Echocardiographic predictors of pulmonary hypertension in patients with severe aortic stenosis

Nikhil Kapoor, Padmini Varadarajan, and Ramdas G. Pai*

Division of Cardiology, Loma Linda University Medical Center, 1234 Anderson Street, #4414, Loma Linda, CA 92354, USA

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Background Pulmonary hypertension complicating severe aortic stenosis increases morbidity and mortality. Causes and mechanisms of this are unclear.

Methods This is a retrospective observational study of 626 patients with severe aortic stenosis who had measurable pulmonary arterial pressure by Doppler echocardiography. Clinical, echocardiographic and pharmacological data were related to the presence of pulmonary hypertension.

Results Of the 626 patients, 119 (19%) had severe pulmonary hypertension defined as pulmonary artery systolic pressure ≥60 mmHg. Patients with severe pulmonary hypertension had a smaller aortic valve area (P < 0.0001), a lower left ventricular ejection fraction (P < 0.0001), a higher mitral E/A velocity ratio (P < 0.0001) indicating a higher filling pressure and a higher prevalence of 3 or 4+ mitral regurgitation (P < 0.001). They were less likely to be on a beta blocker (P = 0.05) or a statin (P = 0.02).

Smaller aortic valve area, left ventricular dysfunction, mitral regurgitation and lack of statin use were independent predictors of severe pulmonary hypertension.

Conclusions Severity of aortic stenosis, left ventricular dysfunction, and mitral regurgitation are risk factors for the genesis of pulmonary hypertension and statins may potentially be protective in patients with severe aortic stenosis.

KEYWORDS Aortic stenosis; Pulmonary hypertension; Statin; Echocardiography

Introduction Aortic stenosis (AS) is common, found in 2–3% of individuals over the age of 65 years. Severe pulmonary hypertension is present in 15–20% of these patients and significantly increases morbidity and mortality.1-4 Small observational series have shown its association with left ventricular (LV) dysfunction and higher LV filling pressures.5-8 Presence of transpulmonary pressure gradient in these individuals indicates the importance of an increase in pulmonary arterial resistance.9 Statins have been reported to have a protective effect against pulmonary hypertension in experimental models of producing pulmonary hypertension.9,10 Our observational study evaluates the risk factors for the development of pulmonary hypertension in patients with severe AS. It also investigates a possible protective effect of statin therapy against the development of pulmonary hypertension.

Methods Patient population Our echocardiographic database between 1993 and 2003 was screened for patients with severe AS defined as an aortic valve area ≤0.8 cm² by the continuity equation. This yielded a total of 740 patients of whom 626 had adequate tricuspid regurgitation velocity signals allowing measurement of pulmonary artery (PA) pressures using simplified Bernoulli equation and estimated right atrial pressure based on inferior vena cava size. Of these, 119 (19%) had severe pulmonary hypertension defined as PA systolic pressure ≥60 mmHg. Clinical, demographic, pharmacologic and echocardiographic data were abstracted from chart review.

Clinical data Following clinical details were abstracted: Systemic hypertension was defined as blood pressure ≥130/90 mmHg or a history of hypertension and being on antihypertensive medications. Diabetes mellitus was defined as fasting blood sugar ≥125 mg/dL or being on antidiabetic agents. Renal insufficiency was defined as serum creatinine ≥2 mg/dL. 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 presence of significant Q-waves on the surface electrocardiogram.

Pharmacological 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. LV ejection fraction 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. Anatomic and Doppler examinations and measurements were performed according to the recommendations of the American Society of Echocardiography. The aortic valve area was calculated using the continuity equation utilizing flow velocities in the LV outflow tract and across the valve. Aortic valve area was indexed to the body surface area. The pulmonary artery systolic pressure was calculated from the tricuspid regurgitation velocity signal using the simplified Bernoulli equation and estimated right atrial pressure based on inferior vena caval (IVC) size. Right atrial pressure was estimated as follows: IVC small and collapsed 5 mmHg, IVC <2 cm in size and collapses >50% with inspiration 10 mmHg, IVC <2 cm in size and collapses <50% with inspiration 15 mmHg, IVC >2 cm in size and <50% collapse or non-collapsing 20 mmHg.

**Statistical analysis**

All the data were initially entered into Microsoft excel program. The data were then imported into Stat View 5.01 (SAS Institute Inc., Cary, NC) program for statistical analysis. Characteristics of patients with and without severe pulmonary hypertension were compared using the Student’s t-test for continuous variables and Chi squared test for categorical variables. Logistic regression model was used to identify the independent predictors of pulmonary hypertension. A P-value of ≤0.05 was considered significant.

