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Prognostic Implications of Functional Mitral Regurgitation in Patients With Heart Failure and Reduced Ejection Fraction

Impacto de la insuficiencia mitral funcional en el pronóstico de pacientes con insuficiencia cardiaca y fracción de eyección reducida

To the Editor,

Functional mitral regurgitation (FMR) occurs in 20% to 30% of patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF).[1,2] In these patients, FMR increases left ventricular (LV) end-diastolic pressure, contributes to LV remodeling, increases pulmonary hypertension, and worsens right ventricular function, all of which are associated with poor prognosis in HF. The clinical course of FMR depends on the type of heart disease, although the factors that determine its onset and the treatment of choice remain unknown. Treatment options include cardiac resynchronization and transplantation, but in most patients with this condition, it is not cured.[3] Percutaneous mitral valve repair has comparable outcomes to surgery for organic mitral regurgitation with reasonable LVEF.[4] Observational studies indicate that percutaneous treatment is beneficial in FMR with reduced LVEF. While randomized study results (ClinicalTrials.gov NCT01772108) are awaited, it would be interesting to identify the patient profile that could benefit from this treatment.

We present the data on FMR from the Spanish HF Research Network (REDINSCOR). From 2007 to 2011, 2507 patients with symptomatic HF were recruited in 18 hospitals.[5] We selected patients with LVEF < 40% with no organic valve disease or hypertrophic cardiomyopathy. Patients were then divided according to whether they had significant FMR (sFMR) (grade II-IV) or nonsignificant FMR (nsFMR) (grade 0-I). The analyses were performed using SPSS 22 and STATA-13.[6]

The study included 1526 patients: most were male (78%) with a history of hypertension (65%) and overweight (body mass index, 28.4). Fifty-seven percent were in functional class III or IV with elevated natriuretic peptide levels despite optimal HF therapy (86% were receiving beta-blockers, 87% were receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, and 64% were receiving aldosterone antagonists). The etiology of ventricular dysfunction was mostly ischemic (57%). At the time of study inclusion, 530 patients (35%) had signs of decompensated HF.

Significant FMR was detected in 746 patients (47%). The group with sFMR had a higher frequency of left bundle branch block, left

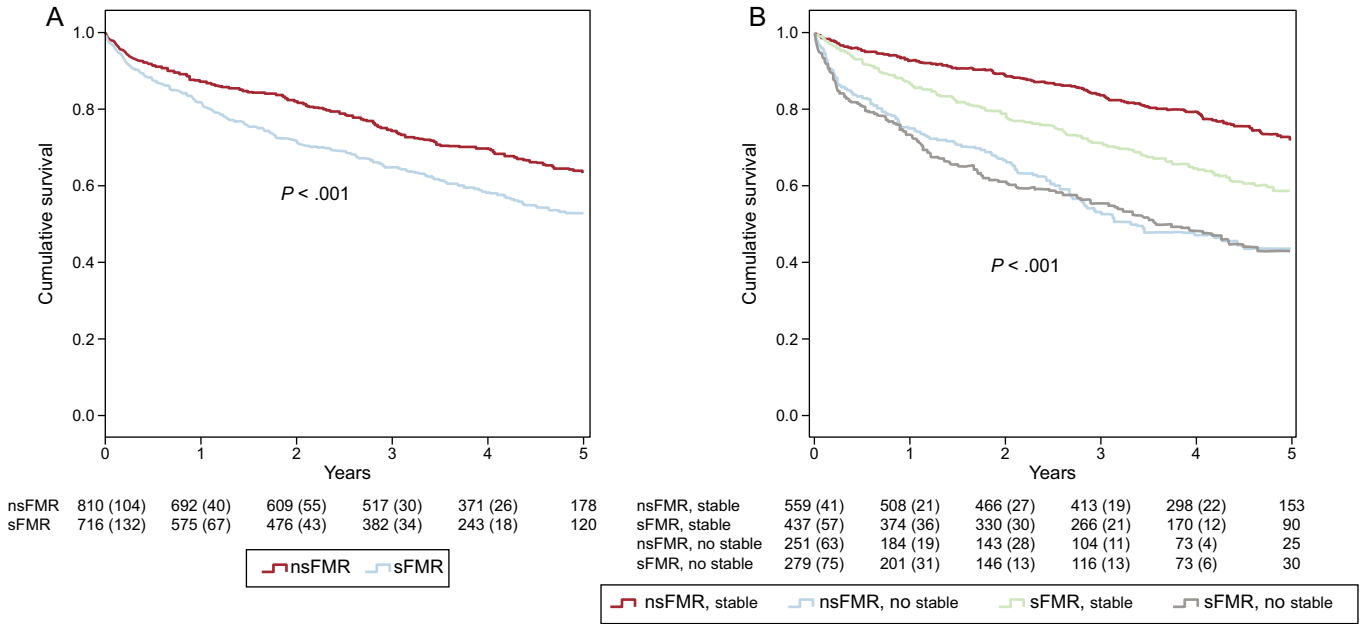

Figure. Kaplan-Meier curves. A: prognosis was worse in patients with sFMR ($P < .001$). B: patients with signs of decompensation (unstable) had lower survival independently of FMR severity. In stable patients, the presence of sFMR identified a group with intermediate prognosis ($P < .001$). FMR, functional mitral regurgitation; nsFMR, nonsignificant functional mitral regurgitation; sFMR, significant functional mitral regurgitation.

