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ORIGINAL RESEARCH

Invasive Hemodynamic Predictors of Survival in Patients With Mitral Stenosis Secondary to Mitral Annular Calcification

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BACKGROUND: The aim of this study was to establish prognostic hemodynamic parameters in patients with mitral stenosis secondary to mitral annular calcification.

METHODS AND RESULTS: A retrospective cohort of 105 patients undergoing transseptal catheterization for hemodynamic evaluation of mitral annular calcification–related mitral stenosis between 2004 and 2020 was studied. Mitral valve gradient (MVG) and mitral valve area (MVA; calculated by the Gorlin formula) were measured using direct left atrial and left ventricular pressures. The median age of the patients was 70.3 years (58.4–76.7 years), and 53.3% were women. The median MVA was 1.7 cm^2 (1.3–2.3 cm^2) and MVG was 7.3 mm Hg (5.3–10.3 mm Hg); left ventricular end-diastolic pressure was 17.6±28.3 mm Hg. During a median of 2.1 years (0.7–4.5 years), there were 63 deaths; 1- and 5-year survival were 76% and 40%, respectively. There was no association between left ventricular end-diastolic pressure and survival. After adjusting for age and comorbidities, both MVA (hazard ratio [HR], 0.50 per cm^2; 95% CI, 0.34–0.73) and MVG (HR, 1.1 per mm Hg; 95% CI, 1.05–1.20) were independent predictors of death. Atrial fibrillation was also independently associated with mortality. When added to a combined model, MVA remained associated with death (HR, 0.51 per cm^2; 95% CI, 0.33–0.79) while MVG was not.

CONCLUSIONS: In patients with mitral annular calcification–related mitral stenosis, survival was poor. MVA and MVG were independently associated with death, but MVA was a better predictor of outcomes.

Key Words: invasive hemodynamics ■ mitral annular calcification ■ mitral stenosis ■ mitral valve area ■ mitral valve gradient

Mitral annular calcification (MAC) is a degenerative process that involves the mitral annulus and impairs its function in supporting the mitral apparatus.[1] MAC can extend into the base of the mitral leaflets, hindering their mobility and leading to mitral stenosis (MS).[1] As opposed to rheumatic MS, as well as other valve diseases,[2] predictors of poor outcomes in patients with MAC-related MS have not been established.

The underlying hemodynamic abnormalities in patients with MAC-related MS are poorly understood. Conventional Doppler parameters have limited application in these patients, attributable to concomitant abnormalities of left atrial (LA) and left ventricular (LV) compliance.[3] Previous studies have shown that both surgical and transcatheter mitral valve replacement (MVR) in patients with severe MAC are associated with high morbidity and mortality.[4,5] Therefore, identification of the high-risk subset of patients with MAC-related MS is critical, as it would aid in the clinical assessment of these individuals and potentially identifies those who would most benefit from surgery or percutaneous intervention.

Using a cohort of patients undergoing invasive hemodynamic assessment of MAC-related MS with transseptal catheterization, the aims of the present study were to:

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CLINICAL PERSPECTIVE

What Is New?

- Prognostic hemodynamic parameters in patients with mitral stenosis (MS) secondary to mitral annular calcification (MAC) have not been established.
- This study evaluated the prognostic impact of invasive transseptal hemodynamic parameters in patients with MAC-related MS.
- In patients with MAC-related MS, mitral valve area and mitral valve gradient measured invasively via direct left atrial and left ventricular catheterization were associated with mortality, but a small mitral valve area was a better predictor of poor outcomes.

What Are the Clinical Implications?

- Transseptal invasive hemodynamics can play a role in quantification of MAC-related MS, as noninvasive quantification can be challenging in this patient population.
- The findings of this study help identify the high-risk subset of patients with MAC-related MS, which could aid in treatment decisions.
- Larger studies with prospective follow-up will lead to better understanding of the impact of mitral valve area and mitral valve gradient on symptom and survival improvement after mitral valve intervention.

Nonstandard Abbreviations and Acronyms

LA	left atrial
LVEDP	left ventricular end-diastolic pressure
MAC	mitral annular calcification
MVA	mitral valve area
MVG	mitral valve gradient
MVR	mitral valve replacement

(1) assess whether invasively measured hemodynamic parameters of MS (ie, mitral valve gradient [MVG] or mitral valve area [MVA]) are predictors of survival in this population; and (2) describe the prevalence of concomitant elevation in LV end-diastolic pressure (LVEDP), as a marker of underlying LV diastolic dysfunction, and to assess its association with prognosis.

METHODS

The authors declare that all of the supporting data are available within the article and supplementary files.

