

Dimensionless Index of the Mitral Valve for Evaluation of Degenerative Mitral Stenosis

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Abstract

Purpose: Degenerative mitral stenosis (DMS) is an increasingly recognized cause of mitral stenosis. The goal of this study was to compare echocardiographic differences between DMS and rheumatic mitral stenosis (RMS), identify echocardiographic variables reflective of DMS severity, and propose a dimensionless mitral stenosis index (DMSI) for assessment of DMS severity. **Methods:** This is a single-center, retrospective cohort study. We included patients with at least mild MS and a mean transmitral pressure gradient (TMPG) ≥ 4 mmHg. Mitral valve area by the continuity equation (MVACEQ) was used as an independent reference. The DMSI was calculated as follows: $DMSI = VT_{ILVOT} / VT_{IMV}$. All-cause mortality data were collected retrospectively. **Results:** A total of 64 patients with DMS and 24 patients with RMS were identified. MVACEQ was larger in patients with DMS (1.43 ± 0.4 cm²) than RMS (0.9 ± 0.3 cm²) by ~ 0.5 cm² ($p = <0.001$) and mean TMPG was lower in the DMS group (6.0 ± 2 vs. 7.9 ± 3 mmHg, $p=0.003$). A DMSI of ≤ 0.50 and > 0.351 were associated with MVACEQ ≥ 1.5 and MVACEQ < 1.0 cm² ($p < 0.001$), respectively. With the progression of DMS from severe to very severe, there was a significant drop in DMSI. There was a non-significant trend towards worse survival in patients with MVACEQ < 1.0 cm² and DMSI > 0.35 , suggesting severe stenosis severity. **Conclusion:** Our results show that TMPG correlates poorly with MVA in patients with DMS. Proposed DMSI may serve as a simple echocardiographic indicator of hemodynamically significant DMS.

Introduction:

Calcification of the mitral valve (MV) annulus and leaflets is an increasingly common cause of MV stenosis (MS).^{1,2} Mitral annular calcification (MAC) has four principal pathophysiological mechanisms: degeneration, atherosclerosis, increased MV stress, and abnormal calcium phosphate metabolism.³ These processes lead to dystrophic calcification, increased lipid peroxidation, and chronic expression of transforming growth factor- β and inflammatory cytokines that promote phenotypic trans-differentiation of valvular interstitial cells into osteoblast-like cells.³⁻⁵ These microscopic changes can eventually cause the macroscopic changes seen with MAC, including a larger, flatter annulus with reduced mitral annular dynamism throughout the cardiac cycle.⁶ As the disease process continues, the dystrophic calcification extends into the left ventricular (LV) inflow tract and onto the MV leaflets, thereby obstructing LV inflow (**Figure 1**).⁷ This disease process has increasingly been recognized as degenerative MS (DMS)

Current guidelines for the management of patients with valvular heart disease define severe MS with a mitral valve area (MVA) < 1.5 cm² independent of the etiology of MS. According to the guidelines,

severe stenosis usually corresponds to a mean transmitral pressure gradient (TMPG) of 5 to 10 mmHg at normal heart rates.⁸ It should be noted that these quantification values have only been validated in patients with rheumatic MS (RMS) and lack similar validation in DMS populations. The anatomic MVA of DMS can be estimated with either electrocardiogram-gated multidetector cardiac computed tomography or three-dimensional echocardiography, but their availability is limited compared to that of two-dimensional echocardiography.^{6,9–11}

Transthoracic echocardiography is widely available, but methods commonly used for evaluating MS severity (*i.e.*, planimetry, pressure half-time, and color flow Doppler) have not been validated for DMS. Planimetry is challenging due to difficulty with obtaining the correct orientation of the image plane.^{11–13} The abnormal LV compliance that frequently accompanies DMS decreases the accuracy of the pressure-half time method and limits its applicability.¹⁰ The applicability of color flow Doppler to DMS is limited by the absence of flow contraction secondary to the MV being distorted into a tubular morphology.^{10,11,14} Continuity equation method is usually limited in DMS due to the frequent co-occurrence of mitral regurgitation (MR), aortic regurgitation, or atrial fibrillation in this population.⁶ There is ample evidence to support the TMPG as a surrogate for stenosis severity in RMS, but it is affected by changes in valve morphology and abnormal atrioventricular compliance as well as volume overload conditions such as end-stage renal disease (ESRD), and hence may not be appropriate for DMS.^{11,14–16}

The goals of this study were to compare echocardiographic characteristics of DMS and RMS, identify echocardiographic variables reflective of DMS stenosis severity, propose a dimensionless index of MS (Dimensionless Mitral Stenosis Index, DMSI) to help with estimation of DMS severity by transthoracic echocardiography, and examine the prognostic determinants of all-cause mortality in patients with DMS.

