Outcomes in Patients With Obstructive Hypertrophic Cardiomyopathy and Concomitant Aortic Stenosis Undergoing Surgical Myectomy and Aortic Valve Replacement

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BACKGROUND: Hypertrophic cardiomyopathy (HCM) and aortic stenosis can cause obstruction to the flow of blood out of the left ventricular outflow tract into the aorta, with obstructive HCM resulting in dynamic left ventricular outflow tract obstruction and moderate or severe aortic stenosis causing fixed obstruction caused by calcific degeneration. We sought to report the characteristics and longer-term outcomes of patients with severe obstructive HCM who also had concomitant moderate or severe aortic stenosis requiring surgical myectomy and aortic valve replacement.

METHODS AND RESULTS: We studied 191 consecutive patients (age 67±6 years, 52% men) who underwent myectomy and aortic valve (AV) replacement (90% bioprosthesis) at our center between June 2002 and June 2018. Clinical and echo data including left ventricular outflow tract gradient and indexed AV area were recorded. The primary outcome was death. Prevalence of hypertension (63%) and hyperlipidemia (75%) were high, with a Society of Thoracic Surgeons score of 5±4, and 70% of participants had no HCM-related sudden death risk factors. Basal septal thickness and indexed AV area were 1.9±0.4 cm and 0.72±0.2 cm²/m², respectively, while 100% of patients had dynamic left ventricular outflow tract gradient >50 mm Hg. At 6.5±4 years, 52 (27%) patients died (1.5% in-hospital deaths). One-, 2-, and 5-year survival in the current study sample was 94%, 91%, and 83%, respectively, similar to an age-sex–matched general US population. On multivariate Cox survival analysis, age (hazard ratio [HR], 1.65; 95% CI, 1.24–2.18), chronic kidney disease (HR, 1.58; 95% CI, 1.21–2.32), and right ventricular systolic pressure on preoperative echocardiography (HR, 1.28; 95% CI, 1.05–1.57) were associated with longer-term mortality, but traditional HCM risk factors did not.

CONCLUSIONS: In symptomatic patients with severely obstructive HCM and moderate or severe aortic stenosis undergoing a combined surgical myectomy and AV replacement at our center, the observed postoperative mortality was significantly lower than the expected mortality, and the longer-term survival was similar to a normal age-sex–matched US population.

Key Words: aortic stenosis ▪ hypertrophic cardiomyopathy ▪ surgery and outcomes
fixed obstruction as a result of calcific degeneration and consequent narrowing of the aortic valve (AV).\textsuperscript{1,2} Simultaneous existence of both conditions in the same patient has been documented, although it is uncommon.\textsuperscript{3–5} However, with the increasing sophistication of imaging techniques and changing clinical demographics, there is a greater recognition of the coexistence of these 2 conditions in the same patient. This presence of sequential LVOT obstruction poses particular diagnostic challenges requiring meticulous imaging (especially Doppler echocardiography) to correctly identify the location of LVOT obstruction (Figure 1). Correct identification and quantification of this combined problem is crucial as it may necessitate a more complex invasive approach, which is the only current definitive therapeutic option as there are no large-scale studies demonstrating a clear survival benefit using medical therapy to relieve LVOT obstruction caused by either AS or HCM.

Surgical myectomy provides excellent long-term survival and freedom from recurrent symptoms in patients with obstructive HCM.\textsuperscript{6–11} It is currently a class I indication to offer surgical myectomy+/−mitral valve surgery to patients with severe LVOT obstruction, who are intractably symptomatic despite maximally tolerated medical therapy.\textsuperscript{1,2} Similarly, surgical AV replacement (AVR) significantly improves survival in patients with severe AS.\textsuperscript{12–21} As a result, the current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines designate a class I indication for AVR in patients with severe AS who present with symptoms or those who demonstrate signs of cardiac dysfunction.\textsuperscript{22,23} In addition, concomitant AVR is also recommended in patients with moderate AS undergoing cardiac surgery for another indications.\textsuperscript{22,23} Over the years, we have recognized the need for performing a combination of surgical myectomy and AVR in multiple patients who present with severe symptomatic obstructive HCM and were incidentally found to have moderate or severe AS. To the best of our knowledge, outcomes data in this intriguing population are unknown. We sought to report the characteristics and longer-term outcomes of such patients.

**METHODS**

The authors will not make their data, analytic methods, and study materials available to other researchers.

