Dynamic Phenotypes of Degenerative Myxomatous Mitral Valve Disease
Quantitative 3-Dimensional Echocardiographic Study

Marie-Annick Clavel, DVM, PhD*; Francesca Mantovani, MD*; Joseph Malouf, MD; Hector I. Michelena, MD; Ori Vatury, MD; Mothilal Sonia Jain, MD; Sunil V. Mankad, MD; Rakesh M. Suri, MD, DPhil; Maurice Enriquez-Sarano, MD

Background—Fibro-elastic deficiency (FED) and diffuse myxomatous degeneration (DMD) are phenotypes of degenerative mitral valve disease defined morphologically. Whether physiological differences in annular and valvular dynamics exist between these phenotypes remains unknown.

Methods and Results—We performed triple quantitation of cardiac remodeling and of mitral regurgitation severity and of annular and valvular dimensions by real-time 3-dimensional-transesophageal-echocardiography. Forty-nine patients with degenerative mitral valve disease classified as FED (n=31) and DMD (n=18) by surgical observation showed no difference in age (65±10 versus 59±13; P=0.5), body surface area (2.0±0.2 versus 2.0±0.2 m²; P=0.5), left ventricular and atrial dimensions (all P>0.55), and mitral regurgitation regurgitant orifice (P=0.62). On average, annular dimensions were larger in DMD versus FED, but height was similar resulting in lower saddle shape. Dynamically, annular DMD versus FED display poorer contraction and saddle-shape accentuation in early systole and abnormal enlargement, particularly intercommissural, in late-systole (all P<0.05). Valvular dynamics showed stable valvular area in systole in FED versus considerable systolic increased area in DMD (P<0.001). Prolapse height and volume increased little throughout systole in FED versus marked increase in DMD (P<0.001).

Conclusions—Our novel observations show that FED and DMD, although both labeled myxomatous, display considerable physiological phenotypic differences. In DMD, the annular increased size and profoundly abnormal dynamics demonstrate DMD-specific annular degeneration compared with the enlarged but relatively normal FED annulus. DMD does not incur more severe mitral regurgitation, despite larger prolapse and valve redundancy, underscoring potential compensatory role of tissue redundancy of DMD (or aggravating role of tissue paucity of FED) on mitral regurgitation severity. (Circ Cardiovasc Imaging. 2015;8:e002989. DOI: 10.1161/CIRCIMAGING.114.002989.)

Key Words: echocardiography, three-dimensional  heart valve diseases  mitral valve insufficiency

Degenerative mitral valve disease (DMVD) is the most common cause of severe organic mitral regurgitation (MR) in Western countries, particularly in patients referred to mitral surgery. DMVD phenotypes, fibro-elastic deficiency (FED) characterized by single-scallop prolapse/flail with other scallops/leaflet often normal or thin versus diffuse myxomatous degeneration (DMD) with generalized valvular thickening, redundant leaflets and chordal elongations (Figure 1), are easily recognizable intraoperatively or by echocardiography but remain poorly understood. Indeed, myxomatous degeneration examined on resected leaflet-segments is similar in both phenotypes, explaining their common classification as DMVD but whether the mechanistic valvular pathophysiology is similar or different in FED versus DMD is unknown. These questions generated a considerable interest for quantitative valvular assessment now possible using 3-dimensional (3D) echocardiography. Morphologically, previous 3D echocardiographic studies have shown that the DMVD phenotypes have different valvular and annular dimensions. However, the advent of 3D echocardiography provided the ability to obtain not only static measurements but also quantitative assessment of the mitral valvular apparatus in a dynamic manner throughout the cardiac cycle. Dynamic imaging coupled with quantitative software demonstrated the dynamic nature of mitral annulus physiology in normal humans, matching the old observations in animals. In contrast, we found DMVD annulus generally of abnormal dynamics, but no analysis of...
DMVD phenotypes for annular or valvular dynamics has been reported. New progress in quantitative methods now allow measurement of mitral annulus, leaflets, and prolapse dimensions, and yield the new possibility of complete dynamic characterization of these DMVD phenotypes. Hence, comprehensive dynamic physiological description of these poorly understood entities is now possible and may provide crucial pathophysiologic insights, offering stronger basis for recent efforts at mechanistic and genetic DMVD characterization. Furthermore, dynamic physiological characterization may provide insights crucial to surgical or interventional repair of each DMVD phenotype. Thus, our objective was, in patients in whom DMVD phenotype was defined by direct intraoperative visualization, to evaluate by quantitative 3D-transesophageal-echocardiography (3DTEE) combined with comprehensive quantitative MR and cardiac remodeling characterization, the static and dynamic characteristics of mitral annulus, leaflets, and prolapse in FED and DMD, throughout the cardiac cycle. The general hypothesis of the study was that, for similar MR severity, annular and valvular dynamics are profoundly different in FED and DMD.

