Atrial Functional Mitral Regurgitation
From Mitral Annulus Dilatation to Insufficient Leaflet Remodeling

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Atrial fibrillation (AF) is the most frequent heart rhythm disorder. The estimated prevalence of AF in the United States in 2010 ranged between 2.7 and 6.1 million and is projected to increase to 12.1 million by 2030.[1] Similar figures have been described in Europe: the estimated prevalence of AF in adults >55 years was 8.8 million in 2010 and projections estimate a prevalence of 17.9 million by 2060.[2] The vast majority of research has focused on the most feared complications of AF: stroke, heart failure, sudden cardiac death, and noncardiovascular death. However, the occurrence of mitral regurgitation (MR) in patients with AF has received much less attention.

See Article by Kagiyama et al

MR is the most frequent valvular heart disease and is a known risk factor for AF.[1] However, the prevalence and pathophysiology of MR among patients with AF remains unexplored. Between 14% and 26.4% of the patients included in landmark clinical trials on direct oral anticoagulants showed significant valvular heart disease other than moderate and severe mitral stenosis or mechanical valve prostheses.[3] The most frequent valvular heart disease was MR with prevalence ranging between 73% to almost 90%.[3] However, no data on the mechanism of MR were provided.

MR is classified as primary (organic), when the mitral leaflets or the subvalvular apparatus are structurally abnormal causing leaflet malcoaptation, or secondary (functional) when the leaflets and subvalvular apparatus are normal and leaflet malcoaptation is caused by global or regional left ventricular (LV) remodeling that displace the papillary muscles, tethering the mitral leaflets, or by reduction of LV closing forces. Depending on the severity and chronicity of MR, the left atrium (LA) dilates in response to the volume overload. This remodeling process involves the posterior part of the mitral annulus, causing dilatation of the mitral annulus and contributing to leaflet malcoaptation and MR. In addition, the LA remodeling paves the substrate for AF which can further beget LA and mitral annulus dilatation and worsen MR. In isolated AF, the mitral leaflets and subvalvular apparatus are structurally normal and therefore, if MR is present, this has been classically classified as functional MR. However, the pathophysiology of MR in isolated AF is ill-defined.

In contrast to functional MR caused by LV dysfunction and dilatation, in MR caused by isolated AF, the LV shows normal dimensions and function, leaving mitral annulus dilatation as the main and unique mechanism causing mitral leaflet malcoaptation. However, this hypothesis has been highly debated. Otsuji et al[4] showed that LV dysfunction and remodeling causing tethering of the mitral leaflets were the main determinants of moderate and severe MR, whereas isolated mitral annulus dilatation was not. In contrast, the echocardiographic study by Kihara et al[5] reported larger dimensions of the mitral annulus and the LA in 12 patients with AF, normal dimensions, and function of the LV and moderate and severe MR as compared with 10 patients without MR. Similar results were reported in a larger study including 170 patients with AF, structurally normal mitral valve and normal LV dimensions and function who underwent multidetector row computed tomography before AF ablation.[6] Compared with patients without MR, patients with moderate and severe MR showed significantly larger intercommissural and anteroposterior diameters, perimeter, and area of the mitral annulus measured with multidetector row computed tomography. Each 1 mm/m^2 increase in the anteroposterior diameter of the mitral annulus was associated with an odds ratio of 1.8 (95% confidence interval 1.35–2.40) of having significant MR after correcting for age, type of AF, hypertension, LV function and dimensions, and LA dimensions. In addition, the study by Gertz et al[7] demonstrated that mitral annulus dimension was the most important determinant of MR in patients with AF (odds ratio 8.39, 95% confidence interval 1.94–36.35). This evidence has led to the concept of atrial functional MR.

The underlying pathophysiology of atrial functional MR has been described by Silbiger[8] and proposes that the LA enlargement displaces the posterior mitral annulus onto the crest of the LV inlet causing (1) reduction of the posterior leaflet area available for coaptation because the ventricular surface of this leaflet is pressed against the crest of the LV and (2) tethering of the posterior leaflet by increasing the annulopapillary muscle distance. In addition, the displacement of the posterior mitral annulus may cause a counterclockwise torque of the anterior mitral annulus across the intertrigonal axis increasing the tethering of the papillary muscles and causing tenting of the anterior mitral leaflet (Figure).[8]

In this issue of *Circulation: Cardiovascular Imaging*, Kagiyama et al[9] propose an additional mechanism in the pathophysiology of atrial functional MR: the concept of insufficient leaflet remodeling. This concept has been

