

## Clinically unrecognized mitral regurgitation is prevalent in lone atrial fibrillation

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### Abstract

**AIM:** To investigate the prevalence of clinically unrecognized mitral regurgitation (MR) in lone atrial fibrillation (AF).

**METHODS:** We studied the prevalence and severity of MR by transesophageal echocardiography (TEE) in patients with "lone" AF as compared to a matched cohort of patients in normal sinus rhythm (NSR) undergoing TEE for other indications besides recognized valvular heart disease.

**RESULTS:** A total of 157 subjects (57 in the AF group and 100 in the NSR group) with structurally normal cardiac valves were included in the study. In the AF group, moderate MR or more was noted in 66% of the

patients, mild MR in 18%, trace or no MR in 16%. In the control group, moderate MR was noted in 6% of patients, mild MR 31%, trace or no MR in 63 % of patients. Moderate MR or greater was significantly more prevalent in the AF group compared to the NSR group (66% vs 6%,  $P < 0.0001$ ).

**CONCLUSION:** Clinically unrecognized moderate MR is prevalent in "lone" AF -either as an etiologic factor leading to "lone" AF or developing after onset of AF.

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**Key words:** Mitral regurgitation; Lone atrial fibrillation; Normal sinus rhythm

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### INTRODUCTION

There is scant data regarding the prevalence of mitral regurgitation (MR) in lone atrial fibrillation (AF). Significant MR from structural valvular abnormality is associated with subsequent development of chronic AF. However, little is known regarding the relationship between lone AF and clinically unrecognized moderate MR in patients with

structurally normal valves. We noted that patients who were referred for transesophageal echocardiography (TEE) guided cardioversion for AF had an unusually higher prevalence of TEE evident moderate MR than a control group who underwent TEE for other indications. We sought to determine the exact prevalence of MR by TEE in patients with lone AF as compared to patients in normal sinus rhythm (NSR) by blinded observation in a cohort of consecutive patients who underwent TEE at our institution.

## MATERIALS AND METHODS

Over a 50-mo period, 57 consecutive patients with a diagnosis of lone AF underwent TEE in our institution to exclude intra-cardiac thrombus prior to external direct current cardioversion. These patients comprised the AF group. Within the same period, a cohort of 100 patients in NSR who underwent TEE for a variety of indications (evaluation for suspected endocarditis, aortic dissection, and pulmonary hypertension) were enrolled as age- and sex-matched controls. At the time of the initial diagnosis, patients in the AF group were < 60 years and were without concomitant heart disease, hypertension or diabetes mellitus. Subjects from both groups were included if they had structurally normal mitral valves. Exclusion criteria included uncontrolled hypertension, heart failure, cardiomyopathy, structural abnormality of any of the valves (including valvular stenosis and mitral valve prolapse), history of cardiac surgery (including valve repair or replacement), and congenital or pericardial heart disease.

Standard TEE with doppler color flow mapping was employed to assess the variables. All measurements were in conformity with the American Society of Echocardiography guidelines, and were verified by two independent, blinded observers. The presence or absence of MR was verified, and its severity was graded semi-quantitatively as follows: 0 (none), 1 (trace), 2 (mild), 3 (moderate), 4 (severe). Any discordance of the severity of MR was resolved by joint reading by the two observers. The following variables were also measured: left ventricle (LV) ejection fraction, LV diameter, left atrial diameter (LA) and mitral annulus diameter in the 4 chamber views.

Patient demographics, severity of MR, and cardiac dimensions between groups were compared with the use of the Student's *t* test for continuous variables, and the Fisher's exact test for categorical variables. A two-sided *P* value of 0.05 or less was considered to indicate statistical significance.

## RESULTS

A total of 157 subjects (57 in the AF group and 100 in the NSR group) with structurally normal cardiac valves were included in the analysis. Both groups were similar in terms of age, sex, and co-morbidities (hypertension, chronic kidney disease and cerebrovascular disease) except for a greater prevalence of diabetes and lung disease in the control group. Baseline characteristics of the sub-

**Table 1** Baseline characteristics of subjects

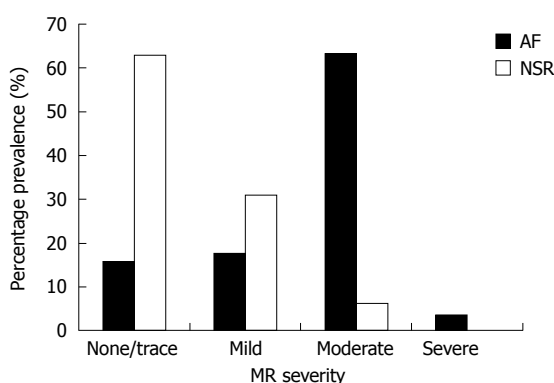
Demographic data	AF group ( <i>n</i> = 57)	NSR group ( <i>n</i> = 100)	<i>P</i> value ( <i>a</i> = 0.05)
Age (mean ± SD)	50.2 ± 7.3	51.7 ± 6.1	0.17 NS
Male sex	39 (68)	66 (66)	0.86 NS
Comorbidities			
Hypertension (controlled)	8 (14)	19 (19)	0.51 NS
Diabetes mellitus	0 (0)	13 (13)	< 0.05
Chronic lung disease	0 (0)	9 (9)	< 0.05
Chronic kidney disease	0 (0)	6 (6)	0.08 NS
Cerebrovascular disease	0 (0)	3 (3)	0.55 NS

AF: Atrial fibrillation; NSR: Normal sinus rhythm; NS: Not significant.

