Aortic Valve Replacement Improves Survival in Severe Aortic Stenosis Associated With Severe Pulmonary Hypertension

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Background. **Severe pulmonary arterial hypertension in patients with severe aortic stenosis (AS) carries a poor prognosis. There are limited data on the effect of aortic valve replacement (AVR) in these patients.**

Methods. **Our echocardiographic database between 1993 and 2003 was searched for patients with severe AS defined as a Doppler estimated aortic valve area of 0.8 cm^2 or less and severe pulmonary hypertension defined as a pulmonary arterial systolic pressure 60 mm Hg or greater. Of the 740 patients with severe AS, 119 (16%) had severe pulmonary hypertension forming the study cohort. The AVR was performed in 36 (30%) of these patients. Survival of patients with and without AVR were compared and adjusted for comorbidities and group differences using the Cox regression model.**

Results. **Characteristics of patients with severe pulmonary hypertension; age 75 ± 13 years, 39% women, left ventricular ejection fraction 41 ± 20%. Patients who underwent AVR had a significantly higher five-year survival of 65% compared with 20% for those treated medically ($p < 0.0001$). The relative mortality risk associated with AVR was 0.28 (95% confidence interval 0.22 to 0.36) and was independent of age, gender, ejection fraction, diabetes, coronary disease, serum creatinine level, and concomitant medical therapy such as beta blockers, angiotensin converting inhibitors, and statins. The benefit of AVR was further supported by sensitivity and propensity score analyses. Patients on conservative therapy had a 30-day mortality of 30% and a one-year mortality of 70%.**

Conclusions. **Aortic valve replacement in patients with severe pulmonary hypertension secondary to severe AS is associated with a huge survival benefit. Medical therapy alone carries a dismal prognosis and AVR should be considered urgently in severe AS patients with severe pulmonary hypertension.**

(Ann Thorac Surg 2007;84:80–6)

Pulmonary hypertension in patients with severe aortic stenosis (AS) is associated with the presence of left ventricular (LV) dysfunction, mitral regurgitation, and higher LV filling pressures [1–4]. In small observational series it has been shown to be associated with high mortality in the absence of aortic valve replacement (AVR). In a series of 47 patients with severe pulmonary hypertension associated with severe AS, 37 patients undergoing AVR had a survival five-year rate of 52% compared with 20% for the 10 patients treated medically [5]. Smaller observational series have reported a potential symptomatic and hemodynamic benefit with AVR in such patients [4, 6, 7]. In view of the paucity of data on outcomes in these patients, we analyzed the effect of AVR in a larger cohort of patients with severe AS and severe pulmonary hypertension from our institution. We constructed a comprehensive database including all clinical comorbidities and pharmacologic therapy, along with echocardiographic and surgical details.

Accepted for publication Feb 28, 2007.

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Patients and Methods

Patient Population

This retrospective cohort study is from a large university medical center. This study was approved by our Institutional Review Board, which waived the need for patient consent because of the retrospective nature of the study. As described previously, our echocardiographic database was searched for patients with severe AS defined as a valve area 0.8 cm^2 or less [8–10]. This yielded a total of 740 patients. Subsets of this database have been used previously [8–10]. Of the 740 patients, 119 patients had severe pulmonary arterial (PA) hypertension defined as PA systolic pressure 60 mm Hg or greater forming this study cohort. Complete clinical, echocardiographic, and pharmacologic data were compiled on these patients from comprehensive chart reviews. Thirty-six of them had AVR. Operative details were obtained in these patients. Decision for AVR was made by treating physicians in conjunction with the patients and not by the investigators. Mean duration of follow-up in patients with AVR was 3.8 years and those without AVR was 1.5 years; the short duration of follow-up in the no AVR group principally due to high short-term mortality.

