Degenerative Mitral Stenosis Versus Rheumatic Mitral Stenosis

Gregg S. Pressman, MD[a,*], Rupesh Ranjan, MD[a], Dong Hyuk Park, MD[b], Chi Young Shim, MD, PhD[b], and Geu-Ru Hong, MD, PhD[b]

Mitral stenosis is classically caused by rheumatic disease (RMS). However, degenerative mitral stenosis (DMS) is increasingly encountered, particularly in developed countries with aging populations. The aim of this study was to compare clinical and echocardiographic characteristics between the 2 entities. One hundred fifteen patients with DMS were identified from an echocardiographic database in the United States and compared with 510 patients with RMS from Seoul, Korea. All subjects had a mitral valve area (MVA) ≤2.5 cm^2 by continuity equation but were otherwise unselected. Patients with DMS were older and had more hypertension, diabetes, chronic kidney disease, and chronic obstructive pulmonary disease than those with RMS. Atrial fibrillation was more common in RMS patients. Mean mitral valve gradient was slightly lower in DMS versus RMS (7.63 ± 3.67 vs 8.50 ± 4.23 mm Hg, p = 0.04) but MVA was strikingly higher in the DMS group (1.35 ± 0.41 vs 0.95 ± 0.38 cm^2, p <0.0001). This appeared to be due to greater stroke volume in the DMS patients (70.4 ± 19.7 vs 55.7 ± 15.5 ml, p <0.0001). Indexed left atrial volume was greater in RMS (82.1 ± 40.3 vs 57.9 ± 21.4 ml, p <0.0001) while estimated pulmonary artery systolic pressure was greater in DMS (49.3 ± 16.5 vs 39.4 ± 13.6 mm Hg, p <0.0001). In conclusion, DMS patients are older and have more comorbidities than RMS patients. DMS presents with greater MVA relative to mean mitral valve gradient than RMS. This appears due to a higher stroke volume in DMS patients. **(Am J Cardiol 2020;125:1536−1542)**

Mitral stenosis is generally due to rheumatic disease (RMS) or severe mitral annular calcification (degenerative mitral stenosis [DMS]). While the former is still widely prevalent in low-income countries, it is now uncommon in developed countries.[1] Conversely DMS, which increases in prevalence with age, is now commonly encountered in clinical practice.[2] We know a great deal about RMS but comparatively little about DMS. Rheumatic disease involves commissural fusion which reduces the mitral orifice to a small circular, or "fishmouth," opening. In this setting Doppler measurements of valve gradient and Doppler-derived valve area have been validated by catheterization studies.[3] By contrast, DMS involves bulky calcific deposits in the mitral annulus which extend onto the leaflets creating a tunnel-like stenosis[4] and displacing the hinge point of the leaflets apically.[5] The orifice at the leaflet tips is not circular at all but roughly crescent shaped (Figure 1). Whether Doppler provides accurate information on valve gradient and valve area is unknown in this setting. This study compares clinical and echocardiographic variables in patients with RMS and DMS.

Methods

For this study we compared 115 DMS patients with severe mitral annular calcium (MAC) and 510 patients with RMS. Both groups had a mitral valve area (MVA) ≤2.5 cm^2 as measured by the continuity equation. MAC patients were identified through review of echocardiogram reports at Einstein Medical Center from September 2007 through April 2018 (inpatient and outpatient) and were otherwise unselected. RMS patients were identified from the echocardiographic database at Severance Cardiovascular Hospital, Seoul, Korea covering the time period from January 2005 through December 2017. Patients with a prosthetic or repaired valve were excluded as were patients with prior balloon valvotomy.

For each echocardiogram the following data was collected:

1. stroke volume, calculated as the product of left ventricular outflow tract (LVOT) area x LVOT velocity-time integral (VTI),
2. mean mitral valve gradient (MVG) obtained by planimetry of the continuous wave Doppler signal through the mitral valve orifice,
3. MVA by 3 methods:
   a. pressure half-time method where MVA = 220/t $^1/_2$
   b. planimetry of the mitral valve orifice on a short-axis view at the leaflet tips
   c. continuity equation where MVA = stroke volume/mitral VTI,
4. net atrioventricular compliance (Cn) defined as 1270* (MVA/E-wave downslope)[6],
5. pulmonary artery systolic pressure (PASP) defined as (4 x tricuspid regurgitant jet velocity2) + estimated right atrial pressure.

[a]Heart and Vascular Institute, Einstein Medical Center, Philadelphia, Pennsylvania; and [b]Division of Cardiology, Severance Cardiovascular Hospital, Seoul, Korea. Manuscript received December 17, 2019; revised manuscript received and accepted February 12, 2020.

