Circulation: Cardiovascular Imaging

EDITORIAL

Mitral Valve Adaptation

Can We Win the Race?

See Article by Nishino et al

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Ischemic mitral regurgitation (IMR) is a common complication of ischemic heart disease that doubles mortality after myocardial infarction (MI) and is a major driving factor increasing heart failure.[1,2] IMR is caused by post-MI left ventricle (LV) remodeling: inferior wall bulging displaces the papillary muscle, tethering the leaflets into the LV cavity, and restricting their closure.[3] The mitral valve (MV) has been thought of as an unchanging structure. However, its ability to adapt to expansion of the remodeling LV is increasingly recognized.[4–7] Although mechanically displacing the papillary muscles without MI causes compensatory MV growth,[8] this adaptive process is altered in the infarcted ventricle by excessive profibrotic processes, impairing closure, and augmenting MR.[9–11] There is a need to understand the timing of compensatory valve growth versus counterproductive fibrosis and the potential effects of therapy on these competing processes.[12] IMR can vary from early post-MI to the chronic stage, but previous studies have mainly focused on IMR in the subacute or chronic setting, and little is known about the mechanism of acute IMR.

The study by Nishino et al[13] in this issue of *Circulation: Cardiovascular Imaging* provides new insights into the mechanism of acute IMR. This sophisticated 3-dimensional echocardiographic study included 80 patients with significant IMR (44 patients with acute IMR; 36 with chronic IMR) compared with 3 different subsets of controls (acute MI without MR, previous MI without MR, and non-MI controls). MR was quantified by vena contracta and regurgitant volume. The authors measured MV complex geometry, LV function, and hemodynamics. LV systolic and diastolic volumes were significantly smaller in acute IMR than chronic IMR despite a comparable degree of regurgitation. The acute IMR group showed a smaller tenting volume and tenting height while the tethering length was not different. Of note, MV tenting in the acute MR group was still larger compared with non-MI controls, indicating that MV tethering occurs even with acute LV dysfunction. The scatter plot between MV tenting volume and MR (vena contracta width) demonstrated that acute IMR develops with smaller tenting compared with chronic IMR. It must be noted that the acute MI tenting volume will be lower than that in chronic IMR for any given tenting height because of the larger annular area in the chronic state.

The authors then pursued a comprehensive analysis of total leaflet area (early systolic value) and the adaptation-related index (total leaflet area to annular area ratio). Although the mitral annulus was remodeled (flattened and dilated) in acute MI, the leaflet area in the acute MR group was comparable to that of acute MI without MR and normal controls. This suggests a lack of valve adaptation in the acute phase, as shown by the smaller leaflet to annular area ratio (Figure). The authors also recognized the impact of hemodynamic factors for developing acute IMR. Systemic blood pressure was significantly higher in the acute versus chronic

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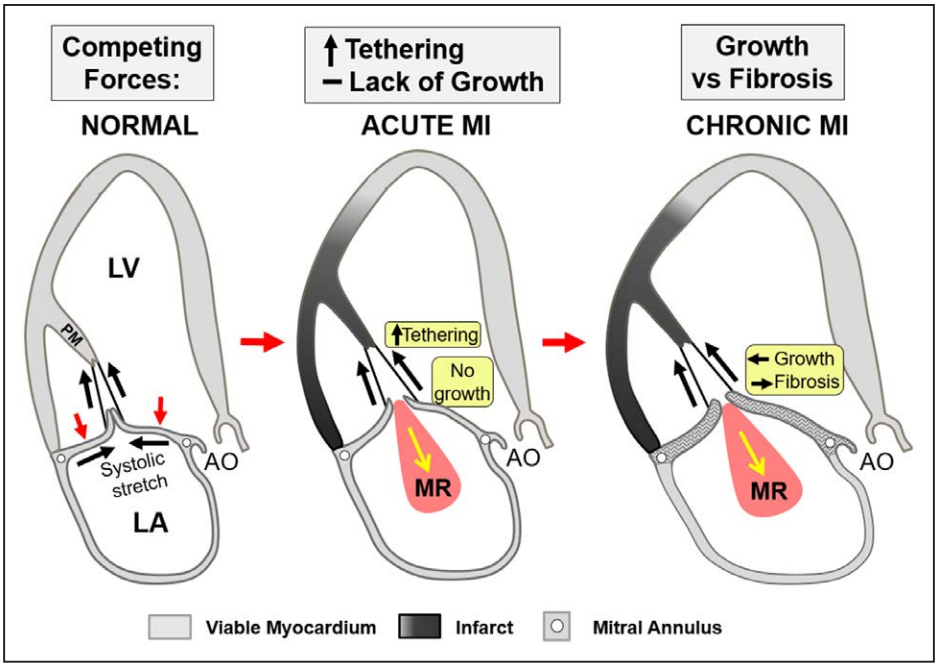

