Mitral effective regurgitant orifice area versus left ventricular ejection fraction as prognostic indicators in patients with dilated cardiomyopathy and heart failure

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Dilated cardiomyopathy; Mitral valve; Regurgitation.

Background. **This study aimed at investigating the relative powers of the quantitative evaluation of functional mitral regurgitation (FMR) and ejection fraction (EF) in predicting the clinical changes and prognosis of dilated cardiomyopathy (DCM) with severe systolic dysfunction.**

Methods. **A total of 81 patients with DCM, EF < 0.40 and at least mild FMR were prospectively evaluated during a mean follow-up of 24 ± 7 months. Twenty cardiac deaths were recorded. At the time of enrolment all patients underwent echocardiographic evaluation of the effective regurgitant orifice area (ERO), EF, left atrial area, and tenting area. In 42/81 patients, the data obtained at enrolment were compared to those measured at a mean follow-up of 10 ± 2 months. A multivariate analysis was performed to determine the best predictor of NYHA class and mortality.**

Results. **There was a correlation between the NYHA class and the ERO (χ^2 = 26.1, p = 0.0001) but not with EF (χ^2 = 4.3, p = 0.22) and at multivariate analysis, the ERO was found to be the main determinant of the NYHA class (r = 0.64, standard error 0.6, p = 0.0001). The NYHA class remained unchanged or improved in 28/42 (67%) and deteriorated in 14/42 (33%) patients. In the first group, the ERO increased from 22.3 ± 10 to 30.2 ± 16.4 mm^2 (p = 0.05) and the tenting area from 5.8 ± 1.8 to 6.8 ± 1.8 cm^2 (p = 0.001); in the second group, the ERO increased from 25.1 ± 5.6 to 39.0 ± 14.5 mm^2 (p = 0.04) and the tenting area from 5.9 ± 2.1 to 7.6 ± 1.8 cm^2 (p = 0.0001), in both groups without significant changes in EF. The mortality was 8.1% in patients with an ERO < 21 mm^2, 30.3% in patients with an ERO of 21-30 mm^2, and 50% in those with an ERO > 30 mm^2. The EF was similar in the three subgroups. At Cox multivariate analysis the best predictors of mortality were the ERO (χ^2 = 13.83, p = 0.0001), EF (χ^2 = 5.48, p = 0.019), and left atrial area (χ^2 = 4.52, p = 0.04).**

Conclusions. **FMR in DCM well correlated with the clinical status of the patients and its worsening was suggestive of progression of the disease. The ERO was found to be the best predictor of the NYHA class and mortality.**

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Introduction

Functional mitral regurgitation (FMR) is a common complication of dilated cardiomyopathy (DCM) and occurs in up to 80% of patients with heart failure (HF)[1]. The presence of FMR in patients with HF contributes to the progression of left ventricular (LV) dysfunction and is a marker of an adverse outcome[2-4]. Mild mitral regurgitation does not appear to be an independent predictor of death in patients with DCM, whereas moderate to severe FMR is correlated with a stepwise increase in overall mortality[5].

FMR has a multifactorial origin related to global and regional LV remodeling, mitral annulus enlargement and dysfunction, left atrial dilation and an altered balance between the tethering and closing forces acting on the mitral leaflets[6-8].

The echocardiographic quantitative evaluation of FMR allows the measurement of the effective regurgitant orifice area (ERO), regurgitant volume and regurgitant fraction. These parameters were found to be strongly related to the morpho-functional alterations that have been considered determinants of FMR itself[9-11].

The ERO proved to be a strong indicator of the clinical status and outcome in patients with previous myocardial infarction and mitral regurgitation[12]. The ERO is also a reliable predictor of survival in patients with organic mitral regurgitation[13]. In selected groups of patients with mild to severe FMR the favorable effect of medical therapy was associated with a decrease in the ERO[14,15].

The LV ejection fraction (EF) has long been recognized as a strong predictor of survival in patients with chronic cardiomyopathy, particularly those with coronary artery disease[16]. In the subset of patients with DCM, however, EF often showed a weaker correlation with the clinical functional class and outcome than left atrial enlargement and Doppler-derived signs of LV diastolic dysfunction[17-20].