See page 1541 for disclosure information.

*Corresponding author: Tel: 215-456-8991; fax: 215-456-3533.
E-mail address: pressmang@einstein.edu (G.S. Pressman).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.02.020

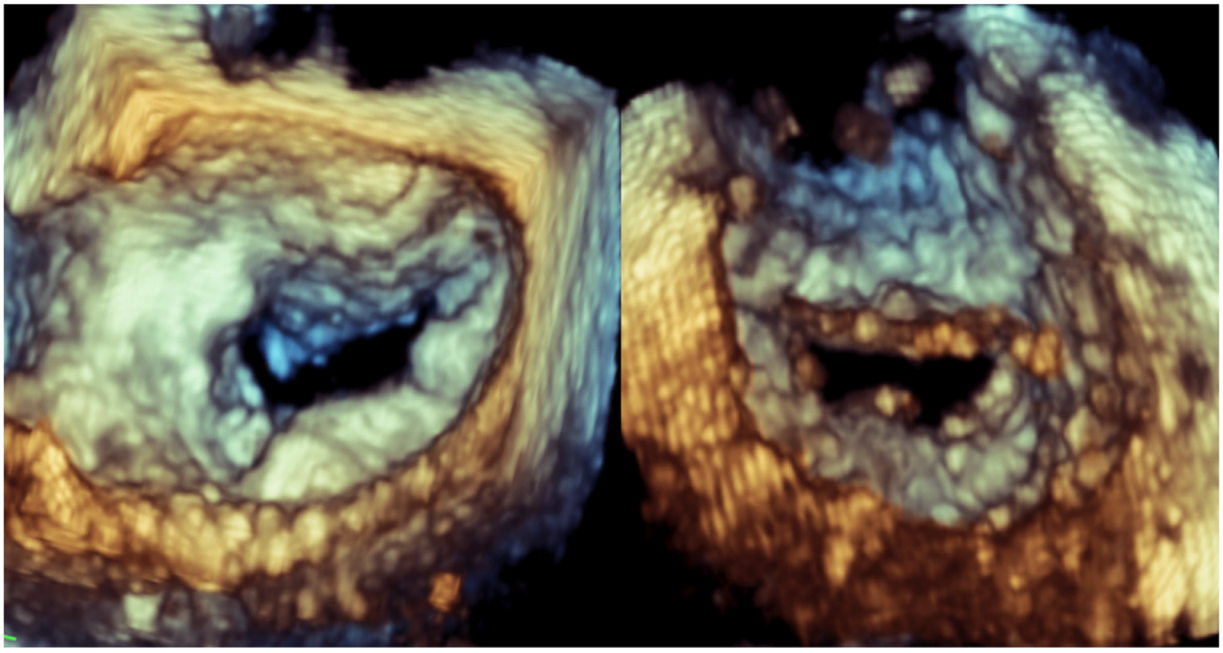

Figure 1. 3D TEE images of a DMS valve. The left panel views the valve from the left atrium. Note the bulky calcifications creating a tunnel-like stenosis. The right panel views the valve from the left ventricle. Note that the commissures are open and that the orifice at the leaflet tips is crescent-shaped. This figure is for illustrative purposes; 3D echocardiography was not employed for this study.

Doppler flow parameters were compared between RMS and DMS patients as were MVAs. The primary analyses included all subjects. Analyses were then repeated after limiting subjects to those with severe mitral stenosis (MVA $\leq$1.5 cm^2) and excluding patients with severe aortic stenosis, $\geq$moderate regurgitation (mitral or aortic), atrial fibrillation, or dialysis. These exclusions were chosen as they can potentially influence net AV compliance, MVA calculations, and PASP estimates.

Demographic data and information on comorbidities were collected from patient records. Hypertension was defined as a chart diagnosis of hypertension or the current use of antihypertensive medication. The presence of diabetes and chronic obstructive pulmonary disease were similarly determined. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 (using the Modified Diet in Renal Disease formula). This study was approved by the Institutional Review Boards of both hospitals.

Continuous data are presented as mean $\pm$ SD and categorical data as numbers and percentages. Nominal variables were compared using chi-squared testing. For continuous variables Student's *t* test or the Wilcoxon test, when values were not normally distributed, were used. For comparisons of MVG and MVA a nonlinear quadratic model provided the best fit. A 2-tailed p value <0.05 was considered to indicate statistical significance. All analyses were performed using JMP version 14.0 (SAS Institute, Cary, North Carolina).

Results

Demographic and comorbidity data are displayed in Table 1. DMS patients were older and had more comorbidities than RMS patients. However, atrial fibrillation was more common in the RMS group. Women predominated in both groups.