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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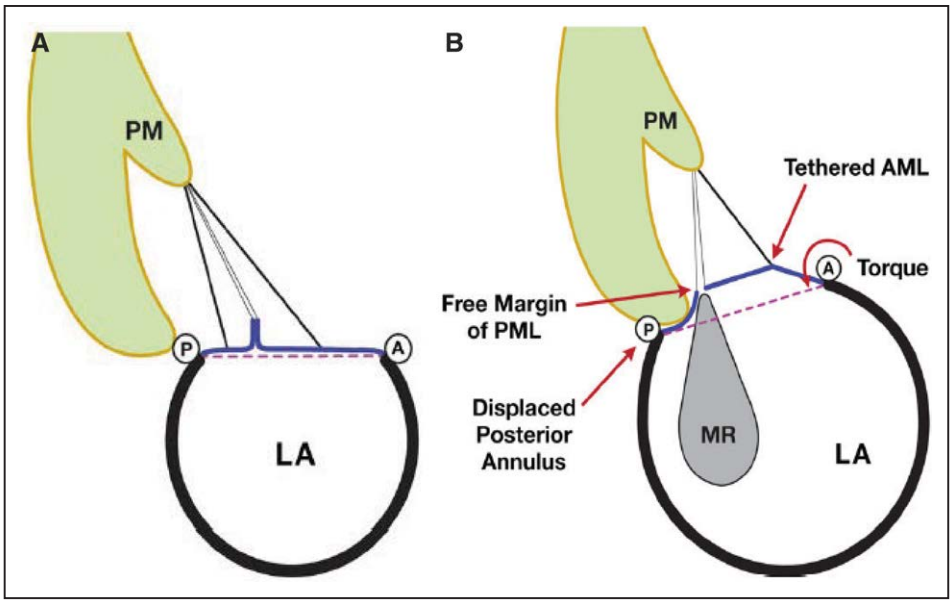

Figure. Pathophysiology of atrial functional mitral regurgitation (MR). **A**, The normal disposition of the mitral valve apparatus: the mitral leaflets rest just at the level of the annular plane (purple dashed line) during systole. In atrial fibrillation (**B**), left atrium (LA) and mitral annulus dilatation displace the posterior mitral annulus (P) above the crest of the left ventricle inlet pressing the posterior mitral leaflet (PML) against and leaving little surface of the leaflet for coaptation. In addition, the distance between the papillary muscle (PM) and the posterior annulus increases leading to posterior leaflet tethering. The anterior mitral annulus follows the displacement of the posterior mitral annulus as consequence of the generated counterclockwise torque across the intertrigonal axis, increasing the distance with the PMs and inducing tethering of the anterior mitral leaflet (AML). Consequently, the mitral leaflet tenting increases and the coaptation point is displaced above the annular plane into the left ventricle further contributing to the malcoaptation and MR. Reproduced from Silbiger[8] with permission of the publisher. Copyright © 2014, John Wiley and Sons.

demonstrated in patients with functional MR because of LV dysfunction and remodeling.[10–12] In patients with heart failure and functional MR, the mitral leaflets show extracellular matrix changes and growth in length proportional to the mitral annulus, LA, and ventricular dimensions and function.[10] Insufficient mitral leaflet remodeling relative to the increase in mitral annulus dimension may lead to MR. This was demonstrated by Chaput et al[11] in 60 patients with inferior LV wall motion abnormalities or dilated cardiomyopathy (29 of them showing significant MR), who underwent 3-dimensional transesophageal echocardiography. Compared with normal individuals, patients with LV dysfunction or remodeling showed 35% increase in the mitral leaflet area. Interestingly, in patients with significant MR, the ratio of mitral leaflet to annular area (representing the mitral annular surface effectively covered by the leaflets) was significantly reduced as compared with patients without MR and normal individuals (1.29±0.15 versus 1.81±0.38 versus 1.78±0.39, respectively; P=0.001) suggesting that insufficient mitral leaflet remodeling to compensate the mitral annulus dilatation may be pivotal in the development of functional MR. In a study including 30 patients with moderate and severe functional MR and 30 patients with comparable LV dimensions and function and LA dimensions but no significant MR, Debonnaire et al[12] showed that patients with significant functional MR had smaller exposed leaflet area relative to total valve area leading to smaller effective coaptation area (1.27±0.03 versus 1.36±0.06; P<0.001). These results are extended to patients with AF and normal LV function in the study by Kagiyama et al.[9] The 3-dimensional geometry of the mitral valve assessed with transesophageal echocardiography of 28 patients with AF and significant MR was compared with that of 56 AF patients without MR and 16 normal controls matched by age and sex. LA dimensions, mitral annulus size, and anterior and posterior mitral leaflets were significantly larger in patients with AF and MR as compared with the other 2 groups. However, patients with MR showed significantly smaller total leaflet area relative to the mitral annulus area compared with AF patients without MR and controls (1.29±0.10 versus 1.65±0.24 versus 1.70±0.29, respectively; P<0.001). Each 1% decrease in the total leaflet area to mitral annulus area ratio was independently associated with significant MR (odds ratio 0.76, 95% confidence interval 0.65–0.89; P<0.001). Therefore, mitral leaflet remodeling seems also present in atrial functional MR. Whether these changes will revert after effective restoration of sinus rhythm remains to be investigated. Probably, patients with AF and significant MR because of annular dilatation and insufficient leaflet remodeling may show more diseased LA with low probability of recovering sinus rhythm. In the present study, AF patients with significant MR showed significantly larger LA as compared with patients without MR. However, it may be interesting to investigate if rhythm control is superior to heart rate control to prevent LA remodeling and MR. In terms of cardiovascular events and survival, rhythm control has not demonstrated to be superior to heart rate control.[13] Ongoing trials are investigating whether catheter ablation, combination therapy, and early therapy of AF results in better outcomes, including salutary effects in LV and atrial remodeling and MR.[13]

