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ABSTRACT

Background/objective The role of factors that increase left atrial pressure or cause acute left atrial dilatation is frequently emphasised in the pathogenesis of atrial fibrillation (AF) in patients with acute myocardial infarction (AMI). This study was designed to test the hypothesis that functional mitral regurgitation (FMR) occurring after AMI may promote AF by producing left atrial volume overload.

Setting Intensive care unit of a tertiary care hospital.

Patients and Methods 1920 patients admitted with AMI were studied. Patients with known AF were excluded. FMR was classified using echocardiography into three groups: none; mild FMR and moderate or severe FMR. The relationship between FMR and AF occurring at any time during the hospital course was examined using multivariable logistic regression.

Results Mild FMR was present in 744 patients (38.8%) and moderate or severe FMR was present in 150 patients (7.8%). AF developed in 51 (5.0%), 83 (11.2%) and 28 (18.7%) patients with no FMR, mild FMR and moderate or severe FMR, respectively (p trend <0.001). In multivariable logistic regression, both mild (odds ratio (OR) 1.6; 95% CI 1.1 to 2.3, $p=0.02$) and moderate or severe FMR (OR 2.1; 95% CI 1.2 to 3.6, $p=0.007$) were independent predictors of AF. There was a significant interaction between the left ventricular ejection fraction and FMR ($p=0.003$) such that mild FMR was predictive of AF only in patients with a reduced (<45%) ejection fraction.

Conclusions There is a graded independent association between the severity of FMR and the new onset of AF in patients with AMI.

Atrial fibrillation (AF) is a common complication of acute myocardial infarction (AMI), with a reported incidence ranging between 6% and 19%.[1–5] Several studies have identified increased inhospital and long-term mortality associated with AF.[4–6]

Although the development of AF is a multifactorial event, the role of factors that increase left atrial pressure leading to acute left atrial dilatation is frequently emphasised in the pathogenesis of new-onset AF in patients with AMI.[2 4]

Functional mitral regurgitation (FMR) is a frequent complication of AMI[7–10] that can produce left atrial volume overload and initiate left atrial remodelling. Therefore, concomitant FMR may be particularly relevant to the development of new-onset AF in patients with AMI. However, there is no information concerning the role of FMR in the development of new-onset AF in the setting of AMI.

We hypothesised that FMR would be associated with an increased risk of new-onset AF in the setting of AMI. To test this hypothesis we performed a post-hoc analysis of an ongoing prospective study on the clinical outcomes of FMR.[7] We studied whether the presence and severity of FMR in the early phase of acute infarction contribute to the development of new-onset AF.

METHODS

Patients

The design of the study has been described in detail previously.[7] The study cohort consisted of patients enrolled in a prospective observational study designed to determine the predictors of post-infarction heart failure. All patients presenting to the intensive coronary care unit with AMI were eligible for entry into the study if they had a diagnosis of AMI according to the American College of Cardiology criteria.[11]

Exclusion criteria included: organic mitral regurgitation, defined as an intrinsic valve disease including severe calcific mitral valve disease, mitral valve prolapse or flail leaflet, healed endocarditis, or chronic rheumatic disease; patients who underwent mitral valve surgery during the index hospitalisation and patients with previously known AF or atrial flutter. The management of patients with FMR was at the discretion of the attending cardiologist, and generally followed the guidelines of the European Society of Cardiology.[12] The investigational review committee on human research approved the study protocol.

Echocardiographic examination

Echocardiography was performed during the hospital stay after a median of 2 days from admission (interquartile range (IQR) 1–3 days). FMR was graded by colour Doppler flow mapping, integrating jet expansion within the left atrium (jet area/atrial area) and jet eccentricity,[13] as previously described.[7] Mitral regurgitation was considered mild when the regurgitant jet area occupied less than 20% of the left atrial area in the absence of a wall jet, moderate in patients with a jet area between 20% and 40%, and severe in patients in whom the jet area was greater than 40% of the left atrial area. FMR was classified into three categories:

no mitral regurgitation (a category that included trace mitral regurgitation (<1 cm^2)); mild FMR and moderate or severe FMR.

Left ventricular ejection fraction (LVEF) was classified according to the criteria of the American Society of Echocardiography as normal (≥55%), mildly reduced (45–54%), moderately reduced (30–44%) and severely reduced (<30%). Left atrial dimensions were obtained using M-mode echocardiography, guided by two-dimensional imaging.