Doppler and echocardiographic variables are displayed in Table 2. E-wave and A-wave velocities, and E:A ratio were similar between the 2 groups. (In the context of mitral stenosis these variables reflect severity of the valve disease and not diastolic function.) Mean MVG was slightly, but significantly, lower in the DMS patients. In both groups mean MVG increased in a nonlinear fashion as valve area decreased (Figure 2). However, MVA was higher in the DMS group, by an average of 0.4 cm^2, no matter which method was used to measure MVA (Figure 3). In addition, MV VTI was lower in DMS, confirming this finding (Table 2). LVOT VTI and stroke volume were significantly greater in the DMS group, consistent with the large difference in MVA between the 2 groups.

LAVI was larger in RMS (Figure 4) when compared with DMS. Interestingly, within the RMS group there was no difference in LAVI between those in atrial fibrillation and those in sinus rhythm (84.4 $\pm$ 41.2 ml vs 79.6 $\pm$ 39.3 ml, p = 0.25). By contrast, in DMS patients LAVI was

Table 1
Demographics and comorbidities

Variable	RMS (n = 510)	DMS (n = 115)	p Value
Men	124 (24%)	36 (31%)	0.12
Age (years)	56.8 $\pm$ 12.5	73.4 $\pm$ 12.6	<0.0001
Hypertension	208 (41%)	77 (67%)	<0.0001
Diabetes mellitus	116 (23%)	57 (50%)	<0.0001
Chronic kidney disease	30 (6%)	41 (36%)	<0.0001
Chronic obstructive pulmonary disease	14 (3%)	13 (11%)	0.0003
Atrial fibrillation	266 (52%)	18 (16%)	<0.0001
Heart Rate (bpm)	71.0 $\pm$ 14.8	74.8 $\pm$ 12.4	0.048

Table 2
Doppler echocardiographic parameters

Variable	RMS (n = 510)	DMS (n = 115)	p Value
Left ventricular outflow tract area (cm^2)	2.97 ± 0.59	2.88 ± 0.54	0.11
Left ventricular outflow tract velocity-time integral (cm)	18.9 ± 4.6	24.6 ± 5.6	<0.0001
Stroke volume (ml)	55.7 ± 15.5	70.4 ± 19.7	<0.0001
E wave (cm/s)	1.84 ± 0.41	1.84 ± 0.47	NS
A wave (cm/s)	1.75 ± 0.41	1.74 ± 0.46	NS
E:A	1.03 ± 0.29	1.10 ± 0.44	0.11
Mean mitral valve gradient (mm Hg)	8.50 ± 4.23	7.63 ± 3.67	0.04
Mitral valve area − Continuity equation	0.95 ± 0.38	1.35 ± 0.41	<0.0001
Mitral valve area − Pressure half-time	1.15 ± 0.35	1.63 ± 0.46	<0.0001
Mitral valve area - Planimetry	1.07 ± 0.29	1.39 ± 0.41	<0.0001
Mitral valve velocity-time integral (cm)	63.9 ± 22.5	54.4 ± 14.7	<0.0001
Net atrioventricular compliance (ml/mm Hg)	4.85 ± 2.40	5.31 ± 2.36	0.07
Left atrial volume index (ml)	82.1 ± 40.3	57.9 ± 21.4	<0.0001
Pulmonary artery systolic pressure (mm Hg)	39.4 ± 13.6	49.3 ± 16.5	<0.0001

significantly greater with atrial fibrillation versus sinus rhythm (70.9 ± 30.4 ml vs 55.0 ± 17.9 ml, p = 0.007). PASP was higher in the DMS group (Figure 5); this difference remained significant even after controlling for MVA and MVG. Cn was numerically greater, but not significantly so, in DMS subjects.

Repeat analyses incorporating all exclusions are displayed in Table 3. MVA and stroke volume remained

