Mitral Valve Prolapse with Mid-Late Systolic Mitral Regurgitation: Pitfalls of Evaluation and Clinical Outcome Compared to Holosystolic Regurgitation

Running title: Topilsky et al.; Mid-late systolic MR

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Abstract:

**Background** - Mitral regurgitation (MR) of mitral valve prolapse (MVP) predominates in late-systole but may be holosystolic (Holo-MR) or purely mid-late systolic (Mid-Late-MR) but the impact of MR-timing on MR left ventricular (LV) atrial (LA) consequences and outcome is unknown. Whether effective-regurgitant-orifice (ERO) by flow-convergence method is similarly linked to outcome in Mid-Late-MR and Holo-MR is uncertain.

**Methods and Results** - We comprehensively and prospectively quantified MR in 111 patients with MVP and Mid-Late-MR and matched them to 90 patients with MVP and Holo-MR for age, gender, atrial fibrillation, ejection fraction and ERO (flow-convergence). Mid-Late-MR vs. Holo-MR groups were well-matched including for comorbidity, blood pressure and heart rate (all p>0.10). Mid-Late-MR vs. Holo-MR caused similar color jet-area, mid-systolic regurgitant flow and peak velocity (p>0.40). Despite identical ERO (0.25±0.15 vs.0.25±0.15 cm², p=0.53), Mid-Late-MR shorter duration (233±56 vs. 426±50 msec, p<0.0001) yielded lower regurgitant volume (24.8±13.4 vs. 48.6±25.6mL; p<0.0001). MR consequences, systolic pulmonary pressure, LV and LA-volume-index (all p<0.001) were more benign in Mid-Late-MR vs. Holo-MR. Under medical management less cardiac events (5-year 15.8±4.6 vs. 40.4±6.1%, p<0.0001) occurred in Mid-Late-MR vs. Holo-MR requiring less mitral surgery. Multivariable analysis confirmed the independent association of Mid-Late-MR with benign consequences and outcomes (all p<0.01). Absolute ERO was not linked to outcome in contrast to regurgitant volume.

**Conclusions** - MR of MVP purely Mid-Late systolic causes more benign consequences and outcomes than holosystolic MR. Assessment may be misleading as jet area and ERO by flow-convergence appear similar to holosystolic MR. However, shorter MR yields lower RVol, consequences and benign outcomes. Instantaneous ERO by flow-convergence should be interpreted in context and in Mid-Late-MR regurgitant volume provides information more reflective of MR severity. Therefore, clinical management and surgical referral should carefully take into account timing and consequences of MR.

**Key words:** echocardiography; mitral regurgitation; valvular regurgitation
Introduction

Epidemiologic data show that mitral regurgitation (MR) is the most frequent valve disease in the U.S. population. The major cause of MR requiring surgical correction is degenerative, characterized mostly by mitral valve prolapse (MVP). The association between aging and higher MR prevalence leads to rapidly increasing population burden of this valve disease. Despite the high feasibility of valve repair and marked decline in operative mortality timing of surgery in asymptomatic patients with MVP remains controversial, as shown also by divergences between U.S. and European guidelines. A critical element of the clinical decision-making process is the MR severity, which in patients with MVP is an essential marker of survival after diagnosis. Furthermore, quantitative MR assessment has taken a central role in the evaluation of patients with MR and MVP. Indeed, these methods are sensitive in detecting MR progression and effective regurgitant orifice (ERO) has been shown in several large prospective series to be independently and strongly associated to outcome under medical management. An ERO ≥40 mm² is now recognized by most scientific societies as the threshold for defining severe MR, and is associated with high mortality, in excess to that expected in the population, and with frequent cardiac events. However, despite the coherence of outcome studies and the wide consensus on the markers of MR severity, there are areas of uncertainty that may have important clinical consequences. MR associated with MVP is dynamic predominant or purely (Mid-Late-MR) in the later phase of systole. Patients with MR that is not holosystolic were not represented in outcome studies, and it is not possible to determine whether such patients incur the same consequences (ventricular, atrial, hemodynamic, outcome) as their counterparts with holosystolic MR (Holo-MR) and whether the measured ERO carries similar implications in Mid-Late-MR.
and Holo-MR. From the theoretical physiologic point of view there is relative equipoise in that regard. On one hand, the MR of MVP predominates in late systole with the largest phasic ERO while the largest regurgitant volume (RVol) is delivered in mid-late systole so that the lack of an early systolic phase to the MR may be negligible and Mid-Late-MR may carry severe consequences. Indeed, our measurements showed that less than 10% of the regurgitant volume occurs in the first 25% of systole in MVP. On the other hand, amputation of a substantial part of systole in generating RVol may affect overall MR severity and lead to overestimation of MR by using the ERO measured at peak MR velocity as the main marker of MR severity. These two opposite concepts are possible and cannot be resolved by review of previous data.

