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ORIGINAL RESEARCH

Atrial Functional Mitral Regurgitation and Exercise-Induced Changes in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Atrial functional mitral regurgitation (AFMR) is prevalent among patients with heart failure with preserved ejection fraction (HFpEF) and associated with adverse outcome, yet this bidirectional association remains underexplored.

OBJECTIVES The purpose of this study was to elucidate the pathophysiological and prognostic significance of AFMR in HFpEF, both at rest and during exercise.

METHODS In this multicenter cohort study, consecutive patients with HFpEF underwent cardiopulmonary exercise testing with echocardiography, with a particular focus on mitral regurgitation (MR) severity assessment in rest and during exercise. Longitudinal follow-up included cardiovascular hospitalizations and all-cause mortality.

RESULTS The study involved 429 patients with HFpEF (age 74 ± 8 years, 65% female). AFMR was observed in 35% of patients at rest (24% mild, 11% ≥ moderate). Increasing AFMR severity correlated with atrial fibrillation, larger left atrium volumes, reduced left atrial function, lower peak oxygen consumption, and increased exercise-induced pulmonary hypertension. After adjusting for age, sex, ventricular and atrial volume and function, moderate or severe MR remained linked with worse outcomes (HR: 4.03; 95% CI: 2.26-7.21; $P < 0.001$). During exercise, MR severity increased in 12% of patients based on guideline-based thresholds. Notably, even in patients without formal reclassification, an absolute increase in effective regurgitant orifice area ≥5 mm^2 during exercise was independently predictive of adverse outcomes (HR: 2.43; 95% CI 1.34-4.41; $P = 0.004$). This increase was not related to systemic blood pressure, chronotropic incompetence, or left ventricular dysfunction.

CONCLUSIONS AFMR is common in HFpEF and independently associated with adverse outcomes when moderate or severe at rest. Even mild, exercise-induced increases carry additional prognostic value, underscoring the relevance of both resting and dynamic AFMR assessment. (JACC Cardiovasc Imaging. 2025;18:1285-1296) © 2025 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFMR = atrial functional mitral regurgitation

CO = cardiac output

CPETecho = cardiopulmonary exercise testing with echocardiography

EROA = effective regurgitant orifice area

GLS = global longitudinal strain

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

ICC = intraclass correlation coefficient

LA res = left atrial strain reservoir

LAVI = left atrial volume index

LVEF = left ventricular ejection fraction

mPAP = mean pulmonary arterial pressure

MR = mitral regurgitation

PISA = proximal isovelocity surface area

RV = right ventricular

TR = tricuspid regurgitation

Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all heart failure (HF) cases and represents one of the most prevalent causes of exercise-induced dyspnea. Functional mitral regurgitation (MR) is frequently observed in patients with HFpEF and is associated with increased symptom burden, higher hospitalization risk, and increased mortality.[1-4] In heart failure with reduced ejection fraction (HFrEF), functional MR arises from left ventricular (LV) dilation and adverse remodeling, which induce papillary muscle displacement, mitral leaflet tethering, and impaired leaflet coaptation. This condition is mainly considered an LV disorder, with therapies aimed at LV remodeling also improving MR severity.[5] In contrast, functional MR in HFpEF primarily arises from adverse left atrial (LA) and annular remodeling, a mechanism referred to as atrial functional mitral regurgitation (AFMR).[6,7]

It remains uncertain whether AFMR is merely a bystander phenomenon and a marker of disease severity or if it constitutes a key pathophysiological contributor to HFpEF and clinical outcome. This perspective is reinforced by the dynamic nature of AFMR, which often improves with decongestive therapies, rhythm restoration, or antihypertensive therapy and rarely progresses to severe AFMR.[8] However, exercise-induced worsening of functional MR in patients with HFrEF correlates with adverse outcomes, highlighting the potential benefits of a valve-centered approach in these patients.[3,9,10] Notably, in many patients with HFpEF, there is a discordance between symptom burden and resting echocardiographic findings, highlighting the potential role of worsening AFMR as a contributing factor to disease progression. To better comprehend the pathophysiological implications of AFMR in patients with HFpEF and its exercise-induced dynamics, we performed a comprehensive echocardiographic evaluation at rest and during exercise in consecutive patients with HFpEF, both with and without AFMR.

METHODS

STUDY POPULATION. This multicenter observational cohort study examined consecutive patients with HFpEF at Ziekenhuis Oost-Limburg (Genk, Belgium) and Jessa Hospital (Hasselt, Belgium) who underwent cardiopulmonary exercise testing with simultaneous echocardiography (CPETecho) between January 2016 and September 2023 due to ongoing symptoms of exertional dyspnea. HFpEF was determined based on an H_2FPEF (presence of atrial fibrillation [AF], 3 points; obesity, defined as body mass index >30 kg/m^2, 2 points; all other criteria [age >60 years, treatment with ≥2 antihypertensive drugs, E/e′ ratio >9, and pulmonary artery systolic pressure >35 mm Hg], 1 point each) score of at least 6 and/or the presence of elevated filling pressures, defined as E/e′ >15, observed during CPETecho. Patients were not considered for the study if they had a left ventricular ejection fraction (LVEF) of <50%, primary mitral valve disease, infiltrative/restrictive/hypertrophic cardiomyopathy, constrictive pericarditis, congenital heart disease, unstable coronary artery disease, LV regional wall abnormalities, more than mild aortic valve stenosis/insufficiency, mitral stenosis, or severe tricuspid valve regurgitation. The study obtained approval from the local ethics committees, and due to its retrospective design, the requirement for written informed consent was waived.

