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Sudden Unexpected Death After Balloon Valvuloplasty for Congenital Aortic Stenosis

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Objectives The aims of this study were to determine the incidence and risk factors of sudden unexpected death (SUD) after balloon aortic valvuloplasty (BAVP) for congenital aortic stenosis (AS) and to assess the effect of exercise restriction.

Background Exercise restriction is recommended for some patients with congenital AS because of a perceived increased risk for SUD. Little is known about the incidence of SUD in those with treated AS or the efficacy of exercise restriction in preventing SUD.

Methods A review was conducted of 528 patients who underwent BAVP for congenital AS at Children's Hospital Boston from 1984 to 2008. Exercise restriction status was ascertained for those ≥4 years of age, censored at aortic valve replacement or transplantation.

Results Median subsequent follow-up was 12.0 years (range 0 to 24.8 years), for a total of 6,344 patient-years of follow-up. There were 63 deaths, with SUD in 6 patients, 5 of which occurred at ≤18 months of age. For patients ≥4 years of age at most recent follow-up with no histories of pulmonary hypertension (n = 422), median follow-up after BAVP was 14.6 years, for 6,019 patient-years of follow-up. Exercise restriction was prescribed in 183 patients (43%; 2,541 patient-years) and no restriction in 220 (52%; 2,691 patient-years); there were insufficient data in 19 patients. There were 17 deaths in this cohort of 422 patients, with 1 SUD (the patient, who was exercise restricted, died during sleep), for an incidence of 0.18/1,000 patient-years (95% confidence interval: 0.01 of 1,000 to 1.01 of 1,000).

Conclusions SUD is extremely rare after BAVP for congenital AS. No beneficial effect of the recommendation for exercise restriction was observed in this longitudinal cohort with 6,000 patient-years of follow-up. (J Am Coll Cardiol 2010;56:1939–46) © 2010 by the American College of Cardiology Foundation

Since first reported 25 years ago (1), balloon aortic valvuloplasty (BAVP) has gradually become the preferred treatment for newborns, children, and young adults with congenital aortic stenosis (AS) at most centers (2–8). Although this treatment is usually effective for acutely relieving left ventricular outflow obstruction, a number of studies of short-term and midterm outcomes of BAVP for congenital AS have demonstrated subsequent progressive aortic valve disease in some patients, both stenosis and regurgitation (3,5–7,9). Long-term outcomes are less well characterized but suggest a steady long-term hazard for aortic valve replacement (AVR) (8–10).

Sudden unexpected death (SUD) has been documented rarely in both symptomatic and asymptomatic patients with severe congenital AS (11,12). Large case series and registries of athletes who died suddenly have included small numbers of patients with congenital AS (13,14). Consensus expert panel recommendations have thus been developed that restrict patients with congenital AS from strenuous exercise and competitive sports to varying degrees, such as the 36th

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Bethesda Conference (15), with similar recommendations endorsed by national organizations, including the American Heart Association and American College of Cardiology (16). In brief, these recommendations restrict asymptomatic patients with moderate AS (defined as a maximal instantaneous Doppler gradient of 40 to 70 mm Hg) from some types of competitive sports, and those with severe AS (maximal instantaneous Doppler gradient >70 mm Hg)

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Abbreviations and Acronyms

AS = aortic stenosis

AVR = aortic valve replacement

BAVP = balloon aortic valvuloplasty

CI = confidence interval

HR = hazard ratio

SUD = sudden unexpected death

from all competitive athletics. Patients with treated AS are restricted from competitive sports on the basis of subsequent residual gradients after intervention by the same criteria.

Few long-term studies, however, have been performed in patients with congenital AS, and the data on which these recommendations are based are largely from case reports and series. In the Second Natural History Study of Congenital Heart Defects, SUD occurred in 25 of 462 patients with congenital AS followed for an average of more than 15 years; however, the majority of these patients had undergone surgical valvotomy (11). The true incidence and risk factors for SUD in patients treated with modern transcatheter techniques are unknown. There is little evidence that exercise increases the risk for SUD in patients with treated congenital AS, and such recommendations are at odds with the known beneficial effects of regular exercise in maintaining cardiovascular health (17). Highly divergent views among physicians at our institution about the appropriateness of exercise and competitive sports restriction in patients followed noninvasively with known congenital AS have thus resulted in significant practice variation. We sought to determine the incidence and risk factors for SUD in a large cohort of patients who underwent BAVP for congenital AS over a 24-year period and to determine if a beneficial effect of exercise restriction in preventing SUD could be demonstrated.