In the present study, we evaluated a series of consecutive patients with DCM and HF with the aim of determining the relative power of quantitative measurements of FMR and EF as markers of the functional state and as independent predictors of cardiac death.

Methods

Patient population. Patients were recruited among those referred to the Outpatients Clinic of the Empoli Hospital from January 1, 2001 to June 30, 2003. The study included 81 consecutive new patients (59 males, 22 females) with a mean age of 68 ± 10 years (range 41 to 82 years).

All patients were screened using the following inclusion criteria:
• chronic HF due to DCM with an EF ≤ 0.40 and a LV end-diastolic diameter > 60 mm at echocardiography;
• at least ≥ 2+ FMR, as evaluated by the commonly adopted semiquantitative echo-Doppler method.

DCM was idiopathic (without clinical and instrumental data diagnostic of coronary heart disease or without significant stenosis at coronary angiography) in 45 (55%) patients and ischemic (previous myocardial infarction) in 36 (45%) patients. Atrial fibrillation was present in 13/81 (16%) and left bundle branch block in 35/81 (43.2%). Patients were receiving standard drug treatment in accordance with the American College of Cardiology/American Heart Association guidelines[21].

At the time of inclusion patients were clinically stable, without recent acute HF, angina, myocardial infarction or the need for revascularization procedures. Other exclusion criteria were significant organic valvular diseases, suboptimal echocardiographic examination, and severe renal or liver disease.

At the time of inclusion all patients underwent clinical and echo-Doppler evaluation. Follow-up information was obtained by review of clinical records, direct interviews and death certificates. The median follow-up was 24 ± 7 months (range 6 to 36 months). During this period, a total of 23 patients died and 20/23 cardiac deaths (worsening HF in 74% and sudden death in 26%) were recorded and evaluated for the analysis.

A second echo-Doppler examination was carried out in 42/81 patients after at least 6 months of standard medical therapy (mean interval 10 ± 2 months). Thirty-nine patients were not reviewed during follow-up because 16/81 died before the first control visit, 14/81 underwent resynchronization therapy, and 9/81 refused to give consent.

Echocardiographic analysis. Two experienced operators carried out all the examinations using a commercially available instrument (Sonos 550, Hewlett Packard, Andover, MA, USA) with a 2.5 MHz phased-array probe.

The LV end-diastolic (EDV, ml) and end-systolic volumes and LVEF were computed using the bi-apical Simpson method in the 2- and 4-chamber views. The end-diastolic left atrial area (LAA, cm^2) was measured in the 4-chamber apical view. The mitral annular inter-commissural and septo-lateral diameters were measured in the 2- and 4-chamber views at end-diastole and averaged to obtain the diastolic annular area = $3.14 \times r^2$ (MAA, cm^2).

The mitral leaflet tenting area (TA, cm^2), the area enclosed between the mitral leaflets and the mitral annulus, was measured from the parasternal long-axis view during early systole.

In all patients, FMR was graded using the following two quantitative methods and the final results were the average of the measured values:
1. quantitative Doppler (feasible in 94% of patients): the mitral and aortic stroke volumes (SV) were calculated as the product of the flow time-integral and the cross-sectional area of the flow tract. The regurgitant volume (ml) was calculated as the difference between these two stroke volumes. The ERO (mm^2) was calculated as the ratio of the regurgitant volume to regurgitant time-integral;
2. proximal isovelocity surface area (PISA) method (feasible in 94% of patients): from the apical approach we measured the distance (r) of the convergence area of mitral flow and mitral plane to calculate both the regurgitant volume ($2 \times 3.14 \times r^2 \times$ aliasing velocity) and the ERO (mm^2) as regurgitant volume/maximal velocity of the mitral regurgitant jet. The regurgitant fraction was calculated as the ratio between the regurgitant volume and the total LV systolic output[22-24].

The reproducibility of these measurements has been previously assessed and showed a narrow intraobserver and interobserver variability[11].

