Original Research

Differences in Echocardiographic Characteristics of Functional Mitral Regurgitation in Ischaemic Versus Idiopathic Dilated Cardiomyopathy: A Pilot Study

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Introduction: Functional mitral regurgitation (FMR) is a common complication in patients with ischaemic (ICM) or idiopathic dilated cardiomyopathy (DCM), as a consequence of left ventricular (LV) remodelling. The aim of this study was to elucidate the differences in FMR between patients with ICM and DCM utilising conventional and tissue Doppler echocardiography.

Methods: We studied 21 patients with ICM and 17 with DCM using conventional and tissue Doppler echocardiography. The severity of FMR was assessed quantitatively and by the PISA method. The 2 groups were similar in terms of NYHA class, LV ejection fraction and pharmacological treatment.

Results: Patients with ICM had higher pulmonary artery systolic pressures (48 ± 16 vs. 38 ± 10 mmHg, $p=0.04$), more severe FMR as assessed by colour Doppler (1.9 ± 0.9 vs. 1.1 ± 0.5, $p=0.006$), and a larger effective regurgitant orifice (0.17 ± 0.07 vs. 0.1 ± 0.05 cm^2, $p=0.003$) and tenting area (2.3 ± 0.8 vs. 1.7 ± 0.7 cm^2, $p=0.02$). In addition, ICM subjects had lower mitral annular systolic (Sm 2.3 ± 0.8 vs. 3.4 ± 0.9 cm/s, $p<0.001$) and diastolic (Em 2.5 ± 1 vs. 3.8 ± 1.5 cm/s, $p=0.005$; Am 3.1 ± 1.4 vs. 4.3 ± 1.7 cm/s, $p=0.02$) myocardial velocities, and a higher ratio of early transmitral filling velocity to early mitral annular diastolic velocity (LV E/Em 42 ± 29 vs. 22.7 ± 7.6, $p=0.008$) compared to DCM patients. Systolic and diastolic mitral annular velocities were significantly correlated with effective regurgitant orifice. Tenting area >1.27 cm^2 exhibited the highest sensitivity and regurgitant volume >24 ml the highest specificity for predicting ischaemic aetiology of LV dysfunction. However, only age and Sm were independent predictors of the diagnosis of ICM rather than DCM.

Conclusions: Mitral apparatus deformity, incomplete closure of mitral leaflets and global remodelling are more prominent in patients with ICM and lead to more severe FMR than in patients with DCM.

Chronic heart failure (CHF) is a major cause of cardiac morbidity and mortality and is usually caused by left ventricular (LV) systolic dysfunction.[1,2] Ischaemic cardiomyopathy (ICM) is the underlying cause of CHF in more than 70% of patients, whereas approximately 25% of patients suffer from idiopathic dilated cardiomyopathy (DCM). The structural basis of heart failure due to cardiomyopathy is LV remodelling, which results in dilatation and further dysfunction of the left ventricle.

Functional mitral regurgitation (FMR) occurs as a consequence of regional or global LV dysfunction, even though the mitral valve is structurally normal, and is a common complication in both ICM and DCM patients.[3-5] When present, FMR accelerates clinical deterioration and increases long-term morbidity and mortality. Several competing geometric and haemodynamic factors have been separately proposed to result in FMR, such as the dilatation of the mitral annulus, the tethering of valve leaflets caused by displaced papillary muscles, and LV dysfunction, which results in reduced transmitral pressure and hence incomplete valve closure.[6,7]

However, whether there are any differences between DCM and ICM patients with reference to the specific mechanisms that lead to FMR remains undetermined. The aim of this study was to elucidate the differences in FMR between patients with ICM and DCM utilising conventional and tissue Doppler echocardiography.

Methods

We studied 38 consecutive patients with CHF who underwent an echocardiographic examination at AHEPA University Hospital from October 2005 till September 2006. DCM was defined as a heart muscle disease of unknown cause and coronary-induced heart failure was recognised when myocardial damage was attributable to severe coronary artery disease. All patients were in New York Heart Association (NYHA) functional class II to IV and underwent diagnostic cardiac catheterisation, coronary angiography and left ventriculography. Informed consent was obtained from all patients in the study population before enrolment.