Methods

We prospectively recruited 49 consecutive patients with severe MR because of DMVD referred to our institution for elective surgical mitral valve repair. The criteria for DMVD diagnosis were (1) the presence in at least 1 scallop of the mitral valve of the features of myxomatous mitral disease with thickening and redundancy; (2) the presence of mitral prolapse as the cause of the MR with or without ruptured chordae; (3) the absence of history or anatomic feature of bacterial endocarditis. These criteria were in all cases confirmed by direct surgical examination of the mitral valve during valve repair. Patients were excluded if they had contraindications to transesophageal echocardiography, uncontrolled atrial fibrillation, presence of mitral stenosis, more than mild other valve disease, or associated pericardial or congenital heart disease. Patients with associated connective tissue disorders, possible bacterial endocarditis, Marfan syndrome, hypertrophic cardiomyopathy, and rheumatic heart disease were also excluded. The study was approved by the Institutional Review Board at the Mayo Clinic and was considered low risk requiring only verbal consent.

All patients underwent a 2D transthoracic echocardiography before surgery with MR quantitation and a 3D transesophageal echocardiography intraoperatively with recording. According to surgical observation, patients were classified in 2 groups as FED or DMD (Figure 1). The anatomic criteria for FED were the general presence of a single scallop involved with myxomatous degeneration and prolapse. If >1 scallop seemed to be involved, then the opposing leaflet was uninvolved, thin, and nonprolapsing. The presence of ruptured chordae was not considered indispensable to FED diagnosis. Anatomic criteria of DMD were the presence on multiple scallops and definitely on both leaflets of myxomatous degeneration with diffuse thickness and redundancy. The final surgical diagnosis of the valvular phenotype was noted on the surgical report and not communicated to the investigator quantitating 3D echocardiography off-line, who did not participate in the performance of intraoperative echocardiography.

Transthoracic Echocardiographic Measurements

All patients underwent a comprehensive 2D echocardiography preoperatively with the use of commercially available ultrasound. Left ventricular and MR quantification were performed according to guidelines of echocardiographic societies, with particular attention to combination of methods and measurement consistency/quality involving also clear delineation of flow convergence. Severity of MR was assessed with the use of effective regurgitant orifice and regurgitant volume.

Three-dimensional Transesophageal Echocardiographic Measurements

TEE was performed intraoperatively, after initial anesthesia induction and endotracheal intubation, before cardiopulmonary bypass or thoracic incisions, and 3DTEE was obtained as recommended. Briefly, full-volume 3D data sets were acquired with the RT3DE imaging probe (model X72) and IE33 echocardiography imaging platform, both from Philips Medical Systems (Philips Medical Systems, Bothell, WA). The images were digitally stored and transferred to a workstation with Q-Laboratory Mitral-Valve-Quantification (QLAB version 9) Software (Philips Medical Systems) for off-line analysis. After storage of 3D data sets, quantitative analysis was promptly performed by an observer blinded to any preoperative and intraoperative Doppler-echocardiographic and surgical findings.