**Study Sample**

The study sample consisted of 191 consecutive symptomatic patients (aged ≥18 years) with a mixed picture of dynamic LVOT obstruction caused by obstructive HCM and fixed obstruction caused by moderate or severe valvular AS who underwent a combination of surgical relief of LVOT obstruction and surgical AVR at our tertiary care center between June 2002 and September 2018. All patients had a diagnosis of HCM before developing significant valvular AS. Appropriate institutional review board approval with waiver of individual informed consent was obtained. Because of a different pathophysiologic profile, we excluded patients undergoing surgery to remove subaortic membrane (n=63) and those who had amyloidosis on eventual histopathologic analysis of postmyectomy tissue\textsuperscript{24} (n=8). By study design, we did not include patients with HCM without concomitant moderate or severe AS (n=7763, which also included 2268 patients who eventually underwent surgical relief of LVOT obstruction). In
addition, patients undergoing surgical or transcatheter AVR for severe AS requiring a concomitant myectomy or alcohol septal ablation (caused by development of intraprocedural systolic anterior motion [SAM] of the mitral valve and LVOT obstruction) were not included (n=9). The diagnosis of obstructive HCM was made by experienced cardiologists based on typical features, with ventricular myocardial hypertrophy (LV wall thickness ≥15 mm) and presence of SAM and severe (>30 mm Hg) dynamic LVOT obstruction. In addition, the diagnosis of concomitant significant AS was made based on the following echocardiographic findings: (1) severe AV calcification with significantly reduced leaflet excursion; and (2) planimetry of the AV suggesting AV area <0.85 cm²/m². Continuity equation and stroke volume index were not utilized to ascertain the type and severity of AS.

Baseline clinical data were manually extracted from electronic medical records. Based on the available preoperative data, Society of Thoracic Surgeons (STS) score (AVR+coronary bypass grafting) was calculated. Chronic kidney disease (CKD) was defined as glomerular filtration rate <30 mL/min. In addition, standard ACC/AHA HCM sudden cardiac death (SCD) risk factors and 5-year ESC SCD risk score were also calculated. History of sudden death was defined as an unexpected sudden collapse occurring <1 hour from symptom onset in otherwise stable patients, followed by successful resuscitation. Because this was a surgical cohort, there were no patients with a prohibitive comorbidity (eg, cancer, advanced neurologic, pulmonary, hepatic, or renal pathologies) at the time that would preclude cardiac surgery. No patient went directly for an operation without being evaluated by a cardiologist (including advanced imaging) at our center and agreement with cardiac surgery. All patients were on maximally tolerated medical therapy at the time of operation.

Follow-up information, including details of AV prosthesis, was collected by manual extraction from electronic medical records and phone calls. Presence of atrial fibrillation was recorded based on history, ECGs, and Holter data. Nonsustained ventricular tachycardia (VT), wide complex tachycardia at ≥120 beats per minute lasting >3 beats but <30 seconds or sustained VT lasting >30 seconds, were recorded based on history and Holter data. Presence of implantable cardioverter-defibrillator and permanent pacemaker were ascertained.

**Echocardiography**

All patients underwent comprehensive echocardiography using commercially available instruments (Philips, General Electric, and Siemens). Maximal end-diastolic LV wall thickness, LV dimensions, and left atrial area were measured according to guidelines. The degree of resting mitral regurgitation and aortic regurgitation were assessed (none to severe), using multiple criteria. Resting dynamic LVOT peak velocity was measured by continuous-wave Doppler echocardiography, and pressure gradient was estimated using the simplified Bernoulli equation. Care was taken to distinguish the “dagger-shaped” late-peaking LVOT waveform from that of mitral regurgitation jet or the continuous Doppler jet of significant AS (Figure 1). In addition, LVOT diameter was measured and AV assessment, including planimetry, were performed according to guidelines. Because of the mixed picture of LVOT obstruction and AS, the continuity equation and stroke volume index
were not utilized to determine severity and type of AS. In addition, all patients underwent transesophageal echocardiography in the operating room to confirm a mixed obstruction picture of obstructive HCM-related LVOT obstruction and at least moderate AS (calcified valve with restricted leaflet motion and planimetered AV area <0.85 cm²/m²) using a similar comprehensive evaluation (including Doppler assessment across AV and LVOT) as described above. 30 While in the operating room, isoprenaline or dobutamine infusion were administered following the completion of myectomy to assess for provokable LVOT gradient.

**Left-Sided Heart Catheterization**

In addition to preoperative coronary angiography, all patients underwent left-sided heart catheterization to confirm the presence of dual obstructive physiology. This was performed using the controlled pullback technique where a guide catheter was positioned across the AV in the left ventricle and the aorta. A 0.035” support wire was put in place in the LV apex to ensure stability of the catheter. Subsequently, a 0.014” pressure wire was placed in the left ventricle through the same guide catheter. Pressure wire– enabled recording of LV pressure while controlled pullback of the guide catheter using support wire allowed measurement of pressure at the LV apex, LVOT, and just distal to the AV.