Published by Elsevier Inc

0003-4975/07/$32.00
doi:10.1016/j.athoracsur.2007.02.094

Clinical Variables

Systemic hypertension was defined as blood pressure greater then 130/90 mm Hg or a history of hypertension and being on antihypertensive medications. Diabetes mellitus was defined as fasting blood sugar greater than 125 mg/dL or being on antidiabetic agents. Renal insufficiency was defined as serum creatinine 2 mg/dL or greater. Coronary artery disease was deemed to be present if any of the following were present: a history of angina pectoris, myocardial infarction, a positive stress test, angiographic evidence of coronary artery disease, coronary intervention, coronary artery bypass surgery, or the presence of significant Q waves on the surface electrocardiogram. Heart failure was diagnosed using Framingham criteria [11].

Pharmacologic Data

Pharmacotherapy at the time of echocardiography was recorded. This was broadly categorized into beta blockers, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, digoxin, and statins.

Echocardiographic Data

All patients had standard two-dimensional echocardiographic examinations. Left ventricular ejection fraction (LVEF) was assessed visually by a level 3 trained echocardiographer and entered into a database at the time of the examination. This has been proven to be reliable and has been validated against contrast and radionuclide LV angiography [12, 13]. Anatomic and Doppler examinations and measurements were performed according to the recommendations of the American Society of Echocardiography [14].

Mortality Data

The endpoint of the study was all cause mortality. Mortality data were obtained from the National Death Index using social security numbers.

Statistical Analysis

All the data were initially entered into the Microsoft excel program. The data were then imported into the Stat View 5.01 (SAS Institute Inc, Cary, NC) program for statistical analysis. Characteristics of patients with and without AVR were compared using the Student t test for continuous variables and the χ^2 test for categoric variables. Survival analysis was performed using various statistical tools such as Kaplan-Meier analysis, Cox regression models (including time varying Cox regression), propensity score matching, and sensitivity analysis as discussed later in the results section. A p value of 0.05 or less was considered significant.

Table 1. Patient Characteristics

Variable	All	No AVR	AVR	p value
Age (years)	75 ± 13	78 ± 12	70 ± 13	0.001
Gender - % male	39	39	41	0.75
Hypertension (%)	39	31	58	0.005
Diabetes mellitus (%)	17	11	31	0.008
Coronary artery disease (%)	43	39	53	0.15
Chronic obstructive pulmonary disease (%)	11	6	22	0.009
Heart failure (%)	69	66	75	0.35
Chronic renal insufficiency (%)	12	12	11	0.89
Aspirin therapy (%)	32	23	53	0.001
Beta blockers (%)	21	17	31	0.09
ACE inhibitor (%)	27	27	28	0.89
Statin therapy (%)	13	10	19	0.14
Digoxin (%)	25	23	31	0.38
LV ejection fraction (%)	41 ± 20	40 ± 21	45 ± 19	0.36
Aortic valve area (cm^2)	0.64 ± 0.18	0.64 ± 0.17	0.65 ± 0.21	0.79
Aortic valve area index (cm^2/m^2)	0.37 ± 0.11	0.38 ± 0.11	0.33 ± 0.12	0.20
PA systolic pressure (mmHg)	69 ± 10	69 ± 8	69 ± 13	0.79
MR grades 3 or 4 (%)	53	55	47	0.41
LV end-diastolic diameter (mm)	52 ± 9	52 ± 8	54 ± 9	0.36
LV end-systolic diameter (mm)	39 ± 10	38 ± 10	40 ± 13	0.59
Ventricular septal thickness (mm)	14 ± 2	13 ± 3	14 ± 2	0.24
LV posterior wall thickness (mm)	12 ± 2	12 ± 2	13 ± 3	0.49
Relative wall thickness	0.51 ± 0.13	0.51 ± 0.14	0.51 ± 0.12	0.99
Mitral E/A velocity ratio	1.71 ± 0.74	1.65 ± 0.79	1.84 ± 0.65	0.34
Mitral E wave deceleration time (ms)	210 ± 126	205 ± 117	222 ± 145	0.56

ACE = angiotensin converting enzyme; AVR = aortic valve replacement; LV = left ventricular; MR = mitral regurgitation; PA = pulmonary arterial.