Study Population

This cohort included consecutive adults (aged ≥18 years) with MAC-related MS undergoing invasive hemodynamic assessment of the degree of mitral inflow obstruction during transseptal cardiac catheterization at the Mayo Clinic (Rochester, MN, or Jacksonville, FL) between January 2004 and February 2020. This study was approved by the Mayo Clinic's institutional review board and only patients providing prior research authorization for use of their medical records were included.

Using an electronic search tool, individuals undergoing transseptal cardiac catheterization whose clinical notes contained the terms *mitral stenosis* or *mitral valve stenosis* were identified. The catheterization procedure logs were manually reviewed by one of the co-authors (W.R.M.) and only patients with a reported MVG were selected (Figure S1). The cause of MS was based on clinical, echocardiographic, and surgical exploration information when available.[6] Exclusion criteria included concomitant percutaneous mitral intervention, rheumatic or postinflammatory MS, prior MVR or repair, New York Heart Association functional status I or II, congenital mitral valve disease, and/or general anesthesia at the time of the procedure (because of its potential effects on hemodynamics). The final cohort included 105 patients (Figure S1).

Clinical data were abstracted from medical charts and included baseline demographics, comorbidities, functional capacity, and echocardiographic data, as well as any surgical or percutaneous interventions performed during follow-up. Survival status was ascertained using the Mayo Clinic registration and Accurint, an institutionally approved electronic location service database used in prior studies.[7,8]

Cardiac Catheterization

Cardiac catheterization was performed in patients in a fasting state under mild sedation and without discontinuation of chronic medications. Transseptal puncture was performed under fluoroscopy guidance in a standard fashion using a femoral vein access. The sidearm of an 8F Mullins sheath was used to measure direct LA pressure. At the operator's discretion, LV catheterization was performed via an anterograde (transmitral) approach using a 7F Berman catheter or retrograde (transaortic) using a diagnostic pigtail or multipurpose catheter. Right-sided heart catheterization was performed using 7F balloon-tipped catheters. Cardiac output was measured using thermodilution method or the direct Fick principle according to the operator's preference, and the Gorlin formula[9] was used to calculate MVA. Hemodynamic data reported herein represent a computer-generated mean of ≥5 consecutive beats obtained at rest and during spontaneous breathing.

Echocardiographic Data

Comprehensive 2-dimensional and Doppler echocardiographic data were obtained in accordance with the American Society of Echocardiography guidelines and data from the most recent transthoracic study before cardiac catheterization abstracted.[10] Reported echo-derived MVA (calculation using the continuity equation or pressure-half method) were obtained from the echocardiography report and reflect the echocardiographer's interpretation at the time of clinical assessment. LV outflow tract (LVOT) obstruction was defined as ≥mild valvular (peak velocity >2.5 m/s, systolic mean gradient ≥20 mm Hg, and/or valve area <1.5 cm^2),[11] subvalvular (dynamic or fixed), or the presence of an aortic prosthesis. Valvular regurgitation was assessed and classified with an integrative approach, according to guidelines.[12] Echocardiographic studies were individually reviewed by one of the investigators (W.R.M.) to assess the extent of MAC.

Statistical Analysis

Continuous data are presented as mean±SD or median (25th–75th percentile) and nominal variables are presented as counts (percentages). Between-group comparisons were performed using Student *t* test or Wilcoxon rank sum test for parametric and nonparametric continuous variables, respectively; chi-square test was used to compare nominal variables. Paired *t* test and linear regression (Pearson correlation) were used to compare invasive and Doppler-derived data.

All-cause survival data were analyzed by Kaplan-Meier method. Because of a lack of established severity cutoffs in this population, patients were categorized according to the median for each variable of interest (MVG, MVA, or LVEDP) for the entire population and groups compared using log-rank test. Cox proportional models were created using clinical variables selected a priori based on their clinical importance. Given the collinearity between MVA and MVG, 2 separate multivariable models were built with each variable included at a time (unless stated otherwise). For the analyses of the association between survival and surgical or percutaneous interventions, these procedures were included in the multivariable models as time-dependent covariates. Statistical analysis was performed with JMP version 11.0 (JMP Statistical Discovery LLC) or SAS version 9.4 (SAS Institute Inc). Statistical significance was defined as $P<0.05$.

RESULTS

Demographic and clinical data are presented in Table 1. The median age of patients was 70.3 years (58.4–76.7 years), and 56 patients (53.3%) were women. Hypertension was present in 79 patients (75.2%), previous/current atrial fibrillation in 42 patients (40%), history of thoracic radiation therapy in 28 patients (26.7%), and ≥moderate restrictive or obstructive lung disease in 27 patients (25.7%). Fifty-two patients had undergone cardiac surgery (coronary artery bypass grafting in 28 patients [26.7%] and prior aortic valve replacement in 35 patients [33%]). Twenty-six (24.8%) patients had New York Heart Association functional class IV. Cardiac catheterization was performed for the evaluation of dyspnea or heart failure symptoms in 70 patients (66.7%) and for the invasive assessment of pulmonary hypertension in 35 patients (33.3%).