**Results**

As shown in Table 1, patients with severe pulmonary hypertension had a smaller aortic valve area (0.64 ± 0.18 vs 0.72 ± 0.17 cm², P < 0.0001) and aortic valve area index (0.37 ± 0.11 vs 0.40 ± 0.10 cm², P = 0.02). These patients also had a lower LV ejection fraction (41 ± 21 vs 56 ± 19%, P < 0.0001), larger LV dimensions (P < 0.0001), a lower relative wall thickness (P = 0.02), higher mitral E/A velocity ratio (P < 0.0001) and a higher prevalence of 3 or 4+ mitral regurgitation (MR) (53 vs 22%, P < 0.0001). They were less likely to be on a beta blocker (21 vs 32%, P = 0.05) or a statin (13 vs 23%, P = 0.02). There were no group differences in the prevalence of comorbidities such as hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency or the use of aspirin or angiotensin converting enzyme inhibitors.

Variables with a P value of ≤0.05 on univariate analysis were entered into a logistic regression model for the prediction of PA pressure >60 mmHg. Lower LV ejection fraction (P < 0.0001), higher degrees of MR (P = 0.0004), smaller aortic valve area (P = 0.03) and lower use of statin therapy (P = 0.05) were independent predictors of higher PA pressure and lower use of beta blockers was of borderline significance (P = 0.09).

**Discussion**

Ours is the largest published series providing insights into mechanisms of pulmonary hypertension in patients with severe AS. Independent risk factors included greater severity of AS, presence of LV dysfunction and MR. The protective effects of statins and possibly beta blockers we found in this study have not been reported previously.

Our data as well as earlier reports indicate that LV dysfunction may be of central importance to the genesis of severe pulmonary hypertension. It may cause both MR and elevated left atrial pressure. Severe degree of AS is more likely to cause LV dysfunction and LV dilatation. Johnson et al. reported PA systolic pressure >50 mmHg in 15 of the 92 patients with severe AS and this was related to LV end-diastolic pressure. Silver et al. in their analysis of 45 patients with severe AS, found PA pressure >50 mmHg in 13 patients and this was related to reduced LV ejection fraction and presence of MR. Eight of the 13 patients in this study had a transpulmonary diastolic gradient of >10 mmHg suggesting reactive element in the genesis of pulmonary hypertension. Buonanno et al. reported a relationship between pulmonary hypertension and LV ejection fraction and end-diastolic pressure in 95 patients.
with severe AS, 15 of whom had PA systolic pressure >50 mmHg.7 Our series is the largest one with 626 patients with PA pressure measurements and 119 with a PA pressure ≥60 mmHg. All had very comprehensive clinical, pharmacological and echocardiographic data compared with other reported series. In addition, effects of concomitant pharmacotherapy on PA pressure in patients with severe AS has not been reported.

The fact that greater degrees of AS, presence of LV dysfunction, development of MR and signs of elevated LA pressure are risk factors for development of pulmonary hypertension have important implications in timing of surgery in patients with severe AS. All of these factors increase the risk of sudden death.8 The potential protective effects of statins and possibly beta blockers merit further investigations. Simvastatin has been shown to reduce pulmonary intimal and medial hyperplasia and reduce PA pressure in hypoxic and chemical models of pulmonary hypertension.9,10 As all our patients had severe AS, the mechanism is not through retardation of AS progression which may occur with statin therapy. Statins have also been shown to reduce LV hypertrophy, but in our series stais had no effect on LV wall thickness. Beta blocker effect is potentially attributable to slowing of the heart rate with improved LV filling and unloading of the pulmonary circulation causing lowering of PA pressure.14

Some of the limitations of the study include its retrospective nature, and variability in the measurement of valve areas and LV ejection fraction. But the echocardiographers were experienced level III readers and the potentially noisy measurements are unlikely to give rise to positive results. Our study population is large and the patients are well characterized in terms of comprehensive clinical, pharmacological and echocardiographic data. In conclusion, severity of AS, LV dysfunction, and MR are risk factors for the genesis of pulmonary hypertension. These need to be carefully monitored in patients with asymptomatic AS. Statins and possibly beta blockers may protect against the development of pulmonary hypertension and warrant further investigations.

References