Effect of Left Ventricular Restrictive filling pattern on survival in ischemic cardiomyopathy: Implications for surgical ventricular restoration.

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Abstract

Background: To evaluate the effects of baseline left ventricular restrictive filling pattern (RFP; E/A>2) in ischemic cardiomyopathy (ICM) patients on prognosis. Methods: Patient data was retrospectively analyzed over a period of 4.5 years to determine the effect of Echocardiographic factors on survival and re-admission for heart failure. 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 diatolic 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, leading to a hypothesis that the eccentric remodelling LV phenotype might benefit with SVR.

Introduction:

Left ventricular (LV) restrictive filling pattern (RFP) is an index of severe diastolic dysfunction in patients with ischemic cardiomyopathy (ICM)[1-3]. It has been shown to be a strong predictor of LV remodelling and adverse clinical outcomes, independent of age and LV ejection 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 is usually persistent 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]. Patients with ICM and baseline RFP have been found to have a higher in-hospital mortality after surgical ventricular restoration (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) the RFP reverted following SVR and these patients fared better than those with reduced RWT and RFP prior to SVR.

There is a need for re-evaluation and framing of stringent criteria in this group of ICM patients with advanced heart failure for surgical therapies like SVR. We conducted a retrospective analysis of patients who presented with heart failure following myocardial infarction. Our aim was to evaluate the effect of RFP on survival in ICM and to facilitate decision making of eligibility for SVR.

Methods:

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

Exclusion criteria were atrial fibrillation or other persistent cardiac rhythm alterations , ventricular paced rhythm , left bundle branch block , any mitral or aortic valve stenosis , 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 out-patient visit. The study protocol was approved by the Institutional Review Board IEC No:171/2021. Informed consent waiver was obtained from the IEC.

Echocardiographic examination was done at baseline 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 and 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.

Statistical Methods

The data are summarized as mean+-SD or n(%) depending on the nature of the data; continuous variables being characterized as mean ±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 readmission 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).

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% 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 maximally tolerated doses of anti-failure medications, which included angiotensin converting enzyme inhibitors angiotensin receptor inhibitors, loop diuretics, spironolactone, cardioselective beta blockers, dual antiplatelet agent, and statins; some patients were taking digoxin and those eligible were taking sacubitril. The clinical characteristics are listed in Table:1. The baseline risk factors were matched between patients with preserved RWT and those with reduced RWT. Preserved RWT was >0.34 (n=70) and reduced RWT was [?]0.34(n=32). 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(Figure 2).

All patients were followed on an outpatient basis up to 4.5 years. The time to readmission 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 (Figure 3). The total number of deaths in the reduced RWT patients was79.4% and 20.6%; p<0.001 in patients with preserved RWT. The patients with re-admissions for heart failure with reduced RWT were 68.2% and 31.8%; p<0.001 in patients with preserved RWT. Information on patients who did not come for follow-up was procured by telephone for clinical update (death and/or hospitalizations). None of the patients underwent SVR, LV assist device, or heart transplant.

Echocardiographic Data:

All patients an echocardiographic demonstrated with 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, (Figure 1). All patients (n=102) had severe diastolic dysfunction as defined by E/A and showed a restrictive filling pattern (E/A[?]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) (Figure 1) 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) (Figure 2).

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.

DISCUSSION :

While studying the left ventricular geometry in heart failure, it was seen that in patients with systolic heart failure, those with eccentric LV remodelling defined as preserved RWT 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, we found that patients with decreased RWT were in more advanced heart failure as assessed by NYHA functional 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 a significantly higher all-cause mortality and significantly greater readmissions 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. Whether there is a measure to identify a sub-set among these patients who may have a better prognosis with definitive therapy needs investigation.

We studied a population of ICM patients with LV systolic dysfunction and severe diastolic dysfunction based of RFP (E/A [?]2). 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.

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]. This can be seen in our patients as none demonstrated significantly greater left atrial measurements although all had RFP.

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).

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 (eg, scarring, loss of viable myocardium, inflammatory response, neurohormonal activation) can render the LV wall less distensible, shifting the pressure–volume relationship to the left. This condition affects also remote, non-infarcted LV regions, possibly triggering myocardial interstitial and replacement fibrosis. This process is common in postinfarction 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 nonuniform 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 patients with RFP at baseline having an RWT >0.34 had less mortality and re-admissions 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. There is a need for high-risk definitive surgeries in these patients with advanced heart failure, many of whom may be in-eligible for cardiac transplantation. Kawajiri et al demonstrated acceptable similar results of high-risk conventional surgery in eligible patients with advanced heart failure compared with ineligible patients with advanced heart failure who received a left ventricular assist device as destination therapy and heart transplantation[24].