Materials and Methods:

This is a single-center, retrospective cohort study that was approved by the Institutional Review Board at Ochsner Medical Center, New Orleans, LA. This retrospective study involving human participants was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Echocardiograms saved in the institutional database (Cardiovascular Imaging System, New Orleans, LA) between 2007 and 2016 were screened with the keywords of MS, MAC, rheumatic, or diastolic doming of the anterior mitral valve leaflet. We obtained demographic and clinical data from electronic medical records (EPIC, Verona, WI, USA), including age, body mass index, gender, history of diabetes, hypertension, chronic kidney disease (eGFR < 60 mL/min per 1.73 m²), ESRD on dialysis, prior radiation exposure, coronary artery disease defined by either history of acute coronary syndrome or abnormal ischemic evaluation, and history of chronic heart failure. Survival and mortality data were obtained retrospectively from electronic medical records in July 2020.

Based on echocardiographic findings, DMS was defined in our study with the presence of severe MAC that extends onto the leaflets causing restricted leaflet mobility and LV inflow obstruction. Eligible studies had at least mild MS reported by transthoracic echocardiogram with a mean TMPG of [?] 4 mmHg. Patients with prior mitral balloon valvuloplasty, ejection fraction < 50%, heart rate [?] 100 bpm, severe aortic stenosis, and more than mild MR or mild aortic regurgitation were excluded. Patients with RMS who met inclusion and exclusion criteria were used as the comparison group. A total of 64 patients with DMS and 24 patients with RMS met the initial inclusion criteria. We excluded patients with ESRD (6 in DMS and 1 in RMS group) for analyses related to valve area and pressure gradient because of possibly increased gradients due to high flow state and volume overload.

Echocardiography studies were performed according to the American Society of Echocardiography guidelines using either GE Vivid E9 and E95 ultrasound system (GE Vingmed, Horten, Norway) and reviewed and verified by a Level III-trained echocardiographer.^{17–19} MAC severity in the DMS cohort was scored as reported in Movva et al.⁶ The MVA by continuity equation (MVA_{CEQ}) was used as the independent reference and calculated with the following equation: $MVA_{CEQ}(cm^2) = (LVOT\ diameter)^2 \times 0.785 \times (VTI_{LVOT} / VTI_{MV})$.¹¹

Continuous-wave Doppler imaging of the MV from the apical four-chamber view was used to obtain the peak and mean TMPG, as well as the velocity-time integral (VTI) of the MV. Peak E (early diastolic velocity), peak A (late diastolic velocity), and deceleration time were measured with pulse wave Doppler of the MV inflow at the MV tips in the apical four-chamber view during diastole. The LV outflow tract (LVOT) diameter was measured in the parasternal long-axis view (inner edge of the septal endocardium to the inner edge of the anterior mitral leaflet in mid-systole). The LVOT VTI was measured by tracing the instantaneous dense modal velocities throughout the systole of the LVOT pulse wave Doppler sample taken 1 cm below the aortic valve in the apical long-axis view. LVOT stroke volume (SV) was calculated with the following equation: $SV_{LVOT} \text{ (cm}^3\text{)} = 0.785 \times \text{Diameter}_{LVOT}^2 \times VTI_{LVOT}$. The DMSI was calculated as follows: $DMSI = VTI_{LVOT} / VTI_{MV}$ (**Figure 2**). Three cardiac cycles were averaged for Doppler-related calculations for patients in sinus rhythm and five cardiac cycles for patients in atrial fibrillation (AF). A level III trained echocardiographer repeated all of the measurements for the study purposes. Two separate level-III trained echocardiographers performed the interclass correlation analysis.