Table 1. Clinical and Echocardiographic Data

Variable	(N = 105)
Age, y	70.3 (58.4–76.7)
Women	56 (53.3)
BMI, kg/m^2	31.7±8.0
NYHA class IV	26 (24.8)
Hypertension	79 (75.2)
Hyperlipidemia	80 (76.1)
Diabetes	42 (40.0)
Coronary artery disease	53 (50.5)
Peripheral artery disease	20 (19.0)
Prior myocardial infarction	10 (9.5)
Prior cardiac surgery	52 (49.5)
Atrial fibrillation	42 (40.0)
History of thoracic radiation therapy	28 (26.7)
Prior stroke	13 (12.3)
Restrictive or obstructive pulmonary disease moderate or greater	27 (25.7)
Chronic kidney disease stage ≥3	29 (27.6)
Hemodialysis	6 (5.7)
Former or current smoker	57 (54.3)
Transthoracic echocardiography	
LV ejection fraction, %	66 (61–71)
RV systolic dysfunction moderate or greater	14 (13.9)
RV systolic pressure, mm Hg	57.7±17.8
LA volume index, mm Hg	48.9±16.0
Aortic regurgitation moderate or greater	12 (12.1)
Mitral regurgitation moderate or greater	14 (14.0)
Mitral valve diastolic mean gradient, mm Hg	9 (7–11)
Tricuspid regurgitation moderate or greater	32 (30.8)
LV outflow tract obstruction	86 (82.7)
LV outflow tract diameter, mm	2.1 (2.0–2.3)
LV/aortic valve systolic mean gradient, mm Hg	20 (13–29)

Values are expressed as mean±SD, number (percentage), or median (25th–75th percentile). BMI indicates body mass index; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; and RV, right ventricular.

Transthoracic Echocardiography

Transthoracic echocardiographic data are summarized in Table 1; the study was performed 2 days [1–10

days] before catheterization. Median LV ejection fraction was 66% (61%–71%) while ≥moderate right ventricular systolic dysfunction was present in 14 patients (13.9%). Mean right ventricular systolic pressure was 59±18 mm Hg. Median MVG was 9 mm Hg (7–11 mm Hg); 14% of patient had ≥moderate mitral regurgitation. Noteworthy, LVOT obstruction was present in 85 patients (81.7%) with an LVOT/aortic valve systolic mean gradient of 21 mm Hg (13–29.5 mm Hg). Native valvular aortic stenosis was present in 41 patients (48.8%), aortic valve prosthesis in 36 patients (42.8%,) and fixed or dynamic subvalvular aortic stenosis in 9 (10.7%). The calcification of mitral annulus extended anteriorly/involved the anterior mitral leaflet in 96 patients (92.3%).

Cardiac Catheterization

Cardiac catheterization data are summarized in Table 2. Mean LA pressure was 22.3±6.6 mm Hg with a mean LA *v* wave of 35.1±6.6 mm Hg. LVEDP was 17.6±28.3 mm Hg, with an LVEDP >15 mm Hg in 64.8% of patients. Right-sided heart catheterization revealed a mean pulmonary artery pressure of 41.4±11.6 mm Hg. The mean cardiac index was 2.6±0.6 L/min per m^2 and calculated pulmonary vascular resistance was 3.9±2.5 WU.

Using the Gorlin formula, the median MVA was 1.7 cm^2 (1.3–2.3 cm^2). During preprocedural echocardiography, an MVA was reported using the pressure half-time method in 52 individuals and continuity equation in 56; MVA by the Gorlin formula was significantly smaller than calculated by pressure half-time (1.7 cm^2 [1.3–2.3 cm^2] versus 2.1 cm^2 [1.5–2.7 cm^2]; *P*=0.02) but larger than calculated by continuity equation (1.7 cm^2 [1.4–2.3 cm^2] versus 1.4 cm^2 [1.2–1.8 cm^2]; *P*=0.01). Median MVG by catheterization was 7.3 mm Hg (5.3–10.3 mm Hg); the correlation coefficient between directly measured and Doppler-derived gradients was 0.66 (*P*<0.01), with gradients obtained by catheterization being lower than noninvasive measures (*P*<0.01).