Figure. Competing valve adaptation factors over time.
Normal leaflet coaptation (**left**) is assisted by the ability of the leaflets to stretch in response to systolic pressure. Acute MI increases leaflet tethering, but without the opportunity for compensatory increases in mitral leaflet area, MR results (**center**). Over time (**right**), there is the additional competition between adaptive growth and profibrotic changes with leaflet thickening and stiffening that limit both systolic stretch and coaptation. Figure courtesy of Mark D. Handschumacher. MI indicates myocardial infarction; MR, mitral regurgitation.

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IMR groups, with lower pulmonary artery systolic pressure, potentially providing a higher transmitral closing force in the acute setting; despite that, MR volumes were comparable.[14,15] Taking these observations together, the authors provide an important message that in an acute MI setting, sudden onset of LV dysfunction may cause loss of MV coaptation even with a milder degree of tenting, and the lack of leaflet adaptation relative to the remodeled annulus and hemodynamic burden could augment significant IMR.

In this technically sophisticated and clinically important study, several additional factors are worth considering. First, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, or diuretics can affect hemodynamics that influence IMR. Second, MV adaptation is best assessed in terms of the total mitral leaflet area of the open valve in diastole,[4,16] independent of systolic leaflet stretch, which assists in valve adaptation to physiological variation in volume loading. Early systolic closure area may be close to that value, with differences relating to systolic stretch (Figure, left) and the initially coapted leaflet portions that are not included in the closed leaflet surface and may not be optimally resolved. In addition to the total mitral leaflet area to annular area ratio measured, the total mitral leaflet area to closure area ratio is important to assess adequacy of MV adaptation in meeting the need for surface a nonplanar surface area that depends on tethering.[4,16] Third, this study raises intriguing questions for longitudinal studies of the evolution of acute to chronic IMR.

This study importantly increases awareness of the need for adequate MV leaflet adaptation in limiting IMR. In chronic IMR, experimental studies have demonstrated that tethering in the presence of MI induces exuberant endothelial-to-mesenchymal transformation. Although modest endothelial-to-mesenchymal transformation can adaptively increase leaflet area, excessive generation of intersitial cells and matrix make the MV thicker and fibrotic, impairing closure and increasing MR.[11] In a large animal model, the angiotensin II receptor antagonist losartan modulates this excessive endothelial-to-mesenchymal transformation and other profibrotic changes.[17] The race to modulate MV adaptation and growth versus fibrosis has just begun; can we win it, by what means and at what time? The authors note that earlier reperfusion is a crucial factor for predicting improvement of IMR along with LV reverse remodeling,[18] but we must also consider the patients with persistent MR despite successful revascularization. Even surgical annular ring repair for chronic IMR often fails: persistent MV tethering causes recurrent MR.[19] For acute IMR, there is no consensus on whether MV surgery is beneficial as opposed to medical therapy alone.[20] Several studies have demonstrated that renin–angiotensin system inhibitors improve long-term event-free survival in patients with significant MR

after acute MI,[21,22] but the benefit was mainly thought linked to reverse LV remodeling; beneficial effects on the MV itself have not been addressed and may be difficult to study without the ability to control LV volume, as in the experimental setting.