Statistical analysis. Data are expressed as mean ± 1 SD. Comparison between groups was made using the Student's unpaired t-test or the Kruskall-Wallis non-parametric rank test. The Student's paired t-test was used to compare basal and follow-up echocardiographic data. Linear regression analysis was used to evaluate the correlation between the NYHA class (as the dependent variable) and variables measuring FMR and local and global LV remodeling (as independent variables). Statistical significance was judged at the 0.05 level. The event rate during follow-up was estimated using the Kaplan-Meier method with follow-up starting at the time of the first echocardiogram and the impact of FMR analyzed in the three subgroups with an ERO < 20, 20-30 and > 30 mm^2 and an EF ≥ 0.30 or < 0.30. The baseline predictors of survival were identified using Cox proportional regression analysis with the stepwise forward method (inclusion criteria p < 0.05).

Results

Characteristics of the patients at the time of inclusion. The baseline clinical and echocardiographic characteristics of the patients are listed in table I.

At the time of enrolment, 53 (65%) patients were in NYHA functional class I-II and 28 (35%) in III-IV. The patients were similar with regard to DCM etiology, ischemic or idiopathic, and the presence of sinus rhythm or atrial fibrillation and of left bundle branch block or normal intraventricular conduction. Patients with left bundle branch block had a slightly lower EF (Table II).

There was a significant correlation between the NYHA class and the ERO and TA but not between the NYHA class and the LV volumes, EF and antegrade SV (Fig. 1).

Multiple regression analysis performed for the most relevant echocardiographic covariates (EF, EDV, antegrade SV, MAA, TA, LAA and ERO) and NYHA class (as dependent variable) showed that the ERO (r = 0.64, standard error 0.6, p = 0.0001) was the only variable correlated with the clinical status of the patients (Table III).

Table I. Clinical and echocardiographic baseline characteristics of the study population.

No. patients	81
Sex (M/F)	59 (73%)/22 (27%)
Mean age (years)	68 ± 10
NYHA class	
I	17 (20.9%)
II	36 (44.4%)
III	19 (23.4%)
IV	9 (11.1%)
Idiopathic/ischemic etiology	45 (55%)/36 (45%)
Left bundle branch block	35 (43.2%)
Atrial fibrillation	16%

	Mean ± SD	Range	95% CI
EF	0.30 ± 0.10	0.11-0.40	0.27-0.32
EDV (ml)	210 ± 69	150-477	197-229
ESV (ml)	149 ± 61	70-422	138-165
MAA (cm^2)	8.2 ± 1.8	4.5-12.6	7.7-8.5
SV (ml)	50.0 ± 15.1	46.5-53.4	22.7-87.7
TA (cm^2)	6.08 ± 1.72	2.8-9.0	5.7-6.4
LAA (cm^2)	23.4 ± 9.4	9-49	22.5-26.3
ERO (mm^2)	24.2 ± 14.1	1-80	17.9-24.6
RV (ml)	35.7 ± 19.4	4-105	30.0-39.5
RF (%)	36.7 ± 15.0	1-72	32.4-40.4

CI = confidence interval; EDV = end-diastolic volume; EF = ejection fraction; ERO = effective regurgitant orifice area; ESV = end-systolic volume; LAA = left atrial area; MAA = diastolic mitral annular area; RF = regurgitant fraction; RV = regurgitant volume; SV = stroke volume; TA = systolic valvular tenting area.

Follow-up. The NYHA class remained unchanged or improved in 28/42 (67%) patients (from 2.6 ± 1.0 to 2.2 ± 0.7, p = NS). We did not find any significant change in LV systolic function (EDV 236 ± 80 to 235 ± 77 ml, EF 0.29 ± 0.6 to 0.29 ± 0.7) and antegrade SV (56 ± 19 to 57 ± 25 ml, p = NS). Quantification of FMR showed a slight but significant increase in the ERO (from 22.3 ± 10 to 30.2 ± 16.4 mm^2, p = 0.05) and TA (from 5.8 ± 1.8 to 6.8 ± 1.8 cm^2, p = 0.001). Taking into account the 14/42 (33%) patients whose functional NYHA class deteriorated from I-II to III-IV (from 1.8 ± 0.6 to 3.4 ± 0.7, p = 0.0001), we found a marked increase in the severity of FMR, as indicated by the ERO (from 25.1 ± 5.6 to 39.0 ± 14.5 mm^2, p = 0.04) and TA (from 5.9 ± 2.1 to 7.6 ± 1.8 cm^2, p = 0.0001), but no significant changes in EF (from 0.30 ± 0.5 to 0.28 ± 0.7, p = NS) and SV.

