studied with baseline RFP. There were 70 males and 95 hypertensives. Diabetes Mellitus was seen in 92 patients. The mean age was 55 ± 15.2 years (Median age: 57 years).

All patients had experienced a prior myocardial infarction (median time lapse from MI to presentation was 6.7 months; 4–43 months), and most of them were in advanced heart failure (New York Heart Association [NYHA] class 3–4 in 75 (75%) of cases). A majority had experienced an anterior wall MI ($n = 84$), whereas 7 patients experienced inferior wall MI. The remaining 8 patients experienced non-ST elevation MI. All patients were receiving guideline directed medical therapy for heart failure. The clinical characteristics are listed in Table 1. A cutoff value of RWT of 0.34 was used because it was the best at identifying an increased LV end-diastolic wall stress (≥ 30 kdyne/cm²) with a sensitivity of 68% and a specificity of 75% in a subgroup of the study patients ($n = 107$) who underwent cardiac catheterization.¹⁸

In our cohort, patients with reduced RWT were in a significantly higher NYHA class and had a significantly greater incidence of anterior wall myocardial infarction. The overall time to mortality (all cause) in patients with preserved RWT was 7 (21.8%) years and in patients with decreased RWT was 3 (4.2%) years $p = 0.99$ (Fig. 2). The time to re-admission for heart failure in patients with preserved RWT was 29 (90.6%) and in patients with reduced RWT was 68 (97.1%) $p = 0.14$ (Fig. 3). The total number of deaths in the reduced RWT patients was 79.4% and 20.6% in patients with preserved RWT; $p < 0.001$. The total number of patients with re-admissions for heart failure with reduced RWT was 68.2% and for patients with preserved RWT was 31.8%; $p < 0.001$. Information on patients who did not come for follow-up procured by telephone for clinical update (death and/or hospitalizations) which was noted in the patient records. None of the patients underwent SVR, LV assist device, or heart transplant.

5. Echocardiographic data

All patients on echocardiography demonstrated severely reduced LVEF, increased LV end diastolic volume index, increased left atrial volume, high systolic pulmonary artery pressure (>40 mm Hg). The echocardiographic parameters are listed in Table 2 (Fig. 1). All patients ($n = 102$) had severe diastolic dysfunction as defined by E/A and showed a restrictive filling pattern ($E/A \geq 2$).

The diastolic function as assessed by the E/A ratio was significantly worse in the patients with reduced RWT as compared to those with preserved RWT (2.8 ± 0.1 versus 2.6 ± 0.05 , $p < 0.001$). The left ventricular internal diameter in diastole (LVIDd), left ventricular internal diameter in systole (LVIDs) was significantly greater in patients with reduced RWT as was the Pulmonary Artery Systolic Pressure (PASP). The left ventricular ejection fraction (LVEF) was significantly lesser in the patients with reduced RWT. When the echocardiographic parameters were followed over 54 months, there was no difference in the LV dimensions, PASP, LA dimensions and LVEF over time. The E/A ratio signifying LV diastolic dysfunction was significantly greater with time (Table 3). Although there was no significant difference in time to survival between patients with preserved RWT and those with reduced RWT, the total all cause death in the patients with reduced RWT was greater than the total all cause death in patients with preserved RWT (79.4% versus 20.6%; $p < 0.001$) (Fig. 2).

Table 1
Clinical characteristics of patients with baseline Left Ventricular Restrictive Filling Pattern.

N = 64	N = 38		P Value
	RWT>0.34	RWT<0.34	
AGE	57.2 ± 13.8	57.1 ± 14.9	0.98
MALES	73.80% (57)	72.50% (25)	0.8
HTN	84.40% (54)	85.70% (37)	0.9
DM	87.20% (36)	86.60% (28)	0.8
NYHA	3.2 ± 1.3	3.9 ± 2	0.6
Old MI	100	100	0.9
Death	20.60% (22)	79.40% (22)	<0.001
Re-Adm	31.80% (34)	68.20% (22)	<0.001
Beta bloc	84% (56)	83% (35)	0.8
ACEI	97% (63)	95.60% (28)	0.8
ARB	23% (26)	18% (24)	0.3
Diuretic	98% (63)	97% (36)	0.4
ARNI	34% (42)	41% (34)	0.5
DAPT	100%	100%	0.9
Statin	100%	100%	0.88
MRA	88% (58)	84% (29)	0.7
BP	124 ± 8 mm Hg	132 ± 6 mm Hg	0.5