Statistical Analysis

We used SPSS statistical software for all analyses (IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp.) with a two-sided P value of less than 0.05 considered statistically significant. A chi-squared test for association was conducted between MV disease (i.e., DMS or RMS) and each categorical/nominal variable; Fisher’s exact test was used instead if a variable had any expected cell frequencies less than 5. The Shapiro-Wilks test was used to assess the normality of continuous variables. Independent groups of continuous variables were compared using Student’s t-test if the variable had a normal distribution or Mann-Whitney U test if the distribution failed to meet this assumption. Mann-Whitney U tests were used to compare MVA_{CEQ} of DMS and RMS while controlling for mean TMPG. DMS patients were stratified based on MVA_{CEQ} ($[?] < 1.0 \text{ cm}^2$, $1.0 \text{ to } 1.5 \text{ cm}^2$, $> 1.5 \text{ cm}^2$) to account for the small sample size, and a Kruskal-Wallis test was used to identify echocardiographic variables significantly impacted by MVA_{CEQ} stratification. Echocardiographic variables were assessed using simple linear regression analysis. A receiver operator characteristic (ROC) curve analysis was created to determine the cutoff value of the DMSI value associated with $MVA_{CEQ} [?] < 1.5 \text{ cm}^2$ and $MVA_{CEQ} [?] < 1.0 \text{ cm}^2$. Cox proportional hazards models were constructed to examine the prognostic determinants of all-cause mortality in patients with DMS.

Results:

Baseline patient characteristics are given in **Table 1**. Patients with DMS were older than RMS patients (77 ± 12 vs. 61 ± 15 y, $p < 0.001$). Study subjects were predominantly females (80% in DMS vs. 83% in RMS, $p = 0.7$). Patients with DMS had a higher prevalence of hypertension (92% vs. 70% in RMS, $p = 0.009$) and chronic kidney disease (53% vs. 29% in RMS, $p = 0.045$). There was a higher prevalence of AF in the RMS group (38% vs. 14% in DMS, $p = 0.034$). Patients with DMS had a lower mean TMPG (6.0 ± 1.8 vs. 7.9 ± 2.9 , $p < 0.003$) and a larger MVA_{CEQ} (1.4 ± 0.4 vs. $0.98 \pm 0.3 \text{ cm}^2$) despite a similar LVOT SV (in the absence of significant MR and aortic regurgitation) (**Table 2**). After the exclusion of patients with ESRD, there were 16 patients in the DMS group with high LVOT flow defined as $LVOT \text{ VTI} > 25 \text{ cm}$. Even after the exclusion of high LVOT flow, the DMS group still had a larger MVA_{CEQ} (1.3 ± 0.4 vs. $1.0 \pm 0.2 \text{ cm}^2$, $p < 0.001$) and lower TMPG (5.6 ± 2 vs. $8 \pm 3 \text{ mm HG}$, $p = 0.001$) compared to RMS group.

The average of mean TMPG in all subjects was 6.3 mmHg. Patients with a TMPG of $> 6.3 \text{ mmHg}$ ($n=39$), had a larger MVA_{CEQ} in the DMS group ($n=24$) than RMS group ($n=14$) (1.4 ± 0.4 vs. $0.8 \pm 0.2 \text{ cm}^2$, $p = 0.001$) (**Figure 3**). The frequency of low flow state defined as SV index $< 35 \text{ ml/m}^2$ was 41% ($n=24$) and 43% ($n=10$) in the DMS and RMS groups, respectively ($p=0.8$). TMPG was significantly lower in the DMS group irrespective of the SV index (**Table 2**). We stratified the echocardiographic variables by the presence of AF in the DMS group. No significant in-between group differences (DMS patients with AF versus without AF) were observed in mean TMPG (mean difference -0.50 mmHg [$-1.9 - 0.90$], $p = 0.475$), LVOT SV (mean difference -7.2 ml [$-17.1 - 2.0$], $p = 0.122$), and DMSI (mean difference 0.02 [$-0.06 - 0.87$], $p = 0.705$).

We stratified DMS patients by MVA_{CEQ} to understand the association of MS severity with other echocar-

diographic variables (**Table 3**). There was a statistically significant gradual increase in E velocity with worsening MS severity defined by MVA_{CEQ} . However, A velocity and E/A ratio did not correlate with MS severity. There was a statistically significant difference in DMSI between all three groups, and it progressively got smaller with severe stenosis.