Inclusion criteria were: symptoms of CHF (dyspnoea, orthopnoea, history of pulmonary oedema); LV systolic dysfunction (ejection fraction <40%); presence of at least mild mitral regurgitation with a structurally normal mitral valve; and sinus rhythm on electrocardiography. Exclusion criteria were: clinical or echocardiographic evidence of other cardiac diseases (recent <3 months myocardial infarction, unstable angina, severe hypertension >170/100 mmHg); mitral regurgitation due to primary organic valve disease, such as rheumatic disease or prolapse; papillary muscle rupture; atrial fibrillation; suboptimal echocardiographic windows leading to incomplete quantification of mitral regurgitation with the PISA method.

Echocardiography

All patients underwent a complete echocardiographic study using a standard ultrasound machine (Vivid 7, GE Vingmed, Horten, Norway) and all images were saved digitally in raw-data format to magneto optical discs for offline analysis.

LV and left atrial (LA) dimensions were obtained by M-mode and two-dimensional echocardiography according to the recommendations of the American Society of Echocardiography.[8] LV ejection fraction was calculated using the biplane method according to the modified Simpson's rule. For the evaluation of LV diastolic function, the transmitral diastolic flow tracing was imaged in the apical four-chamber view using pulsed Doppler echocardiography and the peak early transmitral filling velocity E, peak transmitral atrial filling velocity during late diastole A, their ratio E/A, and deceleration time DT were recorded.

The assessment of mitral regurgitation involved a comprehensive evaluation of both two-dimensional and Doppler colour flow echocardiographic images, according to the guidelines of the American Society of Echocardiography.[8] The severity of FMR was assessed quantitatively using Doppler colour-flow imaging, by indexing the regurgitation jet area to left atrial size using a scale of 0-4+, and by the proximal isovelocity surface area (PISA) method effective regurgitant orifice area (ERO) and regurgitant volume (RV) were calculated.[9,10] Systolic leaflet deformation, defined as tenting area, was measured as the area enclosed between the annular plane and mitral leaflets at late systole from the parasternal long-axis view.[11]

Pulmonary artery systolic pressures were estimated by calculating the systolic pressure gradient between the right ventricle and the right atrium from the maximum velocity of the tricuspid regurgitant jet, using the modified Bernoulli equation, and then adding to this value an estimated right atrial pressure based on the size of the inferior *vena cava* and the change in calibre of this vessel with respiration.

Using colour tissue Doppler imaging the following velocities of the septal mitral annulus were acquired for each patient: peak systolic (Sm), early diastolic motion (Em) and late diastolic motion (Am) velocity. These were used as markers of global systolic or diastolic function. In addition, we calculated the ratio of peak early transmitral filling velocity to the early diastolic velocity of the mitral annulus (E/Em), an index which has been correlated with pulmonary capillary wedge pressure.

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD). Differences between groups were assessed by Student's unpaired t-test. Categorical variables were compared using the χ^2 test. Pearson's correlation coefficients were calculated for pairs of continuous variables. Multivariate logistic regression analysis was used to assess the relationship between the probability of diagnosis of ICM and clinical and echocardiographic variables, and to assess major determinants of FMR severity among measured parameters. A receiver operating characteristic curve (ROC) was constructed to determine cut-off values for tissue Doppler echocardiographic parameters. A two-tailed p-value <0.05 was considered significant. SPSS statistical software (version 12.0, Inc., Chicago, Illinois, USA) was used.

Results

The study included 38 patients with CHF, of whom 21 suffered from ICM and 17 from DCM. The demographic and clinical characteristics of the two groups are shown in Table 1. Patients diagnosed with ICM were older, were more frequently treated with statins and antiplatelets, and more often had a history of diabetes mellitus compared to DCM patients. Standard echocardiographic and pulsed Doppler tissue imaging measurements are shown in Table 2. Importantly, LV ejection fractions were similar between the two groups of CHF patients. Patients with ICM had more severe mitral regurgitation, with a larger systolic mitral tenting area and greater pulmonary hypertension (Table 3). Moreover, tissue Doppler imaging parameters showed significantly lower systolic and diastolic velocities of mitral annular motion and a higher E/Em ratio in patients with ICM (Table 3).