Abbreviations: RWT: Relative Wall Thickness, HTN: Hypertension, DM: Diabetes Mellitus, NYHA: New York Heart Association, MI: Myocardial Infarction, Re-Adm: Re-admission, Beta bloc: Beta Blockers, ACEI: Angiotensin Converting Enzyme Inhibitors, ARB: Angiotensin Receptor Blockers, ARNI: Sacubitril, DAPT: Dual Anti-Platelets, MRA: Mineralocorticoid Receptor Antagonist.

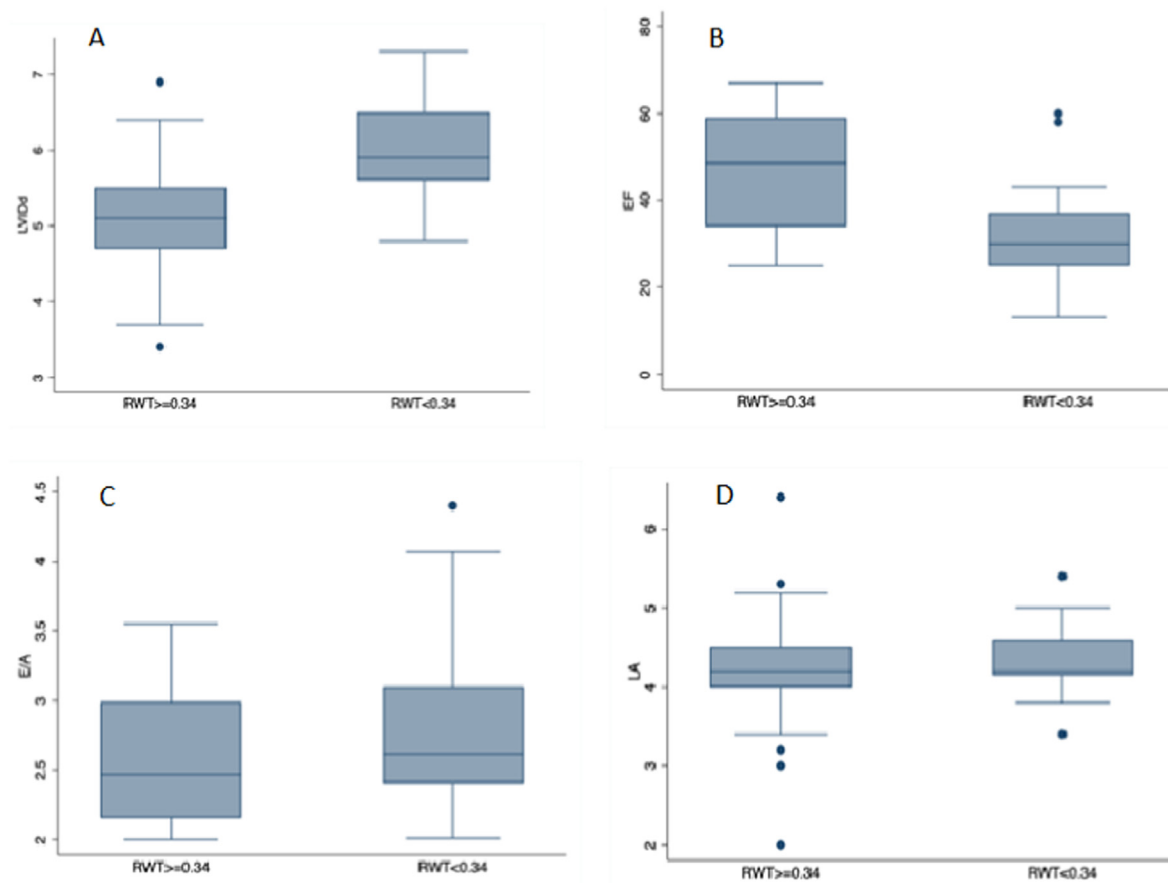
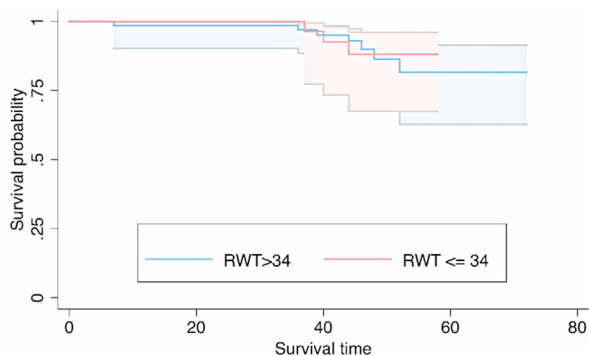