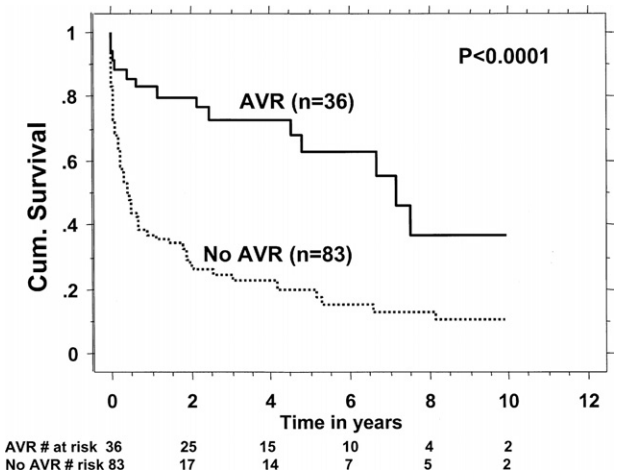

Fig 1. Kaplan-Meier survival curves showing the association of aortic valve replacement (AVR) with better survival in patients with severe aortic stenosis associated with severe pulmonary hypertension.

Results

Baseline Patient Characteristics

The baseline features of 119 patients with severe pulmonary hypertension and severe AS is summarized in Table 1. Of these, 36 patients had AVR and 83 did not receive AVR because of physician or patient preference. As shown in Table 1, patients receiving AVR were younger ($p = 0.001$), and had a higher prevalence of hypertension ($p = 0.005$), diabetes mellitus ($p = 0.0008$), chronic obstructive pulmonary disease ($p = 0.009$), and aspirin use ($p = 0.001$). However, they had similar LVEF, aortic valve area, PA pressure, degree of mitral regurgitation (MR), renal insufficiency, heart failure, and therapy with various cardiac drugs including angiotensin converting enzyme inhibitors, beta blockers, and statins. A logistic regression model was created for the independent predictors of AVR using the significant group differences for independent variables. Only younger age was a predictor of AVR ($p = 0.002$). Adjustment for gender, renal failure, coronary artery disease, LVEF, degree of MR, and PA pressure did not change the model.

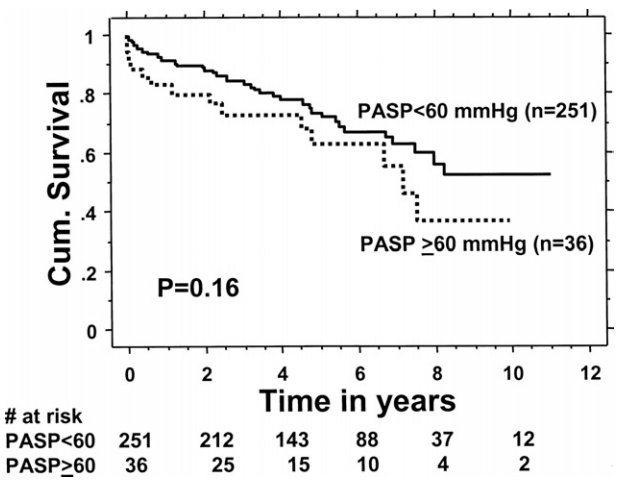

Fig 2. All patients with aortic valve replacement (AVR) (n = 287). Survival curves of AVR patients with pulmonary artery systolic pressures (PASP) partitioned around 60 mm Hg.