A significant association was demonstrated between the two methods of mitral regurgitation assessment ($r=0.84$, $p<0.01$). Significant correlations were also found between ERO and LV end-diastolic diameter ($r=0.38$, $p=0.02$), LA diameter ($r=0.39$, $p=0.01$), tenting area ($r=0.69$, $p<0.001$), and pulmonary artery systolic pressure ($r=0.4$, $p=0.001$). With regard to tissue Doppler indices, ERO showed a significant association with systolic myocardial velocity, Sm ($r=-0.6$, $p<0.001$), diastolic myocardial velocities, Em ($r=-0.41$, $p=0.01$) and Am ($r=-0.4$, $p=0.01$), and finally with the E/Em ratio ($r=0.52$, $p=0.001$; Figure 1).

From multivariate logistic regression analysis, age ($p=0.01$) and Sm ($p=0.01$) were the only variables independently associated with the probability of ICM rather than DCM diagnosis (Table 4). Amongst all FMR echocardiographic indices, tenting area >1.27 cm^2 exhibited the highest sensitivity and RV >24 ml the highest specificity for predicting ischaemic aetiology in patients with LV dysfunction (Table 5, Figure 2).

Discussion

It is well known that FMR is a major determinant of outcome and a marker of poor prognosis in patients with CHF, since a higher degree of FMR is associated with an increase in mortality. Lamas and colleagues

Table 1. Demographic and clinical characteristics of the 38 patients with ischaemic and idiopathic dilated cardiomyopathy.

Parameter	ICM (n=21)	DCM (n=17)	p
Age, years	62 ± 9.8	47 ± 11.7	<0.001
Men/women	19/2	11/6	NS
NYHA (II,III,IV)	2/15/4	2/13/2	NA/NS/NS
LBBB, n	10	4	NS
Arterial hypertension, n	5	3	NS
Hyperlipidaemia, n	7	3	NS
Diabetes mellitus, n	7	0	0.005
Smoking, n	5	5	NS
Medications			
β-blockers, n	15	10	NS
ACEIs/ARBs, n	17	16	NS
nitrates, n	7	0	NA
diuretics, n	18	14	NS
statin, n	11	3	<0.001
digitalis, n	6	5	NS
antiplatelets, n	19	7	<0.001

ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; DCM – idiopathic dilated cardiomyopathy; ICM – ischaemic cardiomyopathy; LBBB – left bundle branch block; NA – not available; NS – non-significant; NYHA – New York Heart Association.

Table 2. Echocardiographic indices of left heart chambers and mitral regurgitation parameters of the 38 patients with ischaemic and idiopathic dilated cardiomyopathy.

Parameter	ICM (n=21)	DCM (n=17)	p
LVEDD (cm)	7.6 ± 1	6.8 ± 0.7	0.01
LVESD (cm)	6.34 ± 1	5.8 ± 0.8	NS
LVEF %	30.5 ± 7	28 ± 7.7	NS
LA (cm)	4.8 ± 0.6	4.5 ± 0.6	NS
CDSA-FMR	1.9 ± 0.9	1.1 ± 0.5	0.006
Tenting area (cm^2)	2.3 ± 0.8	1.7 ± 0.7	0.02
ERO (cm^2)	0.17 ± 0.07	0.1 ± 0.05	0.003
RV (ml)	27.8 ± 17	15 ± 12	0.02

CDSA-FMR – colour Doppler semi-quantitative assessment of FMR; DCM – idiopathic dilated cardiomyopathy; ERO – effective regurgitant orifice area; FMR – functional mitral regurgitation; ICM – ischaemic cardiomyopathy; LA – left atrial end-systolic diameter; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEF – left ventricular ejection fraction; RV – regurgitant volume; NS – non-significant.

showed in the SAVE study that patients with FMR after myocardial infarction had a significantly worse overall prognosis than did patients without FMR. The presence of even mild FMR was an independent predictor of a poor cardiovascular outcome.[12] Moreover, in the chronic phase after myocardial infarction, FMR is associated with increased mortality independently of the degree of LV dysfunction, with the risk of death being directly related to the degree of FMR as defined by ERO and RV.[13] ERO values above 20 mm^2 are independently associated with higher mortality rates. Several other studies also showed a high prevalence of FMR among patients with LV dysfunction and demonstrated its association with poor prognosis.[14-16]

The purpose of the present study was to examine the echocardiographic characteristics of patients with the clinical diagnosis of ICM and DCM, and to identify echocardiographic differences regarding FMR indices between these two groups. In addition, we sought to explore the main determinants of FMR severity. The two groups showed no significant differences in LV function as measured by LV ejection fraction; however, the ICM group had a greater LV end-diastolic dimension. The two groups had significant differences in all echocardiographic indices of FMR. Patients with ICM exhibited more severe FMR, despite having a similar LV systolic ejection fraction to DCM patients.