Figure 1. Intraoperative (A and B) and 3-dimensional-echocardiographic (C and D) views of Mitral valve with fibro-elastic deficiency disease (A and C) or diffuse myxomatous degeneration (B and D). Note the single-scallop involvement of fibro-elastic deficiency versus the diffuse leaflet redundancy and involvement in diffuse myxomatous degeneration.
Three orthogonal mitral annulus images were displayed and modified to optimize visualization of the entire annulus. Mitral annular measurements (annular area, circumference, intercommissural and anteroposterior diameter, and height; Figure 2A and 2B) were obtained 6× during the cardiac cycle, in early, mid-, and late-diastole and early, mid, and late-systole. Early diastole was identified just after mitral valve opening, late-diastole as preceding mitral closure, and mid-diastole as midway between these frames. Early systole was identified as immediately after onset of mitral closure, late-systole at or immediately before aortic closure, and mid-systole midway between these frames. Annular height was the instantaneous maximal vertical distance between highest (anterior or posterior) and lowest (anterolateral or posteromedial) points and used to compute the instantaneous ratio of annular height to intercommissural diameter, a measure of annular saddle shape, associated with reduced valvular stress. After annular delineation, mitral leaflets were traced in multiple slices from medial to lateral commissure, and landmarks placed at the tip of the coaptation zone, so that the entire surface of anterior and posterior leaflets could be defined. From these valvular 3D data, mitral leaflet measurements (3D total valvular area, anterior leaflet area, and posterior leaflet area) and quantitation of leaflet excess movement in relation to annular plane (volume and height of prolapse) were also obtained at end systole (Figure 2C and 2D).

Statistical Analysis
Results were presented as mean±SD for continuous variables and percentages for categorical variables. Differences between patient groups were analyzed with the use of the 2-sided Student t test for continuous variables, Wilcoxon rank-sum test for ordinal variables, the χ² for categorical variables or Fisher exact tests for categorical variables when ≥1 cells have an expected frequency of ≤5. Changes in 3D Doppler-echocardiographic variables were analyzed with the use of a 2-way ANOVA for repeated-measures with 1 factor analyzed as a repeated-measures factor. F tests were used to evaluate the effect of group (FED versus DMD) and the effect of cardiac cycle point and the interactions between group and cardiac cycle point. All pairwise multiple comparison procedures were done with the Holm–Sidak method. A value of P<0.05 was considered statistically significant. The statistical analyses were performed with the Sygmatstat 11.0 software.

Results
Clinical and Operative Characteristics
The clinical characteristics are presented overall in Table 1, left column, and are typical of degenerative MR with mean age in the mid-sixth decade, predominance of men and rare symptoms. As usual with severe MR, blood pressure and heart rate were in the normal range, but many patients had a history of hypertension often requiring treatment. Other comorbidities, such as diabetes mellitus and coronary disease, were rare. Operative characteristics were also typical of the current era with rare associated coronary bypass surgery, and vast predominance of valve repair performed as expected with degenerative MR, during a short cross-clamp time and often using a robotically assisted approach. All patients had competent valves after surgery (equal or less than mild MR). The right columns of Table 1 compare the clinical and operative characteristics of patients classified surgically as FED or DMD. The slightly older age of patients with FED is associated with trends for more frequent diabetes mellitus or the use of diuretics, but otherwise, there is no significant clinical difference, suggesting that the discovery of the degenerative MR phenotype is not detectable clinically.
2D and 3D echocardiographic characteristics of patients with degenerative MR are indicated in Table 2. Overall, 2D hemodynamics show features of severe MR with enlarged left ventricular and left atrial, verified by large regurgitant volume and effective regurgitant orifice. The comparison of hemodynamic characteristics between FED and DMD shows no hemodynamic difference, particularly in regard to the severity of MR, so that no morphological or dynamic difference between these phenotypes can be explained on the basis of the MR severity. Morphologically, there were differences between groups on 2D echocardiography in term of higher prevalence of Bileaflet prolapse and of multiscallop posterior leaflet involvement in the DMD group. Conversely, valvular calcification was not different.