CPETecho. All patients underwent a maximal, symptom-limited bicycle test in a semi-supine position using a tiltable ergometer with simultaneous echocardiographic data acquisition at rest, mid and peak exercise stages. Mid-exercise was defined as reaching the first ventilatory threshold or a heart rate of 90 to 100 beats/min to prevent E and A wave fusion, whereas peak exercise was identified by a respiratory exchange ratio of ∼1.05 and/or symptom onset. Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), tidal volume (V_T), respiratory rate, and minute ventilation (V_E) were measured. A predefined ramp and stress echocardiography protocol was used as previously described.[11,12] Chamber volumes and LVEF were calculated with the modified Simpson method using apical 2- and 4-chamber views and indexed for body surface area. Tissue Doppler was used for measuring myocardial velocities at the septal and lateral sites of the mitral annular and the lateral side of the tricuspid annulus to quantify longitudinal RV function. LA and LV strain were assessed using 2-dimensional speckle-tracking, both measurements were based on end diastole (electrocardiogram-gated onset of the QRS complex) as zero-strain reference point and expressed as absolute values. LA strain was evaluated during the reservoir (LA res), conduit (LA con), and booster (LA boos) phases. Stroke volume was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity-time integral. Cardiac

output (CO) was obtained by stroke volume × heart rate. Agitated colloid (1-3 mL) was routinely injected in the left antecubital vein to enhance the tricuspid regurgitation (TR) velocity signal.[13] The systolic pulmonary arterial pressure was estimated from the continuous wave Doppler velocity of the TR jet, without adding right atrium pressure. The mean pulmonary arterial pressure (mPAP) was calculated based on TR signal using the Chemla equation (mPAP = 0.61 × tricuspid regurgitant velocity + 2).[14] All measurements were averaged over 3 cardiac cycles in sinus rhythm or 5 cycles in case of AF.[15]

EVALUATION OF MITRAL VALVE REGURGITATION. MR was assessed with echocardiography at rest and during exercise, including both mid and peak phases in a semi-supine position. Initially, the severity of MR at rest was graded using a multiparametric approach, incorporating both qualitative and (semi) quantitative markers as recommended by current guidelines.[16,17] MR at rest was classified into: 1) no or trivial MR; 2) mild MR; or 3) ≥ moderate MR. Second, to quantify MR during CPETecho, a strictly quantitative approach was adopted. Changes in MR severity were classified as a decrease, stability, or increase based on variations in the effective regurgitant orifice area (EROA). Only subjects with MR measurements available at a minimum of 2 time points (rest, mid, and/or peak exercise) using the proximal isovelocity surface area (PISA) method were included in the analyses of exercise-induced changes. Differences between EROA measurements at the various time points were calculated, and the maximum difference among these measurements were identified. A significant increase or decrease in MR severity was defined as a shift in classification based on guideline-recommended thresholds for functional MR.[3,16-18]

OUTCOME ASSESSMENT. All patients were followed from the date of CPETecho, with regular follow-up evaluations conducted according to current guidelines.[16,17,19,20] Comprehensive data regarding cardiovascular hospitalizations and all-cause mortality were gathered from electronic health records. The cardiovascular hospitalizations were further categorized as arrhythmic, vascular, or HF related. A HF hospitalization was defined as an unplanned admission requiring treatment with intravenous diuretics or more advanced HF-specific therapies, including inotropic agents or vasodilators.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD if normally distributed or median (Q1-Q3) if otherwise. Categorical data are expressed as numbers and/or percentages. Normality of continuous variables was assessed using the Shapiro-Wilk test. Between-group differences were compared by (un)paired Student's *t*-test, analysis of variance, or Kruskal-Wallis test as appropriate. For categorical variables, chi-square tests were used, with Fisher's exact test applied when expected cell counts were <5. Subsequently, time-to-event Cox proportional hazards models and life tables were used to generate Kaplan-Meier curves, log-rank tests (Mantel-Cox), and HRs for the clinical endpoints. These analyses were stratified by MR severity, both in univariable and multivariable contexts. Multinomial logistic regression models were used to assess clinical and echocardiographic determinants of dynamic MR response (decrease, no change, or increase in EROA during exercise) and univariable and multivariable Cox proportional hazards models were used to investigate the prognostic association between exercise-induced MR changes and event-free survival. As a sensitivity analysis, outcome analyses were repeated after exclusion of patients with AF during CPETecho. All variables with a value of $P < 0.10$ in univariable analysis were considered for inclusion in the multivariable model. Statistical significance was a 2-tailed probability level of <0.05. Interobserver variability was assessed using intraclass correlation coefficients (ICCs) and Bland-Altman analyses for key echocardiographic parameters. All statistical analyses were performed using SPSS version 22 (IBM) and GraphPad Prism version 10 (GraphPad Software).

RESULTS

PATIENT POPULATION. The study population included 429 patients with HFpEF, with a mean age of 74 ± 8 years, 65% being female, and a high prevalence of AF (53%), arterial hypertension (76%), and type 2 diabetes (18%). Forty-one (10%) patients were in AF during the stress test. Median H_2FPEF-score was 6 (4-7) and 243 patients (57%) had E/e' >15 during exercise. The median N-terminal pro-B-type natriuretic peptide level was 320 ng/L (180-650 ng/L); however, data were missing for 137 patients (32%) due to a lack of reimbursement in Belgium.