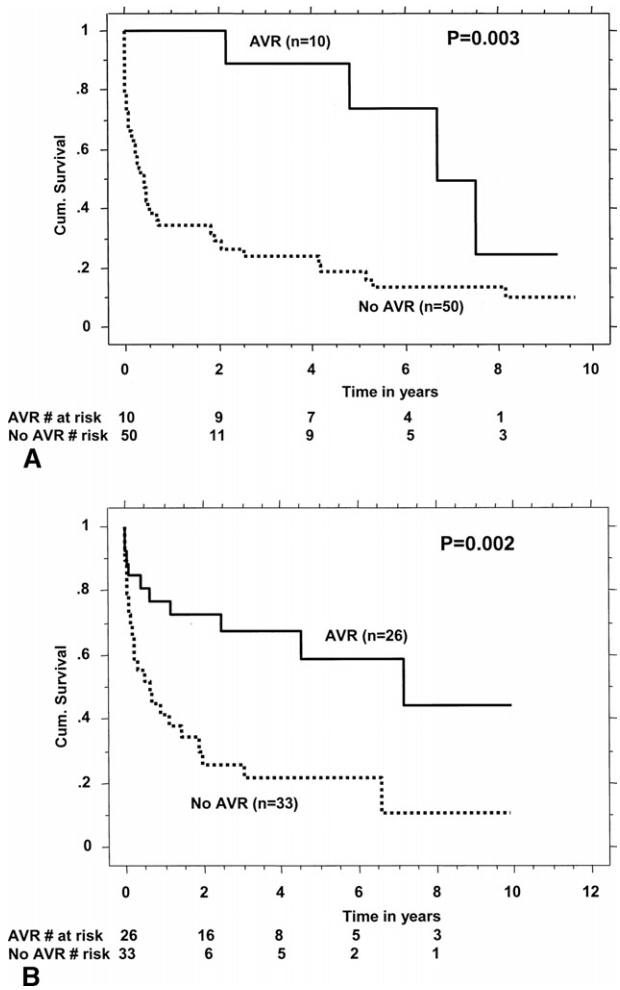

Fig 3. Graphs showing survival of patients with propensity score matching. Note the survival advantage in both strata. (A) Stratum 1. (B) Stratum 2. (AVR = aortic valve replacement.)

AVR and Survival

As shown in Figure 1, patients receiving AVR had a 30-day mortality of 8% compared with 30% for those who did not receive AVR. The one-year survival was 80% and 30%, respectively, for groups with and without AVR. Thus, the survival benefit was huge with AVR in the first year with a relatively low operative mortality. The five-year survival rates for groups with and without AVR were 66 and 20%, respectively ($p < 0.0001$). Even after excluding the 30-day mortality, the survival difference was statistically significant ($p < 0.0001$). Figure 2 shows the survival curves of AVR patients with PA systolic pressure 60 mm Hg or greater compared with the 251 patients at our institution who had AVR for severe AS but had PA systolic pressure less than 60 mm Hg. It is

