Clinically unrecognized mitral regurgitation is prevalent in lone atrial fibrillation

Sanjiv Sharma, Joel Lardizabal, Mark Monterroso, Neil Bhambi, Rohan Sharma, Rasham Sandhu, Sarabjeet Singh

Sanjiv Sharma, Joel Lardizabal, Mark Monterroso, Neil Bhambi, Rohan Sharma, Rasham Sandhu, Sarabjeet Singh, Division of Cardiology, Bakersfield Heart Hospital, Bakersfield, CA 93308, United States

Author contributions: Sharma S designed and executed the study, performed the transesophageal echocardiograms, oversaw the collection and analysis of data, literature search, statistical analysis and wrote the manuscript; Lardizabal J collected and analyzed the data and co-authored the manuscript; Monterroso M collected and analyzed the data; Bhambi N collected and analyzed the data; Sharma R collected and analyzed the data; Sandhu R independently analyzed the transesophageal echocardiograms and analyzed the data; Singh S independently analyzed the transesophageal echocardiograms and analyzed the data.

Correspondence to: Sanjiv Sharma, MD, FACC, FSCAI, Chairman, Department of Medicine, Director, Research and Education, Division of Cardiology, Bakersfield Heart Hospital, 2901 Silsile Ave, Ste 100, Bakersfield, CA 93308, United States. sanjiv1122@yahoo.com

Telephone: +1-661-3238384 Fax: +1-661-3239326

Received: February 21, 2012 Revised: May 15, 2012
Accepted: May 22, 2012
Published online: May 26, 2012

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.
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 subjects 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).

| Demographic data                  | AF group (n = 57) | NSR group (n = 100) | P value (a = 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.

| Measurements                   | AF group (n = 57) | NSR group (n = 100) | P value (a = 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; MR: Mitral regurgitation.

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.

www.wjgnet.com 184 May 26, 2012 | Volume 4 | Issue 5 |
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[3]. AF induces electrical, contractile and structural remodeling of the atrial myocardium that leads to AF progression and permanence[4]. However, lone AF (defined in 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[1-4]. 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[5-8].

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 dilatation 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[9]. Some reports suggest that MR may arise from isolated annular dilatation secondary to lone AF and associated atrial remodeling[10-12]. 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[13,14]. The risk of AF is correlated with increase in LA dimension[15]. 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[16]. 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[17-19].

In our study on subjects with structurally normal mitral valves, none of the subjects had any significant LA enlargement. However, mitral annular dilatation was more frequent in the AF subgroup. It is conceivable that MR follows some mitral annular dilatation and the left atrial dilatation 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[20].

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[21]. Chronic atrial dilation causes atrial conduction delays and a higher contribution of anatomically defined re-entrant circuits, creating a wider excitable gap during AF[22]. Increased left atrial size leads to greater recurrences of “lone” AF[23]. Treatment with ACE inhibitors prevents long term recurrences of “lone” AF and facilitates maintenance of sinus rhythm after cardioversion[24,25]. Cardioversion to NSR reverses the atrial enlargement in patients with AF and MR[26]. There is also an increased amount of atrial fibrosis in AF patients with mitral valve disease than in patients with lone AF[27].

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 dysynchrony 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.