Methods

Patients. Patients with congenital valvular AS who underwent transcatheter BAVP at Children's Hospital Boston from December 1984 through January 2009 were ascertained from the computer database of the Department of Cardiology. Patients who were converted to a functionally univentricular circulation within 30 days of catheterization were excluded. Patients who underwent prior surgical or transcatheter aortic valve intervention before referral to our center were included, as were those with associated congenital cardiovascular anomalies; patent ductus arteriosus in newborns, patent foramen ovale, and atrial septal defects not treated surgically were not considered "associated cardiovascular anomalies." Indications for catheterization and valve dilation were not standardized and may have varied according to patient age, clinical status, era, referring physician, and interventional cardiologist. General guidelines for intervention considered symptomatic status, AS gradient, ventricular function, and the presence and severity of associated anomalies. From 1985, BAVP was the preferred therapy for congenital AS at our center, and surgical aortic valvotomy would have been performed almost exclusively in patients with coexisting anomalies requiring open-heart surgery, or after unsuccessful balloon dilation. The technical details of BAVP have been described previously (2,3,5).

Cross-sectional follow-up was obtained by June 2009. Patients not followed longitudinally at our center were contacted by mail and subsequent telephone call detailing the study. Exercise restriction status was considered relevant for patients ≥4 years of age at most recent follow-up and was ascertained by review of clinical records and/or verified by direct inquiry. Because of complex clinical variation in the nature and degree of restriction from exercise, we simplified our analysis by considering patients "restricted" if their cardiologist had placed any restrictions on exercise or competitive sports participation. Patients with histories of pulmonary hypertension, which was defined as mean pulmonary artery pressure ≥30 mm Hg at an age >30 days, were also excluded from the exercise restriction portion of the analysis, because this represents a known risk factor for sudden death and separate indication for exercise restriction. Most recent follow-up echocardiographic data were collected (before AVR if applicable), and maximal instantaneous AS gradient by Doppler was categorized according to the cutoffs recommended in the Bethesda guidelines: mild, <40 mm Hg; moderate, 40 to 70 mm Hg; and severe, >70 mm Hg (15).

Patients were considered lost to follow-up if there was no available contact information and no known clinical follow-up for >4 years. For these patients (n = 48), vital status and cause of death (if deceased) were ascertained by query of both the Social Security Death Index (maintained by the Social Security Administration) and the National Death Index, a large database maintained by the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and the National Center for Health Statistics.

Data analysis. The primary outcome was SUD in patients with biventricular circulation after BAVP. Secondary outcomes included cardiovascular death and all-cause mortality. Kaplan-Meier analysis with log-rank testing and Cox proportional hazards regression were performed to assess the relationship between predictor variables and time to event, with the start time set at the initial BAVP procedure. Variables significant at the 0.10 level by the log-rank test were considered for inclusion in the multivariate Cox model; a forward selection procedure was used. Variables significant at the 0.05 level on the basis of a likelihood ratio test were retained in the final model. Patients were censored at time of first use of AVR or heart transplantation. Comparisons between patients with and without exercise restriction were performed using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables.

This retrospective study was performed according to a protocol approved by the Committee for Clinical Investigation at Children's Hospital Boston.

Results

Patients. Between December 1984 and January 2008, 563 patients with congenital AS underwent BAVP at Children's Hospital Boston. Thirty-five of these patients were excluded from the present study because they were converted to functionally univentricular circulation during the same hospitalization, either as part of a planned strategy of left-heart rehabilitation or because of circulatory insufficiency after aortic valve dilation. The remaining 528 patients constituted the study cohort. Demographic and diagnostic details of these 528 patients are summarized in Table 1. The median age at BAVP was 1.9 years, and most patients (75%) were ≤10 years of age. The majority had isolated valvular AS (n = 334 [63%]), and most (n = 384 [73%]) had no other cardiac interventions before BAVP.

Most patients (n = 447 [85%]) had pre-intervention peak AS gradients ≥50 mm Hg at catheterization. The peak AS gradient decreased significantly after balloon dilation (median acute decrease, 35 mm Hg; $p < 0.001$ by Wilcoxon signed rank test). Pre- and post-intervention aortic valve hemodynamic variables are summarized in Table 2. Moderate or worse AR was present in 14% of the cohort by angiography acutely after BAVP. Approximately 100 of these 528 patients were included in a previous report that evaluated factors associated with anatomic suitability for biventricular repair in newborns with AS (18).