Thus, to fill these gaps of knowledge and verify the hypothesis that MVP with Mid-Late-MR causes similar left ventricular (LV), atrial (LA) and outcome consequences as MVP with Holo-MR, we prospectively enrolled patients with MVP and Mid-Late-MR and quantified the MR by proximal isovelocity-surface-area method. We then matched these patients to those with MVP and Holo-MR for age, gender, ejection fraction, presence of AFib (AFib) and measured ERO.

Methods

Study Population

Between 2004 and 2006, we enrolled consecutive patients with MVP with mid-late systolic MR (by continuous-wave Doppler) with eligibility criteria identical to our prospective study of holosystolic MR. Thus, all patients had at least mild (by color-flow imaging jet), isolated (without aortic-valve disease) and pure (without stenosis) MR quantified by proximal isovelocity surface area (PISA) method. High-quality flow convergence imaging excluded constrained flow convergences. Patients were excluded if they had functional MR, particularly with pseudo-
prolapse (leaflet overshoot) with restricted motion or structurally normal valves. MR limited to isovolumic relaxation was excluded and in all cases peak MR velocity was easily discernible and measurable. We excluded patients with annular calcification and mean gradient $\geq 5$ mmHg, associated organic aortic or tricuspid disease, previous valve repair or replacement, congenital or pericardial disease or decreased ejection fraction ($<50\%$) for any reason. Age, sex, and cardiac rhythm were not considered eligibility criteria.

**Study Design**

At enrollment, we performed prospective MR quantitation followed by retrospective frequency-matching of cases (Mid-Late-MR) group to control group with MVP and similarly prospectively quantified Holo-MR (by continuous-wave Doppler) previously reported. Gender and AFIB specific mean of age ($\pm 5$ years), ejection fraction (EF, $\pm 5\%$), and ERO ($\pm 5$ mm$^2$) were used (as known major predictors of outcome) to define target matching criteria for control population Holo-MR. This frequency-matching process provides groups with identical distribution of matching criteria but without specific one to one case-control matching. Thus, all patients had MVP with MR $\geq$mild (color-flow) and quantitation of ERO and RVol by Doppler-Echocardiography. The study was powered (80%, 0.05, for a minimum total of 48 events for both groups combined) to detect at least a 30% difference in cardiac events (cardiac death, heart failure or new onset AFib under medical management) between patients with Mid-Late-MR vs. Holo-MR. The study approved by the Mayo institutional review board, was judged low-risk, requiring only oral consent.

**Clinical Assessment and Management**

History and clinical examination were recorded at baseline by patients’ personal physicians at our institution. Coexisting conditions were evaluated by Charlson comorbidity
Congestive heart failure (CHF) was diagnosed based on Framingham Heart Study criteria. NewAFib was diagnosed in patients in sinus rhythm at baseline using ECG tracings. Clinical management was determined independently by patients’ personal physician using all information available. Follow-up information was collected in 2010 after enrollment ended and all baseline data had been obtained. Events used as end-points were all cause mortality and cardiac events (cardiac mortality including sudden death, CHF, new onset of AFib) and need for mitral valve surgery.

**Doppler-Echocardiography**

Complete Doppler echocardiography was performed. Quantitative data promptly stored in a database were not altered throughout the study.

MR quantitation used proximal flow convergence (PISA) method as validated previously. Briefly, color-Doppler images of MR proximal flow convergence used a zoom of the region of interest. We optimized transducer’s position to minimize the angle between regurgitant flow and ultrasonic beam, color-flow scale and baseline shift until flow convergence was clearly visualized. Flow convergences constrained or deformed were not considered acceptable, so that correction by constraint angle was not necessary. Radial distance ‘r’ between first red/blue interface and mitral orifice allowed calculation of regurgitant flow (RFlow). Using continuous wave Doppler, we measured MR peak-velocity, regurgitant time-velocity-integral (RTVI), total systolic duration (including pre-ejection, ejection and relaxation) from mitral closure to opening, MR effective duration from regurgitation beginning to end (mitral opening) and calculated MR normalized duration as ratio of MR effective duration to total systolic duration. Absolute ERO area was calculated as RFlow/MR-velocity and regurgitant volume (RVol) as ERO*RTVI (Figure 1). A time-normalized ERO was calculated as (absolute
ERO)*(MR normalized duration). RVol was also measured by Quantitative Doppler (measurement of mitral and aortic stroke volumes) in 117 patients as previously described. Inter and Intra-observer variability of MR Doppler-echocardiographic quantitation was analyzed in 15 randomly selected patients.