Table
Cox and Fine-Gray Models[a]

	HR/sHR	95%CI	*P*	C-statistic
All-cause mortality, HR				0.70
Functional mitral regurgitation	1.54	1.14-2.08	.005	
Systolic blood pressure, mmHg	0.99	0.98-0.99	.008	
Left ventricular end-diastolic diameter, mm	1.02	1-1.03	.042	
Glomerular filtration rate,[b] mL/min/1.73 m^2	0.99	0.98-0.99	.001	
Elevated natriuretic peptides	2.11	1.45-3.06	.001	
Beta-blocker therapy	0.50	0.33-0.76	.001	
Cardiac mortality, sHR				0.71
Functional mitral regurgitation	1.90	1.36-2.68	< .001	
Systolic blood pressure, mmHg	0.99	0.98-0.99	.011	
Left atrial diameter, mm	1.02	1-1.04	.05	
Glomerular filtration rate,[b] mL/min/1.73 m^2	0.99	0.98-0.99	< .001	
Elevated natriuretic peptides	2.16	1.40-3.34	< .001	
Mortality due to refractory HF, sHR				0.78
Functional mitral regurgitation	2.11	1.32-3.39	.002	
Diastolic blood pressure, mmHg	0.98	0.96-0.98	.001	
Ejection fraction, %	0.95	0.92-0.98	.001	
Left atrial diameter, mm	1.03	1-1.06	.046	
Glomerular filtration rate,[b] mL/min/1.73 m^2	0.98	0.97-0.99	< .001	
Elevated natriuretic peptides	1.97	1.05-3.68	.034	

95%CI, 95% confidence interval; HF, heart failure; HR, hazard ratio; sHR, sub-hazard ratio.
[a] The competing events are noncardiac mortality and mortality not due to refractory HF.
[b] Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

atrial dilatation, and left ventricular dilatation, and worse LVEF. In addition, at the time of inclusion, they had a higher prevalence of decompensated HF, with associated increased natriuretic peptides, hypotension, and renal failure. The variables independently associated with the presence of sFMR were male sex (odds ratio [OR], 0.34; 95% confidence interval [95%CI], 0.25-0.47; $P < .001$), body mass index (OR, 0.94; 95%CI, 0.91-0.97; $P < .001$), decompensated HF (OR, 1.33; 95%CI, 1.01-1.74; $P = .042$), LV diameter (OR, 1.04; 95%CI, 1.02-1.05; $P < .001$), left atrial diameter (OR, 1.05; 95%CI, 1.03-1.07; $P < .001$), blood sodium level (OR, 0.97; 95%CI, 0.94-1.00; $P = .044$), and elevated natriuretic peptides (OR = 1.57; 95%CI, 1.17-2.1; $P = .003$) (area under the curve, 0.70; 95%CI, 0.67-0.74).

Median survival was 3.4 years [interquartile range, 1.7-4.7]. Survival at 1, 3, and 5 years was 84.5%, 69.9%, and 58.5%. Prognosis was worse (Figure A) in patients with sFMR (cumulative survival at 1 year, 81.5% vs 87.1%; at 3 years, 64.9% vs 74.3%, and at 5 years, 52.7% vs 63.5%; $P < .001$) due to mortality from refractory HF.

In the multivariable model, the variables that were independently associated with mortality were decompensated HF (hazard ratio [HR], 1.7; 95%CI, 1.32-2.13; $P < .001$), functional class III-IV (HR, 1.3; 95%CI, 1.01-1.67; $P = .041$), systolic blood pressure (HR, 0.99; 95%CI, 0.98-0.99; $P = .01$), LA size (HR, 1.02; 95%CI, 1.01-1.03; $P = .001$), anemia (HR, 1.34; 95%CI, 1.06-1.69; $P = .013$), glomerular filtration rate (HR, 0.99; 95%CI, 0.98-0.99; $P < .001$), elevated natriuretic peptides (HR, 1.88; 95%CI, 1.38-2.56; $P < .001$), blood sodium levels (HR, 0.97; 95%CI, 0.95-0.99; $P = .038$) and treatment with beta-blockers (HR, 0.51; 95%CI, 0.38-0.68; $P < .001$).