Mitral valvular tenting is a major determinant of FMR and is directly determined by local LV remodelling, and particularly by the displacement of the apical and posterior papillary muscles.[6] The strong correlation found between ERO and tenting area that we found in

Table 3. Conventional and tissue Doppler parameters of the 38 patients with ischaemic and idiopathic dilated cardiomyopathy.

Parameter	ICM (n=21)	DCM (n=17)	p
E, m/s	0.85 ± 0.25	0.8 ± 0.24	NS
A, m/s	0.66 ± 0.3	0.69 ± 0.3	NS
E/A	1.6 ± 0.9	1.48 ± 0.9	NS
DT, ms	184.7 ± 82	172.9 ± 59	NS
Sm, cm/s	2.3 ± 0.8	3.4 ± 0.91	<0.001
Em, cm/s	2.5 ± 1	3.8 ± 1.5	0.005
Am, cm/s	3.1 ± 1.4	4.3 ± 1.7	0.02
Diastolic function:			
Impaired relaxation, n	6	6	NS
Pseudonormal, n	8	4	NS
Restrictive, n	5	5	NS
E/Em	42 ± 29	22.7 ± 7.6	0.008
PASP, mmHg	47.7 ± 16	37.8 ± 10	0.04

Am – peak late diastolic myocardial velocity; DCM – idiopathic dilated cardiomyopathy; DT – deceleration time; Em – peak early diastolic myocardial velocity; ICM – ischaemic cardiomyopathy; NS – non-significant; PASP – pulmonary artery systolic pressure; Sm – peak systolic myocardial velocity.

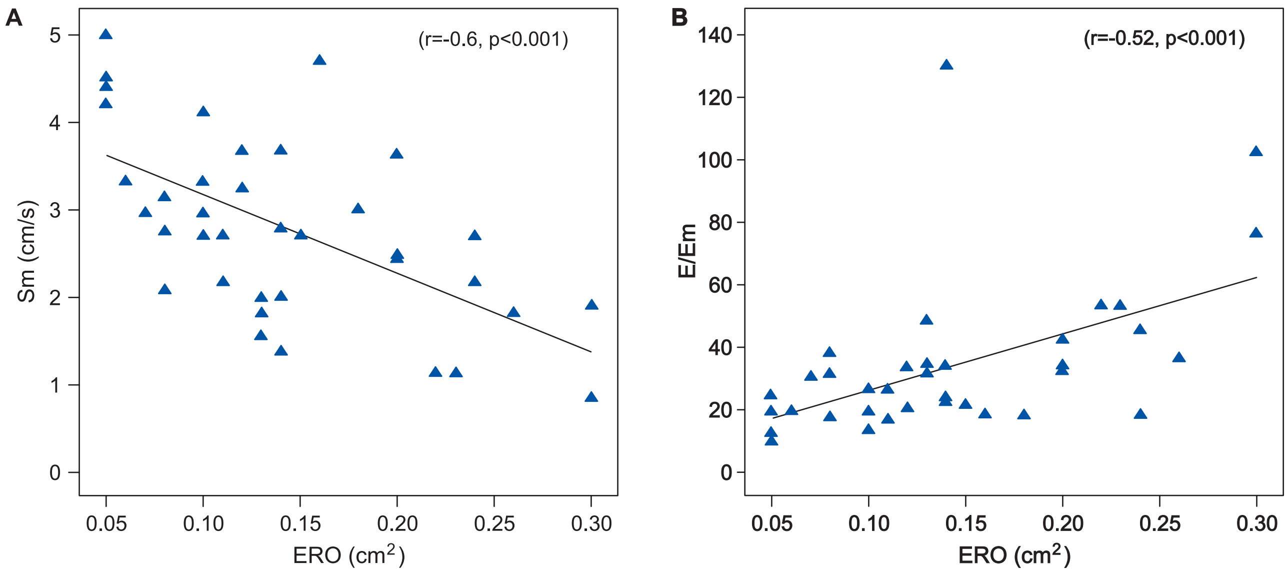

Figure 1. Scatter plots showing the correlation of effective regurgitant orifice area (ERO) with (A) peak myocardial systolic velocity (Sm), and (B) mitral annulus E/Em ratio.