Left ventricular diameters, volumes, ejection fraction, and mass were measured as recommended. LA volume was calculated using biplane area-length method as previously described.

**Statistical Analysis**

Continuous normally distributed parameters were presented as mean±SD and compared using Student’s t-test. Ordinal and/or non-normally distributed variables were presented by median, 1st and 3rd quartiles and compared using the nonparametric Wilcoxon rank-sum test. Categorical data were compared between groups using χ² tests or Fisher’s exact test when appropriate. Comparison of measurements (PISA vs. quantitative Doppler or Intra- and Inter-observer comparisons) relied on linear regression, paired T-tests and Bland and Altman plotting of differences vs. mean values. To analyze the effect of Mid-Late-MR vs. Holo-MR (independent variable) on echocardiographic measures of MR severity and consequences (RVol, LV size indexed, LA volume index, RV systolic pressure, continuous and dichotomous) univariable and multivariable analysis adjusted for age, gender, EF, AFib, ERO and systolic blood pressure were performed. Clinical outcome endpoints were ascertained while patients were under medical management (from diagnosis to surgery or death). Event rates (presented ± standard error) were calculated according to Kaplan–Meier method and compared by log-rank test. Unadjusted and adjusted analyses of time to events were performed with Cox proportional-hazards models. To avoid over-fitting of the model we restricted the independent variables to the presence of Mid-
Late-MR as main variable of interest and age, sex, symptoms, EF, presence of AFib and ERO as main adjusting variables with Charlson comorbidity index and systolic blood pressure added to adjusting variables in a verification model. All P values were two-sided, and values<0.05 indicated statistical significance. All authors participated in designing the study, collecting and analyzing data, and drafting and revising the manuscript.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the 201 patients enrolled in the study, overall and stratified by presence of Mid-Late-MR. Comparison between Mid-Late-MR and Holo-MR verified that the matching process was successful as age, sex, EF, AFib and ERO were equally distributed. Although not part of the matching process, blood pressure, heart rate, prevalence of diabetes or Charlson comorbidity index showed no difference between Mid-Late-MR and Holo-MR. Thus, the matching-process achieved groups, Mid-Late-MR and Holo-MR, with similar comorbidities, ERO and AFib prevalence and thereby differing essentially by the timing of MR. Of note these characteristics, particularly age, are well within the general presentation of patients with MR in the current era.12

MR characteristics

The MR characteristics and the associated LV, LA, hemodynamic and clinical, characteristics are compared between Mid-Late-MR and Holo-MR in Table 2, showing similarities but also marked differences between the two types of MR. Indeed, in addition to similar ERO by design, jet area (in both the 4 chamber and 2 chamber views), regurgitant peak velocity (driving pressure) and regurgitant flow rate were similar in Mid-Late-MR and Holo-MR. Conversely,
regurgitant duration and the ratio of MR duration to total systolic time were shorter in Mid-Late-MR (Figure 1). Shorter MR duration resulted in smaller RTVI and thus smaller RVol in Mid-Late-MR despite similar ERO and driving pressure. Thus, despite the large and similar MR jet, the prevalence of severe MR (RVol ≥ 60 mL/beat) was much lower in Mid-Late-MR (1% vs. 33%, p<0.0001). The adequacy of RVol measurement was confirmed in 117 patients in whom we measured also RVol simultaneously by quantitative Doppler: The correlation between Doppler and flow convergence RVol was r= 0.93, p<0.001, with slope not different from 1.0 (p=0.80), and values of RVol by Doppler and flow convergence RVol showing no difference by paired analysis (45±25 and 44±25 mL/beat, p=0.17) and with Bland-Altman analysis (difference of methods not different from zero throughout range of values). Mean differences for intra- and inter-observer differences for ERO were 0.13 and 1.9 mm2 and for RVol were 2.4 and 2.2 mL/beat, not different from 0 (all p>0.24). Thus, no evidence for measurement errors appeared as source of difference in RVol between Mid-Late-MR and Holo-MR.

In term of MR consequences, smaller RVol in Mid-Late-MR was associated with smaller LV dimensions, mass and LA volume (Table 2). Hemodynamic consequences of MR were also markedly different between Mid-Late-MR and Holo-MR. Mid-Late-MR was associated with lower E-wave diastolic velocity consistent with lower RVol and possibly lower LV filling pressure, as suggested by lower systolic pulmonary pressure. Less frequent systolic reversal in pulmonary veins is also consistent with lower RVol. Clinically, lower severity at presentation with less frequent symptoms in Mid-Late-MR was mirrored by lower intensity of medical treatment by diuretics or Digoxin in the Mid-Late-MR vs. Holo-MR.

