

## Effect of Mitral Regurgitation on Cerebrovascular Accidents in Patients with Atrial Fibrillation and Left Atrial Thrombus

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### ABSTRACT

**Background:** The effect of mitral regurgitation (MR) on the incidence of new cerebrovascular accidents (CVA) and mortality in patients with atrial fibrillation (AF) and left atrial thrombus (LAT) is unknown.

**Objective:** To investigate the effect of MR in patients with AF and LAT on new CVA and mortality.

**Methods:** Eighty nine consecutive patients, mean age 71 years, with AF and LAT documented by transesophageal echocardiography were investigated to determine the prevalence and severity of MR and the association of the severity of MR with new cerebrovascular accidents (CVA) and mortality at 34-mo follow-up.

**Results:** Of 89 patients, 1+ MR was present in 23 patients (26%), 2+ MR in 44 patients (50%), 3+ MR in 17 patients (19%), and 4+ MR in 3 patients (4%). Mean follow-up was 34±28 mo. The Cox proportional hazards model showed that the severity of increased MR did not significantly increase new CVA or mortality at 34-mo follow-up. The only variable predictive of mortality was left ventricular ejection fraction (LVEF), and with every unit increase in LVEF, the risk decreased by 3%.

**Conclusion:** MR occurred in 87 of 89 patients (98%) with AF and LAT. There was no association between the severity of MR and the incidence of CVA or mortality.

Key words: atrial fibrillation, mitral regurgitation, cerebrovascular accidents, transesophageal echocardiography, left atrial thrombus

### Introduction

Atrial fibrillation (AF) is a common and vexing arrhythmia.<sup>1</sup> It is a major risk factor for stroke and mortality in North America.<sup>2,3</sup> The stasis of blood in the left atrium with AF identified by echocardiography is left atrial spontaneous echo contrast (SEC).<sup>4,5</sup> The left atrial SEC in patients with AF leads to a hypercoagulable state in addition to stasis.<sup>6</sup> It is a risk factor for left atrial thrombus (LAT) formation and thromboembolism leading to stroke.<sup>7,8</sup>

There is evidence that the mitral regurgitant (MR) jet agitates the blood in the left atrium and prevents stasis. Karatasakis et al.<sup>9</sup> demonstrated that the presence of significant MR had a protective effect on the incidence of thrombi and embolization. Other studies have failed to reproduce a similar beneficial effect of MR, and there is evidence that platelet activation due to MR may actually enhance the formation of platelet-fibrin thrombus on the mitral leaflet and increase embolization.<sup>10</sup> The effect of MR on thromboembolic risk in patients with AF is controversial. The present study investigates the prevalence of MR in patients with AF and LAT and the effect of severe MR on the incidence of new cerebrovascular accident (CVA).

### Methods

We identified 89 consecutive patients with AF and LAT diagnosed by transesophageal echocardiography (TEE) at Creighton University Cardiac Center. The 89 patients included 49 men and 40 women, mean age 71±10 years (range 38 to 89 years), 58 of the 89 patients (65%) had persistent AF, and 31 patients (35%) had paroxysmal AF. The status of AF during follow-up is not available due to the retrospective nature of the study. LAT was located in the left atrial appendage in 85 patients and in the left atrial body in 4 patients. The patients were divided in 2 groups based on the severity of MR. Group A consisted of patients with MR grade <3+, and group B consisted of patients with MR ≥3+. Table 1 shows the baseline characteristics in both groups and lists levels of statistical significance.

Conventional transthoracic echocardiography was performed in all patients with a Philips Sonos 5500 echocardiographic system and a 2.5 MHz or s4 transducer (Andover, Massachusetts). Left atrial dimension (LAD) was measured in the parasternal long-axis view. A LAD >40 mm in end-systole was defined as enlargement of the left atrium. Left ventricular ejection fraction (LVEF) was calculated from the 4-chamber view using Simpson's rule.