our patients suggests that incomplete mitral leaflet closure is a major determinant of FMR. Nonetheless, it is known that there is a significant difference in mitral valve deformation between the two entities. The pattern of mitral apparatus deformation is asymmetrical in ICM-related FMR, because of unilateral papillary muscle displacement (regional LV dysfunction). In contrast, in DCM global LV dysfunction results in bilateral papillary muscle displacement, which is more symmetrical and shows a funnel-shaped deformity from the medial to the lateral annular side.[7]

In our study ICM patients had a higher degree of systolic valvular tenting, which is responsible for FMR severity.[17,18] A possible explanation of the greater subvalvular remodelling in ICM lies in the difference that we evidenced in myocardial systolic annular velocities between ischaemic and non-ischaemic LV dysfunction. Although the two groups had similar ejection fractions, ICM patients exhibited lower systolic and diastolic mitral annular velocities, which could explain their higher tenting area values. ERO showed significant correlation with systolic myocardial velocity Sm and diastolic myocardial velocities Em and Am, and also with the E/Em ratio, which is associated with increased morbidity and an adverse outcome in patients with CHF and severe secondary mitral regurgitation.[19] Of note is our finding that low mitral Sm values were independently associated with the probability of diagnosis of ICM rather than DCM. The aforementioned LV dysfunction due to global or regional remodelling leads to ventricular dilatation and spherical LV formation. These geometrical distortions result in mitral annular enlargement, papillary muscle displacement and tenting of mitral leaflets, displacing leaflet coaptation towards the apex and away from the mitral annular plane; this leads to mitral deformity, incomplete mitral leaflet closure and FMR. Previous studies showed that LV global remodelling—as indicated by sphericity and LV diameter, but not systolic dysfunction—mainly determines FMR.[17,20-23]

Table 4. Multivariate logistic regression analysis for the prediction of ischaemic cardiomyopathy.

Parameter	B coefficient	RR (CI)	p
Age	0.12	1.13 (1-1.24)	0.01
Sm	-1.58	0.2 (0.05-0.72)	0.01

CI – confidence interval; RR – relative risk; Sm – peak systolic myocardial velocity.

Our ICM cohort also had more severe pulmonary hypertension, which is another factor associated with higher mortality.[24] The significant association between pulmonary artery systolic pressure and ERO clearly underlines the influence of FMR on cardiac haemodynamics. Tissue Doppler imaging provided an assessment of mitral annular motion and revealed significant differences in systolic and diastolic myocar-

Table 5. Sensitivity and specificity of the various mitral regurgitation echocardiographic indices for the identification of ischaemic aetiology in patients with dilated cardiomyopathy. Values are expressed as percentages with 95% confidence intervals shown in parentheses.

Parameters	Sensitivity	Specificity	AUC	p
ERO ≥0.1cm^2	81% (58-94)	59% (33-81)	0.75	0.001
RV ≥24 ml	52% (30-74)	82% (57-96)	0.72	0.008
Tenting area ≥1.27 cm^2	95% (76-99)	41% (19-67)	0.72	0.006

AUC – area under the curve; ERO – effective regurgitant orifice; RV – regurgitant volume.

dial velocities between the two groups. Patients with ICM had significantly lower mitral annular systolic and diastolic velocities, a finding which is in accordance with previous works.[25-27] The mitral septal E/Em ratio, which is associated with an adverse prognosis in both ischaemic and non-ischaemic LV dysfunction and is associated with cardiac mortality and morbidity,[28,29] was significantly elevated in our ICM group. The significant correlations between all tissue Doppler indices and ERO imply that they could be used as univariate predictors of FMR. Likewise, a previous study found that patients with CHF and severe secondary mitral regurgitation from various causes demonstrated significantly lower peak systolic mitral annular velocities and a higher mitral E/Em ratio than CHF patients with no or mild to moderate FMR.[19] A tenting area >1.27 cm^2 showed the highest sensitivity and RV >24 ml the highest specificity for the diagnosis of ischaemic cause of LV dysfunction. However, multivariate logistic regression analysis revealed that amongst all indices, age (p=0.01) and Sm (p=0.01) were the only variables independently associated with the probability of ICM rather than DCM diagnosis.