**Postoperative Echocardiography**

We evaluated postoperative (predischarge) echocardiograms for LV ejection fraction, LVOT gradients, and AV gradients as described above. In addition, we recorded different types of AV prostheses (mechanical or bioprosthetic). We also recorded the effective orifice areas of the prosthetic AV (stroke volume/prosthetic valve velocity time integral) in each patient and indexed it to body surface area. 31

**Surgical Technique**

Date and type of surgical procedures performed were recorded. In addition to AVR, the different operative techniques to relieve LVOT obstruction were recorded as follows: myectomy and myectomy+mitral valve repair+/−papillary muscle (resection/reorientation) surgery. Details of surgical techniques by our group have been previously described. 7,10,11,21,32 The basic technique of myectomy involved muscle resection below the membranous septum, removing muscle over both papillary muscles, and often extending to both trigones. We recorded the type of AV prosthesis as mechanical or bioprosthetic. In addition, concomitant coronary bypass grafting, maze, pulmonary vein isolation, and left atrial appendage ligation/excision were also recorded. The final decision regarding the specific operative technique was made by the attending cardiothoracic surgeon. All myectomy specimens were evaluated by dedicated cardiac pathologists and a diagnosis of HCM was made based on a combination of factors including myocyte disarray, myocyte hypertrophy, small coronary arteriole dysplasia, interstitial fibrosis, and endocardial fibroelastosis. 24

**Outcomes Assessment**

The duration of follow-up ranged between initial surgery to event/last follow-up. Death notification was confirmed by observation of death certificate or verified with a family member. In addition to outpatient clinic/phone call follow-up and electronic medical record documentation, we searched state and nationally available databases and performed obituary searches. The last search was performed in March 2019. Patients were censored at the time of death or last follow-up. Noncardiac cause of death was also recorded, where feasible. The primary end point was death, and no patients were lost to follow-up. In addition, we included a secondary end point of death (excluding documented noncardiac death caused by cancer, liver failure, primary respiratory, or neurologic issues, censoring at the time of event). Patients with an unknown cause of death were included in the secondary outcome, unless the patient’s proximal history, just before death, strongly suggested a noncardiac cause, based on chart review or family discussion. 33 Presence and cause of stroke (transient or permanent) was recorded based on clinical neurologic evaluation and neuroimaging. Arrhythmias, occurring during follow-up (atrial fibrillation, VT, and nonsustained VT) were recorded.

**Statistical Analysis**

Continuous variables are expressed as mean±SD and/or median (interquartile range) and compared using ANOVA (normal distribution) or Mann-Whitney test (non-normal distribution), as appropriate. Categorical data are expressed as percentage and compared using chi-square test. To assess for the association of various predictors with longer-term deaths, univariate and multivariate Cox proportional hazards analysis was utilized. Hazard ratios (HRs) with 95% CIs were calculated. For univariate analysis, variables that are known to be associated with outcomes in patients with HCM (as well as those undergoing cardiac surgery) were studied. Variables that had a significant (P<0.05) association with primary events on univariate analysis were subsequently considered for the multivariate model. No multiplicity adjustment was performed. Additionally, Kaplan-Meier curves were generated to determine the cumulative proportion of patients with events as a function over time, and compared using
RESULTS

The clinical and echocardiographic data of the study sample are shown in Tables 1 and 2. The proportion of patients with standard cardiovascular risk factors such as hypertension (63%), hyperlipidemia (75%), and diabetes (25%) was high, while the proportion of patients with standard HCM risk factors was low (70% had no ACC/AHA HCM SCD risk factors and 79% had ESC 5-year SCD risk score <4%). Mean STS score was 5%±4%; 52% had low (<4%) and 36% had intermediate (4%–8%) STS score. All patients were symptomatic (36% in New York Heart Association class II, 64% in class ≥II, and 19% with concomitant angina) and taking appropriate and maximally tolerated medical therapy. All patients had preserved LV ejection fraction (>55%) and the mean LV mass index was significantly increased at 147±51 g/m². All patients had SAM of the mitral valve, a dynamic LVOT gradient ≥50 mm Hg, and indexed AV area ≤0.85 cm²/m², by study design (51% had moderate [indexed AV area between 0.65 and 0.85 cm²/m²] and 49% had severe AS [<0.65 cm²/m²]). In addition, 26% patients had at least moderate SAM-related mitral regurgitation, while 10% had at least moderate aortic regurgitation. A total of 51 (27%) patients had obstructive coronary artery disease on invasive angiography, and presence of at least moderate AS and severe dynamic LVOT obstruction were confirmed on invasive hemodynamics.