For eligibility for these high-risk surgeries, it is essential to define prognostic criteria.

Analysing survival based on the preoperative LV substrate in the largest registry on SVR the overall 5-year survival was 69%[9]. When survival was analyzed based on the preoperative end-systolic volume index signifying LV dilatation, the patients with ESVI <80 mL/m2 had a 5-year survival of 80%, whereas patients with ESVI of 80 to 120 mL/m2 had a 5-year survival of 70%. The patients with ESVI [?]120 mL/m2 had the lowest 5-year survival at 64%. These findings lead us to infer that SVR in larger ventricles have a relatively worse prognosis. Although the clinical benefits of SVR have been demonstrated in large registries, the STICH trial negated the beneficial effects of SVR when performed concomitantly with coronary artery bypass grafting (CABG)[25]. There were several problems with the conduct of this study; 13% of patients enrolled in the STICH trial had no MI. Myocardial viability was investigated only in 267 patients (26.7%), among whom non-viable myocardium was present in 76 patients only (28.5%). It is known that patients who had, during the postoperative period, a systolic volume <60 mL/m2 had a significantly lower 5-year mortality than patients where the systolic volume was [?]60 mL/m2 (9.8% vs 27.0%). Patients with postoperative volume reduction [?]30%, if compared with patients with volume reduction<30%, had a lower 5- year mortality (13.5% vs 22.1%). The 5-year mortality in CABG alone was 28%, even if not directly comparable to the previous data.[26] These findings imply that a further analysis of the STICH trial found that, with a correct surgical technique and a good surgical indication, survival of patients who had CABG and SVR was definitively high and very likely better than survival of patients who had CABG alone.

Preserved RWT in patients with RFP has identified patients who demonstrate reversal of RFP following SVR and have a better prognosis [23]. SVR in patients with RFP qualifies as a high-risk definitive surgery with an attendant significant mortality and morbidities. For the success of SVR, a discrete area of dyskinesis/akinesis with preserved contractile remote myocardium is a pre-requisite. The nature of the remote myocardium and viability of the border zone is an important determinant for the success of this surgery. The success of SVR depends on the degree of pre-surgical LV remodelling. The greater degree of remodelling was associated with a thinner LV posterior wall and had worse outcomes following SVR.

Extrapolating our findings of medical treatment alone for 4.5 years, we can hypothesize that preserved RWT even in patients with RFP may benefit with SVR. The geometric pattern of LV eccentric remodelling with preserved RWT could have a better prognosis following high-risk definitive surgery like SVR in this population with baseline RFP and severe adverse LV remodelling (Figure 4).

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.

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, leading to a hypothesis that the eccentric remodelling LV phenotype might benefit with SVR.

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26. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM,et al. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg. 2013;146:1139-45.**FIGURE LEGENDSFigure 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.**Figure 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.**Figure 3** : Kaplan-Meier plot of readmission 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. . Readmissions were 29 and 68 in the 2 groups, respectively. Log-rank test P=0.14 for the comparison between the 2 RWT groups.**Figure 4** : Graphical Abstract: Left ventricular function and outcomes in ischemic cardiomyopathy with restrictive filling pattern. Patients with preserved relative wall thickness (RWT) had lesser total number of all-cause deaths and readmissions for heart failure, although the time to survival and time to re-admissions was not significant.

	RWT>.34	RWT<.34	P Value
AGE	57.2±13.8	57.1±14.9	0.98
MALES	73.80%	72.50%	0.8
HTN	84.40%	85.70%	0.9
DM	87.20%	86.60%	0.8
NYHA	3.2±1.3	3.9±2	0.6
Old MI	100	100	0.9
Death	20.60%	79.40%	<0.001
Re-Adm	31.80%	68.20%	<0.001
Beta bloc	84%	83%	0.8
ACEI	97%	95.60%	0.8
ARB	23%	18%	0.3
Diuretic	98%	97%	0.4

	RWT>.34	RWT<.34	P Value
ARNI	34%	41%	0.5
DAPT	100%	100%	0.9
Statin	100%	100%	0.88
MRA	88%	84%	0.7

TABLE:1 Clinical characteristics of patients with baseline Left Ventricular Restrictive Filling Pattern

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.