Mortality. The overall proportional cumulative survival was 79, 68 and 61% at 6, 12 and 24 months respectively (Fig. 2).

Patients with an ERO < 21 mm^2 (37/81) were compared to those with an ERO of 21-30 mm^2 (30/81) and those with an ERO > 30 mm^2 (14/81) for cardiovascular mortality: 3/37 (8.1%) vs 10/30 (33.3%) and 7/14 (50.0%) (p trend = 0.02). In the three subgroups, the mean EF was respectively 0.32 ± 0.10, 0.30 ± 0.09 and 0.27 ± 0.09 (p = NS) (Fig. 3).

Table II. Subgroup comparison.

	ID (n=45)	IS (n=36)	p	No LBBB (n=46)	LBBB (n=35)	p	SR (n=68)	AF (n=13)	p
ERO	23 ± 14	26 ± 13	NS	22 ± 10	26 ± 16	NS	36 ± 13	31 ± 20	NS
MAA	8.3 ± 2.1	8.1± 1.5	NS	8.2 ± 1.6	8.3 ± 1.9	NS	8.1 ±1.8	9.6 ± 2.1	NS
EDV	210 ± 59	221 ± 74	NS	197 ± 71	222 ± 67	NS	212 ± 75	174 ± 70	NS
EF	0.29 ± 0.10	0.28 ± 0.9	NS	0.33 ± 0.9	0.27 ± 0.10	0.03	0.36 ± 0.13	0.31 ± 0.15	NS
LAA	25 ± 11	24 ± 6	NS	21 ± 7	26 ± 9	NS	24 ± 10	24 ± 7	NS

AF = atrial fibrillation; EDV = end-diastolic volume; EF = ejection fraction; ERO = effective regurgitant orifice area; ID = idiopathic etiology; IS = ischemic etiology; LAA = left atrial area; LBBB = left bundle branch block; MAA = diastolic mitral annular area; SR = sinus rhythm.