In stable patients without decompensated HF (n = 996), the presence of sFMR was independently associated with overall mortality, cardiac mortality, and mortality due to refractory HF (Table and Figure B). When FMR was included in the basic model, the integrated discrimination improvement index (added discrimination value due to increased sensitivity without compromising specificity) increased by 1.2% ($P = .003$) for all-cause mortality, 2% ($P < .001$) for cardiac mortality, and 2.5% ($P < .001$) for mortality due to refractory HF.

In patients with reduced LVEF, FMR is a marker of poor prognosis, but its role in decision-making is undefined. This could be partly because FMR severity varies depending on the patient's clinical condition, and partly because performing longitudinal studies that correctly evaluate the role of FMR in each phase of the disease can be difficult. The benefit of reducing FMR severity in advanced HF is uncertain. However, it is possible that in a certain group of patients, the hemodynamic improvement associated with FMR reduction may promote positive remodeling, as can happen with cardiac resynchronization therapy.[3] Our study is the first to analyze the role of the patient's clinical condition in the course of FMR. Our results suggest that stable patients could potentially benefit from a reduction in FMR severity via percutaneous repair, and it would be interesting to study the effects of the procedure in this patient group. Randomized prospective studies are needed.

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Systemic Emboli: The Importance of Transesophageal Echocardiography

Embolias sistémicas. La importancia de la ecocardiografía transesofágica

To the Editor,

Aortic mural thrombus is an uncommon condition with a prevalence of around 1% of all systemic embolisms.[1] The development of a thrombus in an aorta with no predisposing lesions is even less frequent, and the treatment of these cases is controversial.[2]

We present the case of a 45-year-old male smoker with no other cardiovascular risk factors. He had a history of stroke causing an ischemic lesion some years before his current admission, at which time the cardiologic examination was normal. The patient was admitted to our center with diffuse abdominal pain that was more pronounced in the right iliac fossa. He underwent abdominal ultrasound, which yielded normal findings, and abdominal computed tomography (CT), which showed multiple hypodense areas in both kidneys, consistent with renal infarctions.

Based on his history of stroke and the current clinical picture, urgent echocardiography was requested to rule out an intracardiac origin of the embolisms. The echocardiogram showed a nondilated, functionally normal left ventricle, and valvular structures with no anomalies.

Transesophageal echocardiography (TEE) was then carried out, which showed normal heart chambers and no relevant findings. On evaluation of the aorta, a mobile, intra-aortic thrombus, 4 cm in length, was observed (video in the supplementary material) on a vessel wall that showed no evidence of a lesion.

Urgent chest CT study then disclosed a mobile thrombus anchored to the anterior wall of the proximal descending thoracic aorta, posterior to the aortic arch. An atherosclerotic plaque could not be ruled out as the etiologic mechanism (Figure). The angiology and vascular surgery department was consulted, which recommended anticoagulation and posterior re-evaluation.

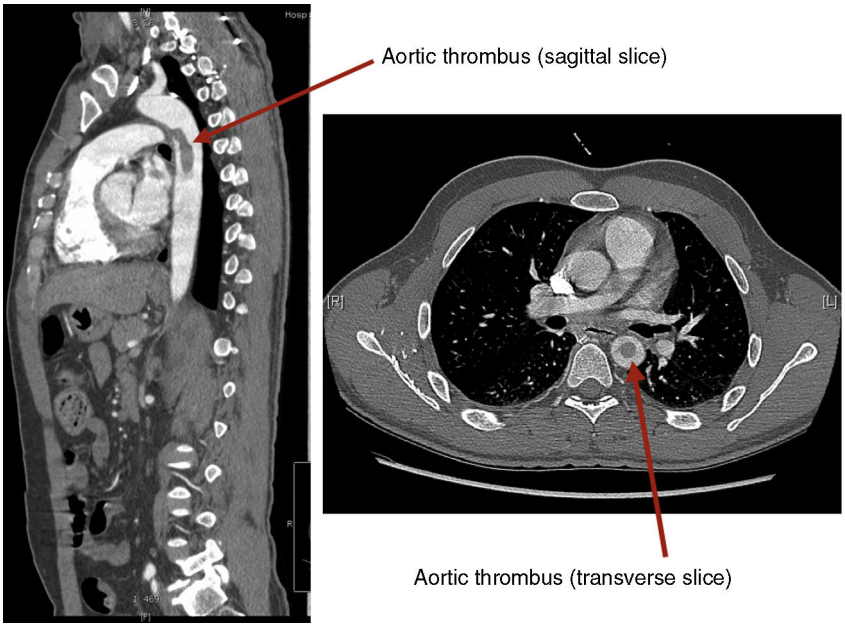

Figure. Sagittal and transverse images of aortic thrombus.