These overall differences between Mid-Late-MR and Holo-MR were confirmed after stratification according to MR measured instantaneous ERO (ERO ≥ or < 0.20 cm²). In
both strata, the differences in echocardiographic measurements between the Mid-Late-MR and Holo-MR remained highly significant (Figure 2). Thus, the lower severity and consequences of MR in MidLate-MR are not related to a different response to a given ERO but are observed irrespective of instantaneous ERO range.

In multivariable analyses, association of Mid-Late-MR with lower severity and consequences of MR was tested, adjusting for age, sex, EF, systolic blood pressure, AFib and measured ERO. Indeed, Mid-Late-MR remained independently associated with smaller RVol as continuous variable (p<0.0001) and with lower odds of RVol≥60 mL (Odds-ratio 0.02[0.001-0.08], p<0.0001). Mid-Late-MR was independently associated with lower LV end-diastolic volume index as continuous variable (p<0.0001) and with lower odds of a value ≥100 mL/m² (0.09[0.03-0.19], p<0.0001). It was also independently associated with lower LV end-systolic volume index (p<0.001) and with lower odds of a value ≥35 mL/m² (0.29[0.13-0.62], p=0.001). Mid-Late-MR was independently associated with lower LA volume index (p<0.0001) and lower odds of LA-index≥60 mL/m² (0.16[0.06-0.39), p<0.0001). It was also independently associated with lower systolic pulmonary pressure (p<0.0001).

Clinical Outcome

All-cause mortality

There were 20 deaths under medical management among the entire series, with survival rates of 98±1% at one year, and 90±3% at five years. The five-year survival rate tended to be lower with Holo-MR vs. Mid-Late-MR but the difference did not reach statistical significance (84±5 vs. 94±3%; p=0.10). Multivariable analysis with limited adjustment for age and ERO did not affect the results and the trend towards lower mortality in patients with Mid-Late-MR did not reach statistical significance (p=0.10). Among the entire cohort, 55 underwent mitral valve surgery,
less in patients with Mid-Late-MR than Holo-MR (19.8% vs. 36.7%; p=0.008). Thus, the combined event of death or need for surgery was more often observed in patients with Holo-MR than Mid-Late-MR (24±5 vs. 6±2% at 1 year and 44±6 vs. 31±6% at 5 years, p=0.02).

**Cardiac Events**

After diagnosis there were 52 cardiac events (death from cardiac causes, admission for congestive heart failure, or new onset AFib) while patients were medically treated, including 16 patients who presented with heart failure and 28 with new AFib. The five-year cardiac event rate was 26±4% overall and was significantly lower in patients with Mid-Late-MR compared to Holo-MR (15.9±4.7 vs. 42.4±6.2; p<0.0001) (**Figure 3**). Each individual event, besides death, was less frequent (at 5 years heart failure 5.8±3.4% vs. 17.0±4.7%; p=0.002; new onset of AFib 7.0±2.5% vs. 21.5±5.2%; p=0.009) in Mid-Late-MR. Mid-Late-MR was strongly associated with lower cardiac event rates in Cox-proportional analysis (**Table 3**), showing a hazard ratio of 0.25 for Mid-Late-MR vs. Holo-MR that was almost unaffected by any adjustment.

Examining the objective echocardiographic variables associated with outcome measured by cardiac events, we tested the absolute ERO, the RVol as well as LA volume index and the ERO normalized for relative regurgitant time. Absolute instantaneous ERO non-normalized to regurgitant time was, in this setting, not associated with cardiac events (hazard ratio 1.2[0.5-2.5] for ERO≥ 0.40 cm², p=0.64), a lack of association unaffected by any adjustment (all p>0.36). Conversely, RVol was associated with cardiac events univariably (hazard ratio 3.42[1.74-6.32], p=0.007 unadjusted for RVol≥60 mL/beat) and in multivariable analysis (3.85[1.94-7.23], p=0.0003 adjusted for age, sex, symptoms, AFib and EF and 3.91[1.93-7.48], p=0.0004 with additional adjustment for systolic blood pressure and comorbidity index). The ERO normalized to relative regurgitant time was also associated with cardiac events univariably (hazard ratio for
normalized-ERO≥40 mm² 3.29[1.34-6.92], p=0.01) and in multivariable analysis with similar adjustments (4.28[1.63-9.9], p=0.005 and 4.38[1.65-10.3], p=0.005 for comprehensive adjustment). LA volume-index≥60 mL/m² was also associated with high event-rates univariably (hazard ratio 3.28[1.75-5.90], p<0.001) and in multivariable Cox-proportional hazards analysis (2.98[1.49-5.77], p=0.003 and 3.18[1.57-6.26], p=0.002 for comprehensive adjustment). Thus, even in the presence of MidLate-MR, there are measures of MR severity and consequences that are strongly linked to outcome, once it is realized that the non-normalized ERO is not useful under such circumstances.