Fig. 1. Representation of differences in Echocardiographic parameters between patients with preserved Relative Wall Thickness (RWT) (>0.34) and patients with reduced RWT (<0.34). The LVIDd was significantly larger in the reduced RWT patients (A), the LVEF was significantly less in the reduced RWT patients (B), while the diastolic function assessed by E/A was significantly greater in the reduced RWT patients (C). There was no significant difference in LA dimensions between the two groups.

The time to re-admission for heart failure was not significant between the two groups. The number of re-admissions for heart failure was greater in patients with reduced RWT (68.2%) than in patients with preserved RWT (31.8%; $p < 0.001$) (Fig. 3).

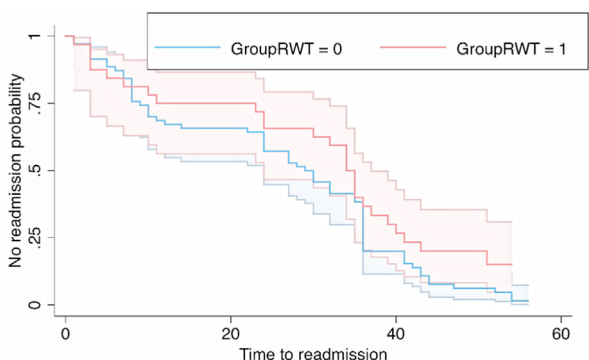
6. Discussion

While studying the left ventricular geometry in heart failure, it was seen that in patients with systolic heart failure, those with



Number at risk	0	20	40	60	80
Group RWT = 0	70	69	50	5	0
Group RWT = 1	32	32	25	0	0

Fig. 2. Kaplan–Meier survival plot of mortality for congestive heart failure. Two lines represent relative wall thickness (RWT) > 0.34 and RWT<0.34 groups. Shaded area represents the 95% confidence interval. The numbers at risk at the beginning of the follow-up time were n = 70 in RWT >0.34 group and n = 29 in RWT<0.34 group. Mortality was 7 and 3 in the 2 groups, respectively. Log-rank test *p* = 0.99 for the comparison between the 2 RWT groups.



Number at risk	0	20	40	60
Group RWT = 0	70	46	13	0
Group RWT = 1	32	24	9	0

Fig. 3. Kaplan–Meier plot of re-admission during the follow-up period. Two lines represent relative wall thickness (RWT) > 0.34 and RWT<0.34 groups. Shaded area represents the 95% confidence interval. The numbers at risk at the beginning of the follow-up time were n = 70 in RWT >0.34 group and n = 29 in RWT<0.34 group. Re-admissions were 29 and 68 in the 2 groups, respectively. Log-rank test *p* = 0.14 for the comparison between the 2 RWT groups.

Table 2
Echocardiographic parameters in patients with RWT> 0.34 and RWT<0.34

	N = 64		N = 38		P value
		RWT>0.34		RWT<0.34	
LVIDd		5.09 ± 0.65		6.03 ± 0.58	<0.001
LVIDs		3.75 ± 0.78		4.95 ± 0.75	<0.001
RWT		0.42 ± 0.12		0.21 ± 0.2	<0.001
E/A		2.57 ± 0.46		2.79 ± 0.59	0.047
DT		110 ± 23		99 ± 12	0.03
PASP		46 ± 16		63 ± 18	0.02
LVEF		46.2 ± 13.6		31.6 ± 10.2	<0.001
LA		4.24 ± 0.59		4.34 ± 0.39	0.36