The echocardiograms were blindly reinterpreted by two investigators to assess the reproducibility of mitral regurgitation grading in randomly selected patients (n=50). In blind echocardiographic reinterpretation, the agreement in mitral regurgitation grading between echo readers was high (Cohen's κ 0.83, 95% CI 0.70 to 0.95).

Definition of new-onset AF

AF was defined as the absence of P waves, coarse or fine fibrillatory waves and irregular RR intervals. New-onset AF was defined as AF detected on an ECG at admission or later during the hospital stay in a patient without a history of persistent or paroxysmal AF or atrial flutter. The minimal time of a counted episode of AF was more than 30 s.[14]

Study endpoints

The primary outcome of interest was the development of new-onset AF during the index hospitalisation. We also assessed the impact of AF occurring during the hospital course and subsequent clinical outcomes including all-cause mortality and the development of heart failure (defined as new-onset heart failure requiring readmission to hospital). Following hospital discharge, clinical endpoint information was acquired by reviewing the national death registry and by contacting each patient individually.

Statistical analysis

Continuous variables are presented as either means (±SD) or medians (with IQR) and categorical variables as numbers and percentages. Baseline characteristics of the groups were compared using the unpaired t test for continuous variables and by the χ^2 statistic for categorical variables.

Univariable and multivariable logistic regression analyses were performed to determine the relationship between candidate variables and new-onset AF during hospital course. The following risk factors were considered in the multivariable procedure: age, gender, history of previous infarction, history of diabetes, history of hypertension, estimated glomerular filtration rate (GFR), Killip class on admission, ST-elevation infarction, anterior location of infarction, coronary revascularisation, LVEF, left atrial size and severity of FMR. LVEF was categorised as preserved (≥45%) or reduced (<45%) and left atrial size as normal size (≤4.0 cm) or enlarged (>4.0 cm). Variables demonstrating an association with AF on univariate analysis at the p<0.1 level were used in a stepwise multiple logistic regression with backwards elimination variable selection.

Because the development of AF in the setting of AMI may be a surrogate of inhospital complications,[2] the analysis of heart failure and mortality included only events occurring after hospital discharge. Consequently, patients who died during hospitalisation were removed from the outcomes analysis.

Kaplan–Meier plots were used to illustrate the crude cumulative incidence of heart failure and mortality according to AF status. The associations between AF and mortality or heart failure were examined through the use of a proportional hazard multivariable regression analysis (Cox regression analysis) while adjusting for appropriate baseline characteristics. The proportional hazard assumption was evaluated and satisfied for these multivariable survival analyses by examining plots of Schoenfeld residuals.

Differences were considered statistically significant at the two-sided p<0.05 level. Statistical analyses were performed using SPSS statistical software version 15.0 (SPSS Inc, Chicago, Illinois, USA) and STATA version 10 (StataCorp, Texas, USA).

RESULTS

Between July 2001 and June 2008, 1920 patients who presented with AMI were enrolled. During the hospital course 162 patients (8.4%) developed AF. In the majority of patients (97%), the AF episode lasted more than 1 h (usually several hours to days). The AF episodes were associated with palpitations, haemodynamic instability, heart failure or angina in 92 patients (57%).

The clinical characteristics of patients according to the presence or absence of AF during the hospital course are listed in table 1. Patients who developed AF during the hospital course were older, more likely to be women and had a higher prevalence of hypertension and lower GFR; they presented with higher Killip class and were less likely to receive coronary revascularisation. Patients with AF had a lower LVEF, larger left atrial dimension and higher frequency of mild FMR and moderate or severe FMR. The median hospitalisation time was significantly longer in patients with new-onset AF compared with patients without AF (8 days (IQR 6–12) vs 6 days (IQR 4–9); Mann–Whitney p<0.001).

Table 1 Baseline clinical characteristics according to the presence or absence of AF during the hospital course