	RWT>.34	RWT<.34	P value
LVIDd	5.09±.65	6.03±.58	<0.001
LVIDs	3.75±.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

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

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 (%)

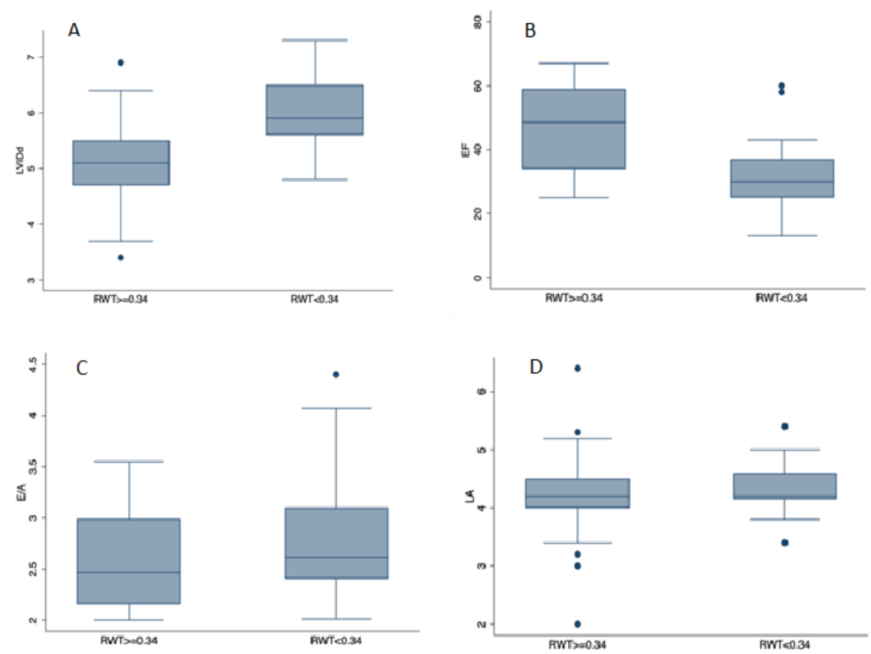
LA: Left Atrium (cms).

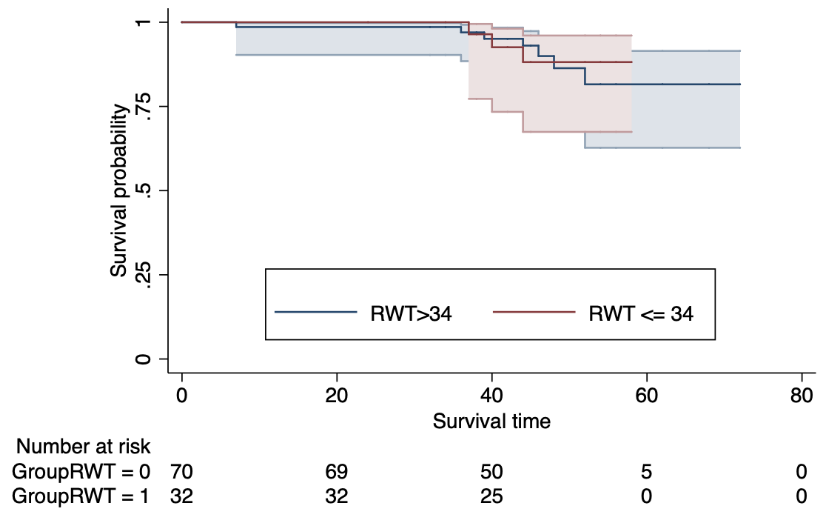
	Groups	**8 months (n=101)**	**14 months (n=98)**	**24 months (n=93)**	**54 months (n=90.)**	**Time X Group Interaction p value**
LVIDd (Cms)	RWT≥0.34	*4.96±.67*	*5.72±.67*	*5.34±.6*	*5.37±.59*	*0.132*
	RWT<0.34	*5.92±.94*	*6.18±0.67*	*6±0.67*	*6.11±.7*	
LVIDs (cms)	RWT≥0.34	*3.66± 0 .72*	*4.40±.86*	*3.97±.69*	*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*±.72	*3.90±.53*	*3.98±.42*	*3.98±.44*	