The type of cardiac surgeries were as follows: AVR+isolated myectomy (n=110, 58%), AVR+myectomy plus mitral/subvalvular apparatus surgery (n=59, 31%), AVR+myectomy+coronary artery bypass grafting (n=29, 15%), and AVR+myectomy+coronary artery bypass+mitral/subvalvular apparatus surgery (n=22, 12%). Bioprostheses were implanted at the aortic position in 171 (90%) patients and 20 (10%) had a mechanical prosthesis implanted. In the subgroup of 91 patients with concomitant mitral valve surgery, 22 (11%) underwent mitral valve replacement, while 59 underwent transaortic mitral valve repairs. In addition, 24 (10%) patients had invasive therapies (surgical maze and/or pulmonary vein isolation) for relief of atrial fibrillation, 29 (15%) patients had excision/ligation of left atrial appendage, and 26 (14%) patients had concomitant ascending aortic surgery. The mean time to discharge was 8±5 days. At the time of discharge, the mean LV ejection fraction, resting LVOT gradient, provoked LVOT gradient, mean AV gradient, and indexed effective aortic orifice area were 60±4%, 10±3 mm Hg (range 0, 18 mm Hg), 19±9 mm Hg (range 0, 28 mm Hg), 14±6 mm Hg (range 8, 20 mm Hg), and 0.94±0.03 cm²/m², respectively. No patients had evidence of patient prosthesis mismatch (indexed effective aortic orifice area <0.85 cm²/m²). At 1 year, 69 patients returned for follow-up and the mean LV ejection fraction, maximal LVOT gradient, mean AV gradient, and indexed effective aortic orifice area were 58±4%, 20±4 mm Hg (range 0, 28 mm Hg), 15±4 mm Hg (range 8, 19 mm Hg), and 0.91±0.04 cm²/m², respectively.

The breakdown of histopathology of myectomy tissue obtained during surgery was as follows: characteristic HCM (n=157 [82%]) and hypertensive heart disease (n=34 [18%]). The baseline characteristics for these 2 subgroups were significantly different (P=0.023), sex (51% versus 52%, P=0.82), maximal LVOT gradient (83±41 versus 84±42, P=0.89), and basal septal thickness (1.9±0.4 versus 1.9±0.3, P=0.92). However, the proportion of patients with hypertension was significantly different (55% versus 100%, P<0.01).

In addition, during follow-up, there were an additional 9 patients (5%) who underwent implantable defibrillator insertion and 32 patients (17%) with pacemaker implantation, respectively. A total of 31 patients (16%) had evidence of atrial fibrillation during long-term follow-up (excluding immediate postoperative atrial fibrillation within 30 days of surgery) and were treated with medications (89% with amiodarone and the rest using rate control). Nonsustained and sustained VT were noted in 15 (8%) and 2 (1%) patients, respectively. There were no ventricular septal defects in the current study sample.

During a mean follow-up of 6.5±4 years (median, 5.9 years [interquartile range, 3.3–8.7 years]), and 52 (27%) patients died. There were 3 (1.5%) in-hospital deaths (versus an expected mortality based on STS score of 5%) and 2 (1%) strokes following surgery. One-, 2-, and 5-year survival in the current study sample was 94%, 91%, and 83%, respectively, similar to an age-sex–matched general US population (Figure 2). Within the sample, there were 5 patients who had a documented noncardiac cause of death (3 cancers, 1 advanced liver disease, and 1 multiorgan failure). There

log-rank statistic. All events, including those occurring in the immediate postoperative period, were included for survival analysis. In addition, the survival of the study sample was also compared with the survival of an age-sex–matched US population (https://www.cdc.gov/nchs/products/life_tables.htm). Since longer-term secondary events and noncardiac death were competing risks, univariate and multivariate survival analysis was performed by competing risk regression analysis using the Fine-Gray proportional subhazards model, and sub-HRs were calculated, along with 95% CIs. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc) and R version 3.4.3 (R Foundation for Statistical Computing). A P value <0.05 was considered significant.
were no patients with a documented appropriate implantable cardioverter-defibrillator discharge during follow-up. During follow-up, 3 (1.5%) patients needed a repeat valve replacement procedure (2 in the aortic and 1 in the mitral position).