In summary, the authors are to be congratulated for highlighting the need to consider the race toward MV adaptation beginning with acute MI, to encourage compensatory valve growth without fibrosis while limiting LV remodeling.

ARTICLE INFORMATION

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REFERENCES

1. Grigioni F, Detaint D, Avierinos JF, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. *J Am Coll Cardiol*. 2005;45:260–267. doi: 10.1016/j.jacc.2004.10.030.
2. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103:1759–1764.
3. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. *Circulation*. 2005;112:745–758. doi: 10.1161/CIRCULATIONAHA.104.486720.
4. 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.
5. Chaput M, Handschumacher MD, Guerrero JL, Holmvang G, Dal-Bianco JP, Sullivan S, Vlahakes GJ, Hung J, Levine RA; Leducq Foundation MITRAL Transatlantic Network. Mitral leaflet adaptation to ventricular remodeling: prospective changes in a model of ischemic mitral regurgitation. *Circulation*. 2009;120(11 suppl):S99–S103. doi: 10.1161/CIRCULATIONAHA.109.844019.
6. Beaudoin J, Handschumacher MD, Zeng X, Hung J, Morris EL, Levine RA, Schwammenthal E. Mitral valve enlargement in chronic aortic regurgitation as a compensatory mechanism to prevent functional mitral regurgitation in the dilated left ventricle. *J Am Coll Cardiol*. 2013;61:1809–1816. doi: 10.1016/j.jacc.2013.01.064.
7. Beaudoin J, Dal-Bianco JP, Aikawa E, Bischoff J, Guerrero JL, Sullivan S, Bartko PE, Handschumacher MD, Kim DH, Wylie-Sears J, Aaron J, Levine RA. Mitral leaflet changes following myocardial infarction: clinical evidence for maladaptive valvular remodeling. *Circ Cardiovasc Imaging*. 2017;10: e006512.
8. Dal-Bianco JP, Aikawa E, Bischoff J, Guerrero JL, Handschumacher MD, Sullivan S, Johnson B, Titus JS, Iwamoto Y, Wylie-Sears J, Levine RA, Carpentier A. Active adaptation of the tethered mitral valve: insights into a compensatory mechanism for functional mitral regurgitation. *Circulation*. 2009;120:334–342. doi: 10.1161/CIRCULATIONAHA.108.846782.
9. Bischoff J, Casanovas G, Wylie-Sears J, Kim DH, Bartko PE, Guerrero JL, Dal-Bianco JP, Beaudoin J, Garcia ML, Sullivan SM, Seybolt MM, Morris BA, Keegan J, Irvin WS, Aikawa E, Levine RA. CD45 expression in mitral valve endothelial cells after myocardial infarction. *Circ Res*. 2016;119:1215–1225. doi: 10.1161/CIRCRESAHA.116.309598.
10. Kunzelman KS, Quick DW, Cochran RP. Altered collagen concentration in mitral valve leaflets: biochemical and finite element analysis. *Ann Thorac Surg*. 1998;66(6 suppl):S198–S205.
11. Dal-Bianco JP, Aikawa E, Bischoff J, Guerrero JL, Hjortnaes J, Beaudoin J, Szymanski C, Bartko PE, Seybolt MM, Handschumacher MD, Sullivan S, Garcia ML, Mauskapf A, Titus JS, Wylie-Sears J, Irvin WS, Chaput M, Messas E, Hagège AA, Carpentier A, Levine RA; Leducq Transatlantic Mitral Network. Myocardial infarction alters adaptation of the tethered mitral valve. *J Am Coll Cardiol*. 2016;67:275–287. doi: 10.1016/j.jacc.2015.10.092.