Characteristics	No AF (n=1758)	AF (n=162)	p Value
Age (years)	60±12	69 ± 12	<0.001
Female gender	365 (21)	50 (31)	0.003
Previous infarction	372 (21)	43 (27)	0.11
Hypertension	873 (50)	103 (64)	0.001
Current smoking	279 (16)	37 (23)	0.02
Diabetes	497 (28)	49 (30)	0.59
Estimated GFR*	87±34	71±27	<0.001
Killip class II–IV	363 (21)	69 (43)	<0.001
Anterior infarction	761 (43)	79 (49)	0.18
ST-elevation infarction	1453 (83)	122 (75)	0.02
SBP on admission (mm Hg)	116±43	127±36	<0.001
Heart rate on admission (bpm)	77±17	83±24	<0.001
Medical therapy at admission			
Antiplatelet agents	1710 (97)	148 (91)	<0.001
β-Blockers	1572 (89)	127 (78)	<0.001
ACE inhibitors/ARB	1518 (86)	132 (82)	0.22
Thrombolytic therapy	389 (22)	33 (20)	0.59
Primary angioplasty	652 (37)	46 (28)	0.03
Coronary revascularisation	888 (51)	63 (39)	0.006
Echocardiography			
Left atrial diameter (cm)	4.0±0.6	4.2±0.5	0.001
Ejection fraction (%)	45±12	41±13	<0.001
Mild FMR	661 (38)	83 (51)	0.001
Moderate or severe FMR	122 (7)	28 (17)	<0.001
Medical therapy			
Antiplatelet agents	1710 (97)	148 (91)	<0.001
ACE inhibitors/ARB	1518 (86)	132 (82)	0.09
β-Blockers	1572 (89)	127 (78)	<0.001

Data are mean±SD or number (%). Continuous variables were compared using the unpaired t test. Categorical variables were compared by the χ^2 statistic.
*Calculated using the abbreviated modification of diet in renal disease equation.
ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; FMR, functional mitral regurgitation; GFR, glomerular filtration rate.

Table 2 Unadjusted and adjusted logistic regression model for AF during the hospital course*

	Unadjusted			Adjusted		
Variable	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age >60 years	4.0	2.7 to 5.9	<0.001	2.8	1.8 to 4.1	<0.001
Female gender	1.7	1.2 to 2.4	0.003	0.9	0.6 to 1.3	0.59
Previous infarction	1.3	0.9 to 1.9	0.11	–	–	–
Diabetes	1.1	0.8 to 1.6	0.59	–	–	–
Smoking	0.9	0.8 to 1.2	0.95	–	–	–
History of hypertension	1.8	1.3 to 2.4	0.008	1.1	0.7–1.5	0.74
eGFR <60 ml/minute	2.5	1.8 to 3.5	<0.001	1.2	0.8 to 1.8	0.37
Anterior infarction	1.2	0.9 to 1.7	0.59	–	–	–
Killip class >I	2.9	2.0 to 4.0	<0.001	1.7	1.2 to 2.4	0.006
LVEF <45%	2.3	1.6 to 3.2	<0.001	2.1	1.2 to 3.6	0.007
Left atrial diameter >4 cm	2.4	1.7 to 3.4	<0.001	1.6	1.1 to 2.3	0.008
Coronary revascularisation	1.3	0.8 to 2.3	0.33	–	–	–
FMR						
None/trivial	1.0 (Referent)	–	–	1.0 (Referent)	–	–
Mild	2.4	1.7 to 3.6	<0.001	1.6	1.1 to 2.3	0.02
Moderate or severe	4.4	2.7 to 7.2	<0.001	2.1	1.2 to 3.6	0.007

*Variables with unadjusted p≥0.1 were not entered into the multivariable analysis. The final model adjusted for age, gender, estimated glomerular filtration rate (eGFR), history of hypertension, Killip class on admission, left atrial dimension and left ventricular ejection fraction (LVEF).
AF, atrial fibrillation; FMR, functional mitral regurgitation; OR, odds ratio.

Association between FMR and new-onset AF

Mild FMR was present in 744 (38.8%) and moderate or severe FMR in 150 (7.8%) patients (moderate FMR in 136 patients and severe FMR in 14 patients). There was a graded increase in the incidence of new-onset AF with increasing severity of FMR. New-onset AF occurred in 51 (5.0%), 83 (11.2%) and 28 (18.7%) patients with no/trivial FMR, mild or mild–moderate FMR and moderate or severe FMR, respectively (p trend <0.001).

Univariable logistic regression showed a significant association between several risk factors and AF during hospital stay, including age greater than 60 years, female gender, reduced estimated GFR, history of hypertension, Killip class greater than I on admission, LVEF less than 45%, enlarged left atrium and FMR (table 2). After multivariable adjustments, only age 60 years or older, Killip class greater than 1, LVEF less than 45%, enlarged left atrium, mild FMR and moderate or severe FMR remained independent predictors of AF (table 2). Similar results were obtained when age, left atrial dimension and LVEF were used as continuous variables in the model. Compared with patients with no/trivial FMR, the adjusted OR for new-onset AF was 1.5 in patients with mild FMR (95% CI 1.1 to 2.2; p=0.03) and 1.9 in patients with moderate or severe FMR (95% CI 1.1 to 3.2; p=0.01).

