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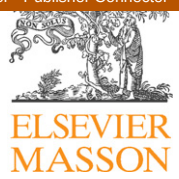

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SCIENTIFIC EDITORIAL

Ischemic mitral regurgitation: New concepts

Insuffisance mitrale ischémique : nouveaux concepts

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Ischemic mitral regurgitation (MR) is caused by altered left ventricular geometry and function [1—3], doubling rates of heart failure and mortality after myocardial infarction [4]. Still common despite improvements in revascularization and medical treatments after myocardial infarction, its treatment remains frustrating and controversial [5—10]. Restrictive annuloplasty, combined with coronary revascularization, is currently the most commonly performed surgical procedure to treat chronic ischemic MR. However, the variable results [6—8], potential for induction of mitral stenosis [9] and high rate of MR recurrence after this strategy suggest the need for a new approach that addresses the subvalvular mitral valve apparatus [11]. Thus, treatment benefit remains hotly debated and would be difficult to resolve as long as existing therapies are incompletely effective in permanently abolishing MR. New therapeutic opportunities are perplexing in their diversity. By exploring such areas of confusion we will try to revisit fundamental principles and achieve more effective solutions.

In ischemic MR, valve leaflets and chordae are structurally normal and MR results from geometrical distortion of the subvalvular apparatus, secondary to left ventricular enlargement and remodelling due to myocardial infarction. Burch et al. [12,13] postulated restricted leaflet motion secondary to papillary muscle dysfunction. However, Tsakiris et al. [14] have shown that papillary muscle dysfunction never produces MR. Moreover, Messas et al. [15] demonstrated that papillary muscle dysfunction can paradoxically decrease ischemic MR.

Thanks to the impressive work performed by Robert Levine (Massachusetts General Hospital, Boston, MA, USA) over the past 10 years, we have an accurate understanding of the characteristics of ischemic MR.

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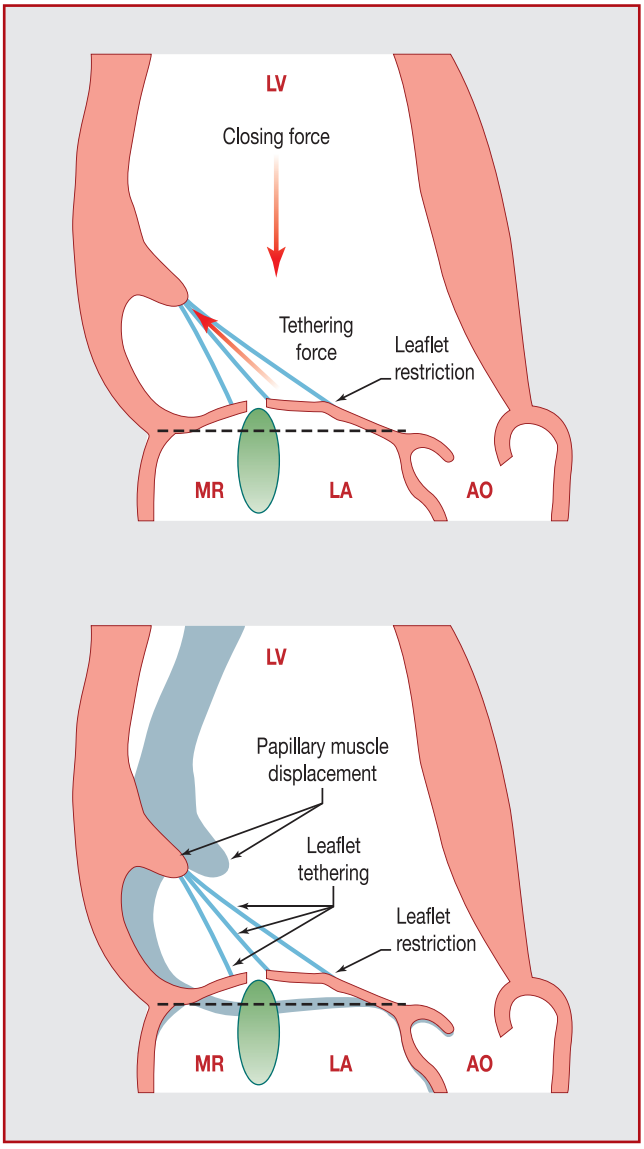

Figure 1. Imbalance between tethering forces — annular dilatation, left ventricular dilatation, papillary muscle displacement, left ventricular sphericity — and closing forces, resulting in the reduction of coaptation surface and causing mitral regurgitation. Ao: aorta; LA: left atrium; PM: papillary muscle; MR: mitral regurgitation.