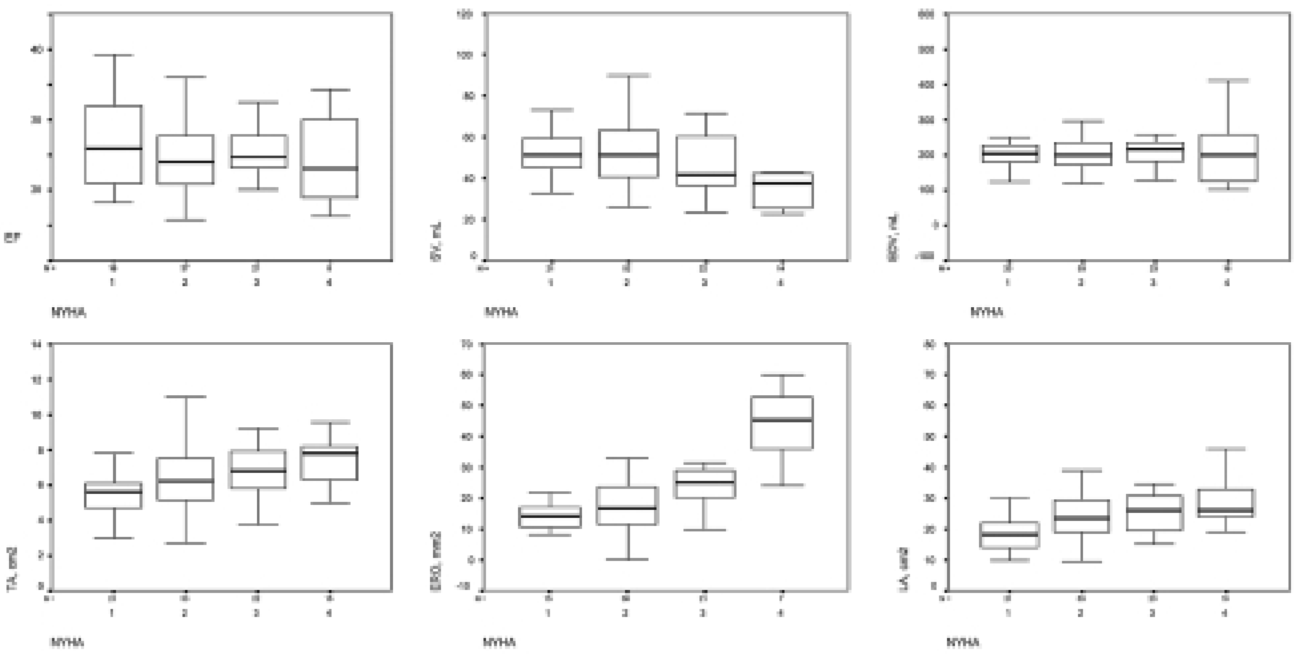

Figure 1. *Correlation between the NYHA class and ejection fraction (EF) (χ^2 = 4.3, p = 0.22), aortic stroke volume (SV) (χ^2 = 7.1, p = 0.07), end-diastolic volume (EDV) (χ^2 = 1.2, p = 0.91), tenting area (TA) (χ^2 = 11.9, p = 0.008), effective regurgitant orifice area (ERO) (χ^2 = 26.1, p = 0.0001), and left atrial area (LA) (χ^2 = 11.2, p = 0.01).*

Table III. Echocardiographic determinants of the NYHA class (univariate analysis).

	r	B	95% CI	p
EF	-0.12	0.003	-0.018 - 0.023	NS
MAA	0.19	0.048	-0.065 - 0.161	NS
SV	-0.29	-0.10	-0.024 - 0.004	NS
TA	0.39	0.075	-0.071 - 0.221	NS
EDV	-0.03	-0.003	-0.006 - 0.001	NS
LAA	0.33	0.004	-0.022 - 0.029	NS
ERO	0.59	0.034	0.014 - 0.054	0.001

NYHA class as dependent variable. CI = confidence interval; EDV = end-diastolic volume; EF = ejection fraction; ERO = effective regurgitant orifice area; LAA = left atrial area; MAA = diastolic mitral annular area; SV = stroke volume; TA = systolic valvular tenting area.

We divided the study population in four subgroups with an EF > or < 0.30 and an ERO > or < 20 mm^2 in order to assess survival during follow-up. The relative Kaplan-Meier survival curves are shown in figure 4.

Independent predictors of mortality. A multivariate Cox proportional analysis with clinical covariates (age, NYHA class, atrial fibrillation, left bundle branch block) and echocardiographic variables correlated with FMR (ERO, TA, MAA, LAA) and LV remodeling (EF, EDV) was assessed in a stepwise forward model. The most important indices of survival were found to be the ERO, EF and LAA (Tables IV and V).

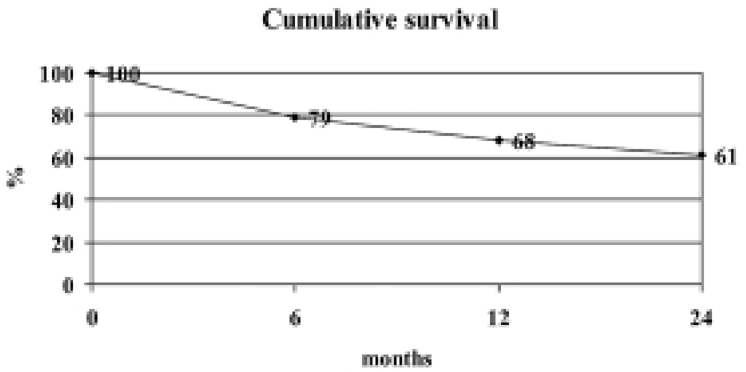

Figure 2. *Graph showing the cumulative survival, as determined using the Kaplan-Meier method, in 81 patients with dilated cardiomyopathy and functional mitral regurgitation.*