There was a significant interaction between mild FMR and LVEF (p=0.003) such that mild FMR was associated with new-onset AF only in patients with reduced LVEF. Stratified analyses demonstrated that mild FMR was an independent predictor of new-onset AF in patients with reduced LVEF (adjusted OR 2.5; 95% CI 1.4 to 4.4, p=0.001), but not in patients with preserved LVEF (adjusted OR 0.9; 95% CI 0.5 to 1.6, p=0.69).

Similar results were obtained in the subgroup of patients without a previous infarction (n=1505). New-onset AF occurred in 41 (4.8%), 62 (11.3%) and 16 (16.7%) patients with no/trivial FMR, mild or mild–moderate FMR and moderate or severe FMR, respectively (p trend <0.001). In a logistic regression model, compared with patients with no/trivial FMR, the adjusted OR for new-onset AF was 1.6 in patients with mild FMR (95% CI 1.1 to 2.3; p=0.01) and 1.9 in patients with moderate or severe FMR (95% CI 1.1 to 3.5; p=0.03).

Impact of new onset of AF on heart failure

Of the 1842 patients who survived the index hospitalisation, 141 had new-onset AF during their hospital stay. The median

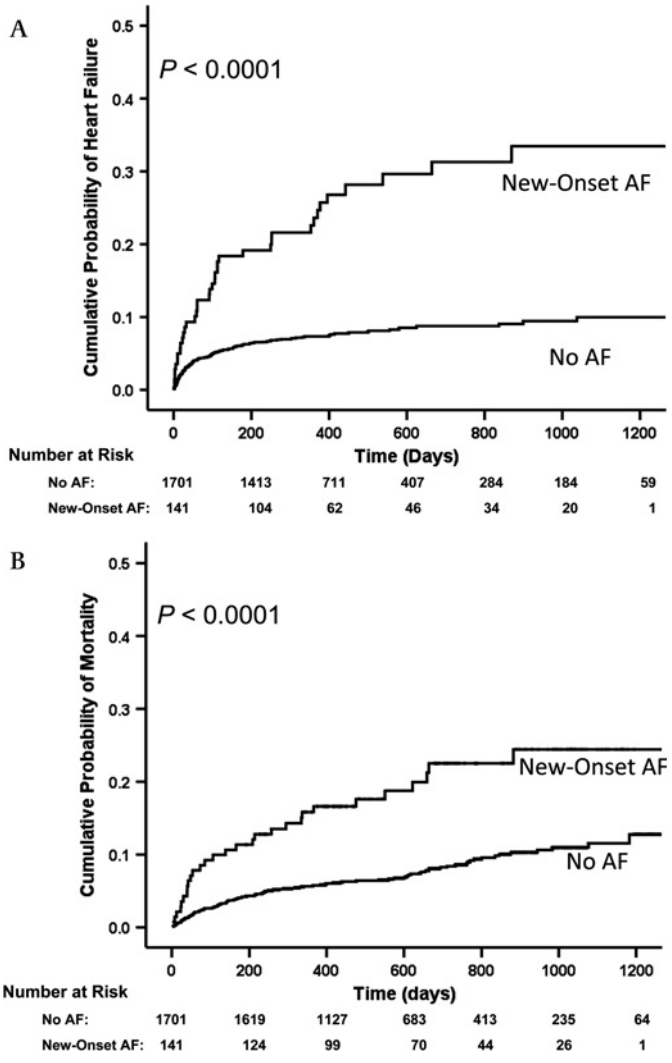

Figure 1 Kaplan–Meier plots showing the crude cumulative incidence of (A) heart failure and (B) mortality after hospital discharge. AF, atrial fibrillation.

duration of follow-up after hospital discharge was 17 months (range 8–35 months). During the follow-up period 38 patients with inhospital AF (27.0%) and 128 patients without AF (7.5%) were re-admitted for the treatment of heart failure. The Kaplan–Meier analysis demonstrated a marked increase in the risk of heart failure among patients who developed new-onset AF during their hospital course (figure 1A), with an unadjusted hazard ratio of 3.7 (table 3). Adjustments for baseline clinical characteristics, LVEF and FMR resulted in a large attenuation of the risk associated with AF, but retained statistical significance (table 3).