The 3D static (obtained by averages over the entire cardiac cycle) measurements of mitral annulus, valves, and prolapse (systolic averages) showed multiple differences. In fact, the only variable that was not different between groups was the average annulus height. Both annular diameters (anteroposterior and intercommissural), as well as annular area and circumference, were larger in DMD than in FED. Conversely, the saddle shape was higher in FED than in DMD. Valvular area, measuring tissue redundancy, was larger for the entire mitral valve and both leaflets in DMD. The depth and volume of prolapse was larger with DMD than with FED. Hence, Table 2 shows the paradox of degenerative MR phenotypes, whereas DMD despite larger valvular redundancy, larger annulus, and larger prolapse shows no larger severity of MR when compared with FED.

Dynamic Mitral Annular Phenotypes
Dynamic changes in mitral annular dimensions over the cardiac cycle are shown in Table I in the Data Supplement. Taken together as degenerative MR, the mitral annulus is dynamic with changes in dimensions over the cardiac cycle and all 6 variables showed phasic changes (P value phase, all \(<0.01\)). In both groups, during diastole, only trivial variations in dimensions were noted and most changes occurred in systole than in diastole (Table I in the Data Supplement). Comparing FED (upper line of each row of Table I in the Data Supplement) and DMD (lower line of each row of Table I in the Data Supplement), the larger annular diameter, area, and circumference in DMD remained so throughout the cardiac cycle (P value group; all 4 \(P<0.01\)). However, the dynamics of mitral annulus behave differently for most measurements, with only the anteroposterior diameter after a similar course in both groups (P interaction=0.16) with brief contraction in early systole returning later to the diastolic value, larger in DMD but after the same course (Figure 3A).

### Static Echocardiographic Characteristics
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A striking difference regarded the intercommissural diameter, which remained stable throughout the cardiac cycle in FED, whereas it enlarged during systole in DMD (Figure 3B), and this difference in behavior was significant ($P_{interaction}<0.001$; Table I in the Data Supplement). This difference of dynamics between the degenerative MR groups resulted in complex dynamics in annular area with a simple and transient early systolic contraction in FED, whereas in DMD, the transient contraction was followed by a late-systolic annular enlargement ($P_{interaction}<0.001$; Figure 3C). The annular circumference dynamics was also different with minimal changes in FED and progressive systolic increase in DMD ($P_{interaction}<0.001$; Figure 3D). The dynamic changes in annular height were superimposable in the 2 groups (Figure 3E) but because of the difference in the intercommissural diameter behavior, the 2 groups had different dynamics in saddle shape, with sustained systolic saddle shape accentuation in FED, whereas in DMD, the brief and modest early systolic saddle shape accentuation was not sustained (Figure 3F).

### Dynamic Mitral Valvular Phenotypes

Mitral leaflet dynamics during systole is presented in Figure 4 and in Table II in the Data Supplement. Surfaces of anterior and posterior leaflets are larger irrespective of timing in DMD than in FED patients (Figure 4A and 4B; Table II in the Data Supplement). However, there are major dynamic differences between degenerative MR types. Indeed, overall surface of leaflets remains constant during systole in patients with FED, whereas it increases considerably in patients with DMD ($P_{interaction}<0.001$). This difference in valvular dynamics is obvious for both leaflets although the increase in leaflet area throughout systole is more pronounced for posterior leaflet in DMD.

Similarly, height and volume of prolapse are larger in DMD irrespective of timing (Figure 4C and 4D; Table II in the Data Supplement). However, there are also considerable dynamic differences between degenerative MR types. Prolapse height and volume increase throughout systole in both groups, but this increase is much larger in DMD versus FED (both $P_{interaction}<0.001$). Thus, despite close height and volume of...
prolapse in early systole, patients with DMD versus FED had much larger prolapse dimension during mid- and late-systole (Figure 4C and 4D).