Discussion

In patients with MVP the dynamic nature of MR during the cardiac cycle is well documented but little attention has been directed towards MVP with MidLate-MR. Previous outcome studies of organic MR either included exclusively holosystolic MR or did not address specific outcome of Mid-Late MR. We report herein the first sizable series of patients with Mid-Late-MR due to MVP with prospective, quantitative assessment and analysis of long-term outcome. Our study shows that purely Mid-Late-MR due to MVP can be particularly misleading. Indeed, compared to Holo-MR, Mid-Late-MR presents with similar jet extent, similarly large flow convergence, similar regurgitant flow and velocity. Therefore, a less-than-comprehensive assessment may lead to erroneously consider it as severe as Holo-MR, particularly if the measured instantaneous ERO is the only quantitative variable considered. However, our study shows that despite the late predominance of MR in MVP, comprehensive assessment reveals the lesser degree and consequences of purely Mid-Late MR. With MR purely involving Mid-Late systole, lower RVol with less LV and LA enlargement, lower pulmonary
pressures and fewer symptoms due to MR are observed. In turn, our study shows that lower volume overload translates into clinical outcomes with markedly lower rates of cardiac events and need for surgical treatment. Hence, the Mid-Late-systolic nature of MR has critical importance in the interpretation of qualitative or quantitative measures of MR severity. In this setting, the measured instantaneous ERO is not independently associated with outcome, in contrast to what is observed with Holo-MR. Hence, other measures of MR severity, RVol in particular, should be used in clinically managing patients with MVP and MR. Therefore, clinical management should carefully take into account timing and consequences of MR and interpret the ERO measurement in context.

**Pathophysiology and clinical presentation**

The historic seminal report on MVP linked late-systolic murmurs to billowing mitral valves, and was later confirmed by echocardiography. Doppler-Echocardiography subsequently demonstrated the dynamic MR of MVP with MVP progression throughout systole even in patients with Holo-MR. Pathophysiologically, as systole progresses, LV volume decreases causing increasing mitral billowing, which compounded by the dysfunctional enlarging mitral annulus, leads to wider ERO, so that most of the RVol penetrates the LA in MidLate-systole. With dynamic ERO measured by the instantaneous flow convergence method, accuracy concerns were raised but ERO measured at peak MR velocity closely reflects average holosystolic ERO and determines outcome. MidLate-MR has not been well studied and the observation that it may have serious clinical consequences raised the issue that marked late-systolic MR predominance makes the differentiation of MR presence in early systole an academic consideration of little clinical significance. This concept is supported by the fact that in MVP, less than 10% of RVol is regurgitated in the first 1/4th of systole. However, our study
shows MR timing, Mid-Late vs. Holosystolic matters very much. Mid-Late-systolic MR of MVP causes less volume overload with much lower RVol than Holo-MR of similar measured instantaneous ERO. This observation is confirmed by the smaller LV, lower LV mass and smaller LA in Mid-Late-MR vs. Holo-MR. Furthermore, the pulmonary pressures are also lower in Mid-Late-MR despite similar ERO, so that an alternative hypothesis of lower RVol due to higher LA pressure is highly unlikely. All forms of adjustment and stratification confirm lower volume overload of Mid-Late-MR consistent with lower E wave velocity, less frequent systolic reversal in pulmonary veins and less frequent symptoms. Consequently, highly dynamic MR of MVP with late predominance should not mislead and hinder the importance of distinguishing Mid-Late-MR from Holo-MR and recognizing its lesser volume overload and clinical consequences.