DMSI accounted for 79% of the variation in MVA_{CEQ} (**Table 4, Figure 4A**), whereas the mean TMPG accounted for only 8% of the variation in patients with DMS (**Figure 4B**). There was also no correlation between DMSI and mean TMPG in the DMS group (**Figure 4C**).

The ROC curve showed that a DMSI of $[?] 0.50$ was associated with $MVA_{CEQ} [?] 1.5 \text{ cm}^2$ (AUROC 0.971, $p = 0.001$) and DMSI of $[?] 0.351$ was associated with $MVA_{CEQ} [?] 1.0 \text{ cm}^2$ (AUROC 0.965, $p = 0.0001$).

The interclass correlation (performed in 8 patients) for mean TMPG was 0.909 (CI 0.546 – 0.982, $p < 0.001$), for MVA_{CEQ} was 0.966 (CI 0.828 – 0.993, $p < 0.001$), and for DMSI was 0.980 (CI 0.899 – 0.996, $p < 0.001$) suggesting excellent reliability for all measurements. The inter-reader variability for MVA_{CEQ} was 13%, mean TMPG was 14%, and DMSI was 7%.

Survival and mortality data were available for all subjects in the DMS group. 27 \pm 18 months of follow-up was available after the echocardiography study used for study enrollment. The all-cause mortality rate was 53% in the DMS group and 41% in the RMS group at an average survival duration of 13 \pm 14 vs. 34 \pm 14 months after the enrolment echocardiography. The Cox hazard regression model revealed that the left atrial volume index and ESRD were independent predictors of mortality in patients with DMS. Kaplan-Meier curve analysis showed a non-significant trend towards worse survival when the cutoff values of $MVA_{CEQ} [?] 1.0 \text{ cm}^2$ and DMSI $[?] 0.35$ were used (**Figure 5**). Other echocardiographic parameters such as $MVA_{CEQ} [?] 1.5 \text{ cm}^2$, mean TMPG $> 7 \text{ mmHg}$, or SV index $[?] 0.35$ did not predict mortality risk.

Discussion:

The results of our study suggest that TMPG correlates poorly with the severity of MS in patients with DMS. Moreover, DMSI may be a viable alternative for the evaluation of DMS. The potential inadequacy of mean TMPG reported here agrees with previous guidelines.^{2,17} However, our results note a significant discordance between TMPG and MVA in DMS patients. Differences in MV morphology and net atrioventricular compliance between DMS and RMS may, in part, explain this observation. The flat plate geometry caused by MAC, compared to the dome-shape of RMS, increases the contraction coefficient.¹⁴ An increased contraction coefficient causes a lower pressure drop across the valve, accounting for the low transvalvular gradient.^{10,11,14} Also, risk factors for an increased net atrioventricular compliance are much more common in the patients with DMS than RMS.^{11,20-23} An increased net atrioventricular compliance accelerates the rate of transvalvular pressure decay, hence lowering the mean TMPG.^{20,24} A recent study suggested the presence of diastolic dysfunction as a potential cause of low TMPG in patients with very severe RMS.²⁵ The above factors may be responsible for lower mean TMPG seen in DMS patients in our study. The use of mean TMPG as an index for MS severity carries a 1B recommendation, but it may not accurately reflect MS severity in the setting of DMS.¹⁵⁻¹⁷

The patients in our RMS and DMS groups were similar to each other regarding some of the hemodynamic (i.e., pulmonary artery systolic pressure, SV index) and structural (i.e., left atrial volume index) parameters. Despite this similarity between groups, DMS was associated with a larger MVA and lower mean TMPG compared to RMS. Consistent with our findings, Pressman et al. recently reported in a retrospective cohort study that DMS is associated with a larger MVA relative to mean TMPG when compared to RMS.²⁶

The DMSI proposed here denotes an increased velocity across the stenotic MV relative of the LVOT velocity. Similar to the continuity equation, the DMSI relies on the rule of conservation of mass. The strong correlation between MVA_{CEQ} and the DMSI relies on the fact that the DMSI is a large component of the MVA_{CEQ} formula. Despite these similarities, this DMSI has several theoretical advantages. It avoids the variability of the LVOT cross-sectional area and reduces error risk driven by LVOT diameter measurement and assumptions of LVOT shape. Thus, the index would be most useful in cases with suboptimal visualization

of the LVOT.