Follow-up. The median duration of vital status follow-up was 12.0 years (range 0.1 to 24.8 years), for a total of 6,344 patient-years of follow-up (Table 3). Among 488 patients who underwent balloon dilation before 2006, clinical follow-up data were available for at least 2 years or until the time of death in all but 6. Among more recent patients, none met our definition of loss to follow-up, although in 6, the most recent follow-up was <2 months after dilation. During follow-up, repeat BAVP was performed in 117 patients (22%), for a total of 149 repeat procedures. AVR (including the Ross procedure) was subsequently performed in 116 (22%). Further analyses of patient and procedural variables associated with long-term valve function and

Table 1 Demographic and Diagnostic Data at Time of First BAVP for Congenital AS, 1984 to 2009 (n = 528)

Variable	Value
Age	
Median (range)	1.9 yrs (1 day to 40.4 yrs)
Group	
<1 month	128 (24%)
1–12 months	121 (23%)
1–10 yrs	147 (28%)
≥11 yrs	132 (25%)
Associated congenital cardiovascular anomalies*	
None	334 (63%)
Coarctation/IAA	95 (18%)
Mitral stenosis†	55 (10%)
Multiple left-heart obstructions‡	38 (8%)
Ventricular septal defect	43 (8%)
Other§	3 (1%)
Pulmonary hypertension‖	37 (7%)
Prior interventions	
None	384 (73%)
Prior intervention for AS	75 (14%)
Surgical valvotomy	57 (11%)
Balloon dilation	21 (4%)
Coarctation/IAA repair	71 (13%)
Ventricular septal defect closure	22 (4%)
Subaortic stenosis procedure	20 (4%)

*Some had more than 1 associated congenital cardiovascular anomaly. †Defined as mean transmitral Doppler gradient ≥4 mm Hg. ‡AS plus at least 2 of the following: coarctation of the aorta, mitral stenosis, and subaortic stenosis. §One case each of transposition of the great arteries, tetralogy of Fallot, and sinus venous atrial septal defect with partially anomalous pulmonary venous return. ‖Defined as mean pulmonary artery pressure at catheterization ≥30 mm Hg, past 30 days of age.

AS = aortic stenosis; BAVP = balloon aortic valvuloplasty; IAA = interrupted aortic arch.

Table 2 Pre-BAVP and Acute Post-BAVP Aortic Valve Function (n = 528)

Variable	Value
Pre-intervention peak AS gradient (mm Hg)*	
Median (range)	65 (0–160)
≤49	78 (15%)
50–79	310 (59%)
≥80	137 (26%)
Acute post-dilation peak AS gradient (mm Hg)†	
Median (range)	28 (0–106)
≤29	269 (51.5%)
30–39	144 (27.5%)
≥40	109 (21%)
Acute post-dilation AR severity‡	
None-trace	275 (52%)
Mild	178 (34%)
Moderate or severe	74 (14%)

*Data missing in 3 patients. †Data missing in 6 patients. ‡Data missing in 1 patient. AR was graded by catheter angiography.

AR = aortic regurgitation; other abbreviations as in Table 1.

Table 3 Most Recent Follow-Up After Post-BAVP for Congenital AS (n = 528)

Variable	Value
Age (yrs), median (range)	17.9 (0–64)
Duration follow-up (yrs), median (range)	12.0 (0–24.8)
Cumulative follow-up (patient-yrs)	6,344
Repeat BAVP*	117 (22%)
AVR	116 (22%)
Age ≥4 yrs at most recent follow-up	422
Exercise restrictions (any)†	183 (43%)
Cumulative restricted follow-up (patient-yrs)	2,541
No exercise restrictions‡	220 (52%)
Cumulative unrestricted follow-up (patient-yrs)	2,691
Restrictive cardiomyopathy	5 (1%)
Heart transplantation	5 (1%)
Death	63 (12%)

*30 patients had >1 repeat dilation. †Exercise restriction considered relevant in those ≥4 years of age at most recent follow-up (n = 454); 32 patients had pulmonary hypertension. Includes any restriction from weightlifting, competitive sports, or exercise. Exercise restriction data were unavailable in 19 patients. ‡Censored at the time of AVR or transplantation.

AVR = aortic valve replacement; other abbreviations as in Table 1.