A previous real-time three-dimensional echocardiography study[7] showed that tenting area was larger in patients with DCM, although the ERO did not differ between the two groups. However, the design of that study was quite different. All patients had significant FMR with mean ERO values of 0.35 cm^2 in ICM patients, compared with 0.17 cm^2 in our study. Moreover, in the above study ICM patients had significantly higher values for LV ejection fraction than DCM patients (28 ± 7% vs. 21 ± 7%, respectively). These differences in the profiles of the study populations

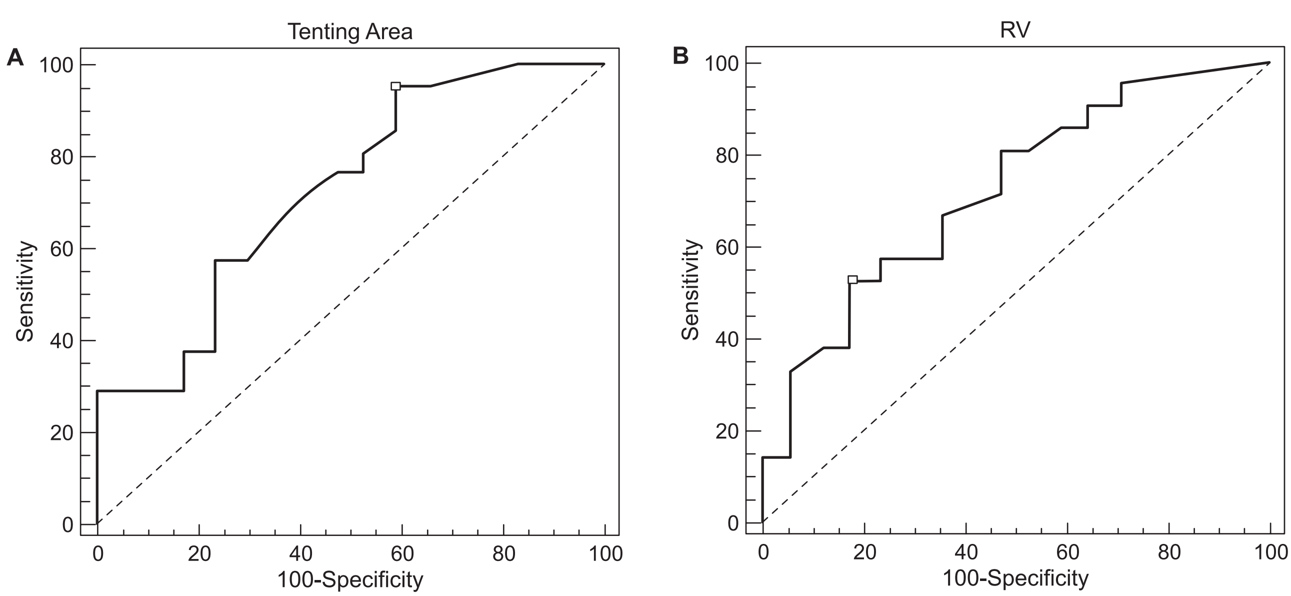

Figure 2. Receiver operating characteristic curves for (A) tenting area, and (B) regurgitant volume (RV), for the prediction of ischaemic aetiology in patients with dilated cardiomyopathy.

could explain the discrepancy between the results from the two studies.

The main limitation of our study is that the patient population was relatively small, thus further studies with larger samples are needed. Moreover, indices of global (sphericity index) or local (papillary-fibrosa distance, regional wall motion score index) remodelling[30-32] were not determined in our cohort. Hence, it could be argued that ICM patients had higher LV end-diastolic dimensions, which could bias the study results by means of their worse baseline status. However, the higher LV end-diastolic dimensions might represent the result and not the cause of the more severe FMR in these patients. Finally, the main purpose of the present study was to compare the echocardiographic characteristics of the two entities after matching the patients echocardiographically (with ejection fraction) and clinically (with functional status expressed by means of NHYA class).

In conclusion, LV remodelling, mitral apparatus deformity and incomplete closure of mitral leaflets were more prominent in patients with ICM and led to more severe FMR than in patients with DCM. Tissue Doppler parameters were correlated with FMR severity, while mitral annular Sm together with age were the only variables independently associated with the probability of ICM diagnosis. Amongst all FMR echocardiographic indices, tenting area had the highest sensitivity and RV the highest specificity for the diagnosis of ICM.

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