For the entire study sample, data on univariate and multivariate Cox proportional survival analysis demonstrating data on the association of various relevant

Table 1. Baseline Characteristics of the Study Sample

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| Age, y                                        | 67±6          |
| Female sex                                    | 100 (52)      |

Standard cardiovascular comorbidities

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| Hypertension                                  | 120 (63)      |
| Hyperlipidemia                                | 144 (75)      |
| Diabetes                                      | 48 (25)       |
| CKD                                           | 11 (6)        |
| Chronic obstructive pulmonary disease         | 23 (12)       |
| History of stroke                             | 17 (9)        |
| Documented coronary artery disease            | 119 (61)      |
| History of prior sternotomy                   | 6 (3)         |
| STS score (%)                                 | 5±4           |
| STS score category                            |               |
| Low risk (<4%)                                | 100 (52)      |
| Intermediate risk (4–8%)                      | 68 (36)       |
| High risk (>8%)                               | 23 (12)       |

HCM-related risk factors

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| Family history of hypertrophic cardiomyopathy | 10 (5)        |
| Family history of SCD                         | 22 (12)       |
| History SCD                                   | 5 (3)         |
| History of nonsustained ventricular tachycardia | 22 (12)     |
| Gene positive for HCM (n=61 tested)           | 20 (33)       |
| History of syncope                            | 42 (22)       |
| History of atrial fibrillation                | 48 (25)       |
| Implantable defibrillator                     | 6 (3)         |
| Permanent pacemaker                           | 8 (4)         |

ACC/AHA HCM SCD risk factors

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| 0                                             | 134 (70)      |
| 1                                             | 46 (24)       |
| ≥2                                            | 11 (6)        |

ESC % 5-y HCM SCD risk score

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| Low risk (<4%)                                | 150 (78)      |
| Intermediate (4–6%)                           | 26 (14)       |
| High (>6%)                                    | 15 (8)        |

Severity of AS, No. (%)

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| Bicuspid aortic valve, No. (%)                | 29 (15)       |
| LVOT diameter                                 | 2.0±0.2 cm    |
| Indexed AVA, cm²/m²                           | 0.72±0.2      |
| Mean AV gradient, mm Hg*                      | 35±6 mm Hg    |

HCM AS Outcomes

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| IV                                            | 3 (2)         |

Values are expressed as mean±SD or number (percentage). ACC/AHA indicates American College of Cardiology/American Heart Association; CKD, chronic kidney disease; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; SCD, sudden cardiac death; and STS, Society of Thoracic Surgeons.

Table 1. Continued

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| LV ejection fraction, %                       | 64±6          |
| LV mass index, g/m²                           | 147±51        |
| Indexed LV end-diastolic dimension, cm²/m²    | 2.3±0.3       |
| Indexed LV end-systolic dimension, cm²/m²     | 1.2±0.3       |
| Maximal LV thickness, cm                      | 1.9±0.4       |
| Maximal posterior wall thickness, cm          | 1.2±0.3       |
| Indexed left atrial dimensions, cm²/m²        | 2.4±0.3       |
| Systolic anterior motion of mitral valve, No. (%) | 191 (100)   |
| Dynamic peak resting LVOT gradient, mm Hg    | 75±43 (range 0–130 mm Hg) |
| Dynamic peak maximal LVOT gradient, mm Hg    | 84±41 (range 52–148 mm Hg) |
| Maximal LVOT gradient ≥50 mm Hg, No. (%)      | 191 (100)     |
| Moderate to severe resting mitral regurgitation, No. (%) | 50 (26)   |
| Bicuspid aortic valve, No. (%)                | 29 (15)       |
| LVOT diameter                                 | 2.0±0.2 cm    |
| Indexed AVA, cm²/m²                           | 0.72±0.2      |
| Mean AV gradient, mm Hg*                      | 35±6 mm Hg    |

Severity of AS, No. (%)

| Variable                                      | Total (N=191) |
|------------------------------------------------|---------------|
| Moderate (indexed AVA 0.65–0.85 cm²/m²)        | 97 (51)       |
| Severe (indexed AVA <0.65 cm²/m²)              | 94 (49)       |
| Moderate or severe resting aortic regurgitation, No. (%) | 19 (10)      |
| Aortic root diameter, cm                      | 3.6±0.6       |
| Ascending aorta ≥4.5 cm, No. (%)               | 26 (6)        |
| RVSP, mm Hg                                   | 34±13         |
| Late gadolinium enhancement on cardiac magnetic resonance (n=65 performed), No. (%) | 35 (52)      |

Values are expressed as mean±SD unless otherwise indicated. AV indicates aortic valve area; LV, left ventricular; LVOT, left ventricular outflow tract; and RVSP, right ventricular systolic pressure.

* Aortic valve (AV) gradient was not utilized to determine severity of aortic stenosis (AS).
predictors with longer-term mortality are shown in Table 3. We demonstrate that standard cardiovascular risk factors such as age (HR, 1.65), CKD (HR, 1.58), and right ventricular systolic pressure (RVSP) on resting preoperative echocardiography (HR, 1.28) were associated with longer-term mortality, but traditional risk factors associated with outcomes in HCM were not. Histopathologic diagnosis of HCM versus hypertensive heart disease was also not associated with longer-term mortality. The type of AV prosthesis was also not associated with longer-term survival. The findings were similar if STS score (a composite of various relevant cardiovascular risk factors associated with mortality) was included in survival analysis instead of its constituent predictors (HR, 1.10).