12. Pierard LA, Magne J. New pharmacological target to treat ischemic mitral regurgitation: thinking outside the box. *J Am Coll Cardiol*. 2017;70:1245–1247. doi: 10.1016/j.jacc.2017.07.751.
13. Nishino S, Watanabe N, Kimura T, Kuriyama N, Shibata Y. Acute versus chronic ischemic mitral regurgitation: an echocardiographic study of anatomy and physiology. *Circ Cadiovasc Imaging* 2018;11:e007028. doi: 10.1161/CIRCIMAGING.117.007028.
14. Kaul S, Spotnitz WD, Glasheen WP, Touchstone DA. Mechanism of ischemic mitral regurgitation. An experimental evaluation. *Circulation*. 1991;84:2167–2180.
15. Schwammenthal E, Chen C, Benning F, Block M, Breithardt G, Levine RA. Dynamics of mitral regurgitant flow and orifice area. Physiologic application of the proximal flow convergence method: clinical data and experimental testing. *Circulation*. 1994;90:307–322.
16. Kim DH, Heo R, Handschumacher MD, Lee S, Choi YS, Kim KR, Shin Y, Park HK, Bischoff J, Aikawa E, Song JM, Kang DH, Levine RA, Song JK. Mitral valve adaptation to isolated annular dilation: insights into the mechanism of atrial functional mitral regurgitation [epub ahead of print]. *JACC Cardiovasc Imaging*. 2017. doi: 10.1016/j.jcmg.2017.09.013. https://0-www-ncbi-nlm-nih-gov.brum.beds.ac.uk/pubmed/29248661. Accessed March 27, 2018.
17. Bartko PE, Dal-Bianco JP, Guerrero JL, Beaudoin J, Szymanski C, Kim DH, Seybolt MM, Handschumacher MD, Sullivan S, Garcia ML, Titus JS, Wylie-Sears J, Irvin WS, Messas E, Hagège AA, Carpentier A, Aikawa E, Bischoff J, Levine RA; Leducq Transatlantic Mitral Network. Effect of losartan on mitral valve changes after myocardial infarction. *J Am Coll Cardiol*. 2017;70:1232–1244. doi: 10.1016/j.jacc.2017.07.734.
18. Nishino S, Watanabe N, Kimura T, Enriquez-Sarano M, Nakama T, Furugen M, Koiwaya H, Ashikaga K, Kuriyama N, Shibata Y. The course of ischemic mitral regurgitation in acute myocardial infarction after primary percutaneous coronary intervention: from emergency room to long-term follow-up. *Circ Cardiovasc Imaging*. 2016;9:e004841. doi: 10.1161/CIRCIMAGING.116.004841.
19. Hung J, Papakostas L, Tahta SA, Hardy BG, Bollen BA, Duran CM, Levine RA. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation*. 2004;110(11 suppl 1):II85–II90. doi: 10.1161/01.CIR.0000138192.65015.45.
20. Alajaji WA, Akl EA, Farha A, Jaber WA, AlJaroudi WA. Surgical versus medical management of patients with acute ischemic mitral regurgitation: a systematic review. *BMC Res Notes*. 2015;8:712. doi: 10.1186/s13104-015-1704-9.
21. Kim K, Kaji S, Kasamoto M, Murai R, Sasaki Y, Kitai T, Yamane T, Ehara N, Kobori A, Kinoshita M, Furukawa Y. Renin-angiotensin system inhibitors in patients with or without ischaemic mitral regurgitation after acute myocardial infarction. *Open Heart*. 2017;4:e000637. doi: 10.1136/openhrt-2017-000637.
22. Okura H, Kataoka T, Yoshida K. Renin-angiotensin system inhibitors in patients with myocardial infarction and secondary mitral regurgitation. *Heart*. 2016;102:694–700. doi: 10.1136/heartjnl-2015-308536.

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