**MR assessment and clinical outcome**

MR assessment is based on guidelines that combine qualitative specific criteria and quantitative criteria.\(^{15}\) Despite these guidelines, assessment of Mid-Late-MR may be particularly misleading. Indeed, among qualitative specific criteria of severe MR figure prominently large jets and large flow convergences. Our study shows that in that regard Mid-Late-MR and Holo-MR have similar appearance by color Doppler and recognizing that these characteristics are only present for part of systole is not easy. Due to pitfalls of color-Doppler, quantitative assessment is recommended\(^{15}\) and a large ERO is now recognized in clinical guidelines as a major marker of severe MR.\(^{8}\) This recognition is based on ERO’s association to physiologic consequences of MR\(^{35}\) and clinical outcome in several prospective studies of organic MR\(^{12-14,16}\). The power of ERO as determinant of outcome is related to the fact that LV energy is transmitted to the LA\(^{36}\) not just as RVol but also as potential energy (pressure), so that ERO is associated with subsequent heart failure and
cardiac events. ERO and RVol are measurable by several methods and the flow convergence method has been validated with excellent correlations to quantitative Doppler. Thus, ERO≥40 mm² is widely considered as a marker of severe MR. However, these validation and outcome studies were conducted in holosystolic MR and have not addressed the issue of Mid-Late-MR due to MVP.

Our study shows that use of a single measurement at peak velocity applied indiscriminately to Mid-Late-MR provides measured EROs that are not associated with outcome and inappropriate for patient management. Indeed, in Mid-Late-MR there is considerable discrepancy between uncorrected ERO≥40 mm² categorizing 15% of patients with “severe MR” while RVol≥60 mL/beat is detected in only 1%. Furthermore, with matched ERO between Mid-Late-MR and Holo-MR as well as matching age, sex and EF, similar blood pressure, heart rate and comorbidity, the outcome of Mid-Late-MR is much more benign than that of Holo-MR and surgery is indicated less frequently. This difference in outcome is confirmed for each specific event (heart failure and new AFib) and in all multivariable models. Additionally, ERO uncorrected to normalized regurgitant time is not associated without come in contrast to previous data in Holo-MR. Thus, patients with MVP and Mid-Late-MR have a generally benign outcome, congruent with the seminal work on MVP and the population-based MVP with minimal MR. Undetected inclusion of patients with Mid-Late-MR may explain the benign outcome observed in some degenerative MR series. Conversely, irrespective of the MR timing, large RVol or large LA-index predict outcome and reflect unbiased severity of MR. It is also possible to correct the ERO for the normalized regurgitant time (fraction of systole occupied by MR) and to obtain information strongly linked to outcome.
Thus, in a very misleading situation, with large regurgitant jet, large flow convergence and large ERO in Mid-Late-MR, it is essential to conform to a comprehensive MR assessment recommended in present guidelines. Low E-wave velocity and absence of pulmonary venous reversal attract attention but are not decisive. Interpretation in context (brief MR duration) of ERO values and a comprehensive assessment of MR with RVol measurement allow appropriate interpretation of the condition severity. Although we favor early surgery in patients with organic, severe MR and reparable mitral valve, we believe that in patients with Mid-Late-MR who have generally a benign outcome for several years following diagnosis, prudent rather than aggressive surgical consideration is in order. However, patients with MVP and Mid-Late-MR should be carefully monitored, as progression of MR and its transformation in Holo-MR may lead to more somber outlook. Therefore, in patients with MVP, MR timing is of critical importance in interpreting ERO measured by flow-convergence method (or other color-Doppler based approaches) so that clinical management and the surgical referral generally reserved to severe MR, should carefully take into account timing and consequences of MR.

**Limitations**

The study was not powered to assess differences in mortality, which is a rare occurrence in patients with Mid-Late-MR so the analysis of this endpoint was prudent with limited adjustment. Therefore, we focused on cardiac events as measures of outcome, as these events are associated with poor survival, even after surgery and represent crucial endpoints. The retrospective frequency matching of Holo-MR group to the prospectively examined Mid-Late-MR group maybe discussed, but is the only approach allowing identical baseline characteristics in these different types of MVP. The PISA method to quantify MR may be criticized but has been
validated and confirmed by our institution and others.\textsuperscript{12, 14, 25} We included only patients with appropriate flow convergence shape so that constrained flow convergence application of constraint-related correction factors cannot explain differences between Mid-Late and Holo-MR. Furthermore, the correlation between flow-convergence and Quantitative-Doppler, based on mitral and aortic stroke volumes was of high quality so that the low RVol observed in Mid-Late-MR is not a technical error but reflects an intrinsically lower volume overload. For outcome, diagnosis of atrial fibrillation by ECG may ignore some paroxysmal arrhythmias but provides specific event ascertainment.

**Conclusions**

Mid-late systolic MR compared to holosystolic MR of similar ERO, yields smaller volume overload and more benign outcome with smaller regurgitant volume, lesser enlargement of LV and LA, less hemodynamic consequences and less cardiac events. As opposed to holosystolic MR, risk stratification in Mid-Late-MR should not rely upon jet extent or uncorrected instantaneous ERO that maybe misleading. Conversely, comprehensive assessment, with attention paid to regurgitation timing and quantitation of regurgitant volume, is linked to outcome and provides appropriate clinical management tools.