**Table 2** Chamber dimensions

Measurements	AF group ( <i>n</i> = 57)	NSR group ( <i>n</i> = 100)	<i>P</i> value ( <i>a</i> = 0.05)
LV ejection fraction (%)	68 ± 6	66 ± 9	0.13 NS
LV end diastolic diameter (cm)	5.4 ± 0.7	5.5 ± 0.5	0.30 NS
LA diameter (cm)	3.7 ± 0.5	3.6 ± 0.6	0.28 NS
Mitral annulus diameter (cm)	4.0 ± 0.4	3.4 ± 0.5	< 0.0001

AF: Atrial fibrillation; NSR: Normal sinus rhythm; LV: Left ventricle; LA: Left atrial; NS: Not significant.



**Figure 1** Percentage prevalence of mitral regurgitation severity between atrial fibrillation and normal sinus rhythm groups. AF: Atrial fibrillation; NSR: Normal sinus rhythm; MR: Mitral regurgitation.

jects are listed in Table 1.

The severity of MR noted in the patients in the AF and NSR cohorts is outlined in Figure 1. In the AF group (*n* = 57), moderate MR or more was noted in 38 patients (66%), mild MR in 10 patients (18%), trace or no MR in 9 patients (16%). In the control group (*n* = 100), moderate MR was noted in 6 patients (6%), mild MR 31 patients (31%), trace or no MR in 63 patients (63%). Moderate MR or greater was significantly more prevalent in the AF group compared to the NSR group (66% *vs* 6%, *P* < 0.0001). All of the subjects had left ventricular ejection fraction > 50%, and there was no difference in LV chamber sizes between groups. LA between the two groups was not statistically significant between the two groups. Mitral annular diameter was statistically greater in the AF group than the NSR group (Table 2).

## DISCUSSION

AF is the most common cardiac rhythm disorder, affecting about 2% of the general adult population and is commonly associated with structural heart disease<sup>[1]</sup>. AF induces electrical, contractile and structural remodeling of the atrial myocardium that leads to AF progression and permanence<sup>[2]</sup>. However, lone AF (defined AF in the absence of demonstrable underlying cardiac disease or a history of hypertension in subjects < 65 years) is uncommon, comprising less than 3% of the total cases of AF<sup>[1-4]</sup>. Numerous mechanisms are postulated in pathogenesis of AF including acute atrial stretch, structural and electrophysiological alterations, systemic inflammation, oxidative stress, autonomic imbalance, atrial fibrosis, or localized atrial myocarditis, genetic predisposition, obesity, sleep apnea, metabolic syndrome, alcohol consumption, endurance sports suggest that apparently “lone” AF may not be necessarily idiopathic or “lone” in many patients<sup>[2-8]</sup>.

In this study, we propose the possibility that clinically unrecognized moderate MR may predispose to occurrence of AF, or alternatively MR develops slowly in patients with AF related to mitral annular dilation as was noted in our subset of patients with AF. We cannot exactly pinpoint the time duration of the existence of AF in our subset of patients, since these patients were all recently or incidentally diagnosed with AF and were referred for TEE guided cardioversion to our clinic. Most of these subjects with lone AF had no transthoracic echocardiography carried out before since their TEE was scheduled essentially within the same week of their diagnosis.

Data are scant on the prevalence of MR in lone AF. In a previous report, using transthoracic 2-dimensional echocardiography, moderate or severe MR was not observed in patients with lone AF<sup>[9]</sup>. Some reports suggest that MR may arise from isolated annular dilatation secondary to lone AF and associated atrial remodeling<sup>[10-12]</sup>. Indeed, in our study, severe MR was not observed frequently. However, in our study utilizing TEE, which is more sensitive in evaluating MR, we noted that moderate MR was present in more than half of the subjects with lone AF, a prevalence that is significantly higher than that of the matched controls.

It is known that significant MR (from degenerative causes or organic valvular abnormalities) is associated with development of chronic AF, at a rate of about 5% per year<sup>[13,14]</sup>. The risk of AF is correlated with increase in LA dimension<sup>[15]</sup>. Even asymptomatic organic MR has been shown to increase the risk of AF and adverse cardiovascular outcomes. MR from organic causes enlarges the left atrium, but most patients are initially asymptomatic because atrial compliance may normalize left atrial pressure even in the presence of severe regurgitation<sup>[16]</sup>. In patients with lone AF, atrial compliance may remain abnormal even after restoration of NSR which could be related to atrial fibrosis in these patients<sup>[17-19]</sup>.