Measurement Variability
In 10 randomly selected patients, blinded repeated measurements were performed to calculate intra- and interobserver variability. Intraobserver variability was 3.3±1.1% for anteroposterior diameter, 4.6±0.3% for annular height, 2.2±2.8% for annular circumference, and 3.3±0.3% for valvular area. Interobserver variability for the same measurements was 5.1±3.7%, 1.4±0.6%, 2.3±6.4%, and 7.4±0.8%, respectively.

Discussion
The present study, based on triple quantitation, dynamic 3DTEE quantitation of annular and valvular alterations coupled with MR and cardiac remodeling quantitation, verifies the hypothesis that, beyond classical appearances, the phenotypes of DMVD, FED, and DMD display considerably different valvular pathophysiology. First, overall larger annular size and larger prolapse volume and height in DMD versus
FED, contrasting to surprisingly similar MR severity, suggest that marked tissue redundancy in DMD is not aggravating but compensatory for MR. In FED, tissue paucity, despite smaller prolapse and annulus, may be aggravating MR, emphasizing the importance of matching tissue resection amplitude to specific phenotype of degenerative MR during valve repair. Second, wider annular enlargement in DMD, despite similar MR and left ventricular and left atrial enlargement as FED, implies primary annular alterations in DMD. This suspicion is supported by profoundly different mitral annulus dynamics in DMD and FED. Indeed, annular dynamics in FED, despite annular enlargement, remains similar to normal. Conversely, mitral annular dynamics is profoundly abnormal in DMD, in early systole (poor contraction and saddle shape accentuation) and in late-systole (anomalous enlargement, particularly intercommissural). Hence, annular contribution to degenerative MR is different in DMD versus FED, involving not only a different balance of annular dilatation/tissue redundancy but also a double annular dysfunction (early- and late-systolic) in DMD. Third, although both DMD and FED cause a lesion similarly labeled mitral valve prolapse, valvular dynamics is profoundly different. FED prolapse is established early and increases little in systole with stable valvular tissue areas. DMD valvular area and prolapse increase considerably throughout systole. DMD systolic redundancy occurs by mobilization of valvular reserve because leaflets unfurl and enlarge like sails in systole versus FED in which there is no mobilization of valvular reserve in systole, irrespective of leaflet examined. These new dynamic physiological insights into degenerative MR phenotypes by quantitative 3DTEE promise essential contributions to valve repair techniques.

Complex Nature of DMVD

DMVD is common but remains described in relatively simplistic terms of its hallmark, the mitral valve prolapse, its severity (bellowing for simple prolapse or flail for unsupported segments) and localization (single versus bileaflet). First 3D insights described mitral annulus as a landmark of peculiar saddle shape used to measure prolapse defining depth. Phenotypes described at surgery were recognized clinically, but histologically no difference could be captured on valvular segments resected during valve repair. Biochemically myxomatous degeneration was conceived as a single tissue repair dysfunction entity. Limitations of bench analysis of DMVD are linked to increasing use of valve repair, which samples resected tissue fragments versus whole valves and to lack of valid animal models. Hence, we are left with little path to uncover whether DMVD phenotypes, DMD versus FED, are negligible morphological variations or are functionally distinct with clinical implications and wide repercussions for genetic, mechanistic, and therapeutic research. Advent of 3D echocardiography using TEE provides excellent display and time resolution to image the entire mitral valve. Our study not only confirms larger annular dimensions in DMD but also provides new dynamic insights warranting definitely separating these phenotypes. Indeed, FED annular dynamics is close to the known normal kinetics (early systolic anteroposterior contraction and saddle-shape accentuation with
stable intercommissural diameter). Conversely, DMD annular dynamics is profoundly abnormal in early systole (diminutive anteroposterior contraction and saddle shape accentuation) and late-systole (marked enlargement abnormally because of intercommissural enlargement). These static (annular enlargement in excess to MR and cardiac remodeling) and dynamic (flatter and dyskinetic annulus) differences suggest intrinsic annular disease in DMD, possibly mechanistically linked to frequent annular disjunction in DMD. This association will require further study because little is known about annular disjunction. Thus, in DMD (contrary to FED), defective annular physiology contributes to MR in early systole because of poor saddle-shape accentuation (flatter annulus) and in late-systole because of marked intercommissural and area enlargement.