The findings of multivariate survival analysis for the primary outcome of death in the subgroup excluding patients with documented obstructive coronary artery disease were similar as follows (total n=140, number of deaths=36): age (for every 10-year increase: HR, 1.61; 95% CI, 1.32–1.79 [P<0.001]), CKD (HR, 1.43; 95% CI, 1.21–1.93 [P<0.001]), and resting RVSP (HR, 1.21; 95% CI, 1.09–1.97 [P=0.02]) were associated with mortality.

Similarly, the findings of multivariate survival analysis for the primary outcome of death in the subgroup of patients with histopathologic diagnosis of HCM were similar as follows (total n=157, number of deaths=43): age (for every 10-year increase: HR, 1.58; 95% CI, 1.27–1.83 [P<0.001]), CKD (HR, 1.37; 95% CI, 1.17–2.04 [P<0.001]), and resting RVSP (HR, 1.22; 95% CI, 1.07–1.91 [P=0.03]) were associated with mortality.

For the entire study sample, the results of multivariate survival analysis using competing risk assumption for the secondary end point (excluding documented noncardiac deaths, n=47) had similar results: age (for every 10-year increase: sub-HR, 1.58; 95% CI, 1.26–1.82 [P<0.001]), CKD (sub-HR, 1.51; 95% CI, 1.27–1.83 [P<0.001]), and resting RVSP (sub-HR, 1.23; 95% CI, 1.09–1.61 [P=0.01]) were associated with the secondary end point.

**DISCUSSION**

The current study describes characteristics and outcomes of patients presenting with a combination of symptomatic severely obstructive HCM and moderate or severe AS undergoing surgical relief of LVOT obstruction and AVR at our tertiary care center. These patients were significantly older than patients with standard HCM\(^1,^2\) with an equal proportion of men and women. There was a high incidence of standard cardiovascular risk factors. On the other hand, the majority of the patients had no ACC/AHA SCD risk factors and the ESC HCM 5-year SCD risk score was low. This was different than the patients with standard obstructive HCM undergoing surgery at our institution, as would be expected.\(^3^,^6\) All patients had significant sequential LVOT obstruction, including severe dynamic LVOT obstruction and at least moderate fixed obstruction caused
by AS (15% also had concomitant bicuspid AV). All patients underwent a combination of surgical myectomy and AVR (42% had additional operations including mitral valve repair/replacement, ascending aortic replacement, or coronary bypass grafting) with an observed in-hospital mortality of 1.5% (significantly lower than the expected mortality of 5%, based on STS score). Unlike a previous report, female sex was not associated with a higher longer-term event rate.37 The pacemaker rate was high, as would be expected from this

Table 3. Univariate and Multivariate Cox Proportional Hazard Analysis for Longer-Term Mortality