Table 2. Cardiac Catheterization Findings

Variable	(N = 105)
Right atrial pressure, mm Hg	12.0±5.2
Mean pulmonary artery pressure, mm Hg	41.4±11.6
LA pressure, mm Hg	22.3±6.6
LA *v* wave, mm Hg	35.1±12.3
LV systolic pressure, mm Hg	147.2±27.1
LVEDP, mm Hg	17.6±28.3
Aortic systolic pressure, mm Hg	128.2±28.3
Aortic diastolic pressure, mm Hg	63.3±12.2
Aortic mean pressure, mm Hg	89.7±18.0
Cardiac index, L/min per m^2	2.6±0.6
Pulmonary vascular resistance, WU	3.9±2.5
Systemic vascular resistance, dynes/seconds/cm^{-5}	1196 (1013–1528)
MVG, mm Hg	7.3 (5.3–10.3)
MVA, cm^2	1.7 (1.3–2.3)

Values are expressed as mean±SD or median (25th–75th percentile). LA indicates left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure MVA, mitral valve area; and MVG, mitral valve gradient.

Survival

During a median of 2.1 years (0.7–4.5 years), there were 63 deaths; survival rates at 1, 3, and 5 years were 76%, 51%, and 40%, respectively. The median follow-up time to an observed mortality rate of 50% was 3.0 years. When stratified by group medians, individuals with MVA ≤1.7 cm^2 had worse survival when compared with those with an MVA >1.7 cm^2 (*P*<0.01). In contrast, those with an MVG >7.3 mm Hg had similar survival compared with the rest of the cohort (*P*=0.97). Similarly, no difference in survival was seen between those with and those without an LVEDP >17 mm Hg (*P*=0.11) (Figure 1).

Results from univariable Cox model analysis for survival are presented in Table 3. After adjusting for age and comorbidities (Table 4), both invasively determined MVA (hazard ratio [HR], 0.50 per cm^2; 95% CI, 0.34–0.73) and MVG (HR, 1.1 per mm Hg; 95% CI, 1.05–1.20) were independent predictors of survival. Atrial fibrillation was also independently associated with outcomes in both models, while pulmonary disease and previous prior cardiac surgery were also predictors of mortality in the model including MVA. Noteworthy, when added to the same model, MVA remained associated with survival (HR, 0.51 per cm^2; 95% CI, 0.33–0.79), while MVG did not (HR, 0.98 per mm Hg; 95% CI, 0.90–1.07).

Twenty-six patients in the cohort underwent mitral valve intervention (24 underwent surgical intervention and 2 underwent transcatheter intervention). After adjusting for age and comorbidities, undergoing percutaneous or surgical mitral valve intervention was associated with increased risk of death during follow-up (HR, 2.4; 95% CI, 1.05–3.28). However, this association was no longer present when MVG (HR, 1.69; 95% CI, 0.88–3.26) or MVA (HR, 1.46; 95% CI, 0.75–2.85) were incorporated into the model.

DISCUSSION

To the best of our knowledge, this is the first study to examine in detail invasive hemodynamic characteristics of patients with MAC-related MS using transseptal catheterization, as well as the association of invasively measured mitral valve quantitative parameters with clinical outcomes. The main findings of the study are that: (1) the overall prognosis was poor, with a 1-year