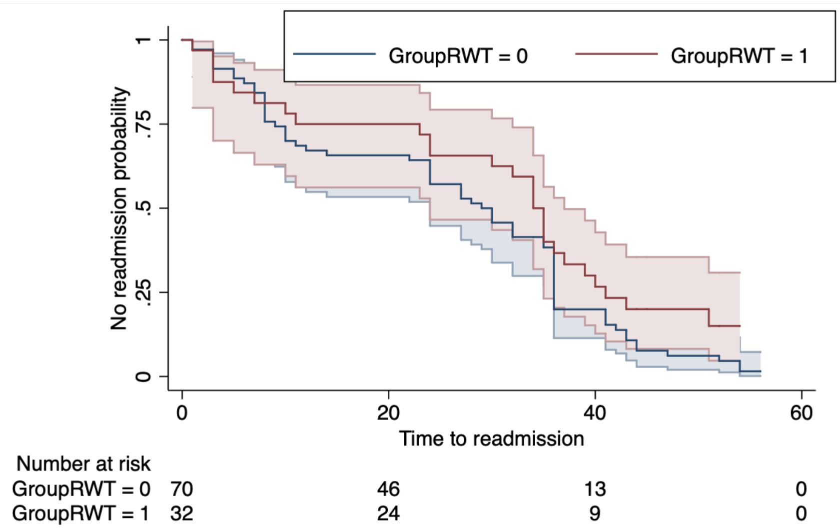
	Groups	**8 months (n=101)**	**14 months (n=98)**	**24 months (n=93)**	**54 months (n=90.)**	**Time X Group Interaction p value**
E/A (ratio)	RWT≥0.34	*2.96±.41*	*2.01±.39*	*2.19±.63*	*2.19±.63*	*0.041*
	RWT<0.34	*2.19±3.80*	*2.13*±5.39	*2.24±.87*	*2.26±.88*	
RWT (cms)	RWT≥0.34	*0.43*±.07	*0.42*±.008	*0.42±.08*	*0.42±.08*	*0.9951*
	RWT<0.34	*0.27±.072*	*0.28±.011*	*0.29±0.05*	*0.28±.06*	

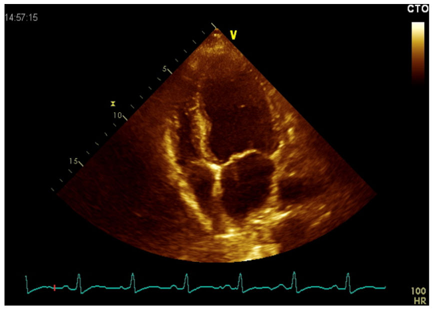
TABLE:3 2 D-Echocardiographic parameters of the 2 groups of ICM patients at follow up, p value from repeated measures ANOVA, time X Group interaction effect

RWT= relative wall thickeness;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)

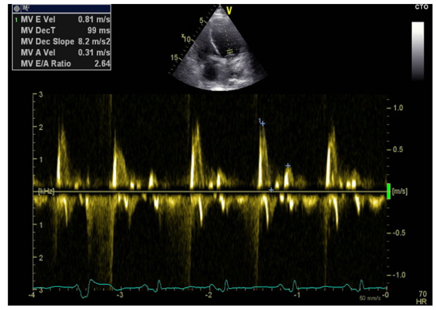



Survival probability
0
.25
.5
.75
1
RWT>34
RWT <= 34
0
20
40
60
80
Survival time
Number at risk
GroupRWT = 0 70 69 50 5 0
GroupRWT = 1 32 32 25 0 0

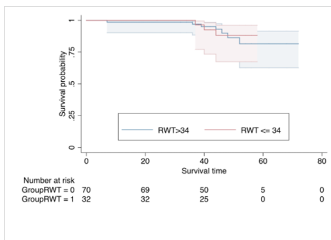

No readmission probability
0
.25
.5
.75
1
GroupRWT = 0
GroupRWT = 1
0
20
40
60
Time to readmission
Number at risk
GroupRWT = 0 70 46 13 0
GroupRWT = 1 32 24 9 0



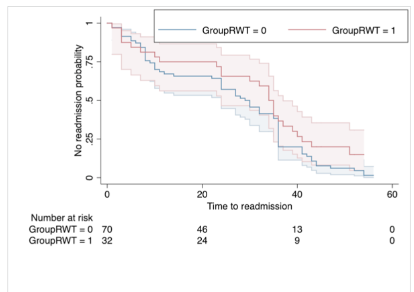
A: Echocardiography 4 Chamber view : Dilated Left Ventricle



B: Left Ventricular Restrictive Filling Pattern E/A>2



C: Time to Survival. RWT 1(<0.34) RWT 0(>0.34)



D: Time to Re-Admission [RWT: Relative Wall Thickness