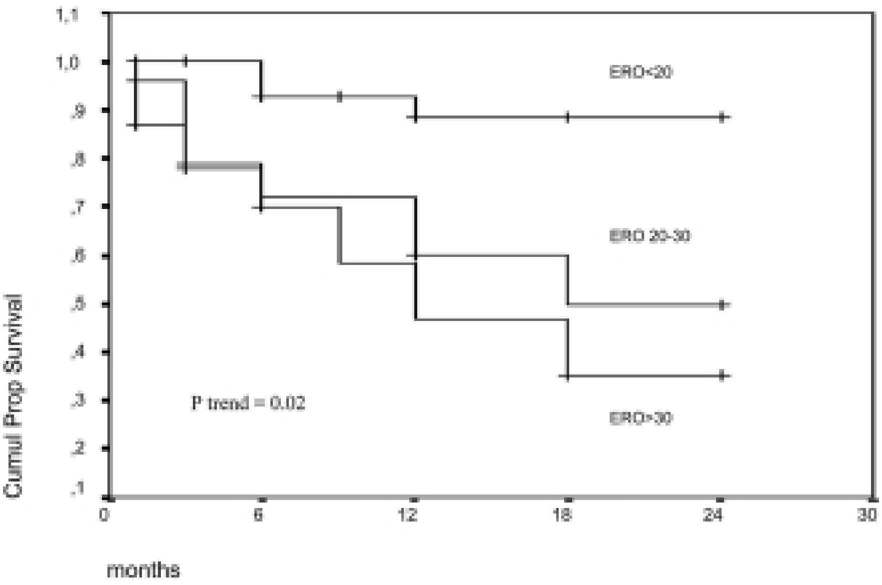

Figure 3. *Kaplan-Meier curves of the cumulative proportional survival in subgroups stratified by the effective regurgitant orifice area (ERO): < 20, 20-30, and > 30 mm². In the three subgroups ejection fraction was respectively 0.32 ± 0.10, 0.30 ± 0.09 and 0.27 ± 0.09 (p = NS).*

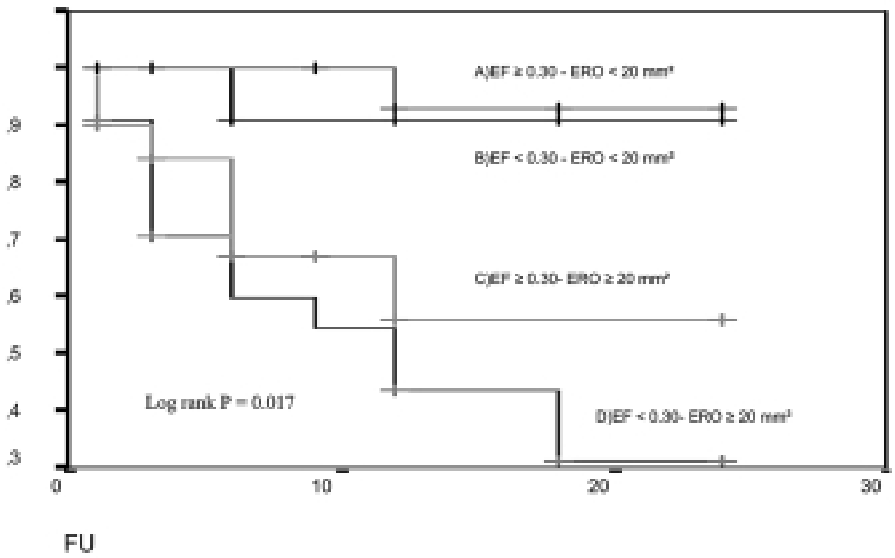

Figure 4. *Kaplan-Meier survival curves in subgroups stratified by ejection fraction (EF) and effective regurgitant orifice area (ERO). A: n = 19, B: n = 19, C: n = 21, and D: n = 22 patients respectively.*

Discussion

Quantitative FMR severity is a reliable indicator of the clinical efficacy of therapy in patients with HF, both those with hemodynamic improvement as well as those, such as our cohort, whose clinical conditions deteriorate in spite of continuous "optimal" medical therapy[13,14,25].

Our results showed that in patients with DCM, a severely depressed LVEF and HF, the degree of FMR, as measured by means of the ERO, was strongly correlated with the NYHA functional class. In our population, patients in NYHA class I-II usually had an ERO < 20 mm² and patients in NYHA class III-IV had an ERO > 20 mm² and no significant correlations were found between the NYHA class and the basal EF, LV volumes and stroke volumes.