Disclosures

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References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics-2017 update: a report from the American Heart Association [published online ahead of print January 25, 2017]. *Circulation.* 2017. doi: 10.1161/CIR.0000000000000485.
2. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751. doi: 10.1093/eurheartj/eht280.
3. Owens RE, Kabra R, Oliphant CS. Direct oral anticoagulant use in nonvalvular atrial fibrillation with valvular heart disease: a systematic review [published online ahead of print December 22, 2016]. *Clin Cardiol.* 2016. doi: 10.1002/clc.22659
4. Otsuji Y, Kumanohoso T, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, Minagoe S, Levine RA, Tei C. Isolated annular dilation does not usually cause important functional mitral regurgitation: comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. *J Am Coll Cardiol*. 2002;39:1651–1656.
5. Kihara T, Gillinov AM, Takasaki K, Fukuda S, Song JM, Shiota M, Shiota T. Mitral regurgitation associated with mitral annular dilation in patients with lone atrial fibrillation: an echocardiographic study. *Echocardiography*. 2009;26:885–889. doi: 10.1111/j.1540-8175.2009.00904.x.
6. van Rosendael PJ, Katsanos S, Kamperidis V, Roos CJ, Scholte AJ, Schalij MJ, Ajmone Marsan N, Bax JJ, Delgado V. New insights on Carpentier I mitral regurgitation from multidetector row computed tomography. *Am J Cardiol*. 2014;114:763–768. doi: 10.1016/j.amjcard.2014.06.005.
7. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski 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. doi: 10.1016/j.jacc.2011.06.032.
8. Silbiger JJ. Does left atrial enlargement contribute to mitral leaflet tethering in patients with functional mitral regurgitation? Proposed role of atriogenic leaflet tethering. *Echocardiography*. 2014;31:1310–1311. doi: 10.1111/echo.12629.
9. Kagiyama N, Hayashida A, Toki M, Fukuda S, Ohara M, Hirohata A, Yamamoto K, Isobe M, Yoshida K. Insufficient leaflet remodeling in patients with atrial fibrillation: association with the severity of mitral regurgitation. *Circ Cardiovasc Imaging.* 2017;10:e005451. doi: 10.1161/CIRCIMAGING.116.005451.
10. Grande-Allen KJ, Borowski AG, Troughton RW, Houghtaling PL, Dipaola NR, Moravec CS, Vesely I, Griffin BP. Apparently normal mitral valves in patients with heart failure demonstrate biochemical and structural derangements: an extracellular matrix and echocardiographic study. *J Am Coll Cardiol*. 2005;45:54–61. doi: 10.1016/j.jacc.2004.06.079.
11. Chaput M, Handschumacher MD, Tournoux F, Hua L, Guerrero JL, Vlahakes GJ, Levine RA. Mitral leaflet adaptation to ventricular remodeling: occurrence and adequacy in patients with functional mitral regurgitation. *Circulation*. 2008;118:845–852. doi: 10.1161/CIRCULATIONAHA.107.749440.
12. Debonnaire P, Al Amri I, Leong DP, Joyce E, Katsanos S, Kamperidis V, Schalij MJ, Bax JJ, Marsan NA, Delgado V. Leaflet remodelling in functional mitral valve regurgitation: characteristics, determinants, and relation to regurgitation severity. *Eur Heart J Cardiovasc Imaging*. 2015;16:290–299. doi: 10.1093/ehjci/jeu216.
13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210.

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