LVIDd: Left Ventricular Internal Diameter in Diastole (cms).
 LVIDs: Left Ventricular Internal Diameter in Systole (cms).
 RWT: Relative Wall Thickness (cms).
 DT: Deceleration Time (msec).
 PASP: Pulmonary Artery Systolic Pressure (mm Hg).
 LVEF: Left Ventricular Ejection Fraction (%).
 LA: Left Atrium (cms).

eccentric LV remodelling with RWT>0.34 demonstrated a better clinical outcome on follow-up, while patients with thinner LV posterior walls (lower RWT) defined as dilated pattern of remodelling similar to dilated cardiomyopathy, demonstrated an independent and incremental risk of adverse outcome.¹⁸

We studied patients with ICM and systolic heart failure with RFP, and found that patients with decreased RWT were in more advanced heart failure as assessed by NYHA functional class. Although we did not study the CVP and other hemodynamic parameters for correlation, we found a robust correlation with the NYHA class. These patients had significantly greater LV diameters and significantly lesser LVEF, demonstrating significantly greater systolic dysfunction than the patients with preserved RWT. The E/A ratio was greater in the patients with decreased RWT signifying greater diastolic dysfunction. The left atrial dimensions were also significantly greater, as was the deceleration time, which are indirect indicators of diastolic dysfunction. When followed over 24 months, there was significantly higher all-cause mortality and significantly greater re-admissions for heart failure in patients with decreased RWT.¹⁹ These findings clearly define a more severe left ventricular remodelling geometry with lower RWT.

Patients with baseline RFP constitute a population with advanced heart failure and severe LV remodelling. There is a need to investigate a defining parameter which may influence prognosis in this sub-group.

We studied a population of ICM patients with LV systolic dysfunction and severe diastolic dysfunction based on RFP (E/A ≥ 2) (n = 102). This cohort signified ICM with greater systolic and diastolic dysfunction. In these patients, those with thinner LV walls, greater LV dilatation and greater pulmonary pressures had greater number of deaths and >2 re-admissions for heart failure, although the survival time and time to re-admission was not significant. All patients studied in our cohort, were followed up on medical management alone as intervention in terms of PCI or surgical revascularization was difficult due to logistic constraints.

RFP is characterized by a reduced and delayed E' and a shortened E deceleration time that reflects slow relaxation and increased LV stiffness. It is not a function of increased left atrial pressure.²⁰

In patients with ICM and LV systolic dysfunction, the mitral pseudo-normal filling pattern or RFP was noted to be a more useful prognostic factor for long-term (2 year) mortality than LVEF in patients presenting with acute heart failure.²¹

Table 3

2 D-Echocardiographic parameters of the 2 groups of ICM patients at follow up, p value from repeated measures ANOVA, time X Group interaction effect.

	Groups	8 months (n = 101)	14 months (n = 98)	24 months (n = 93)	54 months (n = 90.)	Time X Group Interaction p value
LVIDd (Cms)	RWT ≥ 0.34	4.96 ± .67	5.72 ± 0.67	5.34 ± .6	5.37 ± .59	0.132
	RWT < 0.34	5.92 ± .94	6.18 ± 0.67	6 ± 0.67	6.11 ± .7	
LVIDs (cms)	RWT ≥ 0.34	3.66 ± 0.72	4.40 ± .86	3.97 ± .69	3.97 ± .69	0.990
	RWT < 0.34	4.74 ± .83	4.98 ± .69	4.92 ± .68	4.9 ± .7	
LVEF (%)	RWT ≥ 0.34	38.37 ± 6.03	35.27 ± 7.39	36.1 ± 6.1	36.6 ± 6.09	0.836
	RWT < 0.34	31.45 ± 7.53	31 ± 7.5	31.4 ± 7.9	31.4 ± 8.33	
LA (cms)	RWT ≥ 0.34	3.84 ± 0.7	4.17 ± 3.4	3.87 ± .62	3.87 ± .62	0.921
	RWT < 0.34	3.82 ± 0.72	3.90 ± .53	3.98 ± .42	3.98 ± .44	
E/A (ratio)	RWT ≥ 0.34	2.96 ± .41	2.01 ± .39	2.19 ± .63	2.19 ± .63	0.041
	RWT < 0.34	2.19 ± 3.80	2.13 ± 5.39	2.24 ± .87	2.26 ± .88	
RWT (cms)	RWT ≥ 0.34	0.43 ± 0.07	0.42 ± 0.008	0.42 ± .08	0.42 ± .08	0.9951
	RWT < 0.34	0.27 ± .072	0.28 ± .011	0.29 ± 0.05	0.28 ± .06	