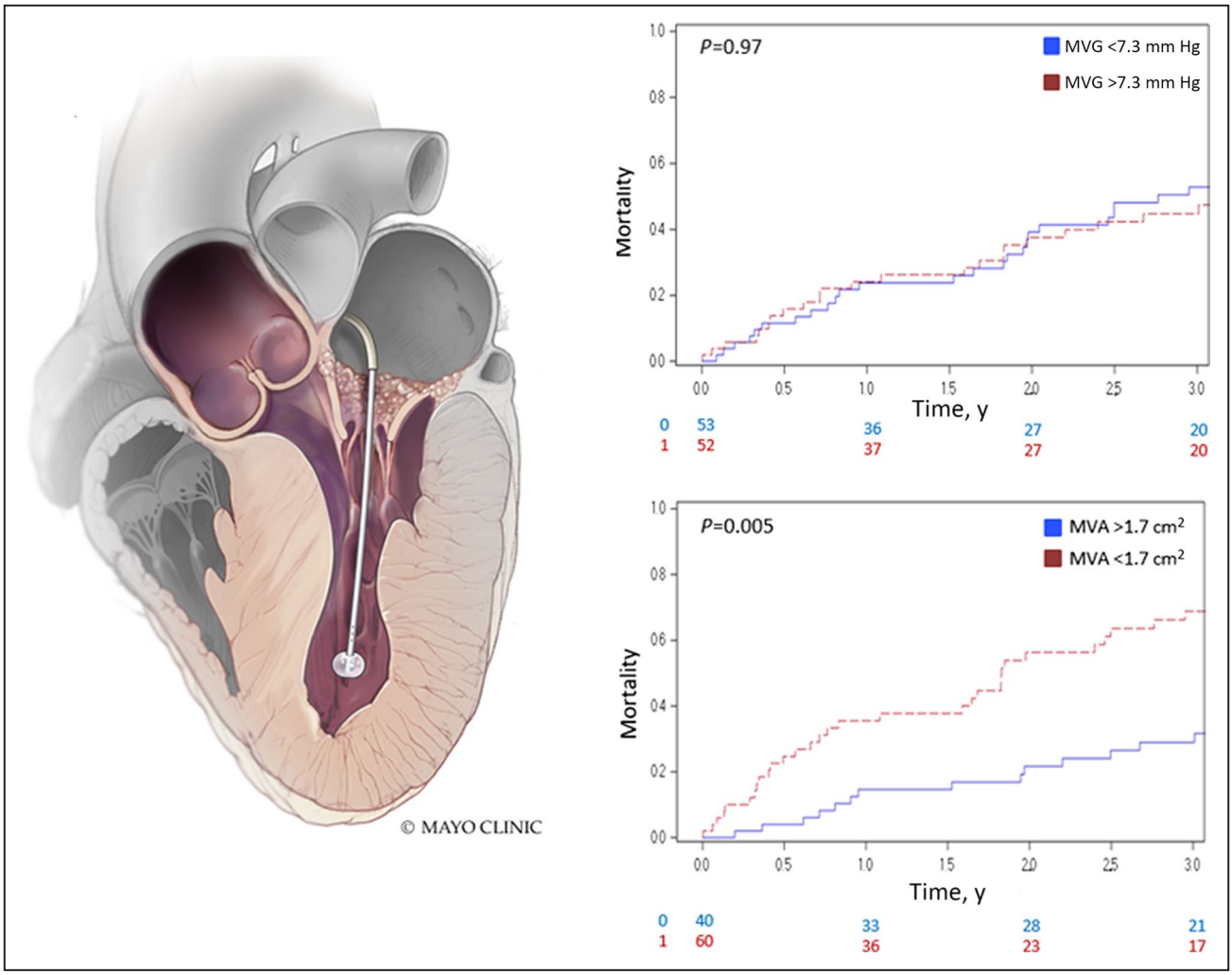

Figure 1. Invasive hemodynamic parameters and survival in mitral annular calcification-related mitral stenosis.
When stratified by MVA, patients who had an MVA <1.7 mm Hg had worse survival. In contrast, those with an MVG >7.3 mm Hg had similar survival compared with the rest of the cohort.

survival of 76%; (2) symptomatic patients with MAC-related MS present with variable degrees of mitral valve inflow obstruction; (3) MVA appeared to perform better than MVG as a predictor of survival; (4) the prevalence of increased LVEDP was high but this not associated with outcomes; (5) concomitant LVOT obstruction was highly prevalent; and (6) patients undergoing mitral valve intervention had higher mortality, but intervention was not associated with mortality when adjusted for MVG or MVA.

Several studies have demonstrated an association between MAC and poor prognosis. In the Framingham Heart Study, identification of MAC was shown to be independently associated with increased incidence of cardiovascular and all-cause mortality.[3] In a different study, patients with severe MAC-related MS (defined by Doppler-derived MVA ≤1.5 cm^2) had 53% and 34% event-free survival at 1 and 3 years, respectively.[6] Others have reported an association between MAC and severe coronary artery disease and stroke.[13–15] Our study showed that MAC-related MS was associated with high all-cause mortality, which is in agreement with prior studies.[3,6,13–15] Given the poor outcomes and the risks associated with surgical and percutaneous interventions in this population, it is therefore critical to identify high-risk subsets of patients who would potentially benefit from mitral valve intervention.

In current practice, quantification of MAC-related MS is challenging and lacks uniformity. Several methods of quantification have been used to evaluate the severity of MAC-related MS. Commonly used methods of quantification rely on the anatomic burden of calcium based on the thickness of the echodense band on M-mode echocardiography,[3] 2-dimensional echocardiography,[16] or circumferential extension of MAC.[15] However, these methods rely on structural rather than functional