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References:


Table 1. Baseline characteristics of patients with mitral regurgitation overall and stratified by the presence or absence of end systolic MR

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=201)</th>
<th>Mid-Late systolic MR (n=111)</th>
<th>Holo systolic MR (n=90)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Matching Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>64.2±15.7</td>
<td>64.0±16.9</td>
<td>64.4±14.4</td>
<td>0.86</td>
</tr>
<tr>
<td>Atrial fibrillation, n(%)</td>
<td>19(9.5)</td>
<td>12(10.8)</td>
<td>7(7.8)</td>
<td>0.46</td>
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<tr>
<td>Male Sex, n(%)</td>
<td>96(48)</td>
<td>51(46)</td>
<td>45(50)</td>
<td>0.56</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>64.4±6.5</td>
<td>64.4±6.7</td>
<td>64.4±6.3</td>
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<tr>
<td>Absolute ERO, mm²</td>
<td>0.26±0.15</td>
<td>0.25±0.15</td>
<td>0.26±0.15</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Non-Matching Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±12</td>
<td>66±13</td>
<td>68±11</td>
<td>0.31</td>
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<td>SBP, mmHg</td>
<td>132±17</td>
<td>130.5±16.4</td>
<td>134.5±18.4</td>
<td>0.10</td>
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<td>Diabetes n(%)</td>
<td>7(3.5)</td>
<td>5(4.5)</td>
<td>2(2.2)</td>
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<td>Charlson comorbidity index*</td>
<td>2.2[0.8,3.7]</td>
<td>2.2[0.8,3.9]</td>
<td>2.1[0.8,3.9]</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Absolute ERO: Effective regurgitant orifice of mitral regurgitation calculated from measurements at peak regurgitant velocity; SBP: Systolic blood pressure; * The comorbidity index is presented as median [25th-75th percentile]
Table 2. Clinical and echocardiographic characteristics in Mid-Late and Holo-systolic MR

<table>
<thead>
<tr>
<th>MR Characteristic</th>
<th>Mid-Late systolic MR (n=111)</th>
<th>Holo-systolic MR (n=90)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERO mm²</td>
<td>0.25±0.15</td>
<td>0.25±0.15</td>
<td>0.53</td>
</tr>
<tr>
<td>Jet area 4C cm²</td>
<td>8.3±3.6</td>
<td>8.0±5.2</td>
<td>0.63</td>
</tr>
<tr>
<td>Jet area 2C cm²</td>
<td>8.2±4.0</td>
<td>8.3±5.1</td>
<td>0.93</td>
</tr>
<tr>
<td>Aliasing velocity cm/sec</td>
<td>37.7±7.6</td>
<td>35.6±9.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Flow convergence radius, cm</td>
<td>0.74±0.2</td>
<td>0.78±0.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Regurgitant flow rate, mL/sec</td>
<td>139.4±80.1</td>
<td>148.6±80.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Regurgitant peak velocity, m/s</td>
<td>5.7±0.6</td>
<td>5.7±0.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Regurgitant TVI, cm</td>
<td>105.5±21</td>
<td>190.2±29.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR duration, msec</td>
<td>233±56</td>
<td>426±50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR duration/systolic time ratio (%)</td>
<td>54.9±10.5</td>
<td>99.7±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVol, mL/beat</td>
<td>25.2±13.5</td>
<td>48.5±25.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV and LA Characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>51.3±6.4</td>
<td>53.9±6.6</td>
<td>0.005</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>32.1±5.1</td>
<td>33.5±5.4</td>
<td>0.06</td>
</tr>
<tr>
<td>LA volume index, mL/m²</td>
<td>39±14</td>
<td>54±21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV diastolic volume index, mL/m²</td>
<td>72±22</td>
<td>102±22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV systolic volume index, mL/m²</td>
<td>25±10</td>
<td>30±12</td>
<td>0.0005</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>103±31</td>
<td>112±25</td>
<td>0.02</td>
</tr>
<tr>
<td>ES mitral annulus diameter (cm)</td>
<td>3.7±0.5</td>
<td>3.8±0.4</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Hemodynamic

Deceleration time msec | 219.5±52 | 207.6±45 | 0.09|
E wave velocity m/sec | 0.78±0.22 | 0.87±0.25 | 0.01|
A wave velocity m/sec | 0.69±0.24 | 0.69±0.22 | 0.96|
E/A ratio | 1.24±0.50 | 1.36±0.61 | 0.17|
PV systolic flow reversal, n(%) | 4(3.6) | 12(18.2) | 0.001|
RVSP, mmHg | 29±7 | 36±10 | <0.0001|
Cardiac index, L/min/m² | 2.93±0.7 | 2.78±0.6 | 0.1|