Table 1. Baseline characteristics in patients with mitral regurgitation (MR) <3+ and ≥3+

variable	MR <3+	MR ≥3+	p
Men	37/69 (54%)	12/20 (60%)	NS
Women	32/69 (46%)	8/20 (40%)	NS
Age (years)	71±10	75±9	NS
LAD (mm)	48±7	52±7	NS
LVEF (%)	41±17	36±19	NS
LAEV (cm/s)	0.24±0.12	0.29±0.19	NS
SEC	63/69 (91%)	16/20 (80%)	NS
INR	2.7±1.1	3.3±1.7	NS
% ASP grade ≥2	43/69 (62%)	15/20 (75%)	NS
CAD	33/69 (48%)	17/20 (85%)	0.004*
Hypertension	18/69 (26%)	2/20 (10%)	NS
Valvular heart disease	8/69 (12%)	1/20 (5%)	NS
Dilated cardiomyopathy	5/69 (7%)	0/20 (0%)	NS
AF of unknown cause	5/69 (7%)	0/20 (0%)	NS

Abbreviations: ASP = aortic atherosclerotic plaque; CAD = coronary artery disease; INR = international normalized ratio; LAD = left atrial diameter; LAEV = left atrial appendage emptying velocity; LVEF = left ventricular ejection fraction; NS = not significant; SEC = spontaneous echo contrast.

The patient was given conscious sedation with intravenous Versed and Fentanyl. A 3.7/5.0 MHz omniplane transesophageal transducer was placed in the posterior pharynx and advanced into the esophagus. The left atrial appendage was initially viewed in the horizontal 0-degree plane and 90-degree vertical plane. LAT was defined as a circumscribed and uniformly consistent echo-reflective mass of a texture different from that of the atrial wall. Off-axis views of the left atrial appendage were also performed to differentiate thrombus from pectinate muscles. SEC was considered present when dynamic “smoke-like” echoes were seen within the atrium that could not be eliminated by changes in gain settings.

Left atrial appendage emptying velocity was measured by putting a sample volume of the pulse Doppler in the left atrial appendage. The severity of MR by color flow imaging was classified into 4 grades; mild (1+), mild-moderate (2+), moderate-severe (3+), and severe (4+) scale as follows:<sup>11</sup>

0 = none (no flow disturbance in receiving chamber)

1+ = mild (disturbed flow localized to the region immediately adjacent to valve closure, may not be seen on every beat, consistent with normal or physiologic regurgitation)

2+ = mild-moderate (disturbed flow filling up to one-third of the cross-sectional area of the receiving chamber, seen on every beat)

3+ = moderate-severe (disturbed flow filling up to two-thirds of the cross-sectional area of the receiving chamber, seen on every beat)

4+ = severe (disturbed flow filling nearly the cross-sectional area of the receiving chamber; distal flow reversal also present).

The aortic atherosclerotic plaque was graded by TEE, and ≥grade II disease was recognized as significant.<sup>12</sup> All TEEs were reviewed by 1 author who was blinded to the clinical information.

Follow-up information was obtained from hospital and clinic records. The patients’ clinical characteristics, embolic events, and anticoagulation status were recorded during follow-up. Ischemic CVA included either a stroke defined as a definite focal neurological deficit of acute onset consistent with a vascular event lasting for >24 h and confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) scans or a transient ischemic attack (TIA) defined as focal neurological deficit of sudden onset that resolved completely in <24 h with a negative CT or MRI.

The TEE database was extracted into a Microsoft Excel datasheet. Descriptive statistics were used to summarize the variables. Student *t* tests were used to check differences in the means of continuous variables; chi-square tests were used to assess the association among categorical variables. Categorizations were based on our preliminary findings.