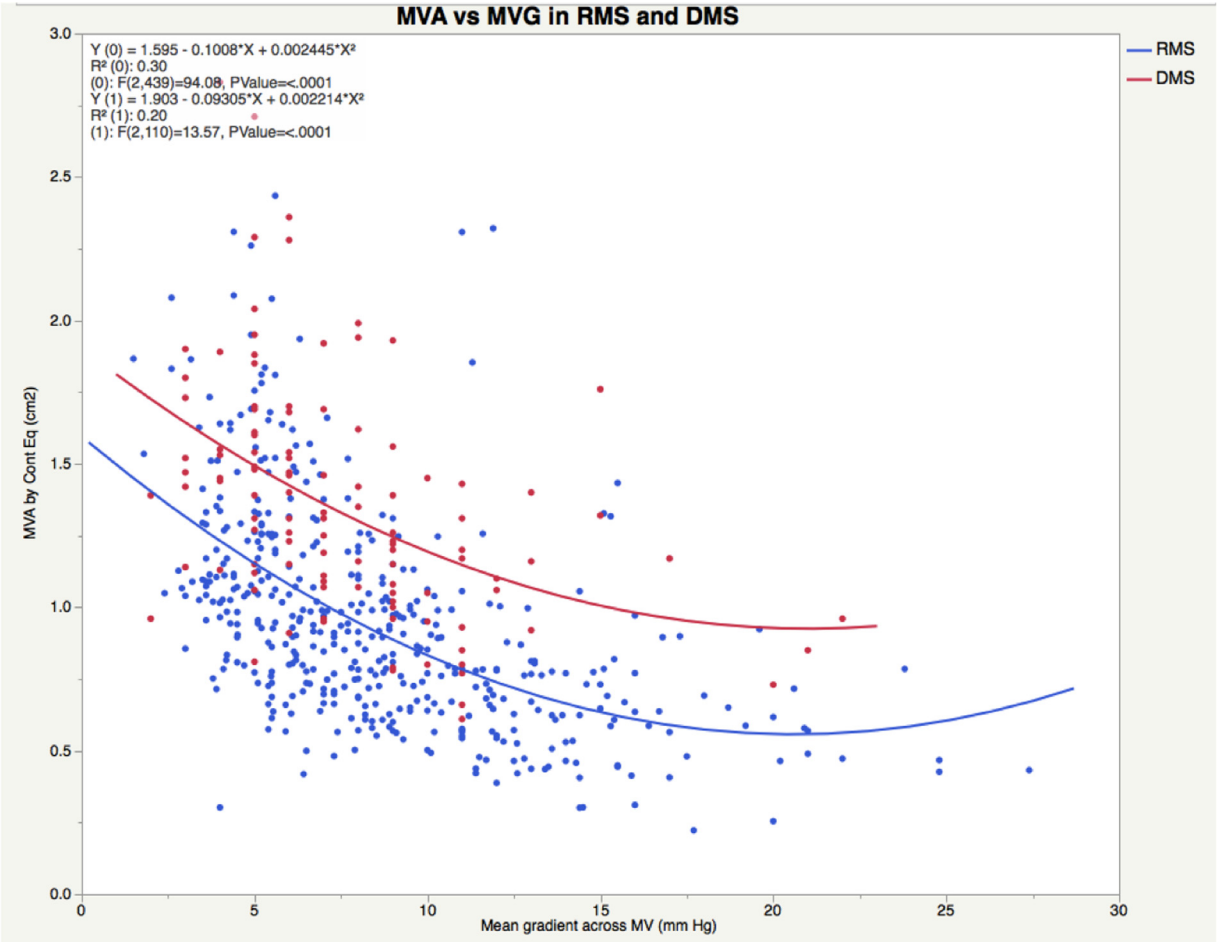

Figure 2. Graph of the mitral valve area (calculated by continuity equation) as a function of mean mitral valve gradient for the entire study group. DMS patients are in red while RMS patients are in blue. It can be readily appreciated that the valve area-valve gradient relationship is displaced upward in the DMS group.