Impact of new onset of AF on mortality after hospital discharge

A total of 29 (20.6%) patients with new-onset AF and 130 (7.6%) without AF died after hospital discharge. Kaplan–Meier analysis (figure 1B) and unadjusted Cox modelling (table 3) showed higher mortality in patients with AF. After adjustments for baseline clinical characteristics and LVEF, the risk associated with AF was markedly attenuated but remained statistically significant (table 3). However, after further adjustment for FMR the development of AF during the hospital course was no longer an independent predictor of post-discharge mortality (table 3).

DISCUSSION

In the present study, we sought to determine whether FMR increases the risk of new-onset AF in the setting of AMI. We demonstrated a positive, graded association between the severity of FMR and the incidence of AF during hospitalisation for AMI. FMR was an independent predictor of AF after controlling for clinical parameters and markers of left atrial volume overload, such as left ventricular systolic function, left atrial size and Killip class. Even mild FMR was associated with an increase in the risk of AF in patients with reduced left ventricular systolic function.

Mechanism of AF in AMI

New-onset AF is a frequent arrhythmia complicating AMI[1–4 6 15] and is associated with an adverse prognosis.[2] The mechanisms that promote the development of AF in the AMI setting are complex and often multifactorial. Many potential mechanisms have been implicated, including pericarditis, atrial ischaemia or infarction, increased catecholamines, metabolic abnormalities, inflammation and increased atrial pressures.[2 16 17] Experimental and clinical observations suggest that increasing atrial pressure and/or causing acute atrial dilatation may play an important role. Experimental studies demonstrated that increased atrial stretch induced by increased atrial pressure shortens the atrial refractory period and greatly increases the vulnerability to AF.[18] In clinical studies, AF is often associated with signs and symptoms of heart failure.[2 4 6 19]

In the present study, all independent predictors of new-onset AF except age (table 2) were markers of increased left atrial filling pressures. In accordance with previous studies,[4 6] we noted that a worse Killip class and reduced left ventricular systolic function were independent predictors of AF, suggesting that elevated left atrial filling pressures are an important underlying mechanism in the development of AF. In addition, we observed a positive graded independent association between FMR severity and new-onset AF.

FMR is of particular interest regarding the development of new-onset AF in the setting of AMI because FMR is common[7 9 10] and because of its ability to produce acute left atrial volume overload and left atrial enlargement. The role of mitral regurgitation as a harbinger of subsequent AF has been reported in patients with rheumatic and degenerative mitral valve disease.[20 21] However, even in patients with haemodynamically significant chronic mitral regurgitation, such as those with flail mitral valve, new-onset AF occurs at a linearised rate of 5% per year.[20] In

Table 3 Cox's proportional hazards model for heart failure and mortality in patients with AF during the hospital course

	Heart failure		Mortality	
Characteristic	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Age (per 10 years)	1.3 (1.1 to 1.5)	0.003	1.3 (1.1 to 1.5)	0.002
Gender	0.8 (0.6 to 1.2)	0.37	0.9 (0.6 to 1.8)	0.89
Previous infarction	1.0 (0.6 to 1.4)	0.81	1.2 (0.8 to 1.7)	0.42
Hypertension	1.1 (0.7 to 1.6)	0.76	1.1 (0.7 to 1.8)	0.61
Diabetes	1.7 (1.3 to 2.3)	<0.001	1.4 (0.9 to 2.0)	0.10
eGRF <60 ml/minute	1.1 (0.8 to 1.6)	0.41	2.7 (1.8 to 4.0)	<0.001
Anterior infarction	1.3 (1.0 to 1.8)	0.05	1.0 (0.7 to 1.4)	0.97
Coronary revascularisation	1.0 (0.8 to 1.2)	0.66	0.8 (0.7 to 1.1)	0.15
Killip class >I	1.8 (1.3 to 2.3)	0.001	1.4 (1.0 to 2.0)	0.04
Echocardiographic parameters				
Left atrial dimension >4 cm	1.6 (1.1 to 2.3)	0.02	0.8 (0.6 to 1.3)	0.44
LVEF <45%	2.1 (1.5 to 3.0)	<0.001	2.5 (1.8 to 3.4)	<0.001
FMR				
None/trivial	1.0 (Referent)	–	1.0 (Referent)	–
Mild mitral regurgitation and Moderate mitral regurgitation	2.2 (1.5 to 3.3)	<0.001	1.6 (1.1 to 2.3)	0.02
Moderate or severe mitral regurgitation	3.1 (1.8 to 5.4)	<0.001	2.2 (1.3 to 3.9)	0.006
AF				
Unadjusted	3.7 (2.6 to 5.3)	<0.001	2.7 (1.8 to 4.0)	<0.001
Adjusted for clinical variables*	2.2 (1.5 to 3.2)	<0.001	1.6 (1.1 to 2.5)	0.02
Adjusted for clinical variables, left atrial size and LVEF	2.0 (1.3 to 2.9)	0.001	1.3 (1.0 to 1.9)	0.02
Adjusted for clinical variables, left atrial size and LVEF and FMR	1.7 (1.2 to 2.5)	0.005	1.4 (0.9 to 2.1)	0.12