| Variable                                         | Univariate                        | Multivariate                     |
|--------------------------------------------------|-----------------------------------|----------------------------------|
|                                                  | HR (95% CI)                       | P value                          | HR (95% CI)                       | P value                          |
| Age (for every 10-y increase)                    | 1.49 (1.22–1.82)                  | <0.001                           | 1.65 (1.24–2.18)                  | <0.001                           |
| Female sex                                       | 1.07 (0.61–1.88)                  | 0.82                             |                                 |                                  |
| History of hypertension                         | 1.65 (0.90–3.00)                  | 0.12                             |                                 |                                  |
| History of dyslipidemia                         | 1.35 (0.75–2.43)                  | 0.31                             |                                 |                                  |
| History of diabetes                             | 1.04 (0.55–1.97)                  | 0.90                             |                                 |                                  |
| History of CKD                                   | 1.96 (1.39–2.74)                  | <0.001                           | 1.58 (1.21–2.32)                  | <0.001                           |
| History of obstructive coronary artery disease   | 1.02 (0.56–1.86)                  | 0.96                             |                                 |                                  |
| History of chronic pulmonary disease            | 1.34 (0.92–2.35)                  | 0.42                             |                                 |                                  |
| History of atrial fibrillation                   | 1.45 (1.76–1.75)                  | 0.24                             |                                 |                                  |
| Sympathy                                        | 1.45 (0.79–2.64)                  | 0.41                             |                                 |                                  |
| NYHA class II vs ≥III                            | 1.08 (0.59–1.97)                  | 0.79                             |                                 |                                  |
| Family history of SCD                           | 1.01 (0.39–1.57)                  | 0.99                             |                                 |                                  |
| Family history of hypertrophic cardiomyopathy   | 1.63 (0.39–6.89)                  | 0.50                             |                                 |                                  |
| Medical therapy for hypertrophic cardiomyopathy | 0.71 (0.27–1.86)                  | 0.48                             |                                 |                                  |
| History of nonsustained ventricular tachycardia  | 1.17 (0.52–1.66)                  | 0.70                             |                                 |                                  |
| STS score*                                       | 1.10 (1.04–1.15)                  | <0.001                           |                                 |                                  |
| ESC risk score                                   | 1.05 (0.93–1.19)                  | 0.43                             |                                 |                                  |
| ACC/AHA risk factors (0 vs ≥1)                   | 1.13 (0.87–1.89)                  | 0.65                             |                                 |                                  |
| LV ejection fraction                             | 1.03 (0.98–1.07)                  | 0.26                             |                                 |                                  |
| Maximal LV thickness                             | 1.17 (0.56–2.46)                  | 0.67                             |                                 |                                  |
| Indexed left atrial size                         | 1.03 (0.89–1.33)                  | 0.54                             |                                 |                                  |
| Moderate or severe mitral regurgitation vs less  | 1.06 (0.56–2.01)                  | 0.99                             |                                 |                                  |
| Moderate or severe aortic regurgitation vs less  | 1.03 (0.63–1.89)                  | 0.76                             |                                 |                                  |
| Maximal LVOT gradient (for every 10-mm Hg increase) | 1.02 (0.96–1.08)                  | 0.59                             |                                 |                                  |
| Indexed LV mass (for every 10-g/m² increase)     | 1.04 (0.98–1.11)                  | 0.16                             |                                 |                                  |
| Indexed LV end-systolic diameter                 | 1.01 (0.96–1.04)                  | 0.83                             |                                 |                                  |
| RVSP (for every 10-mm Hg increase)               | 1.22 (1.02–1.46)                  | 0.01                             | 1.28 (1.05–1.57)                  | 0.01                             |
| Indexed AVA (for every 0.1-cm²/m² decrease)     | 1.03 (0.97–1.06)                  | 0.52                             |                                 |                                  |
| AVR+myectomy                                     | Reference                         |                                  |                                 |                                  |
| AVR+myectomy+CABG                                | 1.21 (0.83–1.59)                  | 0.46                             |                                 |                                  |
| AVR+myectomy+CABG+mitral valve surgery           | 1.37 (0.83–1.42)                  | 0.31                             |                                 |                                  |
| Concomitant ascending aortic replacement         | 1.14 (0.79–1.49)                  | 0.62                             |                                 |                                  |
| Aortic valve mechanical vs bioprosthesis         | 1.15 (0.73–1.78)                  | 0.53                             |                                 |                                  |
| Indexed prosthetic effective aortic valve orifice area | 1.01 (0.98–1.03)                  | 0.78                             |                                 |                                  |
| Maximal postoperative LVOT gradient              | 0.99 (0.98–1.01)                  | 0.62                             |                                 |                                  |
| Mean postoperative aortic prosthetic gradient   | 1.00 (0.99–1.01)                  | 0.69                             |                                 |                                  |
| Histopathologic diagnosis of HCM vs hypertensive heart disease | 1.24 (0.82–2.41) | 0.62                             |                                 |                                  |
| Postoperative pacemaker implantation             | 1.12 (0.64–1.51)                  | 0.73                             |                                 |                                  |

ACC/AHA indicates American Heart Association/American College of Cardiology; AVA, aortic valve area; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; ESC, European Society of Cardiology; HR, hazard ratio; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; and SCD, sudden cardiac death.

*When Society of Thoracic Surgeons (STS) score (a composite of established cardiovascular risk factors) was substituted for age and kidney disease, the findings on multivariate analysis were similar.
older group of patients undergoing myectomy (which itself results in left bundle branch block in all cases) and AVR. Interestingly, on histopathologic analysis of the myectomy specimens in the current study, while 18% had a diagnosis of hypertensive heart disease, the majority (82%) had features that were characteristic of HCM, with similar baseline characteristics and long-term outcomes. As demonstrated in the current study, longer-term survival is associated with standard cardiovascular risk factors such as increasing age, CKD, and higher RVSP, likely caused by dual obstructive physiology and not by pure HCM-related risk factors. Hence, it appears that despite having histopathologic features suggestive of HCM, the pathophysiologic impact of sequential LVOT obstruction (dynamic caused by HCM and fixed caused by AS) is potentially greater than what is seen in a patient with standard obstructive HCM. While purely speculative, it could be that in such patients, afterload mismatch, commonly seen in AS, in addition to excessive hypertrophy, might predispose this patient population to subendocardial ischemia with its downstream ramifications. The findings were similar even in the subgroup where concomitant coronary artery disease was excluded. An important observation is that the longer-term survival of patients was similar to a normal age-sex-matched US population. Hence, it is crucial to recognize concomitant significant AS in such patients, because the natural history of significant AS without AVR is dismal.