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Table 4 Comparison of Exercise-Restricted Versus Unrestricted Patients After BAVP for Congenital AS (n = 403)*

Factor	Exercise Restricted (n = 183)	Unrestricted (n = 220)	p Value
Age at BAVP (yrs)	4 (0–29)	3 (0–35)	0.09
Associated CHD	58 (32%)	73 (33%)	0.83
Pre-intervention peak AS gradient (mm Hg) (n = 181,219)	65 (10–160)	65 (6–130)	0.59
Acute post-dilation peak AS gradient (mm Hg) (n = 181,218)	30 (0–90)	28 (0–106)	0.36
Acute post-dilation AR severity			0.47
None-trace	87 (48%)	118 (54%)	
Mild	65 (35%)	68 (31%)	
Moderate or severe	31 (17%)	34 (15%)	
Cumulative follow-up (patient-yrs)†	2,541	2,691	—
Follow-up (yrs)	14.4 (0.2–24.8)	12.1 (0.0–24.4)	0.01
Repeat BAVP	43 (24%)	52 (24%)	—
AVR	60 (33%)	45 (20%)	—
Most recent echocardiographic AS gradient (MIG, mm Hg)‡	44 (0–120)	41 (0–115)	0.60
Mild (<40)	66 (41%)	86 (45%)	0.73
Moderate (40–70)	78 (48%)	89 (46%)	
Severe (>70)	17 (11%)	17 (9%)	
Most recent echocardiographic AR ≥ moderate‡	49 (27%)	56 (26%)	0.82
Transplantation	1 (1%)	1 (<1%)	—
Death (any)	11 (6%)	6 (3%)	—
SUD	1 (<1%)	0 (0%)	—

Data are expressed as median (range) or as number (percent). The p values are not reported for time-dependent variables. *Includes patients ≥4 years of age at most recent follow-up, with no histories of pulmonary hypertension. Exercise restriction data were unavailable in 19 patients. †Censored at the time of AVR or transplantation. ‡Data were available in all but 50 patients: 22 restricted and 28 unrestricted.

CHD = congenital heart disease; MIG = maximal instantaneous gradient by Doppler; SUD = sudden unexpected death; other abbreviations as in Tables 1 to 3.

reintervention after BAVP are the subject of another study and were not further investigated for the purposes of this report.

Exercise restriction. Among 422 patients ≥4 years of age at most recent follow-up and without pulmonary hypertension, median follow-up after BAVP was 14.6 years, for total 6,019 patient-years of follow-up (Table 3). Exercise restriction was able to be defined from medical records and/or patient inquiry in 403 patients (not available in 19), with 183 (43%) exercise restricted and 220 (52%) not restricted. No cases of "crossover" from exercise restricted to unrestricted, or vice versa, were noted. Cumulative follow-up in the 2 groups was similar: 2,541 patient-years for exercise-restricted patients versus 2,691 patient-years for those unrestricted.

Exercise-restricted and unrestricted patients did not differ with regard to baseline demographics, anatomic features, or peri-BAVP hemodynamic status (Table 4). The median duration of follow-up was longer in the exercise-restricted group (14.4 years vs. 12.1 years), although as noted previously, the cumulative patient-years of follow-up were similar. The proportion of patients who had undergone repeat BAVP before cross-sectional follow-up was similar in both groups (24%), although more had undergone AVR in the restricted group (33%) than the unrestricted group (20%). Measures of aortic valve function by echocardiography at most recent follow-up showed a modestly but not significantly higher AS gradient in those restricted from exercise (median maximal instantaneous gradient, 44 mm Hg vs. 41 mm Hg; p = 0.60). In both restricted and unrestricted patients, the distribution of AS gradients was skewed, but most patients had moderate or severe AS in both groups (Fig. 1). The proportion of patients with severe AS (maximal instantaneous Doppler gradient ≥70 mm Hg) was not significantly different between exercise-restricted and unrestricted patients (11% vs. 9%, p = 0.73). The proportion of patients with moderate or worse aortic regurgitation was similar in both groups.

Deaths. Sixty-three of 528 patients died during follow-up, with death from cardiovascular causes in 50 patients. Twenty of these occurred within 1 month of BAVP. Survival over time was 95 ± 1% at 5 years, 93 ± 1% at 10 years, and 88 ± 2% at 20 years by Kaplan-Meier analysis, with a steep early hazard for death, followed by a steady hazard (Fig. 2). Among patients ≥4 years of age at most recent follow-up (n = 423), there were 20 total deaths, 17 of which occurred in patients in whom exercise restriction status could be ascertained (Table 4, Figs. 3 and 4).