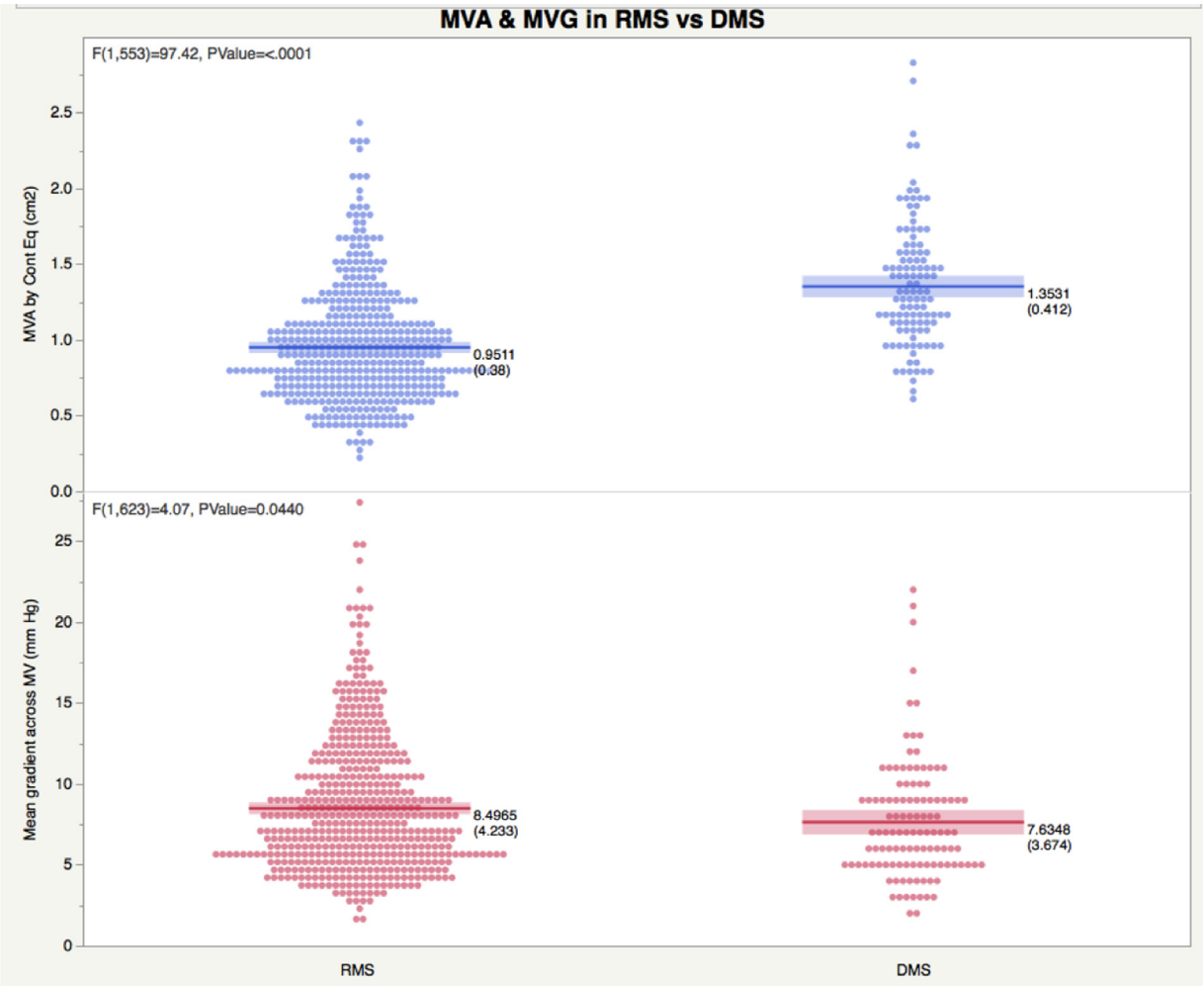

Figure 3. Plots depicting mitral valve area (top panel) and mean mitral valve gradient (bottom panel) in both RMS and DMS patients. Note that while mean mitral valve gradient is only slightly lower in DMS vs RMS patients, mitral valve area is substantially greater in DMS vs RMS.

greater in the DMS group; mean MVG remained numerically lower in DMS but the difference was no longer statistically significant. On multivariate analysis, controlling for age, sex, rhythm (sinus vs atrial fibrillation), and mean MVG, stroke volume remained significantly different between the 2 types of mitral stenosis ($p = 0.0002$).

Discussion

DMS is an increasingly common cause of mitral stenosis in the Western World.[2,7] Yet, little is known about this type of mitral stenosis in comparison with that due to RMS. There are major differences in demographics and associated comorbidities between the 2. Patients with RMS are younger while DMS patients are more often hypertensive and diabetic, and have more chronic kidney disease and coronary artery disease[8].

Valvular geometry is also different between the 2 types of valve pathology. Rheumatic disease classically leads to a dome-shaped mitral valve with a roughly circular or "fishmouth" orifice. In this case the defining anatomic lesion is commissural fusion while the valve leaflets may remain flexible. By contrast, in DMS the commissures remain open. Stenosis occurs because of bulky calcium deposits in the annulus that extend onto the basal portion of the leaflets making them rigid. This displaces the valvular hinge points away from their annular attachments toward the midportion of the valve. Thus, stenosis is created at the level of the annulus[4] and leaflet bases (Figure 6). Distinct from RMS the commissures remain open and the orifice at the leaflet tips is crescent shaped (Figure 1).

Because DMS patients are older and have more comorbidities they are expected to have more myocardial disease than RMS patients. In particular, diastolic dysfunction likely plays a greater role in the disease pathophysiology. In keeping with this, estimated PASP was higher in the DMS group vs RMS. Yet, indexed left atrial volume was higher in RMS. This might be due to the smaller MVA and/or greater prevalence of atrial fibrillation in the RMS group. Additionally, DMS patients would be expected to have a stiff, noncompliant atrium because of greater age and burden of comorbidities. RMS patients, at least early in the disease, might have greater atrial compliance.