The papillary muscles — normally located parallel to the left ventricular long axis and perpendicular to the leaflets — efficiently balance forces generated by ventricular pressure on the leaflet surface. Ischemic or heart failure causes the myocardial segments underlying the papillary muscles to bulge posteriorly and outward, displacing the papillary muscles, so that they pull the leaflets nonperpendicularly, away from their normal coaptation (Fig. 1). The distance between the papillary muscle tips and the annulus also increases, drawing the leaflets into the left ventricle and restricting their motion towards closure [16,17]. Two-dimensional echocardiography has demonstrated apically restricted leaflet motion, called 'incomplete mitral leaflet closure' [18,19]. The displacement of the leaflet attachments causes papillary muscle wall dysfunction or 'tethering' of the papillary muscles. Inferior dyskinesis contributes also to increased leaflet tethering [19].

Tethering is one facet of a unifying principle of mitral valve function: leaflet motion is determined by the three-dimensional geometry of the leaflets and their attachments relative to the surrounding flow field. Furthermore, ischemic MR reflects a basic imbalance between the size of the remodelling left ventricle and the mitral valve, which is tethered by chordal connections to displaced papillary muscles and cannot close effectively. This dichotomy is a simplification. Recent works have determined whether and how the mitral valve adapts to such mechanical stresses and why such adaptation fails to prevent MR, and how we may augment leaflet area therapeutically. Clinical data from Chaput et al. [20] indicate leaflet area averages 35% greater in patients with left ventricular dysfunction compared with normal healthy controls, thus demonstrating that the mitral valve undergoes adaptive and dynamic changes. Chaput et al. [20] and Dal-Bianco et al. [22] have implemented a large-animal model for studying the effects of mechanical stretch on the mitral valve, independent of myocardial infarction and MR that may produce confounding effects. The adaptation of the mitral valve using controlled tethering stretch over 2 months in the beating sheep heart without myocardial infarction or MR, established under bypass, has been performed in sheep. Stretch consistently increased the leaflet area, measured over time by three-dimensional echo, and augmented leaflet thickness by histopathology. Mitral valve area increased by 17% over 2 months with evidence of a process of active cellular adaptation involving endothelial—mesenchymal transformation, beginning along the atrial endothelium and penetrating into the valve interstitium. The potential mechanism for leaflet adaptation involving increased leaflet length and interstitial thickness includes the generation of transforming growth factor beta by mechanically stretched valve interstitial cells and myocytes [21], which induces endothelial—mesenchymal transformation in stretched excised mitral valves [22]. These adaptive processes in the stretched mitral valve are similar to those involved in embryonic valve growth and development that can be reactivated in such conditions. The still unmet question is why this adaptive mechanism does not fully compensate the leaflet tethering? Some paracrine factors are likely to be involved and are the subject of investigation.

Surgery for ischemic MR remains challenging. Standard surgical therapy includes annular ring reduction, which aims to improve leaflet apposition by correcting posterior annular dilatation. Operative mortality is higher than in organic MR and the long-term prognosis is worse. Although often effective initially, long-term failures are increasingly recognized. Indications for surgery and the preferred surgical procedure in patients with ischemic MR remain controversial, mainly because of the persistence and high recurrence rate of MR after mitral valve repair and the absence of evidence that surgery prolongs life [7]. Experienced centres consistently report important persistent and recurrent MR, often months after surgery, in 30% or more of patients, casting doubt on whether satisfactory early results represent success [7,9,23—25]. Severe ischemic MR is not usually improved by revascularization alone, and the persistence of residual MR carries an increased mortality risk. Several preoperative