The DMSI is relatively flow independent in the absence of significant valvular regurgitation. Therefore it would not be affected by the heart rate or flow state. The concept of the velocity ratio was previously described in the assessment of prosthetic aortic and mitral valve stenoses.^{27–29} The former utilized the ratio of LVOT VTI to prosthetic valve VTI with < 0.30 denoting severe prosthetic aortic valve stenosis, and the latter utilized ratio of mitral prosthesis VTI to LVOT VTI denoting > 2.5 as a significant valve dysfunction.²⁹ Furthermore, the dimensionless index for the native aortic valve is calculated as a ratio of LVOT VTI to aortic valve VTI. Moreover, an index of < 0.25 is consistent with severe aortic valve stenosis.

A recent study by Cho et al. including RMS patients with very severe MS (MVA [?] 1 cm²) undergoing MV replacement showed that patients with low mean TMPG ([?] 10 mmHg) were more likely to be older, and females, and have diabetes or AF compared to those with high mean TMPG ([?]10 mmHg).²⁵ The authors noted that this might be related to higher atrial compliance and lower atrial pressure seen in RMS patients. Interestingly, LV SV was higher in the low mean TMPG group in the study mentioned above. The frequency of low-flow state (SV index < 35 ml/m²) was similar in our DMS and RMS groups. Therefore, between-group differences (mean TMPG and MVA_{CEQ}) observed in our study is unlikely to originate from differences in flow-states. We did not perform further subgroup analyses for patients with low-flow states because of the small sample size. Cho et al. reported an association between AF and low mean TMPG in patients with RMS.²⁵ Absence of such a relationship in our study might be due to the small number of patients with AF in our DMS group (14%).

Our study shows that mean TMPG does not correlate well with MVA_{CEQ} and that a practical tool such as DMSI proposed in this study may serve as a simple echocardiographic parameter in the identification of patients with significant DMS.

Our survival analysis indicated that patients with DMS have a poor prognosis, and more than 50% of the patients with DMS died over an average of 13 months. The small sample size was a limitation for the detailed evaluation of predictors of mortality among patients with DMS. According to the cox-regression model, the left atrial volume index and ESRD were the only two independent predictors of mortality among DMS patients. A non-significant trend towards increased mortality risk was observed with MVA_{CEQ} [?] 1.0 cm² and DMSI [?] 0.35. Other echocardiographic parameters such as MVA_{CEQ} [?] 1.5 cm², mean TMPG > 7 mmHg, or SV index [?] 0.35 did not predict mortality risk.

Medical management of DMS includes heart rate control, and diuretic therapy that may cause provide some symptomatic relief.² Surgical treatment for severe DMS is significantly challenging due to older age of these patients with multiple comorbidities.² Emerging transcatheter approach for mitral valve replacement is feasible, but further advancement is needed to improve outcomes.³⁰

Limitations

This is a single-center study of MS patients obtained. The generalizability of our results will require a multicenter study where this new parameter can be validated. The study design diminishes the reliability of results from linear regression modeling in this study. Due to the small sample size, we had to use stratification to control for confounding and could account for the effect of diastolic dysfunction on the echocardiographic characteristics. There are significant differences in the demographic profile of the two groups. DMS group had a high frequency of chronic kidney disease and ESRD. We excluded patients with ESRD and hyperdynamic LV from analysis to minimize confounding.

Our study utilized the continuity equation method as an independent standard. The continuity equation valve area in the DMS population was comparable to that of 3-Dimensional MVA in one study.¹⁰ The retrospective nature of our study prevented us from using an alternative imaging modality to corroborate these findings, which is a significant limitation.

In the presence of significant MR and aortic regurgitation, our results may not be applicable. Therefore, DMSI should be avoided in the assessment of stenosis severity if there is more than mild MR or AR. Also, VTI

can show beat-to-beat variability with irregular heart rhythm. Thus, in the setting of cardiac arrhythmia, DMSI can only be reliable if the average of multiple VTI values is used.

Our study included a limited number of DMS patients with AF. Therefore, our results may not accurately capture the impact of AF on TMPG and transmitral flow, both of which were shown to be affected by AF in RMS patients.²⁵ Given the retrospective nature of the data, the ROC curves shown are the best-case scenario and that association strength may be variable in a larger cohort of patients. Also, there is a lack of validation of these cutoff values.