Clinical Characteristic

| NYHA class | I | 92% | 69% | <0.0001 |
|           | II | 7%  | 29% |          |
|           | III | 1% | 2%  |          |
| Beta-Blocker use (%) | 30% | 37% | 0.3 |
| Diuretics use (%) | 8%  | 20% | 0.01 |
| Digoxin use (%) | 2%  | 23% | <0.0001 |

| NYHA class | I | 92% | 69% | <0.0001 |
|           | II | 7%  | 29% |          |
|           | III | 1% | 2%  |          |
| Beta-Blocker use (%) | 30% | 37% | 0.3 |

4C: Four Chamber view; 2C: Two chamber view; EDD, ESD: end-diastolic end-systolic diameters; ERO: Effective regurgitant orifice; LA: Left atrium; LV: left ventricle; MR: mitral Regurgitation; NYHA: New-York Heart association PV: pulmonary veins; RVol: regurgitant volume; RVSP: right ventricular systolic pressure
Table 3. Cox hazard unadjusted and adjusted analysis of MR-timing (Mid-Late vs. Holosystolic MR) link to cardiovascular events.

<table>
<thead>
<tr>
<th>Cardiac events</th>
<th>Hazard Ratio For MidLate systolic MR</th>
<th>95 percent interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable analysis</td>
<td>0.25</td>
<td>0.12-0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.26</td>
<td>0.13-0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Comprehensive adjustment†</td>
<td>0.25</td>
<td>0.12-0.50</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Adjustment was for age, ejection fraction, symptoms (≥NYHA II), presence of atrial fibrillation.
† Adjustment was for age, ejection fraction, symptoms (≥NYHA II), presence of atrial fibrillation systolic blood pressure and comorbidity index.

Figure Legends:

Figure 1. Example of quantitative and qualitative estimation of MR in a patient with holosystolic MR (panels A, B and C) and with mid-late systolic MR (panels D, E and F). Panels A and D show the timing of MR signal, peak velocity and time velocity integral (TVI-marked by the white line) using continuous wave Doppler. Note the holosystolic signal (panel A) contrasting with a mid-late systolic signal (panel D). The flow convergence imaging is shown in the central panels B and E, demonstrating a similarly large zone of flow convergence, allowing calculation of similar mid-systolic regurgitant flow and effective regurgitant orifice. The color-flow jet in the 2 chamber view is shown in panels C and F and appears quite similar in the patients with holosystolic (panel C) and mid-late systolic (panel F) MR.

Figure 2: Comparison of regurgitant volume (left panels), left atrial (LA) volume index (second from left panels), right ventricular (RV) systolic pressure (third from left panels) and left
ventricular (LV) end-diastolic volume index (right panels) between patients with Mid-Late-systolic MR (Mid-Late-MR) and holosystolic MR (Holo-MR) stratified by measured ERO (ERO<0.2; upper row; ERO≥0.2 cm² lower row). For all strata and all variables represented, Mid-Late-MR was associated with lesser consequences as compared to Holo-MR.

**Figure 3:** Cardiac events (cardiac death, congestive heart failure or new onset Afib) under medical management in patients with Mid-Late-MR compared to HS MR. The values indicated for each line are cardiac event rates (±standard error) at five years. Note that there are significantly less cardiac events in patients with mid-late systolic MR as compared to patients with holosystolic MR with the same ERO.
The graph shows the cardiovascular event rate over years for two types of MR: Holo-systolic MR and Mid-late systolic MR. The event rate for Holo-systolic MR is significantly higher compared to Mid-late systolic MR, with a p-value of <0.0001.

- **Holo-systolic MR**
  - Year 0: 0%
  - Year 4: 40.4 ± 6.2%

- **Mid-late systolic MR**
  - Year 0: 0%
  - Year 4: 15.9 ± 4.7%

### Table: Number of Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Holo-MR</strong></td>
<td>90</td>
<td>56</td>
<td>48</td>
<td>38</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td><strong>Mid-Late-MR</strong></td>
<td>111</td>
<td>94</td>
<td>87</td>
<td>84</td>
<td>59</td>
<td>25</td>
</tr>
</tbody>
</table>
Mitral Valve Prolapse with Mid-Late Systolic Mitral Regurgitation: Pitfalls of Evaluation and Clinical Outcome Compared to Holosystolic Regurgitation
Yan Topilsky, Hector Michelena, Valentina Bichara, Jospeh Maalouf, Douglas W. Mahoney and Maurice Enriquez-Sarano

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