echocardiographic predictors of recurrent ischemic MR and treatment failure, after undersized annuloplasty, have been identified and are indicative of severe tethering, associated with a poor prognosis. These include end-diastolic left ventricular diameter > 65 mm, mitral diastolic annulus diameter ≥ 37 mm, posterior mitral leaflet angle > 45° (indicating a high posterior leaflet restriction), distal anterior mitral leaflet angle > 25°, systolic tenting area > 2.5 cm^2, coaptation distance between the annular plane and the coptation point > 10 mm, end-systolic interpapillary muscle distance > 20 mm, and systolic sphericity index > 0.7 [26].

Intraoperative MR underestimation contributes to the impression of recurrence but is only part of the problem. The mitral valve is caught in a tug-of-war between the dilated annulus and the displaced papillary muscles. Reducing annular size alone leaves persistent tethering to the displaced left ventricular wall. Bach and Bolling [27] indicate that ischemic MR is a ventricular — not a valvular — problem. Calafiore et al. [23] have shown that annuloplasty failure is predicted by greater preoperative leaflet tethering. Most importantly, the ventricle is a moving target and often continues to remodel and dilate, which renders initial repair ineffective, as quantitatively confirmed by Hung et al. [9]. Bach and Bolling introduced the most common, and increasing, practice of implanting rings one or two sizes smaller than predicted by measuring the fibrous intertrigonal annulus [27]. However, as mentioned by Tahta et al. [24], this attempts to compensate for the fundamental problem, but not correct it. McGee et al. [7] reported high-grade recurrent MR in 35% of patients 6 months after surgery, highest for pericardial annuloplasty but still 25% for Cosgrove and complete Carpentier rings, with no significant difference between large and small rings. Rings also shift the posterior annulus anteriorly, but the posterior leaflet remains tethered posteriorly, so its anterior excursion is markedly restricted; nearly rigid, it coapts poorly [9,28]. Modified approaches include asymmetrical annuloplasty, first introduced by David [28], to reduce the largest leaflet gap, located medially because the inferomedial papillary muscle is most affected, bringing the vulnerable commissural point closer to the papillary muscles to relieve tethering. Furthermore, undersized annuloplasty does not improve long-term survival in patients with chronic ischemic MR [5].

Such insights led to a novel surgical approach for chronic ischemic MR. Subvalvular tethering can be relieved by modifying ventricular, leaflet or chordal structures (Fig. 2). An alternative approach involves modifying the chordal tethering mechanism directly, in ways suggested by valve anatomy [17] and clinical observations [18,19,29]. Fine marginal chordae position the leaflet tips and prevent prolapse: thicker intermediate basal chordae insert closer to the leaflet bases. With increased tethering, the basal anterior leaflet near the annulus becomes nearly rigid and is tented apically by these basal chordae. The more distal leaflet pivots around the 'knee' where these chordae attach, but only its tip can then approach the posterior leaflet, which decreases the coaptational surface that normally seals the orifice. Messas et al. [30] therefore proposed that cutting a limited number of these critically positioned basal chordae can decrease ischemic MR: chordal cutting by eliminating apical tenting, and relieving leaflet tethering, eliminates the anterior leaflet bend and can make the leaflets less