The causes of death for the whole cohort included congestive heart failure (primarily infants with circulatory failure after BAVP; n = 27), operative complications during or after aortic or mitral valve surgery (n = 9), pneumonia or sepsis (n = 4), accidental death (n = 3), acute catheterization complications (n = 2), and drug overdose (n = 2); a complete list is provided in Table 5. Five patients underwent heart or heart-lung transplantation, 4 of whom sub-

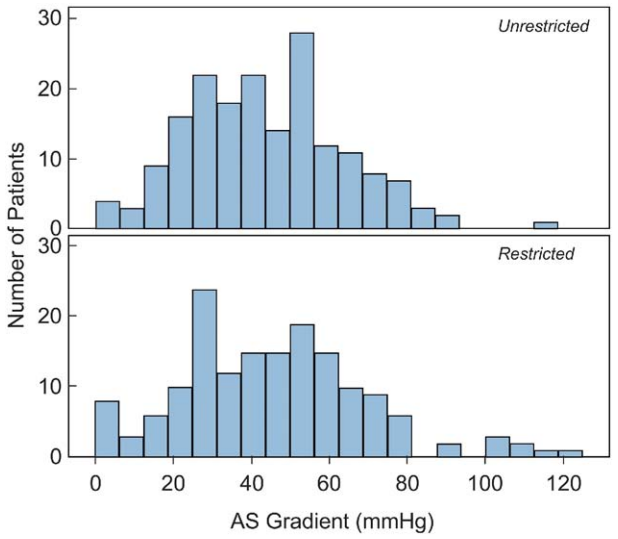

Figure 1 **AS Gradient at Most Recent Follow-Up**

Histograms demonstrate the maximal instantaneous gradient by Doppler echocardiography at most recent follow-up in unrestricted and exercise-restricted patients. Follow-up data were not available in 28 of 220 unrestricted and 22 of 183 exercise-restricted patients. AS = aortic stenosis.

sequently died. Among patients with diagnoses of pulmonary hypertension, 46% died during follow-up, compared with 6.7% of those without this diagnosis.

In multivariate analysis, age <30 days at BAVP (hazard ratio [HR]: 5.7; 95% confidence interval [CI]: 3.2 to 10.1; $p < 0.001$), presence of multiple left-sided obstructive lesions (HR: 11.9; 95% CI: 5.9 to 24.4; $p < 0.001$), and BAVP during the first decade of experience (HR: 5.9; 95% CI: 2.3 to 15.1; $p < 0.001$) were the only pre-procedural or

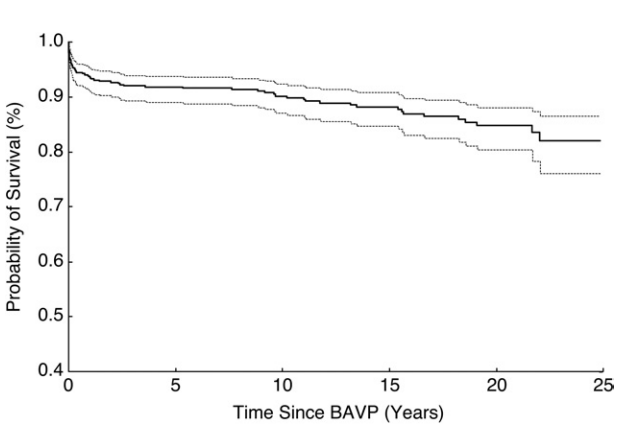

Figure 2 **Survival After BAVP for Congenital AS**

Kaplan-Meier survival analysis of entire cohort of patients who underwent balloon aortic valvuloplasty (BAVP) for congenital aortic stenosis (AS) from 1984 to 2009 (n = 528). **Solid line** represents estimated probability of survival, with **dashed lines** demonstrating 95% confidence bands.