Perhaps the most interesting finding in the present study is the discrepancy between the transmitral gradient and MVA when comparing RMS and DMS. Although the mean

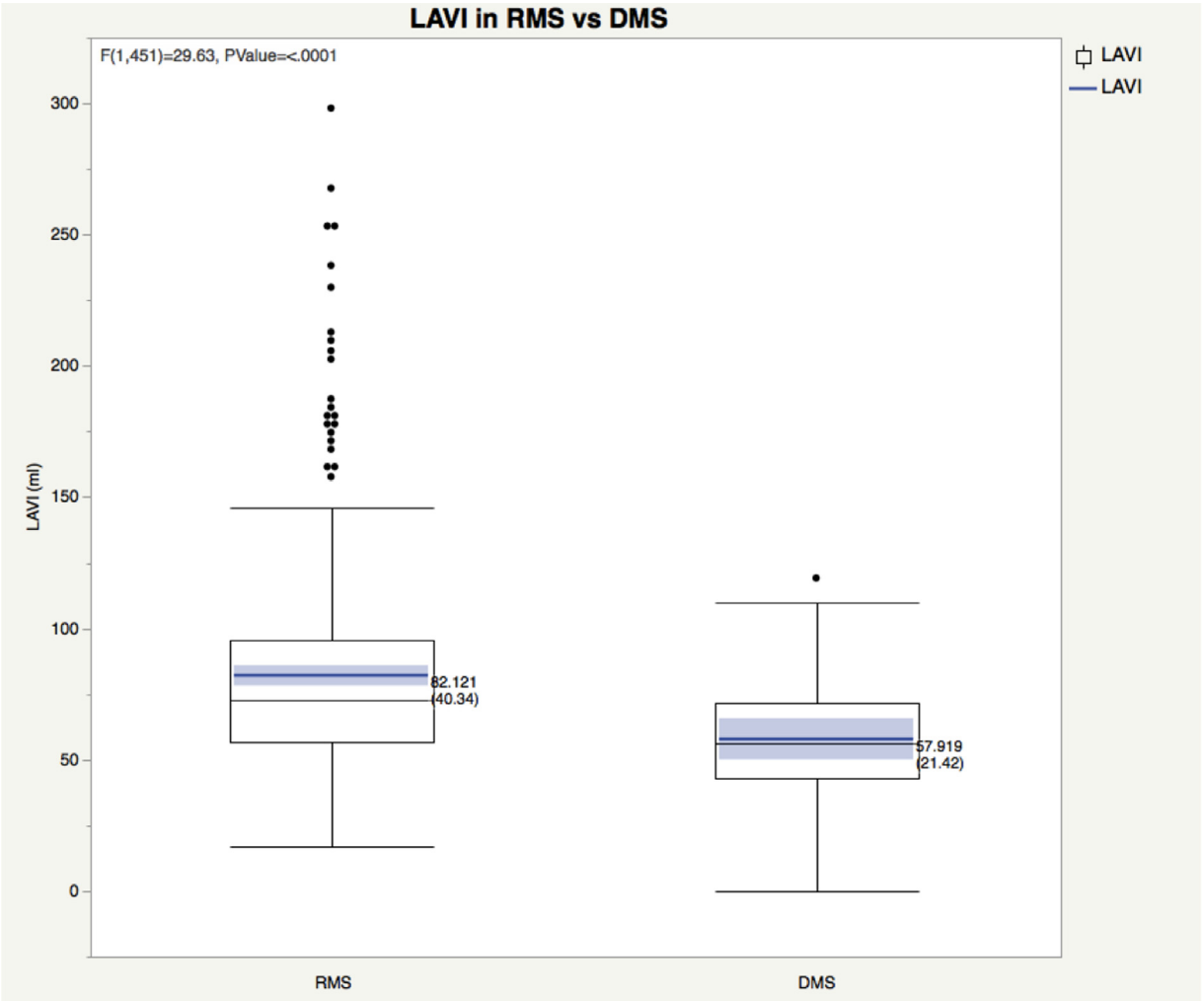

Figure 4. Indexed left atrial volume area in RMS vs DMS patients. Note the number of outliers with very high left atrial volume among the RMS patients.

gradient was only slightly different between the 2 groups, valve area was substantially larger in the DMS patients. This gradient-area discrepancy might be explained by the higher stroke volume in the DMS patients: greater stroke volume leads to increased flow across the mitral valve and higher mean gradients. Another possible explanation relates to differences in age and comorbidities between groups - these could produce differences in atrial and ventricular compliance leading to different gradient-valve area relationships in the 2 groups. The importance of this finding is that the same MVG heralding severe RMS might not indicate severe stenosis in MAC patients. If confirmed, this would mean we cannot apply the same MVG guidelines to assess DMS as are used in assessing severity of RMS.