In the context of blood ejection from LVOT into the aorta, multiple pathophysiologic conditions that result in fixed or dynamic obstruction need to be recognized. While AS (valvular narrowing) and subaortic membrane (narrow LVOT) result in a fixed profile of obstruction, obstructive HCM (as a result of SAM of mitral valve and dynamic LVOT obstruction) can occur as a result of a complex interplay of basal septal hypertrophy, narrow LVOT, mitral valve/papillary muscle abnormalities, and a steeper LV inflow to outflow (aorto-LVOT) angle. While it is not common to observe both AS and HCM simultaneously in the same patient, there are patients in whom these conditions coexist. This presence of sequential LVOT obstruction poses particular diagnostic challenges requiring meticulous imaging (especially Doppler echocardiography [Figure 1]) to correctly identify the location (valvular or subvalvular) and type of LVOT obstruction (fixed or dynamic). In many cases, invasive hemodynamics may need to be considered for a complete elucidation of the dual problem.

Correct identification of this dual obstructive physiology is also crucial for accurate diagnosis, as it might have implications on family screening, follow-up recommendations, and therapeutic options. The current study demonstrates that an experienced setup in terms of expertise in clinical management, advanced imaging invasive hemodynamic assessment, and cardiac surgery is required. In symptomatic patients who require advanced therapies, it necessitates an altered and a more complex (in the majority of cases, an invasive) approach. A previous study has reported 2% mortality in 47 patients with severe AS (of 3523 patients) who underwent AVR and concomitant myectomy for the primary indication of severe AS. This is unlikely the current study where the primary cause was HCM. While there are small studies on disopyramide and emerging data on novel therapeutic agents that can modulate dynamic LVOT obstruction, there are currently no large-scale studies demonstrating that medical therapy is associated with a survival benefit in patients with obstructive HCM and, particularly, severe AS. AVR and surgical myectomy are considered class 1 indications and definitive therapies to relieve fixed and dynamic obstruction in symptomatic patients with severe AS and obstructive HCM, respectively, with excellent longer-term survival.

The current study demonstrates that in a carefully selected group of symptomatic patients with concomitant fixed and dynamic LVOT obstruction a combination of myectomy and AVR had excellent surgical results and longer-term survival similar to an age-sex-matched normal US population. However, any suggestion of performing such a complex combined operation has to be balanced against procedural risk and overall experience of the center (including imaging and surgical expertise) at managing these complex patients. The current study also highlights the importance of high volume and experience in invasive management of AS and HCM in patients with severe LVOT obstruction. In recent years, the paradigm of invasive management of AS is rapidly shifting towards transcatheter AVR. With increasing sophistication of percutaneous procedures, it is conceivable that many such patients (especially those with higher STS score and appropriate septal arterial perforator/LVOT anatomy) could be treated using a combination of alcohol septal ablation and transcatheter AVR. However, in such patients, a surgical approach has advantages over a percutaneous approach because of its ability to address multiple problems simultaneously, including dynamic LVOT obstruction (using myectomy or mitral/papillary muscle-based procedures), significant AS, and concomitant coronary artery disease. The results of the current study could serve as a benchmark for future comparison of myectomy+surgical AVR versus transcatheter AVR+alcohol septal ablation strategies. However, this requires further investigation.

**Limitations**

This was an observational study from a single tertiary center, which could have potential selection bias. The findings of this study should not be extrapolated to
patients with severe AS and a narrow LVOT caused by basal septal hypertrophy who need a concomitant myectomy to expand the LVOT. The results of all testing were available to all clinicians at the time of decision-making, introducing further bias. Multimodality imaging was not routinely performed and, hence, data were available in all patients. In addition, given the overall expertise involved with both imaging and invasive management of LVOT obstruction, our results might not be generalizable to other lesser experienced centers. We did not include patients needing emergent ASA during TAVR, as this was only performed as a bailout procedure attributable to unexpected development of intraprocedural SAM and LVOT obstruction. We report all-cause mortality, which is more objective than trying to ascertain a specific cause of death.46 However, the findings were similar when patients with documented noncardiac causes of death were excluded. Finally, the current study only tested associations, not causality.

CONCLUSIONS

In a large HCM and valve practice, it is not uncommon to encounter patients who have symptoms from dual obstructive physiology (significant obstructive HCM and AS). It is crucial to identify the presence of sequential obstruction to the flow of blood from the left ventricle to the aorta by careful imaging and hemodynamic assessment. In patients presenting with a combination of severe symptomatic obstructive HCM and moderate or severe AS undergoing a combined surgical myectomy and AVR at our tertiary care center, the observed postoperative mortality was significantly lower than the expected mortality, and longer-term survival was similar to a normal age-matched US population. These findings need additional validation.

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