MR ASSESSMENT. Among the cohort, 278 (65%) had no or trivial MR, 102 (24%) had mild MR, and 49 (11%) had ≥ moderate MR. MR severity during rest was classified using a multiparametric approach, incorporating both qualitative and quantitative markers as appropriate. In this context, the median vena contracta and effective regurgitant orifice were 2 mm (Q1-Q3: 1-3 mm), 6 mm^2 (Q1-Q3: 4-11 mm^2) for mild MR, and 4 mm (Q1-Q3: 3-6 mm), 19 mm^2 (Q1-Q3: 13-25 mm^2) for ≥ moderate MR, respectively. Despite lower absolute quantitative values, the overall

TABLE 1 Baseline Characteristics of the Total Population and Stratified by MR Severity

	Total (N = 429)	No MR (n = 278)	Mild MR (n = 102)	≥ Moderate MR (n = 49)	*P* Value
Age, y	74 ± 8	73 ± 8	75 ± 8	77 ± 6	**0.003**
BMI, kg/m^2	28 ± 5	29 ± 5	28 ± 5	27 ± 5	**0.029**
Female, %	278 (65)	175 (63)	73 (72)	30 (61)	0.099
Rest heart rate, beats/min	68 ± 12	69 ± 12	66 ± 12	69 ± 11	0.125
Systolic BP, mm Hg	143 ± 20	142 ± 20	144 ± 21	146 ± 20	0.372
Diastolic BP, mm Hg	78 ± 14	78 ± 13	78 ± 15	78 ± 16	0.970
Comorbidities					
Atrial fibrillation, %	227 (53)	136 (49)	57 (56)	34 (69)	**0.028**
Hypertension, %	324 (76)	206 (74)	77 (75)	41 (84)	0.267
Diabetes mellitus, %	78 (18)	50 (18)	26 (25)	12 (24)	0.445
Laboratory and spirometry					
Hemoglobin, g/dL	13 ± 2	13 ± 2	13.0 ± 2	13 ± 2	0.088
Creatinine, mg/dL	1.12 ± 0.63	1.14 ± 0.64	1.09 ± 0.33	1.29 ± 71	0.311
NT-proBNP, pg/mL	320 (180–650)	300 (140–500)	430 (210–880)	660 (398–1325)	**<0.001**
FEV_1 (L)	1.8 ± 0.6	1.9 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	0.099
FVC (L)	2.3 ± 0.8	2.4 ± 0.8	2.3 ± 0.7	2.2 ± 0.7	**0.048**
Medications, %					
Beta-blocker	310 (73)	193 (69)	78 (76)	39 (80)	0.159
ACEI/ARB/ARNI	261 (61)	168 (60)	60 (59)	33 (67)	0.614
MRA	213 (50)	128 (46)	55 (54)	30 (61)	0.082
Diuretic	139 (32)	71 (25)	36 (35)	32 (65)	**<0.001**
SGLT2 inhibitor	121 (28)	73 (26)	31 (30)	17 (35)	0.384

Values are mean ± SD, n (%), or median (Q1-Q3), unless otherwise indicated. **Bold** indicates values of $P < 0.05$, which are considered statistically significant.

ACEI = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BP = blood pressure; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter 2.

multiparametric assessment confirmed ≥ moderate MR. Table 1 summarizes the baseline characteristics according to MR. Patients with increasing severity of MR at rest were generally older, had a lower body mass index, more frequent AF, higher maintenance diuretic need, and a slightly reduced forced vital capacity measured by spirometry. Kidney function, concomitant medication use, resting heart rate, and blood pressure were comparable between the groups.

REST ECHOCARDIOGRAPHY. Although LVEF and RV function were preserved in all patients, LV global longitudinal strain (GLS) was generally reduced with no significant differences observed between those with and without AFMR (Table 2). Patients with more severe MR at rest showed larger LV volumes, with a higher frequency of increased left-sided filling and pulmonary pressures compared with HFpEF patients without MR. Across the study population, left atrial volume index (LAVI) progressively increased with MR severity, rising from 29 ± 13 mL/m^2 in patients without MR to 36 ± 13 mL/m^2 with mild MR, and reaching 46 ± 13 mL/m^2 in those with ≥ moderate MR ($P < 0.001$). Moreover, LA function (LA res in particular) also decreased with increasing resting MR severity (Figure 1). The prevalence of LA dysfunction, defined as LA res <18%, was 49% in patients with no MR, 69% in patients with mild MR, and 87% in patients with ≥ moderate MR ($P < 0.001$). LA res was correlated with LAVI ($r = 0.32$, $P < 0.002$) and history of AF ($r = 0.24$, $P < 0.001$).

CPETecho. Most patients underwent a maximal cycling test, with a mean respiratory exchange ratio during peak exercise of 1.07 ± 0.10. In general, there was significant CO augmentation, increasing from 4.6 ± 1.2 L/min at rest to 8.6 ± 2.6 L/min at peak exercise ($P < 0.001$). Pulmonary limitation was absent, as indicated by a mean maximal ventilation during exercise/maximum voluntary ventilation (VE/MVV) ratio of 61% ± 17% and a minimum recorded oxygen saturation of 96% ± 2%. The mean ventilation to carbon dioxide output (Ve/VCO_2) slope was elevated (33 ± 7), and the mean mPAP/CO slope was 4.2 ± 2.2 mm Hg/L/min. Values stratified by MR severity are listed in Table 3. Patients with increasing MR severity at rest produced less power (W), had a lower peak heart rate, reduced VO_2 peak, higher left-sided filling pressures, and an increased mPAP/CO slope during exercise while corrected for age and sex