After 1 year of follow-up, clinically stable patients did not show any significant changes in LV volumes and EF while quantitative evaluation of FMR showed a slight but significant increase of the ERO and an enlargement of the TA. This subclinical increase in mitral regurgitation and LV local remodeling is probably suggestive of a "silent" evolution of the disease, despite optimal standard medical therapy.

On the contrary, patients with worsening clinical conditions presented with a marked increase in the ERO and related echocardiographic parameters (TA),

Table IV. Predictors of death at Cox univariate analysis.

Variables	χ^2	df	p
Age	0.64	1	0.42
LBBB	6.69	1	0.01
AF	0.92	1	0.33
EF	9.41	1	0.002
NYHA class	17.99	3	0.0001
EDV	1.84	1	0.18
LAA	0.35	1	0.55
TA	8.54	1	0.003
ERO	16.64	1	0.0001

NYHA class, LBBB and AF as categorical variables. AF = atrial fibrillation; EDV = end-diastolic volume; EF = ejection fraction; ERO = effective regurgitant orifice area; LAA = left atrial area; LBBB = left bundle branch block; TA = systolic valvular tenting area.

Table V. Predictors of death at Cox multivariate analysis.

Variables	χ^2	β	SEE	p
ERO	13.83	0.09	0.03	0.0001
EF	5.48	-0.06	0.04	0.019
LAA	4.52	-0.08	0.02	0.04

EF = ejection fraction; ERO = effective regugitatnt orifice area; LAA = left atrial area; SEE = standard error of the estimate.

again without significant changes in EF, LV volumes and stroke volume.

Severe FMR has been considered a pre-terminal complication of chronic HF[2].

Our results confirmed that an ERO > 20 mm^2 is suggestive of poor survival at 24 months and above all that an ERO > 30 mm^2 had an incremental predictive value on mortality. At Cox multivariate analysis, the ERO was found to be a better predictor than both EF and LAA. This finding is in contrast with previous data indicating that the severity of mitral regurgitation, as determined on the basis of semiquantitative Doppler methods, had a weaker predictive value than EF or left atrial size[17,18]. This difference may reflect the greater accuracy of quantitative evaluation of FMR. In any case, our results showed that EF and LAA had a lower prognostic impact.

In our study, the prognosis was better in the group of patients with an ERO < 20 mm^2 regardless of the degree to which the EF was reduced while the absolute mortality was high when the ERO exceeded 20 mm^2 with a greater impact of the decrease in EF: about 70% of patients with an ERO > 20 mm^2 and an EF < 0.30 died within 24 months.

In the setting of DCM with FMR, LV systolic shortening depends on a complex interaction between aortic impedance, mitral regurgitant flow impedance, LV preload and contractility, so that EF should not be considered a reliable indicator of the LV function. As suggested by our results, an increase in the regurgitant volume may modify clinical disability even in the absence of significant changes in EF and SV. The impact of the degree of FMR on the functional class and prognosis highlights, in our opinion, the prevalent role of "backward failure" in these patients.

Finally, in patients with DCM and an already severely depressed EF, quantitative evaluation of the degree of FMR by measurement of the ERO appears to be a stronger marker of the clinical status and a more powerful prognostic indicator than EF, which provides little incremental information on the clinical outcome.

Study limitations. The main limitations of the study are the small sample size and the small number of echocardiographic checkups during follow-up. At the time of enrolment, all patients were already on heterogeneous medical therapy and differences among subgroups were not considered in the statistical analysis. Our protocol did not include specific measurements of functional capacity, such as the walking distance or peak oxygen consumption.

Some variables such as the diastolic filling patterns and deceleration time or right ventricular function were not considered with sufficient frequency during early echocardiographic examinations to warrant inclusion in multivariate analysis.

The PISA method presents some limitations due to the shape of the convergence area and the optimal regulation of the aliasing velocity[26]. In clinical practice, PISA is accepted as an accurate method for the quantitative evaluation of FMR. In our study this method yielded highly reproducible values that were found to be comparable to those reported in previous studies.