Table 2. Multivariate analysis for new cerebrovascular accident

	B	SE	Wald	p
Gender	-2.22	1.48	2.25	0.13
Age	0.07	0.08	0.85	0.36
Persistent AF	0.72	1.15	0.39	0.53
SEC	-1.72	1.65	1.08	0.30
LAD	-0.25	0.11	4.95	0.03
LVEF	-0.03	0.04	0.74	0.39
LAEV	-25.1	11.5	4.77	0.03
Cardioversion	0.71	1.39	0.26	0.61
Severity of MR	1.32	0.80	2.70	0.10

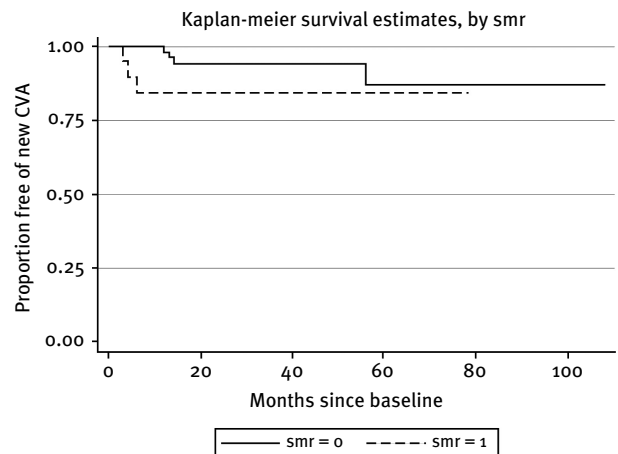
Abbreviations: LAD = left atrial diameter; LAEV = left atrial appendage emptying velocity; LVEF = left ventricular ejection fraction; SEC = spontaneous echo contrast.

Regression analysis was used to assess the association between independent and outcomes variables. Multivariate analysis was used to control for possible confounders. All data analyses were done using STATA 9 statistical software (Stata Corporation, College Station, TX, USA). Table 2 shows the multivariate analysis for new cerebrovascular accidents with adjustment by gender, age, persistent AF, spontaneous echo contrast, left atrial diameter, left ventricular ejection fraction, left atrial appendage emptying velocity, cardioversion, and severity of MR.

## Results

The mean duration of follow-up was  $34 \pm 28$  mo. Eighty-seven of 89 patients (98%) had MR. The degree of MR was 1+ in 23 patients (26%), 2+ in 44 patients (50%), 3+ in 17 patients (19%), and 4+ in 3 patients (4%). Of the 20 patients with MR grade  $\geq 3+$ , 19 (95%) had ischemic MR and 1 (5%) had MR secondary to mitral valve prolapse. Seven of 89 patients (8%) had a new CVA after LAT demonstrated by TEE. The annual incidence of new CVA in patients with AF and MR was 2.4% per year. Using the Cox proportional hazards model, we did not find any significant difference by MR severity in the incidence of CVA and mortality. The hazard ratio (HR) for new CVA was not decreased with increased severity of MR (HR = 2.7; 95% confidence interval [CI]: 0.6–12.2; Figure 1). The HR for mortality was not decreased with increased severity of MR (HR = 1.9; 95% CI: 0.9–4.3; Figure 2). The only variable predictor of mortality in this population was LVEF, and with every unit increase in LVEF, the mortality decreased by 3%.

A total of 51 patients (61%) were on warfarin anticoagulation before LAT demonstrated by TEE, and 17 patients (19%) had a CVA in the past. A total of 73 patients (82%)



smr = 0 is equal to mitral regurgitation  $<3$

smr = 1 is equal to mitral regurgitation  $\geq 3$

CVA: cerebrovascular accident

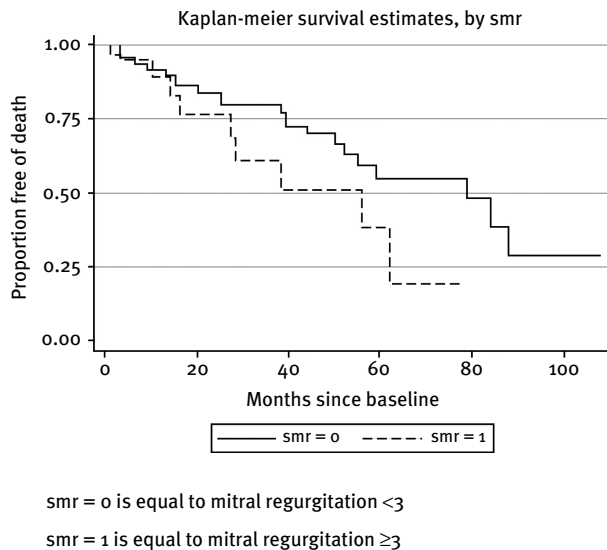
Figure 1. Kaplan-Meier cerebrovascular accident (CVA) free survival of patients with and without significant MR (smr). There was no significant difference in CVA free survival rate between the patients with and without MR  $\geq 3+$ . smr = 0 is equal to mitral regurgitation  $<3$ ; smr = 1 is equal to mitral regurgitation  $\geq 3$ .