This study has certain limitations. We compared a largely African-American population with DMS to a Korean population with RMS. This was necessitated by the paucity of RMS and rising prevalence of DMS in the United States, whereas the opposite situation pertains in Korea. It is possible that unrecognized racial/ethnic differences could in part explain our findings. However, these differences would be unlikely to explain the substantially altered MVA/MVG relation illustrated in Figure 2. In addition, while Doppler

Table 3
Doppler echocardiographic parameters with all exclusions*

	RMS (n = 446)	DMS (n = 30)	p Value
Stroke volume (ml)	54.0 ± 14.1	65.6 ± 16.6	<0.0001
Mean mitral valve gradient (mm Hg)	8.90 ± 4.26	7.63 ± 2.19	0.10
Mitral valve area − Continuity equation	0.86 ± 0.27	1.19 ± 0.21	<0.0001

* Severe aortic stenosis, ≥moderate regurgitation (mitral or aortic), atrial fibrillation, or dialysis

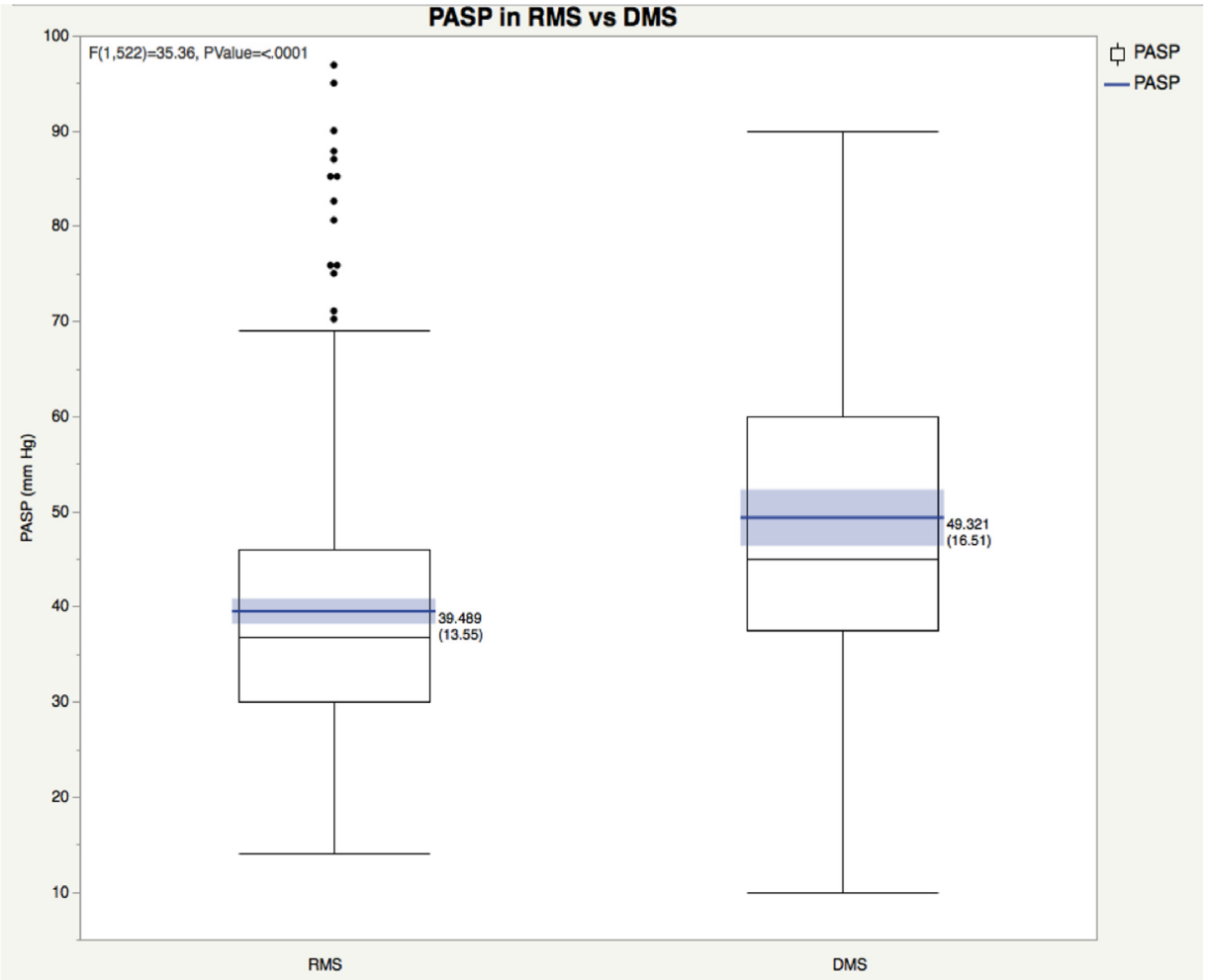

Figure 5. Pulmonary artery systolic pressure in RMS vs DMS patients. Mean values are 10 mm Hg higher among DMS patients as compared to RMS patients.