The presence of at least mild MS on the official echocardiography report was an eligibility criterion for our study. Moreover, some interpreters may avoid calling MS in the setting of MAC since these patients usually have normal-appearing leaflet excursion on 2D echocardiography. Therefore, our subjects might not represent the full spectrum of DMS. It is also a limitation that men were underrepresented in our DMS and RMS groups.

Conclusion

Our results suggest that TMPG correlates poorly with MVA in patients with DMS. The DMSI, which denotes an increased velocity across the stenotic MV relative of the LVOT velocity, may serve as a useful and practical screening tool in the evaluation of DMS. Future studies using multimodality imaging techniques and evaluating clinical outcomes are needed to validate and further explore these findings.

Author Contributions:

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References:

1. Oktay AA, Gilliland YE, Lavie CJ, Ramee SJ, Parrino PE, Bates M, et al. Echocardiographic Assessment of Degenerative Mitral Stenosis: A Diagnostic Challenge of an Emerging Cardiac Disease. *Curr Probl Cardiol.* 2017/01/10. 2017;42(3):71–100.
2. Sud K, Agarwal S, Parashar A, Raza MQ, Patel K, Min D, et al. Degenerative Mitral Stenosis: Unmet Need for Percutaneous Interventions. *Circulation.* 2016;133(16):1594–604.
3. Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral Annulus Calcification. In: *J Am Coll Cardiol.* 2015. p. 1934–41.
4. Alexopoulos A, Bravou V, Peroukides S, Kaklamanis L, Varakis J, Alexopoulos D, et al. Bone regulatory factors NFATc1 and Osterix in human calcific aortic valves. *Int J Cardiol.* 2010 Mar;139(2):142–9.

5. Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. *Circulation*. 2006;113(6):861–6.
6. Pressman GS, Movva R, Topilsky Y, Clavel M-A, Saldanha JA, Watanabe N, et al. Mitral Annular Dynamics in Mitral Annular Calcification: A Three-Dimensional Imaging Study. *J Am Soc Echocardiogr*. 2015;28(7):786–94.
7. Iwataki M, Takeuchi M, Otani K, Kuwaki H, Yoshitani H, Abe H, et al. Calcific extension towards the mitral valve causes non-rheumatic mitral stenosis in degenerative aortic stenosis: real-time 3D transoesophageal echocardiography study. *Open Hear*. 2014/09/15. 2014;1(1):e000136.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American college of cardiology/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63(22):e57-185.
9. Eleid MF, Foley TA, Said SM, Pislaru S V, Rihal CS. Severe Mitral Annular Calcification: Multimodality Imaging for Therapeutic Strategies and Interventions. *JACC Cardiovasc Imaging*. 2016;9(11):1318–37.
10. Mejean S, Bouvier E, Bataille V, Seknadji P, Fourchy D, Tabet JY, et al. Mitral Annular Calcium and Mitral Stenosis Determined by Multidetector Computed Tomography in Patients Referred for Aortic Stenosis. *Am J Cardiol*. 2016/07/29. 2016;118(8):1251–7.
11. Chu JW, Levine RA, Chua S, Poh KK, Morris E, Hua L, et al. Assessing mitral valve area and orifice geometry in calcific mitral stenosis: a new solution by real-time three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2008/07/14. 2008;21(9):1006–9.
12. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease—current management and future challenges. *Lancet*. 2016;387(10025):1324–34.
13. Weyman AE, Weyman AE. Principles and practice of echocardiography. Lea & Febiger Philadelphia; 1994.
14. Gilon D, Cape EG, Handschumacher MD, Jiang L, Sears C, Solheim J, et al. Insights from three-dimensional echocardiographic laser stereolithography. Effect of leaflet funnel geometry on the coefficient of orifice contraction, pressure loss, and the Gorlin formula in mitral stenosis. *Circulation*. 1996;94(3):452–9.
15. Faletra F, Pezzano A, Fusco R, Mantero A, Corno R, Crivellaro W, et al. Measurement of mitral valve area in mitral stenosis: Four echocardiographic methods compared with direct measurement of anatomic orifices. *J Am Coll Cardiol*. 1996;28(5):1190–7.
16. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014/03/03. 2014;129(23):2440–92.
17. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10(1):1–25.
18. Ryan T, Berlacher K, Lindner JR, Mankad S V, Rose GA, Wang A. COCATS 4 Task Force 5: training in echocardiography. *J Am Coll Cardiol*. 2015;65(17):1786–99.
19. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019 Jan;32(1):1–64.
20. Schwammenthal E, Vered Z, Agranat O, Kaplinsky E, Rabinowitz B, Feinberg MS. Impact of atrioventricular compliance on pulmonary artery pressure in mitral stenosis: an exercise echocardiographic study.