were on warfarin after LAT was demonstrated by TEE, and 16 patients (18%) were not on warfarin because of a bleeding contradiction. There was no significant difference in the international normalized ratio (INR) level at the first wk after TEE between the patients with and without MR  $\geq 3+$  (Table 1). New CVA occurred during follow-up in 3 of 20 patients (15%) with MR  $\geq 3+$  and in 4 of 69 patients (6%) with  $<3+$  MR (p not significant). There was no significant association between SEC and incidence of CVA or between SEC and mortality. A previous history of CVA was not a significant predictor for recurrent CVA. Thirty-two patients received cardioversion with no significant effect on new onset CVA.

## Discussion

Previous studies suggest that patients with AF and MR have a reduced incidence of CVA, assuming that the regurgitating jet washes out and prevents the formation of LAT and thromboembolism. Our study demonstrated that 23% of 89 patients with AF and LAT had significant MR, and that significant MR was not associated with a decreased incidence of CVA in patients with AF and LAT. The main difference between our study and previous studies is that our study population consisted of a high risk group with AF and LAT at baseline.

It has been postulated that MR will increase the risk of thromboembolism because the jets of MR lash at the thrombus and make the thrombus drop out from the left



**Figure 2.** Kaplan-Meier survival of patients with and without significant MR (smr). There was no significant difference in survival rate between the patients with and without MR ≥3+. smr = 0 is equal to mitral regurgitation <3; smr = 1 is equal to mitral regurgitation ≥3.

atrial wall. However, 96% of the LATs in our patients were located in the left atrial appendage and hence were protected from the regurgitant jet. Except for coronary artery disease prevalence, there were no significant differences in baseline characteristics between patients with ≥3+ MR and <3+ MR. Increased severity of MR was also not associated with increased mortality.

The role of anticoagulation in patients with MR and AF is controversial. While some studies recommend not using warfarin in patients with AF and severe MR,<sup>13</sup> other studies have shown a significant benefit from warfarin.<sup>14</sup> In the MR group, previous stroke is more frequent in patients without warfarin treatment than in patients with low-dose warfarin treatment.<sup>14</sup> Possible mechanisms for the marked reduction in thromboembolism are a decrease in intra-atrial coagulation activity and formation of platelet-fibrin thrombus on the leaflet. Wada et al.<sup>14</sup> reported that in patients with AF and significant MR, warfarin therapy (mean INR of 2.6) is associated with an almost 10-fold decrease in the relative risk of thrombus formation. There is need for a large randomized trial to assess the risk/benefit of long-term anticoagulation in patients with AF and significant MR. We currently lack substantial evidence to not give warfarin to these patients.

#### Limitations

Patient selection was based on a retrospective cohort design and involved data extraction from records. Because of a relatively small number of patients studied, we may not have sufficient power to have valid statistical analysis of

some of the variables. Because of the small number of patients with cerebrovascular events it is difficult to exclude a B-type error. Further studies with a larger number of patients having a longer follow-up duration are indicated. Furthermore, whether using left atrial volume instead of dimensions would influence the results in the assessment of the true atrial size is unclear since atrial volumes were not calculated in this retrospective study.

#### Clinical Implications

In our study the prevalence of MR was high in patients with AF and LAT. There was no association between the severity of MR and incidence of CVA. Our study does not support withholding long-term anticoagulation with warfarin in high risk patients with AF and MR. Randomized, controlled trials with a larger number of patients are needed to assess the risk and benefit of long-term anticoagulation in this patient population.

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