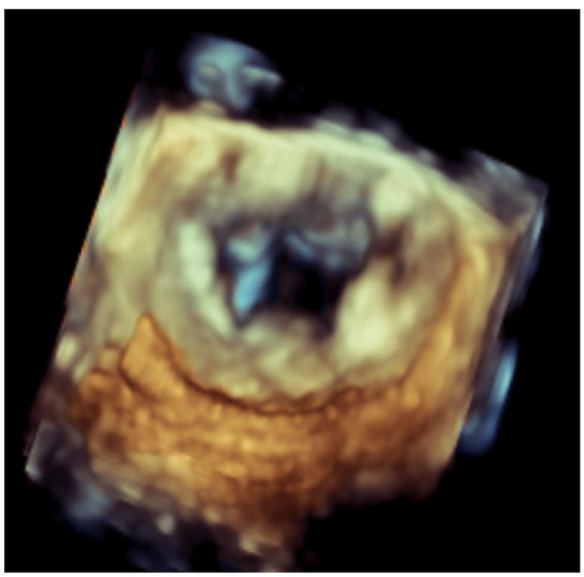

Figure 6. 3D TEE image (as viewed from the left atrium) of a DMS patient illustrating the tunnel-like stenosis created by bulky calcium deposits at the annular level. This figure is for illustrative purposes; 3D echocardiography was not employed for this study.

echocardiography has been validated in RMS its use has not been validated for assessment of DMS. The unique geometry of the DMS valve might affect the accuracy of Doppler measurements.

In summary, the clinical profile of DMS is quite different from that of RMS. DMS patients are older and have more comorbidities. They also have a different hemodynamic profile with a shifted mean gradient/MVA relationship. This appears to be due to higher stroke volume in these patients as compared with RMS. Finally, DMS patients have a higher pulmonary pressure while RMS patients tend to have larger left atrial size.

Disclosures

The authors have no conflicts of interest to disclose.

This research was approved by the Einstein Healthcare Network IRB and the IRB of Severance Hospital. The need for informed consent was waived due to the retrospective nature of the research.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution

Gregg S. Pressman: Conceptualization, Manuscript preparation and revision, Supervision. Rupesh Ranjan: Methodology, Investigation, Data curation. Dong Hyuk Park: Investigation, Data curation. Chi Young Shim: Conceptualization, Reviewing. Geu-Ru Hong: Conceptualization, Reviewing.

1. Chandrashekhar Y, Westaby S, Narula J. Mitral stenosis. *Lancet* 2009;374:1271–1283.
2. Sud K, Agarwal S, Parashar A, Raza MQ, Patel K, Min D, Rodriguez LL, Krishnaswamy A, Mick SL, Gillinov AM, Tuzcu EM, Kapadia SR. Degenerative mitral stenosis: unmet need for percutaneous interventions. *Circulation* 2016;133:1594–1604.
3. Nishimura RA, Rihal CS, Tajik AJ, Holmes DR Jr. Accurate measurement of the transmitral gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol* 1994;24:152–158.
4. Chu JW, Levine RA, Chua S, Poh KK, Morris E, Hua L, Ton-Nu TT, Hung J. 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;21:1006–1009.
5. Muddassir SM, Pressman GS. Mitral annular calcification as a cause of mitral valve gradients. *Int J Cardiol* 2007;123:58–62.
6. Nunes MC, Hung J, Barbosa MM, Esteves WA, Carvalho VT, Lodi-Junqueira L, Fonseca Neto CP, Tan TC, Levine RA. Impact of net atrioventricular compliance on clinical outcome in mitral stenosis. *Circ Cardiovasc Imaging* 2013;6:1001–1008.
7. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the euro heart survey on valvular heart disease. *Eur Heart J* 2003;24:1231–1243.
8. Atar S, Jeon DS, Luo H, Siegel RJ. Mitral annular calcification: a marker of severe coronary artery disease in patients under 65 years old. *Heart* 2003;89:161–164.