TABLE 2 Resting Cardiac Structure and Function

	Total (N = 429)	No MR (n = 278)	Mild MR (n = 102)	≥ Moderate MR (n = 49)	*P* Value
LVEF, %	61 ± 9	62 ± 9	60 ± 9	59 ± 9	0.060
LVEDV indexed, mL/m^2	49 ± 17	48 ± 13	51 ± 16	57 ± 17	**<0.001**
LVESV indexed, mL/m^2	20 ± 8	18 ± 7	21 ± 9	24 ± 10	**<0.001**
LAVI, mL/m^2	33 ± 14	29 ± 13	36 ± 13	46 ± 13	**<0.001**
E/e'	14 (11-18)	13 (11-17)	15 (12-19)	17 (13-20)	**<0.001**
TAPSE, mm	17 ± 5	16 ± 6	17 ± 5	18 ± 5	0.146
sPAP, mm Hg	26 ± 7	24 ± 6	27 ± 6	32 ± 9	**<0.001**
LV GLS, %	15 ± 3	15 ± 3	15 ± 3	14 ± 3	0.053
LA res, %	16 ± 7	17 ± 7	15 ± 6	12 ± 5	**<0.001**
LA con, %	9 ± 4	9 ± 4	9 ± 4	8 ± 3	0.060
LA boos, %	7 ± 5	8 ± 5	7 ± 5	4 ± 4	**<0.001**
Tricuspid regurgitation					**<0.001**
Mild	174 (41)	96 (35)	51 (50)	27 (55)	
Moderate	30 (7)	13 (5)	11 (11)	6 (12)	

Values are mean ± SD, median (Q1-Q3), or n (%), unless otherwise indicated. **Bold** indicates *P* values <0.05, which are considered statistically significant.

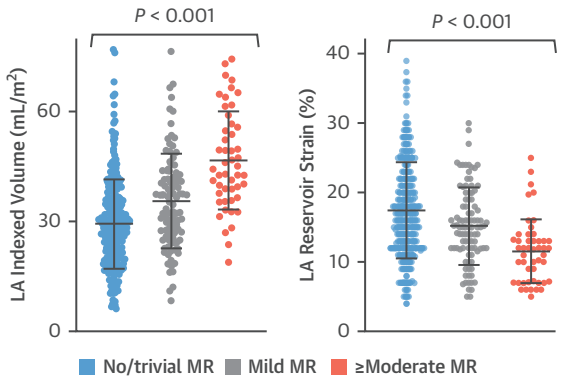
E/e' = ratio of early mitral inflow velocity to early diastolic mitral annular velocity; LA boos = left atrial booster; LA con = left atrial conduit; LA res = left atrial strain reservoir; LAVI = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LV GLS = left ventricular global longitudinal strain; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; other abbreviation as in Table 1.

(Figure 2). No differences in systolic or diastolic blood pressure were observed during exercise. The mPAP/CO slope correlated with LA res function ($r = -0.14$, $P = 0.004$), peak VO_2 ($r = -0.29$, $P < 0.001$), MR severity ($r = 0.26$, $P < 0.001$), and age ($r = 0.179$, $P < 0.001$), but not with sex ($r = -0.063$, $P = 0.191$).

REST AND EXERCISE-INDUCED MR. The feasibility of the quantitative PISA method varied by MR severity, being lower in mild MR (42% at rest, 58% mid-exercise, 55% peak exercise) and higher in moderate or severe MR (96%, 94%, and 90%, respectively). Among patients without MR at rest, 5 (1%) developed MR during exercise. EROA measurements at multiple time points were available for 113 patients (26%) of whom 18 (16%) experienced a reclassification based on guideline-recommended grading: 13 (12%) worsened and 5 (4%) improved 1 grade (Central Illustration). Regardless of reclassification, 41 (36%) showed an absolute EROA increase of ≥5 mm^2 and 18 (16%) had a decrease of >5 mm^2. In the remaining 54 patients (48%), MR remained stable (Figure 3, case examples in Supplemental Figure 1). The characteristics of patients exhibiting exercise-induced changes in MR were largely comparable to those without changes, except for differences in body mass index and a history of hypertension (Supplemental Table 1). Other clinical variables, including medication use, resting and exercise blood pressures, LV longitudinal function, pulmonary pressures, RV function, and peak heart rate, were similar across groups.

IMPACT OF MR ON CLINICAL OUTCOMES. The median follow-up duration was 28 (17-40) months, during which 105 patients (24%) were hospitalized and 27 patients (6%) died. Of the recorded hospitalizations, 13 were due to vascular causes (mainly myocardial infarctions and a 2 cerebral strokes), 56 were related to HF, and 37 were associated with arrhythmogenic events, almost exclusively AF-related. Kaplan-Meier analysis, stratified by the severity of MR at rest, is shown in Figure 4 (log-rank $P < 0.001$). The unadjusted HR for the composite primary endpoint was 2.1 (95% CI: 1.3-3.3; $P = 0.002$) for mild MR and 4.5 (95% CI: 2.9-7.3; $P < 0.001$) for ≥ moderate MR. When considering HF hospitalization as the sole outcome measure, the HRs were 1.90 (95% CI: 0.9-3.6; $P = 0.053$) for mild MR and 2.2 (95% CI: 1.3-4.2; $P = 0.021$) for ≥ moderate MR. When covariates such as age, sex, LVEF, tricuspid annular plane systolic excursion, pulmonary pressure, LAVI, LV GLS, and LA res were included (Table 4), only ≥ moderate MR remained independently associated with worse outcomes, whereas the association with mild MR was no longer significant. This finding persisted after further adjustment in the subgroup of patients with available N-terminal pro-B-type

FIGURE 1 Correlation of LA Volume and Strain With MR Severity



This figure shows that increasing MR severity in heart failure with preserved ejection fraction is linked to larger indexed LA volumes and impaired LA function, reflected by reduced reservoir strain. LA dysfunction (LA res <18%) was markedly more common in patients with ≥ moderate MR, supporting a strong association between atrial functional MR and atrial myopathy. LA = left atrial; LA res = left atrial strain (reservoir phase); MR = mitral regurgitation.

natriuretic peptide levels (HR: 2.57; 95% CI: 1.08-6.21; $P = 0.04$).