Our study also provides new insights into mitral leaflets’ physiology. In FED, prolapsing segment volume and height appear early and progress little throughout systole. FED valvular tissue area (including that of prolapsing leaflet) is smaller than in DMD and does not increase through systole. Conversely, DMD prolapse is larger and markedly increase through systole. Simultaneously, DMD valvular tissue area not only is larger but also increases markedly, implying recruitment of valvular reserve. DMD leaflets behave as sails unfurling under the wind, described anatomically as hooding and consistent with reduced valve stiffness of myxomatous infiltration. The difference in valve reserve is central to DMD paradox of larger, deeper, and severely progressive prolapse with larger, flatter annulus, contrasting with similar MR severity as FED. FED, despite smaller prolapse and smaller, more saddle-shaped annulus not enlarging in systole, has no overt valve reserve and reaches similar effective regurgitant orifice as DMD. Thereby, larger valve reserve probably plays a compensatory role, preventing larger effective regurgitant orifice of MR that one would expect in DMD. However, imbalance between progression of annular enlargement and tissue availability probably explain MR progression with further annular enlargement. MR of FED and DMD is dynamic, increasing from early- to late-systole, and fits increasing prolapse magnitude during systole in both forms, but in each phenotype, dynamic MR reflects evolving combination of increasing prolapse severity counteracted by valve reserve coverage.

### DMVD Phenotype and Mitral Valve Repair

Mitral valve repair is key to improved long-term outcome of patients with degenerative MR and is the preferred treatment of MR. Ability to perform durable repair is also conditional to offer surgery in asymptomatic patients with DMVD. Although repair techniques are largely derived from description by Carpentier, there is no specific recommendation for FED versus DMD. Although quadrangular resection of posterior leaflet has been the staple of mitral repair, recently surgeons have offered more limited triangular resections or even advocated respect of valve tissue rather than resect. Controversies on these approaches have not been based on valvular data, which are not measured during surgery and remain qualitatively judged. Furthermore, full surgical judgment on excess tissue may not be easy on a flaccid heart, apart by mitral expert surgeons because our study shows considerable unfurling and expansion of valvular tissue in DMD during systole. Hence, our study provides quantitative basis to procedural repair choices, opening wider use of preoperative 3DTEE. Annuloplasty decreases enlarged annular size but should be titrated to balance correcting annular dilatation to available tissue excess. Annuloplasty of DMD also corrects annular late-systolic enlargement by reanchoring mitral annulus to ventricular myocardium. Although annuloplasty of FED remains surgical dogma, FED annulus less severely enlarged and maintaining its dynamics, probably explains acceptable results of percutaneous repair without annuloplasty in inoperable patients with FED by mitral clip. Posterior valvular resection, judicious in DMD to ensure smooth coaptation line, should be prudent in FED where relative tissue paucity is the rule. Excess tissue resection in FED may result in posterior leaflet tissue gaps with wide open indentations between scallops potentially causing residual MR. Subvalvular support by artificial chordae is durable and popular, but its adjustment is not always simple to compensate for valvular and subvalvular tissue redundancy. In view of our data, artificial chordal supports warrant adaptation to the specific pathophysiology of FED versus DMD, particularly excess valvular tissue in end-systole. Whether adaptation and individual tailoring to patients’ needs are improved by comprehensive 3DTEE measurements and whether specifically designed annuloplasty rings improve repair results require further studies and clinical trials. Hence, specific annular and valvular dynamics of DMVD phenotypes are critical to recognize and to reconcile with the principles and tools of valve repair, to achieve the goals of new valvular guidelines (ie, high immediate and durable success of valve repair).