References

1. Smolens IA, Bolling SF. Secondary mitral regurgitation. In: Crawford MH, DiMarco JP, Paulus WJ, eds. Cardiology. 2nd edition. St Louis, MO: Mosby International, 2001.
2. Conti JB, Mills RM. Mitral regurgitation and death while awaiting cardiac transplantation. Am J Cardiol 1993; 71: 617-8.
3. Lamas GA, Mitchell GF, Flaker GC, Smith SC, Gersh BJ, Basta L, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Circulation 1997; 96: 827-33.
4. Charanit SR, Nishimura RA, Hatle LK, Bailey KR, Tajik AJ. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. Relation to symptoms and prognosis. Circulation 1994, 90: 2772-9.
5. Tcheng JE, Jackman JD, Nelson CL, et al. Outcome of patients sustaining acute ischemic mitral regurgitation during myocardial infarction. Ann Intern Med 1992; 117: 18-24.
6. Otsuji Y, Handschumacher BS, Schwammenthal E, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation 1997; 96: 1999-2007.
7. He S, Fontaine AA, Schwammenthal E, Yoganathan AP, Levine RA. Integrated mechanism for functional mitral re-

gurgitation. Leaflet restriction versus coapting force: in vitro studies. Circulation 1997; 96: 1826-33.
8. Kwan J, Shiota T, Agler DA, et al. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation. Circulation 2003; 107: 1135-45.
9. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction. Circulation 2000; 102: 1400-6.
10. Dujardin KS, Enriquez-Sarano M, Bailey KR, Nishimura RA, Seward JB, Tajik AJ. Grading of mitral regurgitation by quantitative Doppler echocardiography: calibration by left ventricular angiography in routine clinical practice. Circulation 1997; 96: 3409-15.
11. Gianfaldoni ML, Venturi F, Petix NR, et al. Quantitative assessment of functional mitral regurgitation in dilated cardiomyopathy: morphological and functional relations. Ital Heart J Suppl 2002; 3: 738-45.
12. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation. Long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001; 103: 1759-64.
13. Enriquez-Sarano ML, Tajik AJ, Messika-Zeitoun D, et al. The effective regurgitant orifice area is predictive of survival in patients with organic mitral regurgitation. (abstr) J Am Coll Cardiol 2003; 41 (Suppl A9): 510A.
14. Capomolla S, Febo O, Gnemmi M, et al. Beta-blockade therapy in chronic heart failure. Diastolic function and mitral regurgitation improvement by carvedilol. Am Heart J 2000; 139: 596-608.
15. Rosario LB, Stevenson LW, Solomon SD, Lee RT, Reimold SC. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduction of the regurgitant orifice area. J Am Coll Cardiol 1998; 32: 1819-24.
16. Packer M. Prolonging life in patients with congestive heart failure. Circulation 1987; 75 (Suppl IV): IV1-IV3.
17. Gradman A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. J Am Coll Cardiol 1989; 14: 564-70.
18. Rossi A, Cicoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 2002; 40: 1425-30.
19. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol 1994; 24: 132-9.
20. Giannuzzi P, Temporelli PL, Bosimini E, et al. Independent and incremental value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. J Am Coll Cardiol 1996; 28: 383-90.
21. Hunt SA, Backer DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 guidelines for the evaluation and management of heart failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. Circulation 2001; 104: 2996-3007.
22. Enriquez-Sarano M, Bailey KR, Seward JB, Tajik J, Krohn MJ, Mays JM. Quantitative Doppler assessment of valvular regurgitation. Circulation 1993; 87: 841-7.
23. Enriquez-Sarano M, Seward JB, Bailey KR, Tajik AJ. Effective regurgitant orifice area: a noninvasive Doppler development of an old hemodynamic concept. J Am Coll Cardiol 1994; 23: 443-51.
24. Schwammenthal E, Chen C, Benning F, Block M, Breithardt G, Levine RA. Dynamics of mitral regurgitation flow and orifice area: physiologic application of the proximal flow convergence method. Clinical data and experimental testing. Circulation 1994; 90: 307-21.
25. Lowes B, Gill EA, Abraham WT, et al. Effects of carvedilol on left ventricular mass, chamber geometry and mitral regurgitation in chronic heart failure. Am J Cardiol 1999; 83: 1201-5.
26. Enriquez-Sarano M, Miller AF, Hayes SN, et al. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. J Am Coll Cardiol 1995; 25: 703-9.