Moreover, exercise-induced increase in MR EROA ≥5 mm² was also associated with worse outcomes (HR: 2.43; 95% CI: 1.34-4.41; $P = 0.004$), independent of baseline severity, whereas an exercise-induced improvement in MR (EROA >5 mm²) had a neutral effect (HR: 0.89; 95% CI: 0.37-2.1; $P = 0.892$). In addition, MR progression—defined per guideline-based severity criteria—was also linked to poorer outcomes (HR: 2.61; 95% CI: 1.30-5.21; $P = 0.007$), although this analysis was limited by a small sample size (n = 13). A sensitivity analysis excluding patients in AF during CPETecho (n = 41) showed consistent direction and significance of the HR for both the impact of rest AFMR severity and exercise-induced changes in AFMR, as presented in Supplemental Tables 2 and 3.

INTRACLASS CORRELATION COEFFICIENT. Measurements were performed by 2 authors (S.D. and W. LH.), both fully certified in transthoracic echocardiography. In 20 patients, interobserver variability was assessed against a third observer (S.M.F.) as shown in Supplemental Figure 2. For LV outflow tract MR velocity-time integral, used to calculate stroke volume, the ICC values were 88%, 95%, and 89% for rest, low, and peak exercise, respectively. The mean difference in rest based on Bland-Altman analysis was 0.2 cm/s (95% limits of agreement: −2.7 to +3.1). The systolic pulmonary arterial pressure measurements showed an ICC of 89% with a mean bias of 1.7 mm Hg (95% limits of agreement: −4.9 to +4.0). For myocardial deformation parameters, LV GLS and LA res had ICC values of 67% and 80%, respectively. PISA radius at rest, mid, and peak exercise demonstrated ICCs of 66%, 85%, and 86%.

DISCUSSION

This study highlights the prevalence and prognostic value of AFMR in HFpEF, a frequently overlooked yet closely interrelated pathology: 1) AFMR is present in one-third of patients with HFpEF and is associated with impaired LA function, reduced exercise capacity, a steeper mPAP/CO slope during exercise, and

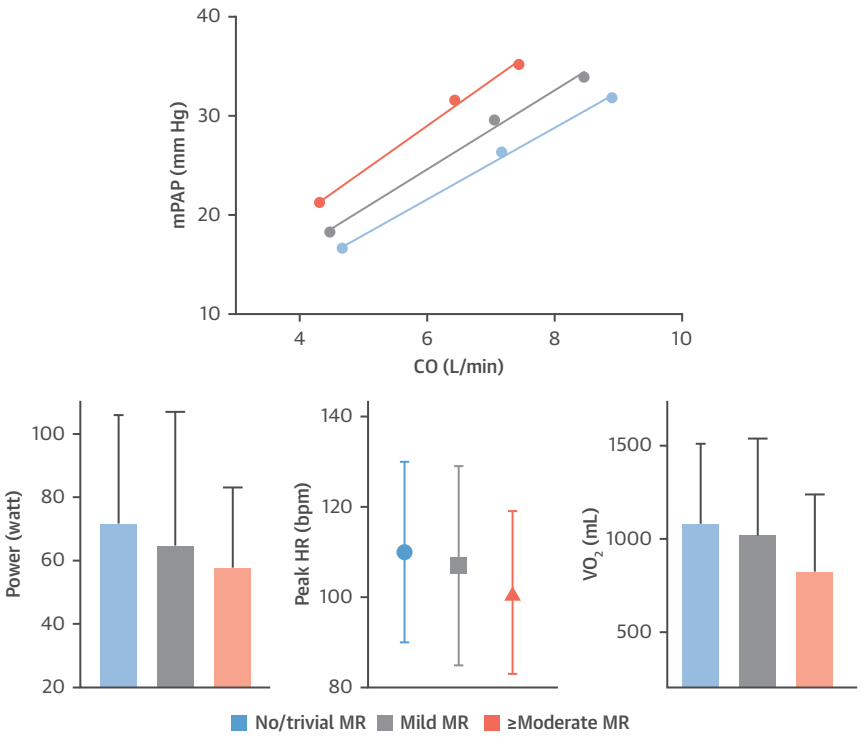
TABLE 3 Characteristics Derived From Stress Echocardiography and CPET

	Total (N = 429)	No MR (n = 278)	Mild MR (n = 102)	≥ Moderate MR (n = 49)	*P* Value
Peak heart rate, beats/min	108 ± 21	110 ± 20	107 ± 22	101 ± 18	**0.016**
Peak power, Watt	68 ± 36	72 ± 34	65 ± 42	58 ± 25	**<0.001**
VO_2 peak, mL	1044 ± 418	1088 ± 389	1026 ± 511	832 ± 406	**<0.001**
Systolic BP, mm Hg	177 ± 27	179 ± 28	178 ± 24	166 ± 26	0.061
Diastolic BP, mm Hg	81 ± 15	82 ± 14	81 ± 15	76 ± 19	0.311
TAPSE peak, mm	22 ± 6	22 ± 6	22 ± 6	22 ± 5	0.877
E/e' mid	15 (12-19)	14 (11-17)	15 (13-20)	17 (14-22)	**<0.001**
Cardiac index peak	4.6 ± 1.3	4.7 ± 1.3	4.6 ± 1.4	4.3 ± 1.1	0.073
sPAP peak, mm Hg	51 ± 10	49 ± 9	52 ± 10	54 ± 12	**<0.001**
mPAP/CO	4.2 ± 2.2	3.9 ± 1.9	4.5 ± 2.2	5.2 ± 3.5	**<0.001**
Ve/VCO_2 slope	33 ± 7	33 ± 6	33 ± 6	34 ± 7	0.351

Values are mean ± SD or median (Q1-Q3), unless otherwise indicated. **Bold** indicates *P* values <0.05, which are considered statistically significant.

