EDITORIAL COMMENT

Mitral Valve Adaptation in Ischemic Heart Disease*

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Literature is the art of discovering something extraordinary about ordinary people, and saying with ordinary words something extraordinary.

—Boris Pasternak (1)

The same can be said about scientific insights. In fact, profound scientific discoveries are often based on systematic approaches to the most mundane observations. Our knowledge of physical world is very much based on observing how ball rolls down an inclined plane made by Galileo. Likewise, our knowledge about fundamental biological laws of heredity is based on observing the color of pea flowers (2). In cardiology, profound insights in the prognosis after acute myocardial infarction (MI) were gained by simply looking at ventricular size (3). Further observations on why some patients do, and some do not, develop mitral regurgitation (MR) after MI led to an understanding of how local left ventricular (LV) remodeling affects mitral valve (MV) geometry by tethering of otherwise “normal” leaflets. Findings from our group have contributed to this field, by describing that, for the same amount of valve tethering, ischemic MR is more severe than functional MR in dilated cardiomyopathy (4). Still, our observations did not explain why, or even recognize this as a question, and the current paper fills this void. But before we delve into innovations of this paper, a review of the biology behind MV function is necessary.

MV competency is dependent on the orchestrated function of the mitral leaflets, chordae tendinae, papillary muscles, subjacent LV myocardium, and fibromuscular annulus (5). At an ultrastructural level, there is a well-organized network of extracellular components across the leaflets that contribute to its highly precise spatial and temporal biomechanical properties (6). This network shows adaptive capacity, first being expressed during embryological development. In embryos a subset of endocardial cells transition from endothelial cells to mesenchymal cells in response to transforming growth factor beta (TGF-β) proteins (7, 8), resulting in organized lamellar and fibrous tissue (9). This cellular array changes as we grow and age in response to chronic mechanical loading (10). Changes in leaflet distensibility are also reversible in nonpathologic states. Wells et al. (11) demonstrated in a pregnant bovine model that changes in extensibility varied depending on the state of pregnancy (early vs. late). Whether the observed alterations to structural and material MV properties were in response to the physiological cardiovascular changes of pregnancy or the changes in hormonal milieu could not be separated, but the findings supported the postulation of an adaptable MV structure. Thus, we know that structure and distensibility of mitral leaflets change with growth, with aging, and during pregnancy. But what about in pathologic conditions?

A common dogma has been that MR in ischemic heart disease and idiopathic cardiomyopathy, so called “functional MR,” is a consequence of ventricular disease (i.e., mitral annular dilation, displaced papillary muscles, reduced transmitral closing pressure) in the setting of “normal” MV leaflets (12–15). However, Timek et al. (16) elegantly demonstrated in an ovine tachycardia-induced cardiomyopathy (a model for nonischemic cardiomyopathy), that MV leaflets elongate. In their subsequent experiment, Rausch et al. (17)
showed that tethering imposed by an inferior MI also leads to mitral leaflet elongation, albeit to a smaller degree. Again, this is in concordance with the prior observations of milder MR for the same amount of valve tethering in functional (nonischemic), versus ischemic cardiomyopathy. Thus a central question is the mechanism of the This topic was originally explored by Dal-Bianco et al. (18) in an ovine model of valve tethering by apical retraction of papillary muscle tips, which resulted in increased mitral leaflet area and thickness. The authors then demonstrated that the mechanical stress-induced MV changes were an active consequence of cell activation and matrix production. By flow cytometry, they found a number of endothelial cells (CD31+) coexpressing α-smooth muscle actin (α-SMA) in the tethered leaflets (18). This is important as α-SMA coexpression indicates reactivation of embryonic development pathways. This ability of embryonic pathway reactivation was further confirmed in vitro when MV endothelial cells treated with TGF-β1, TGF-β2, or TGF-β3 expressed α-SMA.

The next question was whether ischemic myocardial injury modulates leaflet response to valve tethering. In the current issue of the Journal, Dal-Bianco et al. (19) address this question by expanding on their previous work by introducing 2 modifications of the tethered MV model described previously. In a first modification, an apical MI (used instead of posterior/inferior MI in order not to modify mitral apparatus) was introduced. In a second, an apical MI was introduced while a surgical mesh was implanted to limit LV remodeling. The authors show that the presence of MI, even when LV remodeling is prevented, dramatically up-regulates embryonic development pathways, neovascularization, and TGF-β and hematopoietic cell expression, and increases valve thickness. In other words, ischemic heart disease dramatically alters the way MV leaflets react to mechanical stimulus brought about by MV tethering.

These findings are insightful and clinically relevant; 7.6 million Americans have a history of MI and ischemic MR develops in approximately 50% of patient after myocardial injury (20,21), and the presence of MR after MI is associated with a doubling in mortality (22,23). Despite its clinical impact and decades of investigation, the treatment of functional regurgitation remains controversial. MV surgery does not lead to LV reverse remodeling or survival benefit (24,25). The 2015 American Heart Association/American College of Cardiology (26) valvular heart disease practice guidelines reflect the dearth of suitable treatment options of chronic secondary MR with Class I recommendations limited to guideline-directed medical therapy for heart failure and cardiac resynchronization therapy to qualifying patients.

In this context, the findings of the current study by Dal-Bianco et al. (19) should prompt further investigation into the pathways of MV remodeling. Simply put, the authors show that mitral leaflets are not dead tissue. Perhaps, its biological response can be modulated. Indeed better insights into how to prevent or reverse maladaptive response of the MV may identify new therapeutic targets in order to optimize leaflet tissue characteristics and valvular function before the development of substantial MR.

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REFERENCES


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