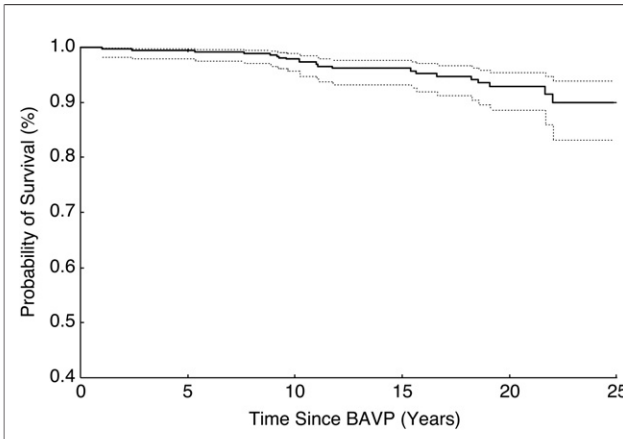

Figure 3 **Survival After BAVP for Congenital AS for Those More Than 4 Years of Age at Most Recent Follow-Up**

Kaplan-Meier survival analysis of patients ≥4 years of age, with no histories of pulmonary hypertension, who underwent balloon aortic valvuloplasty (BAVP) for congenital aortic stenosis (AS) (n = 422). **Solid line** represents estimated probability of survival, with **dashed lines** demonstrating 95% confidence bands.

acute post-procedural predictors of subsequent cardiovascular death.

Sudden deaths. Of the 63 deaths in the entire cohort, 6 were considered SUD (Table 6). Five of these patients died at ≤18 months of age and 3 at <2 months of age. Only 1 SUD occurred in the group ≥4 years of age at most recent follow-up, a 28-year-old asymptomatic patient who was restricted from competitive sports, who died suddenly during sleep. Thus, the minimal incidence of SUD in the cohort ≥4 years of age was 18 of 100,000 patient-years (95% CI: 1 of 100,000 to 101 of 100,000). Although patient follow-up for the purpose of SUD was censored at time of

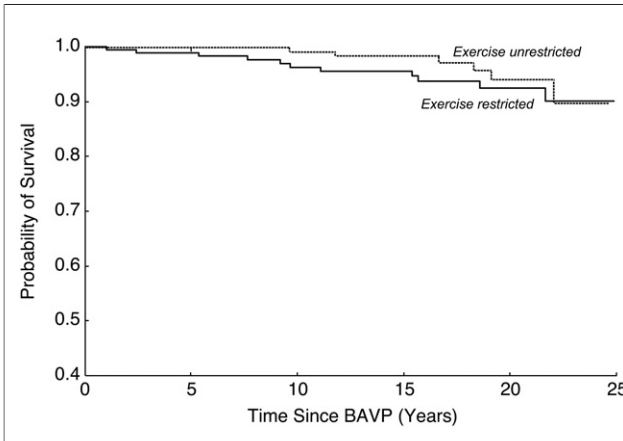

Figure 4 **Survival by Exercise Restriction Status After BAVP for Congenital AS**

Kaplan-Meier survival analysis of patients who had undergone balloon aortic valvuloplasty (BAVP) for congenital aortic stenosis (AS) and were ≥4 years of age at most recent follow-up, with no histories of pulmonary hypertension, by exercise restriction status (any restriction from exercise or competitive sports was considered restricted). **Solid line** indicates patients restricted from exercise, and **dashed line** represents those unrestricted. Log-rank test p = 0.30.

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Table 5 Deaths After BAVP for Congenital AS (n = 528)

Variable	n (%)
Deaths	63 (12%)
Accident	3 (5%)
Acute catheterization procedural*	2 (3%)
Congestive heart failure†	27 (43%)
Drug overdose	2 (3%)
Endocarditis	1 (1.6%)
Heart transplantation complications	4 (6%)
Leukemia	1 (1.6%)
Pneumonia and/or sepsis	4 (6%)
Post-operative cardiac surgery complications	9 (14%)
Respiratory failure (Duchenne muscular dystrophy)	1 (1.6%)
Ruptured aortic aneurysm (Turner syndrome)	1 (1.6%)
Stroke (mechanical AVR, warfarin noncompliance)	1 (1.6%)
SUD	6 (10%)
Tracheal reconstruction surgery complications	1 (1.6%)

*One death due to occlusive aortic flap raised over left coronary ostium, the other to lethal ventricular arrhythmia. †Primarily infants with circulatory insufficiency after BAVP.
Abbreviations as in Tables 1, 3, and 4.

AVR or transplantation by study design, SUD did not occur in any patients censored for this reason.