**REFERENCES**

1. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR, Istrup DM, Frye RL. The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med* 1987; 317: 669-674
2. Potpara TS, Lip GY. Lone atrial fibrillation: where are we now? *Hoop Pract (Minneapolis)* 2011; 39: 17-31
3. Kopecky SL, Gersh BJ, McGoon MD, Chu CP, Istrup DM, Chesbro JH, Whisnant JP. Lone atrial fibrillation in elderly persons: a marker for cardiovascular risk. *Arch Intern Med* 1999; 159: 1118-1122
4. Falk RH. Atrial fibrillation. *N Engl J Med* 2001; 344: 1067-1078
5. Parvez B, Darbar D. Lone AF - etiologic factors and genetic insights into pathophysiology. *J Atr Fibrillation* 2010; 1: 675-684
6. Roski M, Dzaua M, Chudzik M, Cyganekiewicz I, Bartczak K, Drozdz J, Wranicz JK. Risk factors for atrial fibrillation: Not always severe heart disease, not always so ‘lone’. *Cardiol J* 2010; 17: 437-442
7. Korantzopoulos P, Liu T, Miltonis HJ, Li G, Goudevenos JA. ‘Lone’ atrial fibrillation: hunting for the underlying causes and links. *Int J Cardiol* 2009; 131: 180-185
8. Kozlowski D, Budrejko S, Lip GY, Rysz J, Mikhailidis DP, Raczk G, Banach M. Lone atrial fibrillation: what do we know? *Heart* 2010; 96: 496-503
9. Zhou X, Otsuji Y, Yoshifuku S, Yuasa T, Zhang H, Takasaki K, Matsukida K, Kisanuki A, Minagoe S, Tei C. Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular regurgitation. *Circ J* 2002; 66: 913-916
10. Vohra HA, Whistance RN, Magan A, Sadeque SA, Livesey SA. Mitral valve repair for severe mitral regurgitation secondary to lone atrial fibrillation. *Eur J Cardiothorac Surg* 2012; Epub ahead of print
11. Khira T, Gillonov AM, Takasaki K, Fukuda S, Song JM, Shiota M, Shiot A. Mitral regurgitation associated with mitral annular dilatation in patients with lone atrial fibrillation: an echocardiographic study. *Echocardiography* 2009; 26: 885-889
12. Silbiger JJ. Mitral regurgitation in lone atrial fibrillation: more than a matter of annular size. *Echocardiography* 2010; 27: 218; author reply 219
13. Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, Boone J, Sheldon R, Dorian P, Newman D. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2005; 149: 489-496
14. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. *J Am Coll Cardiol* 2002; 40: 84-92
15. Parkash R, Green MS, Kerr CR, Connolly SJ, Klein GJ, Sheldon R, Talajic M, Dorian P, Humphries K. The association of left atrial size and occurrence of atrial fibrillation: a prospective cohort study from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2004; 148: 649-654
16. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, De- taint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ, Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005; 352: 875-883
17. Donal E, Ollivier R, Veillard D, Hamonic S, Pavin D, Daubert JC, Mabo P. Left atrial function assessed by transesophageal echocardiography in patients treated by ablation for a lone paroxysmal atrial fibrillation. *J Eur Heart Rhythm* 2010; 11: 845-852
18. Tondo C. Atrial fibrillation and lone atrial fibrillation: an ominous association from the beginning? *Heart Rhythm* 2010; 7: 1482-1483
19. Kottkamp H. Atrial fibrillation substrate: the “unknown species” – from lone atrial fibrillation to fibrotic atrial cardio-myopathy. *Heart Rhythm* 2012; 9: 481-482
20. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlin ski FE, Keane MG, Silvestry FE. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol* 2011; 58: 1474-1481
21. Deroubaix E, Folliguet T, Rücker-Martin C, Dinanian S, Boixel C, Validire P, Daniel P, Capderou A, Hatem SN. Moderate and chronic hemodynamic overload of sheep atria induced by reversible cellular electrophysiological abnormalities and atrial vulnerability. *Am J Cardiol* 2004; 94: 1918-1926
22. Neuberger HR, Schotten U, Blaauw Y, Vollmann D, Eijs bouts S, van Hunnik A, Allessie M. Chronic atrial dilation, electrical remodeling, and atrial fibrillation in the goat. *J Am
Zacà V, Galderisi M, Mondillo S, Focardi M, Ballo P, Guerrini F. Left atrial enlargement as a predictor of recurrences in lone paroxysmal atrial fibrillation. *Can J Cardiol* 2007; 23: 869-872.

Grecu M, Olteanu RO, Olteanu SS, Georgescu CA. Does treatment with ACE inhibitors prevent the long term recurrences of lone atrial fibrillation after cardioversion? *Rom J Intern Med* 2007; 45: 29-33.

Belluzzi F, Sernesi L, Preti P, Salinaro F, Fonte ML, Perlini S. Prevention of recurrent lone atrial fibrillation by the angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. *J Am Coll Cardiol* 2009; 53: 24-29.

Gosselink AT, Crijns HJ, Hamer HP, Hillege H, Lie KI. Changes in left and right atrial size after cardioversion of atrial fibrillation: role of mitral valve disease. *J Am Coll Cardiol* 1993; 22: 1666-1672.

Geuzebroek GS, van Amersfoorth SC, Hoogendijk MG, Kelder JC, van Hemel NM, de Bakker JM, Coronel R. Increased amount of atrial fibrosis in patients with atrial fibrillation secondary to mitral valve disease. *J Thorac Cardiovasc Surg* 2011; Epub ahead of print.