### Limitations

Comprehensive measurements with MR quantitation and dynamic 3DTEE mitral quantitation were applied to a limited but sufficient sample required to quantitatively compare DMVD phenotypes. Our intent was to verify for the first time the contrasting mitral valvular and annular dynamics of the phenotypes of DMVD. As such, it has profound implications for mechanistic and genetic research into DMVD and provides insights into specific principles of degenerative MR repair. However, as such it is not applicable in clinical practice as each patient’s set of measurements requires hours of processing incompatible with immediate clinical application. To develop individualized valve repair planning, which would allow matching of surgeons’ skills to patients’ needs, it is essential that future software versions be developed to enhance automatic (or semiautomatic) processing of 3DTEE data sets. The present hypothesis-driven analysis should represent a strong incentive to develop and make clinically applicable such software improvements.

### Conclusions

Our study provides hitherto unknown insights into pathophysiology of phenotypes of DMVD, demonstrating that DMD and FED, despite similar MR severity and cardiac remodeling, are profoundly different, not just for valvular morphology but most importantly for valvular and annular dynamic...
physiology. The paradox of larger prolapse with larger and flatter annulus in DMD versus FED, contrasting with similar MR severity, points toward larger tissue redundancy as compensatory rather than aggravating MR in DMD. In addition, DMD annulus is dynamically abnormal, enlarging in systole through intercommisural enlargement, further suggesting intrinsic annular involvement, in contrast to FED characterized by smaller annulus of almost normal kinetics. Valvular dynamics is also strikingly different, with no evidence of valvular reserve in FED, whereas in DMD, considerable valvular reserve and redundancy is deployed and unfurled during systole. These phenotypic differences extending beyond mere dimensional differences should lead to mechanistic and genetic studies to develop strategies preventing the progression of MR and to phenotype-specific corrections during valve repair of patients with degenerative MR.

**Disclosures**

None.

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Degenerative mitral regurgitation is the most frequent cause requiring mitral surgery. In the repair era, pathological examination of the entire mitral valve is exceedingly rare, leaving an essential physiological role to 3-dimensional echocardiography. This study has highlighted 2 clinically important lessons: (1) the difference between diffuse myxomatous disease and fibro-elastic deficiency, poorly known in the absence of large pathological data, is affirmed; it is not limited to the type of prolapse (bi versus single leaflet) or valve thickness. Dynamic valvular and annular mitral physiology is different. Hence, reality of fibro-elastic deficiency and diffuse myxomatous disease as independent conditions, instead of variants, is confirmed and opens the door to future genetic/physiological analysis to identify causal genes and familial assessment after probands are identified and (2) the link of valvular/annular physiology to mitral regurgitation severity was analyzed quantitatively. We assumed that more tissue redundancy would be associated with prolapse severity and with more severe mitral regurgitation. In fact, the opposite is true; diffuse myxomatous disease with severe prolapse is covered by markedly redundant tissue, whereas in fibro-elastic deficiency, there is tissue paucity that fails to cover the less severe prolapse and the result is a similar mitral regurgitation effective regurgitant orifice. This information can help future investigation into surgical approaches related to the debate of resect versus respect in mitral repair. Relative tissue paucity, if recognized, could warrant limited mitral tissue resection and orient toward other valve supports; additionally for cardiologists, 3D-quantitative analysis may facilitate prerepair evaluations particularly if the analysis software can be automated.
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Supplemental Material For
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**Table SM1: 3D Echocardiographic Variables – Annular Measurements**

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Degree of freedom: 1 for group analysis, 2 for phase analysis and 2 for group*phase interaction analysis.
Table SM2: 3D Echocardiographic Variables – Leaflets and Prolapse Measurements

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<th></th>
<th>Early-Systole</th>
<th>Mid-Systole</th>
<th>Late-Systole</th>
<th>p-value Group</th>
<th>p-value Phase</th>
<th>p-value Group*Phase Interaction</th>
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<td><strong>Anterior Leaflet Area, mm²</strong></td>
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<td>DMD</td>
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<td><strong>Total Leaflet Area, mm²</strong></td>
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</table>

Degree of freedom: 1 for group analysis, 2 for phase analysis and 2 for group*phase interaction analysis.