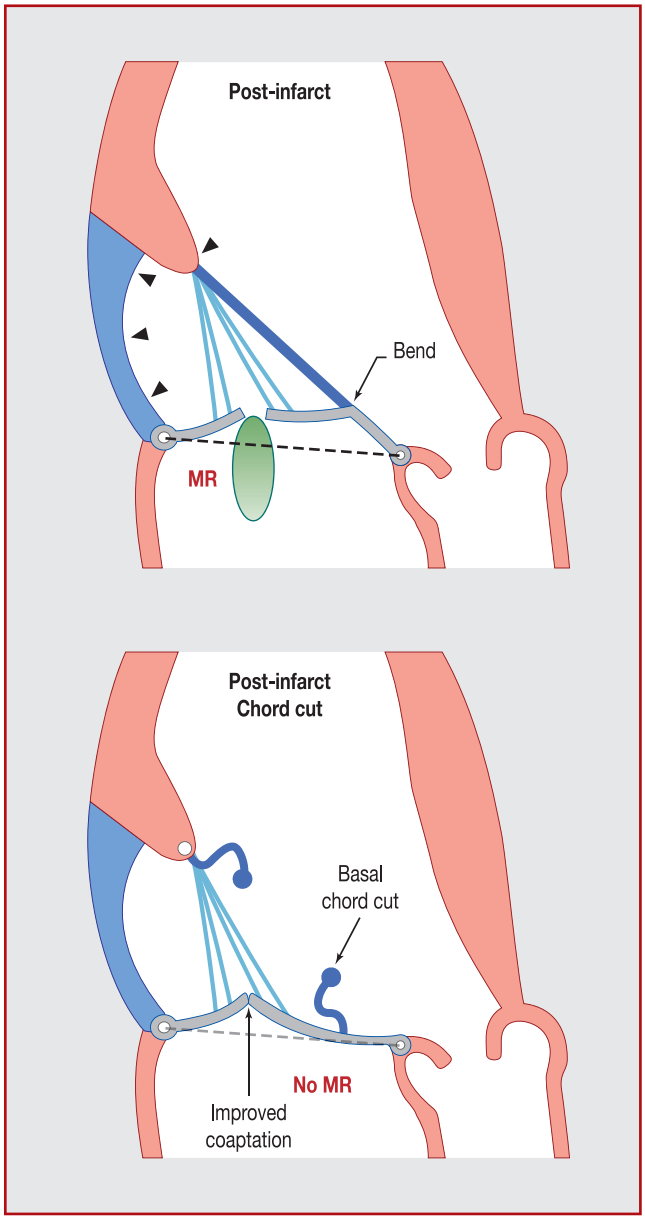

Figure 2. Left panel: anterior leaflet bend by papillary muscle displacement and leaflet tethering producing mitral regurgitation (MR). Right panel: restoration of coaptation after basal chordal, relieving tethering on the anterior leaflet.

taut, thus improving leaflet mobility and coaptation and reducing MR The intact marginal chordae continue to prevent prolapse. These major series of large-animal models experiments on chordal cutting therapy to relieve mitral valve tethering and ischemic MR showed incremental benefits from chordal release without any adverse effects over several months on ventricular remodelling in a sheep model of acute [30] and chronic [15,31] ischemic MR. As the leaflet tethering is applied on both annular and papillary muscle levels, the same team used an experimental chronic ischemic MR sheep model to study the potential benefit of associating undersized ring annuloplasty with chordal cutting. The association of both techniques improved results due to improved coaptation and reduced left ventricular

remodelling with an incremental improvement over isolated undersized annuloplasty [11]. Clinical data from Borger et al. [32] have shown that chordal cutting improves mitral leaflet mobility and decreases MR recurrence in patients, without any adverse effects on left ventricular function.

Finally, the tethering mechanism provides both annular and subvalvular targets for therapy, including reversing left ventricular geometric changes and leaflet or chordal modification. The likelihood of repair will be enhanced by the availability of different options, obviating the need for valve replacement. Detailed mapping of geometric substrates should allow tailoring of the ideal combination of annular, ventricular and chordal approaches to achieve the best result in each patient.

Conclusion

Understanding mechanisms of functional MR has led to improved therapies targeted to the primary causes. New therapeutic options have the potential to provide a more flexible approach, adaptable to patients with diverse ventricular and valvular changes. The guiding principle is to achieve a comprehensive repair that addresses tethering at both ends of the leaflets. Leaflet tissue adaptation is also of interest and contributes to the mechanism of MR. Therefore, in the near future, we expect that a combination of leaflet tissue biomechanic properties and three-dimensional subvalvular mitral valve apparatus analysis will help to resolve this last frontier in valve disease.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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