Discussion

In this long-term observational cohort of 528 patients who underwent BAVP for congenital AS, we found an extremely low rate of SUD; there were only 6 cases in more than 6,300 patient-years of follow-up. Although the small number of patients with SUD precluded formal statistical analysis for associated variables, SUD was more common in the young, with 5 of 6 cases occurring in infants ≤18 months of age and 3 of the 6 cases in those ≤45 days of age. Patients with neonatal AS requiring BAVP early in life may thus be at higher risk than older children for SUD, a finding that has not been reported to date and may have implications for clinical follow-up.

Among patients ≥4 years of age at most recent follow-up, in whom exercise restriction could reasonably be postulated to have a beneficial or protective effect, we found only a single occurrence of SUD in more than 6,000 patient-years of follow-up. Cumulative patient-years of follow-up were roughly similar in the group of patients restricted in any fashion from exercise and those unrestricted (2,541 patient-years vs. 2,691 patient-years), and we could find no differences between these groups in baseline characteristics (such as age at initial BAVP, frequency of associated cardiovascular anomalies, or pre-intervention AS gradient), or acute procedural results (post-intervention AS gradient, degree of AR). There were no obvious differences in subsequent outcomes, with 24% of patients in both groups requiring repeat BAVP and similar number requiring heart transplantation (1 patient in both groups). Although the median AS gradient by most recent echocardiogram was slightly higher in the exercise-restricted group (44 mm Hg vs. 41 mm Hg), and although the exercise-restricted group was more skewed toward higher gradients, as shown in Figure 1, the majority of patients in both groups would be classified as having moderate or greater AS by the Bethesda guidelines. A similar proportion in both groups had moderate or worse aortic regurgitation by most recent echocardiogram. There were more AVR procedures in the restricted group (33% vs. 20%), although given the known steady risk for AVR in this population (8–10), this may be at least partially explained by a longer median follow-up time in the exercise-restricted group (14.4 years vs. 12.1 years). Thus, within the constraints of this retrospective study, although some differences between the 2 groups, such as AS gradient at most recent follow-up, exist, the decision to restrict patients from exercise or sports participation did not appear to be determined by clinical factors alone but in large part by the practice pattern of the treating cardiologist, presumably informed by his or her interpretation of national guidelines such as the Bethesda Conference (15). The issue of how patients followed such recommendations could not be ascertained by this study design. Despite a large number of patient-years of follow-up, we did not observe a beneficial effect of the recommendation for exercise restriction in preventing SUD.

This study included only patients with congenital AS who had undergone BAVP. Patients with congenital AS

Table 6 SUD After BAVP for Congenital AS

Patient #	Age at BAVP*	Age at Death	Associated CHD	Residual AS†	Residual AR‡	Circumstances of Sudden Death
1	2 days	14 days	Isolated valvular AS	35	Mild	At home, no preceding symptoms. Autopsy performed, no clear etiology found.
2	1 day	30 days	Isolated valvular AS	40	Trivial	At home, no preceding symptoms. Autopsy not performed.
3	2 days	45 days	Isolated valvular AS	40	Mild	At home, no preceding symptoms. Autopsy not performed.
4	24 days	18 months	D-loop TGA, underwent arterial switch operation	35	Mild	At home, no preceding symptoms. Autopsy not performed.
5	1 day	11 months	Multiple left-sided obstructions, pulmonary hypertension	40	Moderate	At home, fever and respiratory symptoms. Autopsy performed, sepsis listed as primary cause of death.
6	6 yrs	28 yrs	Aortic coarctation, underwent coarctation repair	65	Moderate	At home while sleeping, no preceding symptoms. Autopsy not performed.

*Age at first BAVP procedure. Patients 5 and 6 had more than 1 BAVP. †At most recent follow-up, Doppler maximal instantaneous gradient. ‡At most recent follow-up.
TGA = transposition of the great arteries; other abbreviations as in Tables 1, 2, and 4.

who underwent surgical valvotomy as primary treatment of their disease, or with AS not severe enough to require intervention, were not included. At our center, surgical valvotomy was primarily used in an earlier treatment era, before the advent of BAVP in the mid-1980s, and since that time has been used nearly exclusively for patients undergoing surgical repair of other significant congenital heart lesions, which may modify the subsequent natural history, or for BAVP treatment failures. Patients with congenital AS who did not undergo BAVP during the study period were primarily those with milder forms of the disease, and they were not included in this report for a number of reasons, including the known inaccuracy of noninvasive Doppler determinations of the severity of AS in children (19) as well as the presumed lower risk for SUD in those with mild disease as informed by previous natural history studies (11). As congenital valvular AS often worsens over time, the number of patients followed at our center with significant AS in which BAVP was not undertaken over the 24-year time period of this study was relatively small. Our study focused on a group with severe enough AS by invasive measurement to require BAVP, which represents a population with the most severe disease and presumably the highest risk for SUD.