Table 3. Univariate Analysis for Survival

Variable	HR (95% CI)	*P*-value
Age, y	1.01 (0.99–1.04)	0.35
Male sex	0.67 (0.41–1.11)	0.12
BMI, kg/m^2	0.98 (0.95–1.01)	0.25
NYHA class IV	1.45 (0.83–2.51)	0.19
Hypertension	0.81 (0.45–1.43)	0.46
Hyperlipidemia	1.61 (0.82–3.17)	0.17
Diabetes	0.83 (0.50–1.39)	0.48
Coronary artery disease	1.62 (0.98–2.69)	0.06
Peripheral artery disease	1.11 (0.61–2.03)	0.73
Prior myocardial infarction	1.14 (0.49–2.66)	0.76
Prior cardiac surgery	1.76 (1.05–2.95)	0.03
Atrial fibrillation	1.87 (1.13–3.10)	0.02
Prior stroke	2.24 (1.18–4.27)	0.01
History of thoracic radiation therapy	1.14 (0.65–2.03)	0.64
Restrictive or obstructive pulmonary disease	1.77 (1.01–3.08)	0.04
Chronic kidney disease stage ≥3	0.93 (0.54–1.61)	0.80
Former or current smoker	1.65 (0.98–2.78)	0.06
Transthoracic echocardiography		
LV ejection fraction, %	0.98 (0.97–1.01)	0.18
RV systolic dysfunction moderate or greater	2.14 (1.13–4.01)	0.02
RV systolic pressure, mm Hg	1.01 (1.00–1.03)	0.01
LA volume index, mm Hg	1.04 (1.01–1.05)	<0.01
Aortic regurgitation moderate or greater	1.19 (0.54–2.62)	0.67
Mitral regurgitation moderate or greater	1.42 (0.69–2.91)	0.34
Mitral valve diastolic mean gradient, mm Hg	1.08 (0.99–1.15)	0.05
Tricuspid regurgitation moderate or greater	1.91 (1.14–3.21)	0.01
LV outflow tract obstruction	1.49 (0.74–2.98)	0.24
LV/aortic valve systolic mean gradient, mm Hg	0.99 (0.97–1.02)	0.93
Cardiac catheterization		
Right atrial pressure, mm Hg	1.05 (0.98–1.10)	0.06
Mean pulmonary artery pressure, mm Hg	1.01 (1.00–1.04)	0.05
LA pressure, mm Hg	1.04 (1.01–1.08)	0.02
LA *v* wave, mm Hg	1.02 (1.00–1.03)	0.08
LV systolic pressure, mm Hg	1.00 (0.99–1.01)	0.78
LVEDP, mm Hg	0.98 (0.93–1.102)	0.24
LVEDP >17 mm Hg	0.66 (0.39–1.10)	0.11
Aortic systolic pressure, mm Hg	0.98 (0.99–1.01)	0.63
Aortic diastolic pressure, mm Hg	0.98 (0.96–1.02)	0.05
Aortic mean pressure, mm Hg	0.99 (0.97–1.00)	0.15
Cardiac index, L/min per m^2	0.64 (0.43–0.94)	0.03
Pulmonary vascular resistance, WU	1.04 (0.95–1.24)	0.38
Systemic vascular resistance, dynes/seconds/cm^{-5}	1.00 (0.99–1.00)	0.91
MVG, mm Hg	1.08 (1.01–1.14)	0.02
MVG >7.3 mm Hg	0.99 (0.60–1.68)	0.97
MVA, cm^2	0.54 (0.37–0.75)	<0.01
MVA >1.7 cm^2	0.41 (0.24–0.69)	0.01

BMI indicates body mass index; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; MVA, mitral valve area; MVG, mitral valve gradient; NYHA, New York Heart Association; and RV, right ventricular.

assessment of the mitral annulus/leaflets. Although intuitive, whether a large burden of calcified annulus is translated into hemodynamically significant stenosis has not been validated and is a limitation of these methods. More recent studies incorporated echocardiographic hemodynamic quantification of MS in MAC to classify severity. Tsutsui et al[17] used mean and peak MVG as well as MVA using pressure half-time to quantify the severity of MAC-related MS. A study by Kato et al[6] from our institution used transthoracic echocardiography–derived MVA ≤1.5 cm^2 using the continuity equation to define severe MS. In this subgroup of patients, a mean gradient ≥8 mm Hg was shown to be independently associated with mortality, whereas MVA was not.

Given its availability, noninvasive nature, and high accuracy, echocardiography has been the diagnostic modality of choice for the assessment of valvular disease. However, the quantification of MAC-related MS by echocardiography has several potential challenges.[18] Heavy calcification can limit adequate planimetry measurement of MVA even if 3-dimensional echocardiography is used. As seen in our study, patients with MAC commonly have concomitant LV diastolic dysfunction, which limits the use of the pressure half-time method for determination of the valve area. In contrast, the use of the continuity equation to quantify MVA in MAC-related MS might be limited by difficulties in accurately measuring the LVOT diameter caused by the presence of anterior MAC. Moreover, the prevalence of LVOT obstruction and small LVOT might lead to subaortic flow acceleration, affecting the calculated LV stroke volume by Doppler.