CO = cardiac output; CPET = cardiopulmonary exercise testing; mPAP = mean pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; Ve/VCO_2 = ventilation to carbon dioxide output; VO_2 = oxygen consumption; other abbreviations as in Tables 1 and 2.

FIGURE 2 **Exercise Dynamics Stratified by MR Severity**



This figure highlights that patients with ≥ moderate MR show lower peak VO_2, higher mPAP, steeper pulmonary pressure slopes, reduced peak cardiac output, and elevated filling pressures during exercise—indicating a greater hemodynamic burden and reduced exercise tolerance associated with AFMR. bpm = beats per minute; CO = cardiac output; HR = heart rate; mPAP = mean pulmonary artery pressure; VO_2 = oxygen consumption; other abbreviation as in Figure 1.

poorer clinical outcomes; 2) moderate or severe MR remained an independent risk factor for adverse events, whereas mild MR likely reflects underlying LA disease; and 3) exercise-induced MR changes, although infrequent, provided additional prognostic insights.

AFMR accounts for ~25% of all moderate or severe MR cases, driven by LA and mitral annular dilation with preserved LV size and function.[4] It is mainly observed in the setting of HFpEF and AF, 2 interrelated conditions sharing risk factors and an LA-centered pathophysiology. Consistent with prior studies, we found AFMR in one-third of patients with HFpEF.[1,2,21,22] Increasing AFMR severity was associated with progressive LA enlargement and declining LA function, while LV performance remained stable, highlighting the key mechanistic role of atrial remodeling. Nearly half of our cohort also has a history of AF, with prevalence increasing as MR severity worsens, peaking at 69% in moderate or more AFMR. These patterns reemphasize the close interrelationship among AF, MR, and HFpEF.

Even mild AFMR doubled the risk of cardiovascular hospitalization and all-cause mortality, consistent with findings by Tamargo et al,[2] who observed similar outcomes despite excluding moderate or severe MR.[2] Harada et al[23] confirmed these results using invasive exercise echocardiography, excluding patients with severe MR and including only 2 cases of moderate MR.[23] Across all 3 studies, worsening resting MR paralleled progression of LA myopathy. Notably, the association between mild MR and outcomes weakened after adjusting for LA myopathy, again consistent with Tamargo et al,[2] suggesting that mild AFMR primarily reflects LA disease severity rather than directly driving pathophysiology. However, even small regurgitant volumes can have a significant prognostic impact in a noncompliant LA and LV with

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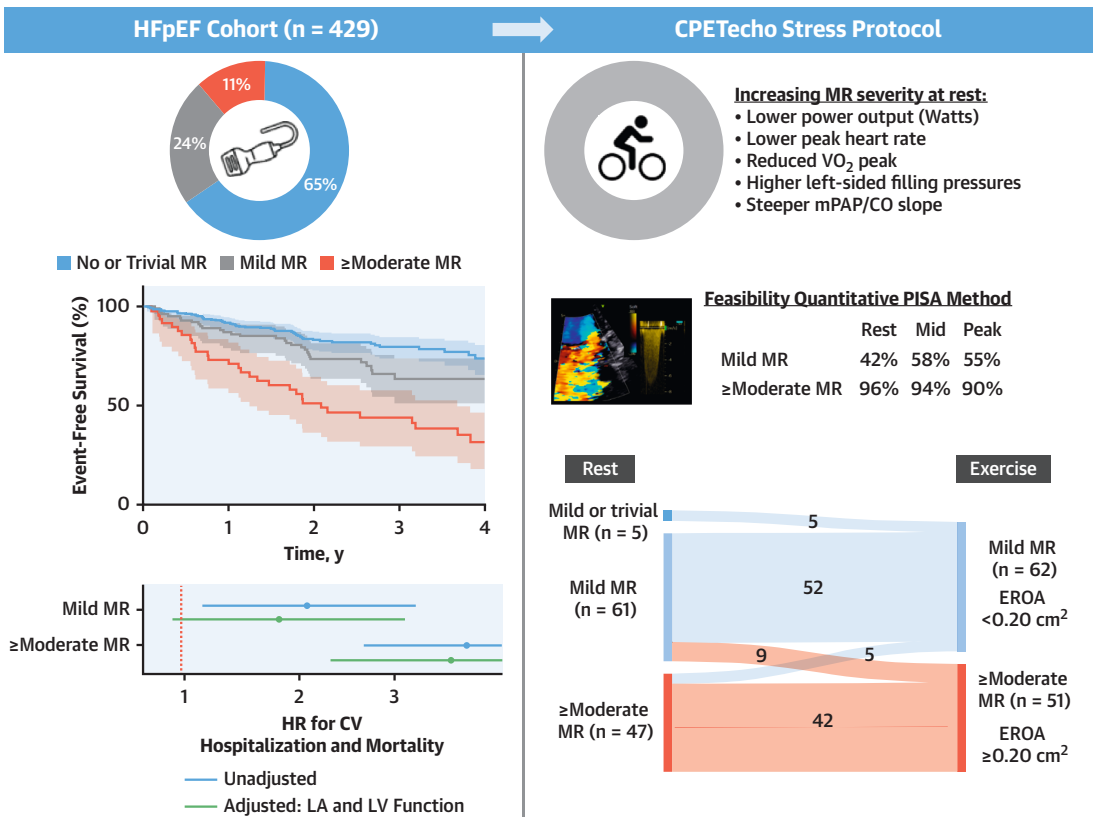
CENTRAL ILLUSTRATION **Impact of Atrial Functional Mitral Regurgitation and Exercise-Induced Changes in Patients With HFpEF**