*Clinical variables included age, gender, previous infarction, hypertension, diabetes, estimated glomerular filtration rate (eGFR), anterior infarction, coronary revascularisation and Killip class at admission.
AF, atrial fibrillation; FMR, functional mitral regurgitation; HR, hazard ratio; LVEF, left ventricular ejection fraction.

contrast, patients with FMR and AMI had higher AF rates developing within a few days.

In patients with AMI and FMR, the non-compliant left atrium results in an increase of left atrial pressure, particularly if a concomitant acute decrease in left ventricular systolic function is also present. Increasing evidence suggests that atrial stretch induced by increased atrial pressure may precipitate AF through an effect on atrial refractoriness.[18 22] Acute atrial stretch may be relevant to AF episodes occurring during acute changes in haemodynamic conditions such as AMI and acute pulmonary embolism.[23] Experimentally, in animal models, AF has been shown to be easily inducible when intra-atrial pressure is raised acutely, presumably via the stretch-activated ion channels that are present in cardiac tissue and are activated by increased intra-atrial pressure.[18 24–26] At the whole heart level, blockade of stretch-activated channels diminishes AF inducibility.[25 26]

The role of left atrial enlargement as a risk factor for subsequent AF has been reported in patients with and without valve disease.[20] In patients with degenerative mitral regurgitation in sinus rhythm at diagnosis, left atrial enlargement precedes and predisposes to the development of AF.[20 27] In the present study, left atrial enlargement was an independent predictor of AF, although differences in left atrial size between patients with and without AF were small. The larger left atrial size in the AF group may represent a pre-existing predisposing factor and may also be partly due to an acute left atrial dilation in patients with reduced left ventricular systolic function or FMR. However, FMR remained an independent predictor of AF after adjustments for left atrial size.

AF and clinical outcomes

The prognostic significance of AF in patients with AMI is controversial. Although most studies have found that AF is an independent predictor of inpatient and longer-term mortality,[4 5 28] other studies did not reach this conclusion.[29 30] In addition, some studies were unable to determine whether the AF was new-onset or pre-existing.[1] Major differences between different studies make it difficult to compare the results directly. Heart failure and other factors known to affect prognosis adversely after AMI were frequently found in patients with AF.[2 4 5 28] However, most studies were unable to establish a temporal relationship between the time of AF and the occurrence of inhospital complications and adjusted only for patient history and arrival findings.[1 4]

Previous studies frequently did not adjust for the degree of left ventricular dysfunction[1 4 6] and none considered the impact of FMR. FMR is a frequent complication of AMI and has been recognised as an important risk factor for mortality, adverse cardiac remodelling and the development of post-infarction heart failure and increased mortality.[7 9 10] Furthermore, FMR that produces left atrial volume overload can acutely increase left atrial pressure and promote left atrial remodelling. In the present study, AF was not an independent predictor of mortality after adjustments for two important determinants of left atrial filling pressures: left ventricular systolic function and the degree of FMR. In addition, adjustments for these variables markedly attenuated the association between AF and heart failure after hospital discharge. Concomitant FMR may thus contribute to the adverse outcome associated with AF in the setting of AMI.

Study limitations

Our study has several limitations. FMR is a dynamic lesion, and its severity may vary over short periods of time due to ongoing ventricular remodelling. The use of colour Doppler for determining the severity of mitral regurgitation may not be accurate due to a variety of technical and haemodynamic limitations.[13] It is thus possible that misclassification of mitral regurgitation severity occurred in some patients. However, we were able to demonstrate a graded association between FMR severity and new-onset AF.

CONCLUSION

The present study demonstrates a graded independent association between the presence and severity of FMR and the development of new-onset AF in patients with AMI. Concomitant FMR contributes to the adverse clinical outcome associated with AF in the setting of AMI.

Competing interests None.

Ethics approval This study was conducted with the approval of the Rambam Medical Center.

Contributors All authors have participated in either the conception or design or the study or in the analysis and interpretation of its results.

Provenance and peer review Not commissioned; externally peer reviewed.

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