Circulation. 2000 Nov;102(19):2378–84.

21. Ukita Y, Yuda S, Sugio H, Yonezawa A, Takayanagi Y, Masuda-Yamamoto H, et al. Prevalence and clinical characteristics of degenerative mitral stenosis. *J Cardiol*. 2016 Sep;68(3):248–52.
22. Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PHM, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and atherosclerosis in community dwelling elderly. The Cardiovascular Health Study (CHS). *Am Heart J*. 2006;151(1):39–47.
23. Codolosa JN, Koshkelashvili N, Alnabelsi T, Goykhman I, Romero-Corral A, Pressman GS. Effect of Mitral Annular Calcium on Left Ventricular Diastolic Parameters. *Am J Cardiol*. 2016 Mar;117(5):847–52.
24. Flachskampf FA, Weyman AE, Guerrero JL, Thomas JD. Calculation of atrioventricular compliance from the mitral flow profile: analytic and in vitro study. *J Am Coll Cardiol*. 1992;19(5):998–1004.
25. Cho I-J, Hong G-R, Lee SH, Lee S, Chang B-C, Shim CY, et al. Differences in Characteristics, Left Atrial Reverse Remodeling, and Functional Outcomes after Mitral Valve Replacement in Patients with Low-Gradient Very Severe Mitral Stenosis. *J Am Soc Echocardiogr*. 2016 Aug;29(8):759–67.
26. Pressman GS, Ranjan R, Park DH, Shim CY, Hong GR. Degenerative Mitral Stenosis Versus Rheumatic Mitral Stenosis. *Am J Cardiol*. 2020;125(10):1536–42.
27. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Hear Journal-Cardiovascular Imaging*. 2016;18(3):254–75.
28. Rusinaru D, Malaquin D, Maréchaux S, Debry N, Tribouilloy C. Relation of dimensionless index to long-term outcome in aortic stenosis with preserved LVEF. *JACC Cardiovasc Imaging*. 2015;8(7):766–75.
29. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography’s Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction. *J Am Soc Echocardiogr*. 2009;22(9):975–1014.
30. Yoon SH, Makkar R. Transcatheter Mitral Valve Replacement in Patients with Severe Mitral Annular Calcification. *Interv Cardiol Clin*. 2019;8(3):301-312.

Figure Legends

Figure 1. Transthoracic Echocardiogram showing severe Mitral annular calcification (MAC) and Degenerative Mitral stenosis (DMS). Parasternal Long axis (A) showing calcification of the posterior mitral annulus (arrow) and color flow acceleration across the mitral valve; Parasternal short axis (B) showing an extensive calcification of posterior mitral annular ring (arrow); Apical 4 chamber view (C) shows the extension of calcium on to the mitral valve leaflets (arrowheads) causing restriction; Continuous wave doppler across Mitral valve (D) shows a peak and mean gradient of 24 and 12 mmHg consistent with severe degenerative Mitral stenosis)

Figure 2. DMSI (Dimensionless Mitral Stenosis Index) sample calculation.

$LVOT\ VTI\ (27\ cm) / MV\ VTI\ (78\ cm) = DMSI\ (0.35)$. LVOT-left ventricular outflow tract; MV VTI-Mitral valve velocity time integral; DMSI- Dimensionless Mitral Stenosis Index

Figure 3 . MVA_{CEQ} stratified by high (≥ 7 mmHg) and low (< 7 mmHg) TMPG.

Figure 4.

A. Linear regression analysis of MVA_{CEQ} as a function of the DMSI in DMS patients

B. Linear regression analysis of MVA_{CEQ} as a function of the mean TMPG in DMS patients

C. Linear regression analysis of mean TMPG as a function of DMSI

Figure 5.

Kaplan-Meier survival curve using a cutoff value of $< 1 \text{ cm}^2$ for MVA_{CEQ} (A) and < 0.35 for DMSI (B) in patients with DMS.

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