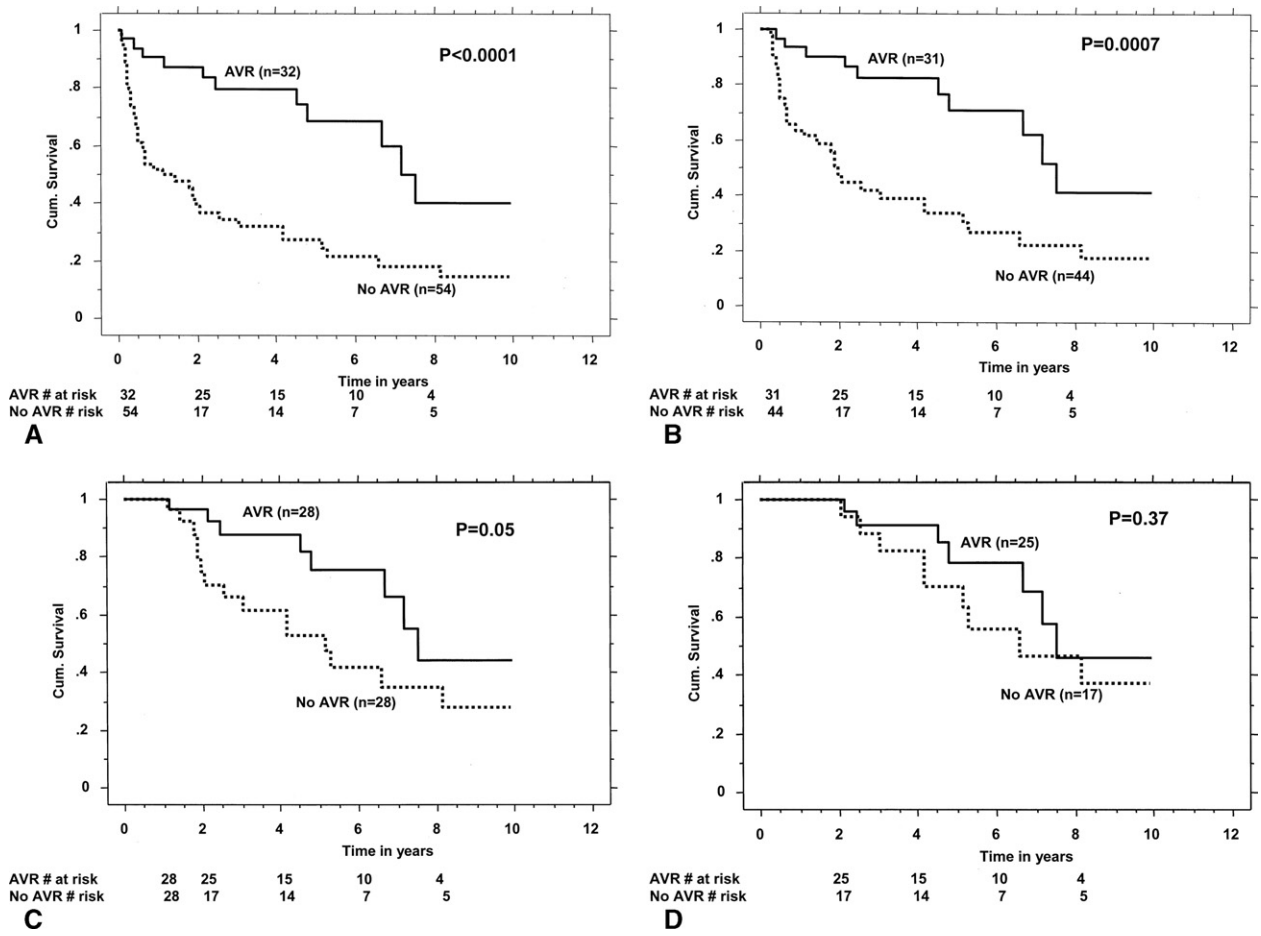

Fig 4. Results of sensitivity analysis showing persistence of survival benefit of aortic valve replacement (AVR) with elimination of observations up to one year. (A) First 30 days eliminated. (B) First 90 days eliminated. (C) First one year eliminated. (D) First two years eliminated.

noteworthy that the survival curves were not statistically different indicating the benefit of AVR irrespective of PA pressure. Survival curves of the AVR patients with PA systolic pressure 60 mm Hg or greater was not statistically different from those with PA pressure less than 40 mm Hg.

Cox Regression Analysis

The risk ratio for mortality with AVR by Cox regression analysis was 0.28 (95% confidence interval 0.16 to 0.50, $p < 0.0001$). The risk ratio after adjusting for group differences such as age, mean transvalvular gradient, hypertension, diabetes, chronic pulmonary disease, and aspirin use was 0.30 (95% confidence interval 0.17 to 0.50, $p < 0.0001$). The survival benefit remained significant ($p < 0.0001$) with the Cox regression models adjusting for all the eight clinical comorbidities listed in Table 1 alone, or adjusting for all clinical comorbidities and pharmacotherapy or clinical comorbidities, pharmacotherapy, and echocardiographic variables.

Propensity Score Analysis

Patients were divided into two strata based on the probability of receiving AVR for each patient based on the 18 covariate characteristics. Only two strata were used because of sample size. Logistic regression analysis was used to calculate this propensity score. Stratum 1 was least likely to receive AVR and stratum 2 most likely to receive AVR. Aortic valve replacement was associated with a survival benefit in both strata (Fig 3). As can be expected, the survival curves for the non-AVR group was the worst in stratum 1, but AVR seemed to offer a larger survival benefit in these patients. It is also interesting that the survival curves in the AVR groups were very similar in both the strata.