In our study on subjects with structurally normal mi-

tral valves, none of the subjects had any significant LA enlargement. However, mitral annular dilation was more frequent in the AF subgroup. It is conceivable that MR follows some mitral annular dilation and the left atrial dilation takes a longer time to develop and does not become apparent in the early stages of lone AF. Whether AF exerts some anatomical effect on the mitral annulus remains hypothetical, since the number of patients is small. It is also possible that the atrial dyssynchrony produces an anatomically variable contraction of the mitral annulus leading to varying degrees of mitral closure with an irregular R-R interval, possibly predisposing to slow development of MR. One study suggests development of “functional MR” in patients with AF that improves when sinus rhythm is restored<sup>[20]</sup>.

Atrial hypertension and stretch induced by MR may also be a likely explanation for development of “lone” AF. In animal models, LA dilation of moderate severity has been shown to result in significant changes in the cellular action potential and calcium current in the atrial myocardium rendering the atria vulnerable to AF<sup>[21]</sup>. Chronic atrial dilation causes atrial conduction delays and a higher contribution of anatomically defined re-entrant circuits, creating a wider excitable gap during AF<sup>[22]</sup>. Increased left atrial size leads to greater recurrences of “lone” AF<sup>[23]</sup>. Treatment with ACE inhibitors prevents long term recurrences of “lone” AF and facilitates maintenance of sinus rhythm after cardioversion<sup>[24,25]</sup>. Cardioversion to NSR reverses the atrial enlargement in patients with AF and MR<sup>[26]</sup>. There is also an increased amount of atrial fibrosis in AF patients with mitral valve disease than in patients with lone AF<sup>[27]</sup>.

Theoretically, it seems plausible that moderate MR may be a risk factor for the development of lone AF, primarily by causing mechanical stretch of the left atrium (“left atrial hypertension”). Or conversely, AF may predispose to slow development of “silent” MR that may progress with time. It is also conceivable that the MR is a transient atrial dyssynchrony predisposed phenomenon that resolves after NSR is restored; but we do not have longitudinal TEE follow-up on our patients to make that assumption. Lastly, it is conceivable that the greater degree of MR noted on TEE may be related to the greater sensitivity of TEE to evaluate MR; however the presence of a control group should have normalized for that observation bias. Our study suggests that clinically unrecognized moderate MR may be prevalent in patients with lone AF. Whether moderate unrecognized MR may be an etiologic factor related to development of “lone” AF or vice versa needs to be studied in long-term longitudinal studies.

This was a single-center, nonrandomized, retrospective, single time point observational study. Hence, it was not designed to prove causality. The basis of our study was to explore an association between “silent” unrecognized moderate MR and “lone” AF. Our observations are subject to the same limitations imposed by retrospective study designs, and it is possible for bias to exist during the review process. It is conceivable that AF, by induc-

ing atrial wall motion dyssynchrony, may by itself induce MR. Moderate MR may be a more likely explanation for development of “lone” AF. The etiologic basis of this hypothesis would require long term longitudinal follow-up studies of patients with moderate MR who are in NSR at the time of the initial diagnosis of moderate MR. Another limitation of our data relates to the greater sensitivity of recognizing moderate MR with TEE, though this bias was possibly neutralized by inclusion of the control group of patients who were in NSR.

In our study utilizing TEE, moderate MR is prevalent in patients with lone AF. Longitudinal studies may be required to explore whether “silent” unrecognized moderate MR leads to development of “lone” AF or vice versa.

## COMMENTS

### Background

Clinically significant mitral regurgitation (MR) often leads to development of atrial fibrillation (AF). However, whether a stage of clinically unrecognized moderate MR (preceding development of clinically obvious significant MR) in patients with structurally normal valves can also lead to development of AF is not known.

### Research frontiers

MR and AF are common cardiac conditions that often co-exist. Moderate MR is often clinically unrecognized as it is asymptomatic. “Lone” AF often occurs in patients without any preceding established cardiac disease. Whether there is an etiologic relationship between moderate MR and “lone” AF has not been studied. In the present study the authors demonstrate that clinically unrecognized moderate MR often co-exists in patients with lone AF and there may be an etiologic relationship between these two entities.

### Innovations and breakthroughs

The study highlights the relationship between the presence of AF without any clinically obvious cardiac disease and clinically unrecognized moderate MR. It highlights that a clinically unrecognized stage of moderate MR may be a preceding step before the clinical manifestations become obvious in the form of development of AF. It is also possible that atrial dyssynchrony induced by AF may make MR more manifest by echocardiography.

### Applications

By understanding the relationship between moderate MR and lone AF, the study generates interest in whether a therapeutic strategy for preventing progression of MR by afterload reduction therapy may be of benefit in preventing onset of AF.

### Terminology

“Lone” AF is defined as AF in the absence of demonstrable underlying cardiac disease or a history of hypertension. MR is the presence of leakage of the mitral valve that is present in trace to mild degree almost universally on echocardiography. However, moderate or severe MR is more uncommon and is sometimes associated with presence of other heart disease.

### Peer review

It is well written, concise paper and interesting.

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