The current study is the first to explore the prognostic value of invasive hemodynamic parameters via direct LA and LV measurement. Our results show that MVA measured by the Gorlin equation in this population was predictive of all-cause mortality. This was in agreement with previously published noninvasive hemodynamic data in patients with calcific MS, which showed that MVA <1.5 cm^2 was associated with worse survival compared with an MVA between 1.5 cm and 4.0 cm.[26] Interestingly, in contrast to MVA, our study showed no difference in survival when patients were classified according to the median MVG. A number of individuals from our cohort with mildly or moderately elevated MVG were found to have overall findings

Table 4. Multivariable Model

	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MVA, per unit change	0.50 (0.34–0.74)	<0.01	…	…
MVG, per unit change	…	…	1.12 (1.05–1.20)	<0.01
Age, per year	1.01 (0.99–1.04)	0.33	1.01 (0.99–1.04)	0.34
Coronary artery disease	1.18 (0.66–2.11)	0.57	1.20 (0.68–2.14)	0.53
Atrial fibrillation	2.07 (1.19–3.59)	0.01	2.40 (1.37–4.20)	<0.01
Restrictive or obstructive pulmonary disease	1.87 (1.04–3.38)	0.37	1.74 (0.97–3.10)	0.06
Prior cardiac surgery	1.92 (1.05–3.53)	0.04	1.71 (0.96–3.05)	0.07

HR indicates hazard ratio; MVA, mitral valve area; and MVG, mitral valve gradient.

consistent with mild MS based on invasively measured MVA (Figure 2) In these individuals, a large LA *v* wave appeared to be the major driver for MVG with minimal (or even absent) end-diastolic LV–LA pressure gradient, a well-known marker of severe MS,[19] being present. Rather than significant MS, such patients appeared to have a combination of LA noncompliance, LV diastolic dysfunction, and/or, for a smaller subset, anemia/high-flow state as the source of large atrial *v* wave and LA hypertension. Therefore, if mitral valve intervention is being considered, cardiac catheterization with direct LA pressure measurement might prove helpful in the hemodynamic assessment of MAC-related MS.

The current analysis also provided novel insights into other hemodynamic and anatomic parameters. The median LVEDP in this study population was 17.6±28.3 mm Hg, supporting the concomitance of MAC-related MS and LV diastolic dysfunction in this subgroup of patients. Interestingly, LVEDP was not associated with mortality; however, this finding may have therapeutic implications. The presence of elevated LVEDP may limit symptomatic improvement post-MVR, and this has been shown in patients with rheumatic MS undergoing mitral balloon valvuloplasty.[20]

There was a high prevalence of LVOT obstruction in our study. Prior studies have also shown that the presence of LVOT obstruction was associated with development of MAC, such as in patients with hypertrophic obstructive cardiomyopathy.[21] This association could also be related to basal septal hypertrophy, which can