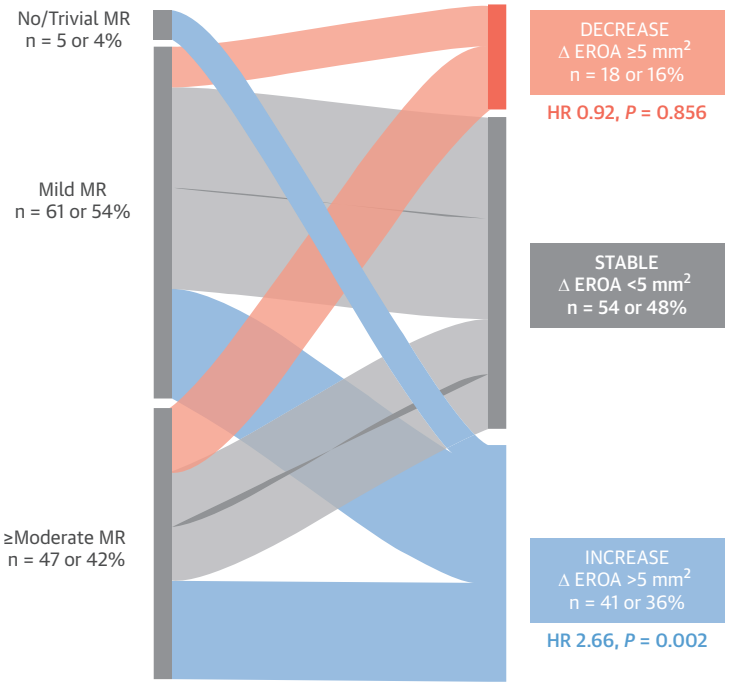
Dhont S, et al. JACC Cardiovasc Imaging. 2025;18(12):1285-1296.

(Left) A total of 35% of patients had AFMR (24% mild, 11% ≥ moderate). Kaplan-Meier curves reveal worse event-free survival with moderate or severe MR. HRs for adverse outcomes are displayed, both unadjusted and adjusted for LA/LV function. (Right) The CPETecho protocol is outlined, linking higher resting MR severity with reduced exercise capacity, elevated filling pressures, and a steeper mPAP/CO slope. Quantitative MR assessment during exercise was most feasible in ≥ moderate MR. The lower portion of the right panel visualizes the dynamic changes in MR during exercise demonstrating limited variability based on guideline-based thresholds for EROA. AFMR = atrial functional mitral regurgitation; CO = cardiac output; CPETecho = cardiopulmonary exercise testing with echocardiography; EROA = effective regurgitant orifice area; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; LV = left ventricle; mPAP = mPAP, mean pulmonary arterial pressure; MR = mitral regurgitation.

restrictive physiology.[6,24,25] In contrast, moderate or greater MR tripled the risk of the composite endpoint, independent of LA function and other covariates, supporting a valve-centered clinical approach in this subgroup. Notably, these associations remained consistent after exclusion of patients with AF during CPETecho. Targeting AFMR through rhythm control, pharmacotherapy, or valve interventions could offer new therapeutic avenues in this HFpEF phenotype, although randomized trials are needed to confirm efficacy and causality.[26-33]

In patients with HFrEF, cycling can exacerbate the imbalance between valve tethering and closure forces, leading to a ≥1-grade increase in functional MR severity in up to 35%, closely correlating with worse outcomes.[3,9,18,34] An EROA increase of ≥13 mm² has been identified as a key warning sign.[3,18] In contrast, AFMR in HFpEF shows limited dynamic variability during isotonic exercise. In our study, EROA quantification was feasible in ~50% of mild and ~90% of moderate or severe AFMR cases, with good reliability. Only 12% demonstrated an

FIGURE 3 Graphical Representation of MR Dynamics During Exercise

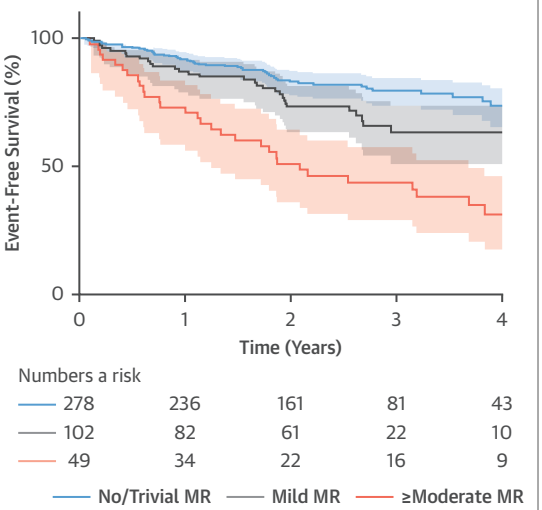


This figure shows that 36% of patients had an exercise-induced EROA increase ≥5 mm², which was independently linked to worse outcomes. Even mild dynamic worsening of atrial functional MR adds prognostic value, underscoring the importance of MR assessment during exercise. EROA = effective regurgitant orifice area; other abbreviation as in Figure 1.