RWT = relative wall thickness; EF = ejection fraction; LA = left atrial; LVIDd: Left ventricular diameter in diastole; LVIDs: Left ventricular diameter in systole; E/A ratio (Early mitral filling/late mitral filling).

In a meta-analysis of patients presenting with heart failure the overall effect of RFP on all-cause mortality was studied. A total of 3024 patients in 27 studies were identified and in an average follow-up of 3 months and 5 years, 1284 (42%) patients had RFP at baseline. The odds ratio for death associated with restrictive filling pattern was 4.10 (95% CI 3.34, 5.04), $p < 0.00001$. There was no significant heterogeneity within this group of studies ($p = 0.53$). In this meta-analysis, over 40% of HF patients displayed a restrictive filling pattern, which was associated with more than four times higher mortality.²²

RFP is associated with worse prognosis in ICM. The greater degree of LV remodelling with structural and functional alterations after MI can render the LV wall less distensible, shifting the pressure–volume relationship curve to the left. This condition also affects remote, non-infarcted LV regions, and triggers myocardial interstitial fibrosis. This process is common in post-infarction dilated ICM, where the increased LV radius provokes elevated abnormal stress on the relatively thinner LV wall. Some authors opine that the geometric phenotypes of LV remodelling as such cannot be applied to patients with ICM who have non-uniform wall thickness. More advanced imaging techniques, such as cardiac magnetic resonance imaging, might provide more precise details regarding LV structure for scarring, hypertrophy and dimensions in these ICM patients.

Medical management of this sub-set of patients has not shown any mortality benefit.²² Despite this, in our series of patients with RFP at baseline having an RWT >0.34 had less mortality and readmissions for heart failure when compared to those with reduced RWT. Although our series is small, the presence of preserved RWT (the geometric LV eccentric remodelling pattern) in our patients with RFP tended to have a better prognosis at 4.5 years. RWT may not correlate with duration of heart failure, although the diastolic function improved partially in patients with preserved RWT during follow-up.

Although we have not studied patients with dilated cardiomyopathy, it has been reported that even in patients with dilated cardiomyopathy, the prognosis of patients with severe diastolic dysfunction (RFP) is impacted by the RWT. Here, a RWT <0.34 correlated with poor clinical outcomes.¹⁸

For eligibility for these high-risk surgeries, it is essential to define prognostic criteria as evidenced by registry data of surgical ventricular restoration[9, 24, 25, 26].

Preserved RWT in patients with RFP has identified patients who demonstrate reversal of RFP following SVR along with a better prognosis[23].

In a cohort of ICM patients with baseline RFP, the patients with lower RWT signifying a geometric pattern of LV dilated remodelling

fared worse than those patients with preserved RWT signifying a geometric pattern of eccentric remodelling.

7. Limitations

This study has several limitations. It is a very small, strictly selected patient series with a preponderance of male subjects. Doppler-derived LV filling pattern can be influenced by multiple factors, including heart rate, loading conditions, and left-sided valvular disease. We excluded patients with moderate-to-severe mitral regurgitation or aortic stenosis and those with a pacemaker. Heart rate and blood pressure data were not collected. The lack of cardiac magnetic resonance imaging data is a limitation in the assessment of the extent of baseline ischemia and replacement fibrosis. Further, due to the small sample size, we could not establish any significance in the time to death and time to re-admission between patients with preserved RWT and reduced RWT.

8. Conclusions

In this pilot study on ICM patients in advanced heart failure and baseline RFP, the presence of preserved RWT indicative of eccentric remodelling demonstrated a better clinical outcome than in patients with reduced RWT.

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Informed consent

Waiver was obtained from the IEC as this is a retrospective study.

Declaration of competing interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2022.04.007>.

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