Sensitivity Analysis

Sensitivity analysis was carried out by serially eliminating patients with duration of observations 30 days or less, 90 days or less, 1 year or less, and 2 years or less sequentially in an effort to minimize the effect of unmeasured and unmeasurable variables on survival. As can be seen from Figure 4, AVR was associated with a significantly better survival in all four analyses ($p < 0.0001$). This supports an inference that AVR had a beneficial effect on survival even after excluding patients who might have been deemed nonsurgical based on initial evaluation.

AVR Subgroup

Of the patients undergoing AVR, 16 had coronary artery bypass surgery, 6 had mitral valve (MV) replacement, and 4 had mitral valve repair. Survival was similar in patients with and without coronary artery disease, with and without coronary artery bypass surgery, and with or without diabetes mellitus. Of the AVR patients, 17 had 3 or 4+ MR and MR was predictive of a higher PA pressure. The 10 patients undergoing MV repair or replacement had a higher EF (55 ± 15 vs 41 ± 19%, $p = 0.04$), higher PA systolic pressure (76 ± 22 vs 66 ± 7 mm Hg, $p = 0.05$) and were nonsignificantly younger (65 ± 10 vs 72 ± 14 years, $p = 0.16$). Three of these patients had 3 or 4+ MR and the rest had 2+ MR. In patients undergoing MV repair or replacement, 30-day mortality was 10% and five-year survival was 90%. Patients not having concomitant MV procedure had a 30-day mortality of 11% and a five-year survival of 57% ($p = 0.12$ vs MV surgery group). It is possible that the observed better survival in the MV surgery group may be due to their favorable morbidity profile or a chance occurrence due to the small sample size. Patient groups with and without MV procedure had similar degrees of preoperative MR.

Comment

This observational series confirms that AVR can be performed with an acceptable operative mortality and that it confers a huge survival benefit in severe AS patients with associated severe pulmonary hypertension. Our series is larger than all the other reported series and has, additionally, comprehensive echocardiographic and pharmacologic data which have potential prognostic implications.

Comparison to Other Studies

Johnson and colleagues [4] were the first to report, in 1988, that AVR can be performed in patients with pulmonary hypertension. In their series of 15 patients with a PA systolic pressure greater than 50 mm Hg, 13 underwent AVR. There were no operative deaths, there was one late death, and 11 of the 12 patients were in functional class I. Tracy and colleagues [6] showed the safety of AVR in these patients with no operative mortality. Snopek and colleagues [7] performed AVR in 11 patients with severe pulmonary hypertension with one operative death. In the survivors, there was a dramatic improvement in both PA systolic and wedge pressures. The largest reported series so far is by Malouf and colleagues [5]. In their series of 47 patients with severe AS and severe pulmonary hypertension, 37 underwent AVR. Mortality was 80% in the medically treated patients, the operative mortality was 16%, and the five-year survival was 52% in the surgically treated group. The operative mortality in our series was 8%. We had a five-year survival of 66% in the surgically treated group compared with 20% in the medically treated patients. The survival curves in operated severe pulmonary hypertension patients were similar to operated patients with no severe pulmonary hypertension. This is interesting and is very likely due to a beneficial effect of AVR on PA and LV filling pressures in these patients. Our findings are similar to those of Malouf and colleagues [5] and also confirms earlier observations that AVR can be performed with an acceptable mortality in these patients. One of the most impressive findings of our study is that the 30-day mortality in the medically treated patients is 30%. This emphasizes a need for emergent AVR in these patients in view of 1% per day mortality if not operated upon.

In terms of physician behavior, presence of significant coronary artery disease was a trigger for AVR and older age was predictive of medical therapy. The majority of decisions for nonsurgical management were made by cardiologists in conjunction with the patients, presumably assuming they were too sick for surgical therapy. Patients also seemed to have concerns in terms of quality of life post-AVR and a fear of physical and neurological deterioration.