increase in MR grade, whereas 4% showed a decrease based on EROA measures. These findings align with earlier, smaller studies that lacked quantitative MR classification or exercise capacity indices.[23,35,36] Harada et al[23] reported even less MR variability, although their cohort included only 2 patients with moderate MR at rest, no severe cases, and testing was performed in a supine position. Despite limited numbers, an increase in MR during exercise remains strongly associated with adverse outcomes and a decrease appears reassuring. Specifically, an absolute EROA increase of >5 mm² may signal higher risk, consistent with thresholds observed in randomized trials of functional MR.[10,34,37,38]

The mechanism of atrial FMR centers on LA remodeling, as also demonstrated by our data. However, the factors driving dynamic changes in AFMR severity remain incompletely understood. Our findings argue against major contributions from systemic blood pressure or chronotropic incompetence. Although a recent study suggested that impaired longitudinal LV function during exercise may contribute to worsening MR, this was not confirmed in our cohort.[39] Potential roles for microvascular

FIGURE 4 Kaplan-Meier Curves for Cardiovascular Hospitalization and Mortality Stratified by MR Severity



Kaplan-Meier curves show that patients with ≥ moderate MR had significantly higher risk of cardiovascular hospitalization and mortality ($P < 0.001$). These findings confirm the prognostic value of atrial functional MR and support its role in clinical risk stratification. Abbreviation as in Figure 1.

TABLE 4 Variables Associated With the Composite Endpoint (CV Hospitalizations and All-Cause Mortality)

	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
Age, y	1.02 (1.00-1.05)	0.073[a]	1.00 (0.98-1.03)	0.872
Male	0.98 (0.66-1.47)	0.932		
Mild MR	2.10 (1.32-3.45)	**0.002**[a]	1.97 (0.99-3.22)	0.055
≥ Moderate MR	4.58 (2.88-7.68)	**<0.001**[a]	4.03 (2.26-7.21)	**<0.001**
LVEF	0.98 (0.96-1.01)	0.169		
LAVI	1.03 (1.01-1.04)	**<0.001**[a,b]		
TAPSE	1.00 (0.97-1.04)	0.812		
Rest sPAP	1.04 (1.02-1.07)	**<0.001**[a]	1.01 (0.98-1.04)	0.525
LV GLS	0.94 (0.87-1.01)	0.159		
LA res	0.95 (0.92-0.98)	**0.003**[a,b]	0.99 (0.95-1.03)	0.992

Bold indicates values of $P < 0.05$, which are considered statistically significant. [a]Variables included in the multivariable model (significance level <0.100). [b]Due to multicollinearity between LAVI and LA reservoir strain, only LA reservoir strain was included in the multivariable model.

Abbreviations as in Tables 1 to 3.

coronary disease and alterations in mitral annular dynamics remain plausible, underscoring the need for further mechanistic studies using advanced multimodality imaging.

STUDY LIMITATIONS. Quantifying MR, particularly during exercise, remains challenging. The PISA method often underestimates MR severity in AFMR due to the elliptical shape of the regurgitant orifice. Furthermore, a significant proportion of patients present with AF and varying R-R intervals, making reproducible MR measurements difficult even under optimal conditions. However, the presence of a central regurgitant jet in AFMR enhances the feasibility of PISA and facilitates quantitative assessment, providing easily exchangeable data and offering a unique contribution of this study. Particularly during exercise, we emphasize the relative progression compared with the resting state rather than focusing solely on absolute values. Future advances in 4-dimensional echocardiography and multimodality imaging may enhance these methods but remain complex during exercise. Moreover, only patients with persistent symptoms of dyspnea for whom the underlying cause was not readily apparent were referred for CPETecho, which may have introduced a selection bias, potentially leading to an underrepresentation of patients with severe AFMR. Diagnosing HFpEF in patients with exertional dyspnea but no signs of congestion requires right heart catheterization, often with exercise testing if resting pressures are normal. Alternatively, the H_2FPEF score (≥6) indicates >90% probability of HFpEF, although its sensitivity may be limited in early disease stages despite high specificity. Use of sodium-glucose cotransporter 2 inhibitors was low (28%) despite a Class I recommendation, reflecting delayed reimbursement in Belgium, which only began in 2023 near the study's end.

CONCLUSIONS

AFMR is prevalent in patients with HFpEF and is independently associated with adverse outcomes when moderate or severe at rest. Assessment of exercise-induced changes is both feasible and reproducible. Even mild increases in AFMR during exercise—without meeting formal criteria for severity reclassification—carry additional prognostic value beyond resting assessment. These findings underscore the clinical importance of evaluating both static and dynamic components of AFMR in patients with HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: AFMR is prevalent in heart failure with HFpEF and is associated with impaired LA function, reduced exercise capacity, and worse clinical outcomes.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Moderate or severe AFMR at rest remains an independent predictor of worse survival, even after adjusting for LA and LV function, highlighting its role beyond a mere marker of disease severity.

TRANSLATIONAL OUTLOOK: Although guideline-based classification suggests that exercise-induced MR progression is uncommon, even a slight increase is associated with worse clinical outcomes, emphasizing the need for dynamic MR assessment.

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KEY WORDS **atrial functional mitral regurgitation, CPETecho, dynamic valve disease, heart failure with preserved ejection fraction, stress echocardiography**

APPENDIX **For supplemental figures and tables, please see the online version of this paper.**