The appreciation of mitral valve prolapse (MVP) has evolved from clinical recognition to surgical classification to guide repair; echocardiographic analysis, and specificity with 3-dimensional (3D) depiction and most recently genetic and molecular studies. Two manifestations of degenerative mitral valve disease (DMVD) with involvement of multiple scallops of both leaflets and fibroelastic deficiency (FED), with generally thin leaflets except for myxoid degeneration of one or a few scallops of a single leaflet, generally the posterior. From both mechanistic and surgical perspectives, it remains unresolved whether these are 2 distinct phenotypes or a spectrum, and whether the localized thickening in FED is primary or secondary to the adjacent turbulent blood flow emerging from a scallop with deficient chordal restraint.

See Article by Clavel et al

Clavel et al., in this issue of Circulation: Cardiovascular Imaging, have now contributed information from dynamic quantitative 3D echocardiography relevant to this question in patients undergoing reconstructive surgery that allows visual classification. Despite comparable mitral regurgitation (MR) severity consistent with surgical selection, in addition to previously described static anatomic characteristics, namely enlarged annulus and excess valvular tissue, cyclic annular dynamics are blunted in DMVD and systolic leaflet area changes are reduced in FED. These findings raise the possibility of primary alterations of the mitral annulus and biomechanical differences in the leaflet tissue with excess distensible tissue in DMVD versus relatively deficient and less extensible tissue in FED. These variations could reveal differences in mechanism and require differences in surgical approach.

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cells contribute to normal valve matrix homeostasis with low turnover. During embryonic development and myxomatous degeneration, valvular interstitial cells are activated to myofibroblasts that expressing smooth muscle-associated contractile proteins, metalloproteinases, and inflammatory cytokines that rapidly remodel the extracellular matrix, produce collagens, proteoglycans, and growth factors such as transforming growth factor-β, and lead to thicker, more extensible valves. Therefore, leaflet stretch caused by initial prolapse and accentuated by annular flattening, may lead to cellular activation that potentially increases prolapse. This may also explain why myxomatous degeneration is usually limited to the prolapsing leaflet scallop in FED.

Valve Tissue Reserve: Beneficial or Detrimental?
Valvular redundancy in DMD versus paucity in FED may affect degree of regurgitation: excess but nonflail leaflet tissue may increase the leaflet coaptation zone, actually reducing MR, whereas limited leaflet tissue and extensibility may limit coaptation. Factors that determine whether leaflets are too long or small in relation to the left ventricular remodeling need to be considered, as in functional MR, with decreased valve reserve because of leaflet thickening with restricted motion, and hypertrophic cardiomyopathy, with elongated leaflets disproportionate to the reduced cavity size that can explain the coexistence of MVP.

Should Mitral Annulus Dynamics Help to Redefine DMVD Phenotypes?
Barlow disease is characterized by excess connective tissue, with redundant, thickened and yellowish leaflets, marked annulus dilatation, elongated chordae, disrupted collagen and elastic layers, and excess acid mucopolysaccharides. FED is characterized by decreased connective tissue, deficient in collagen, elastin and proteoglycans, thin, smooth and translucent leaflets without excess tissue and only moderate annulus dilatation and thin, slightly elongated chordae; localized myxomatous degeneration and thickening occur within the flap scallop, mainly the posterior leaflet. To date, however, clear echocardiographic definitions of those entities have not been standardized or validated; moreover, histopathologic features are not always conclusive; finally, the surgical classification remains difficult or impossible in some patients. Thus, dynamic changes of the mitral annulus might be helpful in the near future (when semiautomatic analysis available) to approach the differential diagnosis between DMD and FED, subject to the caveats above about annular changes being secondary to variations in prolapse themselves and therefore in force intersections between leaflets and annulus. It is also important to recall the marked phenotypic variations seen within kindreds with heritable MVP, suggesting that variations in prolapse severity and extent may occur despite a common haplotype and relate to additional factors.

Which Potential Consequences for Surgical Management?
Surgical MV repair involves removal, restraint, or reconstruction of a part or whole valve scallop that is most redundant. Fixing the lesion requires understanding the mechanisms and mechanics needed to achieve physiological repair. The considerable amount of information obtained with dynamic 3D transesophageal echocardiography quantification should allow guiding valve reconstruction procedures, whether surgical or interventional, by addressing yet unanswered questions such as: Should we respect or resect excess tissue in MVD when considering the possible role of compensatory mechanism of reduced regurgitation by the excess tissue in MVD and conversely the degree of increased regurgitation because of tissue paucity in FED? What is the mechanism of postrepair posterior leaflet tethering and how to prevent it? What is the long-term consequence of edge-to-edge suturing or clipping? What is the best technique of commissural reconstruction and the functional consequences of papillary muscle repositioning in commissural prolapse? The detection of leaflet reserve, as proposed by Clavel et al, may affect decisions on adjusting leaflet and annular interventions to provide the optimal repair for all patients with DMVD.

Future Directions
This new functional approach based on 3D transesophageal echocardiography complements the functional approach introduced in the beginning of reconstructive valve surgery. It should open a new era in valve surgical analysis and repair, but also might have consequences for the diagnosis of DMD and FED. Current areas of investigation are focused on genetic analyses and new treatment modalities, either targeting annular collagen to reduce annular diameter using directly applied radiofrequency energy or through novel molecular and cell-based therapies targeting underlying mechanisms to limit disease progression and adverse impact on myocardial function. Deriving valve-specific progenitor cells from induced pluripotent stem cells generated from somatic cells of patients harboring genetic valve disease might provide invaluable early disease models predicting how mutations cause DMVD. Understanding valve and annular adaptations could create opportunities for physiological interventions, for example, by modulating transforming growth factor-β, which seems to have a major regulatory role in leaflet homeostasis. Determining whether DMD and FED are truly distinct phenotypes or part of a spectrum will benefit from genome-wide association studies underway, advanced imaging techniques, and immunohistochemical studies of the molecular and cellular events to which echocardiography provides a structural window.

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References


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