AVR Group

This study is too small a group for subset analysis, but it is worth noting that patients with 2+ or greater MR may potentially benefit from MV surgery. Though the difference did not reach significance, there was a trend for high mortality if MV surgery was not performed. This finding is clinically important and warrants further attention. We suggest that in severe AS patients with severe pulmonary hypertension undergoing AVR, serious consideration should be given for the surgical correction of 2+ or greater MR in view of this potential survival benefit and the fact that MR plays an important role in the genesis of pulmonary hypertension in these patients.

Study Limitations

This is a retrospective observational study and assignment to AVR was not randomized. We had very comprehensive data on all the patients including pharmacologic data not reported in prior studies. This is important as agents such as statins, beta blockers, and angiotensin converting enzyme inhibitors have potential survival effects in these patients, as many had coronary artery disease. However, because of the retrospective study nature, the duration and intensity of these therapies could not be quantified. We attempted adjustment for group differences using the Cox regression model, propensity score analysis, and sensitivity analysis, but effects of some unmeasurable variables on mortality cannot be ruled out. Though the propensity score analysis corrects for measured variables, it is possible that some unmeasured or unmeasurable medical morbidities might have augmented the medical mortality. These can be controlled only in a randomized trial, which is improbable.

Clinical Implications and Conclusions

Our study confirms that AVR can be performed with an acceptable mortality in severe AS patients with severe pulmonary hypertension. The AVR in these patients is

associated with an impressive survival benefit. Medically treated patients have a dismal prognosis. In our experience there is general reluctance on the part of the physicians to refer sicker AS patients for AVR. Our study confirms that presence of severe pulmonary hypertension should not constitute a contraindication to AVR. As MR, smaller aortic valve area, lower EF, and elevated LV filling pressures are predictive of pulmonary hypertension, presence of any of these risk factors or pulmonary hypertension, which can be monitored by echocardiography, should be considered seriously as indications for AVR in patients with severe AS.

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INVITED COMMENTARY

In this article, Pai and colleagues [1] describe their institutional experience with aortic valve replacement in the setting of severe pulmonary hypertension. This is a follow-up study of two previous reports from these authors who are now focusing on the pulmonary hypertension cohort. This is a welcome addition to the surgical literature, as there is a paucity of data on this challenging patient population.

The mortality follow-up was obtained from social security numbers and the national death index. Accordingly it is difficult to discern to what degree surgeon selection bias may have played as a role in avoiding unsavory surgical candidates (eg, the patients undergoing aortic valve replacement [AVR] were often younger). Nonetheless, the 30-day mortality in nonoperated patients was striking at 30% compared with operated patients at 8%. Again, astute clinical judgment could partially explain the high early mortality in nonoperated patients and not as the authors suggest "a need for emergent AVR in these patients in view of a 1% per day mortality." However, when the authors stratified patients with propensity analysis according to the likelihood of undergoing AVR they demonstrated a significant survival benefit with surgery. Furthermore, when they censored the early deaths, which should remove those patients who would have been judged to be a prohibitive operative risk, a survival benefit still remained.

The good news for patients with pulmonary hypertension is that if they were successfully managed through surgery there were no significant differences in the Kaplan-Meier survival curves in the patients with severe pulmonary hypertension compared with those without it. The key then is how to safely guide these patients through their perioperative course. There are now numerous adjuncts available including intravenous milrinone, nesiritide, inhaled nitric oxide, and prostacyclin, and on the horizon, intravenous endothelin-1 antagonists. Our group and others have transitioned patients to oral phosphodiesterase inhibitors such as sildenafil [2, 3]. Much work remains to be done in identifying the optimal perioperative treatment strategies in randomized trials, and also in more accurate reporting to the national Society of Thoracic Surgeons' database to better define the prevalence.

This report probably confirms most surgeons' inherent bias that this patient group can be operated on with reasonable perioperative mortality. I encourage the authors to share their findings with the cardiology community. As the authors themselves noted, "The majority of decision[s] for nonsurgical management [were] made by the cardiologists in conjunction with the patients presumably assuming they were too sick for surgical ther-

0003-4975/07/$32.00
doi:10.1016/j.athoracsur.2007.04.053