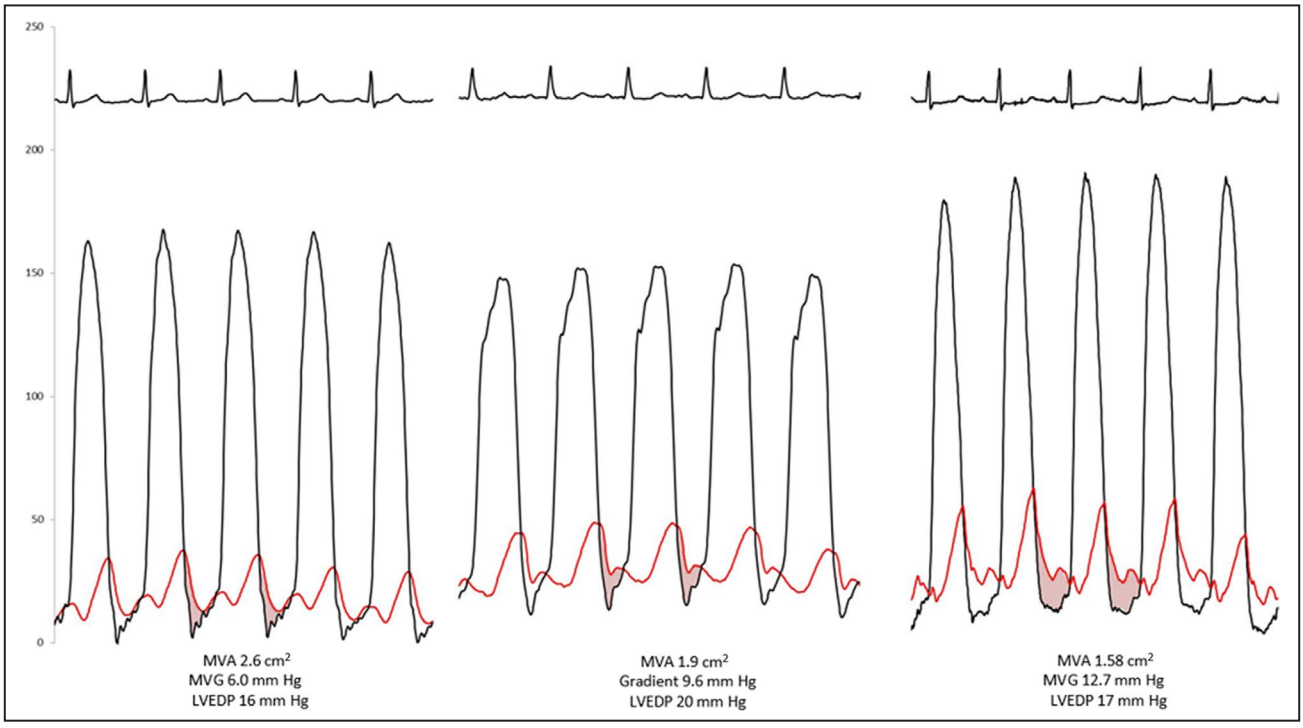

Figure 2. Hemodynamic phenotypes in patients with mitral annular calcification–related mitral stenosis (MS).
Patients can present with mildly/moderate elevated mitral valve gradient (MVG) with less than severe MS by mitral valve area (MVA; left), high MVG driven by a large left atrial (LA) *v* wave caused by elevated left ventricular (LV) end-diastolic pressure (LVEDP) but less-than-severe MS by MVA (middle), and high MVG with severe MS by MVA with end-diastolic separation of LA and LV pressures (right).

develop in these patients as a result of comorbidities such as hypertension, coupled with further narrowing of the LVOT from the anterior annular calcium bulk.[22] Perhaps most important for the management of these patients, 25% of our cohort had an LVOT diameter of ≤20 mm. LVOT obstruction *after* MVR has been shown to be an independent risk factor for mortality and occurred in 11.5% of patients undergoing transcatheter MVR.[5] Therefore, identification of baseline LVOT parameters in this patient population is of particular significance because of its implications postintervention.

Future Directions

The study results have important implications in the patient selection for mitral valve intervention. Previously published studies revealed high morbidity and mortality associated with treatment of severe MAC, whether surgically or percutaneously. Accurate quantification of MAC-related MS severity with validated parameters would be important for identifying patients who could potentially benefit from treatment and can potentially improve outcomes. For example, patients with more preserved MVA without significant mitral regurgitation might not benefit from mitral valve intervention, since the effective orifice area of the implanted prosthesis might not significantly differ from the native valve opening.

Although not the focus of our study and also acknowledging the small number of patients undergoing mitral valve intervention in our cohort, no difference in survival was seen when adjusted for the degree of mitral inflow obstruction. Whether mitral valve intervention improves survival or, perhaps as important given the age group, alleviates symptoms requires further investigation. Similarly, it would be natural to expect that patients with underlying LV diastolic dysfunction and concomitant diastolic dysfunction would have worse outcomes. It is possible that these patients would have similar survival but might have a less positive response to mitral valve intervention in terms of symptomatic improvement as one "overloads" the left ventricle as the mitral obstruction is relieved.

Last, as invasive diagnostic procedures are reserved for select cases, it is critical for the care of this patient population that future studies are performed in order to define the optimal method to quantitate MVA noninvasively both via cross-sectional imaging and echocardiography and correlate these measurements with cardiac catheterization data, Additionally, the measurement of MVG by Doppler has not been validated with concomitant Doppler-catheterization studies.

Limitations

This was a retrospective study that carries inherent selection bias. This might have contributed to the prevalence of concomitant LVOT obstruction and high comorbidity burden in our cohort. Selection bias could have also impacted outcomes related to mitral valve surgery and intervention. Older patients may be underrepresented as they were less likely to undergo transseptal hemodynamic given its risks. Data on the impact of mitral valve intervention on symptomatic improvement was not available for this study, limiting the full understanding of the potential benefit of mitral valve intervention in this patient population. Despite the relatively large cohort, the sample size limited our statistical analyses. The validity of the Gorlin equation in MAC-related MS has been discussed and we acknowledge these concerns.[23] However, MVA calculation using this formula is a well-established, universally used parameter in cardiac catheterization. Echocardiographic and catheterization measurements were not simultaneous, which could have affected MVG (and thus Doppler-derived MVA) caused by change in loading conditions.

CONCLUSIONS

In patients with MAC-related MS undergoing transseptal invasive hemodynamic assessment, although Gorlin-derived MVA and MVG were associated with all-cause mortality, MVA might be a better predictor of outcomes in this population. Concomitant elevated LVEDP and LVOT obstruction were highly prevalent but not associated with prognosis. Further studies are needed to validate these findings and correlate noninvasive parameters with their invasive counterparts.

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Supplemental Material

Figure S1

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