Case series (12) and large cohort studies (11) have suggested that patients with symptoms and the highest AS gradients are at higher risk for SUD. Although such retrospective data have been used to inform national guidelines regarding exercise restriction and restriction from competitive athletics (15,16), patients with severe, symptomatic, untreated AS are rarely encountered clinically in the current era. This study of patients with congenital AS managed with more contemporary BAVP techniques would indicate that the absolute risk for SUD is extremely low, with a reasonably long cohort follow-up in both exercise restricted and unrestricted patients. In contrast, there has been mounting evidence that regular exercise offers a number of health benefits, including improved survival and lower risk for cardiovascular events (17) in normal patients and improved functional capacity and quality of life even in patients with severe congenital heart disease (20–22). Rhodes et al. (23) found a significant positive impact of regular exercise on behavior, emotional state, and well-being in patients with severe congenital heart disease. Although the intent of competitive sports restriction is not to preclude regular exercise for the maintenance of cardiovascular fitness, patients may interpret such restriction as an indication that vigorous exercise may be detrimental to their health, which might have unintended negative consequences that surpass any positive benefit. The full impact of restriction from competitive athletics on patients, including long-term cardiovascular risk factors (such as sedentary life-style and body mass index), exercise capacity, and psychological well-being, has not been well studied to date but deserves further evaluation, particularly in light of the lack of a clear beneficial effect on SUD.

Overall, the risk for cardiovascular death after BAVP was not associated with acute post-procedural hemodynamic status. However, there were some significant predictors of subsequent cardiovascular death, most notably the presence of multiple left-heart obstructions (HR: 11.9), a subset of patients with congenital AS known to have significant associated mortality (24–26). Many of these patients also had pulmonary hypertension, which was also associated with mortality in this study; 46% of patients diagnosed with pulmonary hypertension at some point during follow-up died, compared with 6% in patients without this diagnosis. Patients undergoing BAVP during the first decade of experience had a higher risk for cardiovascular death than those treated in subsequent years. Patients undergoing BAVP as neonates also had a higher risk for cardiovascular death (HR: 5.7), often early after BAVP, which may be a marker of more severe or progressive disease.

Study limitations. One of the primary limitations of this study is that the rarity of SUD in patients of exercising age managed with BAVP precluded insight into 1 of our central clinical questions: does exercise restriction prevent SUD in patients with congenital AS? Other limitations to this study are the retrospective study design and extended enrollment period, logistic considerations that may limit the applicability of our findings. Similarly, although general clinical guidelines for intervention were followed, criteria for referral for catheterization or BAVP were not standardized, and practice likely varied over time and among practitioners. Hemodynamic variables likely changed over time in some patients, but we did not attempt to account for the potential time variance in AS or aortic regurgitation. As a retrospective evaluation, the clinical decision making that informed restricting or not restricting a given patient from competitive sports or exercise was often not available, only the prescription itself; we also did not verify the actual activity levels of the patients. Other clinical information that might factor into the decision to restrict from exercise, such as electrocardiographic changes, were not available in many patients and thus were not included in the analysis. Furthermore, the complex variation in types and levels of exercise restriction, including changes in restriction status, precluded a more complex analysis of the data. Also, many of the patients in this cohort were primarily followed elsewhere, and inquiry of the National Death Index and Social Security Death Index was required to ascertain vital status in some patients; although these are highly sensitive tools for ascertaining deaths and causes of death in most studies (27), it is possible that a small number of deaths were either missed or misclassified. However, given the rarity of SUD in this study, most of the methodological limitations noted likely had little impact on our primary conclusions.

Conclusions

SUD is extremely rare after BAVP for congenital AS. Infants may be at somewhat higher risk for SUD after

BAVP. No beneficial effect of the recommendation for exercise restriction was observed in this longitudinal cohort with 6,000 patient-years of follow-up. Current guidelines that restrict some patients with congenital AS from sports participation may overestimate the beneficial impact this practice has in preventing SUD.

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Key Words: aortic regurgitation ■ aortic stenosis ■ aortic valve replacement ■ exercise restriction ■ sudden death.