Frequency, Characteristics, and Outcome of Patients with Aortic Stenosis, Left Ventricular Dysfunction, and High (Versus Low) Trans-Aortic Pressure Gradient*

Diab Mutlak MD, Doron Aronson MD, Jonathan Lessick MD DSc, Shimon A. Reisner MD, Salim Dabbah MD and Yoram Agmon MD

Echocardiography Laboratory and Heart Valves Clinic, Department of Cardiology, Rambam Health Care Campus, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Trans-aortic pressure gradient in patients with aortic stenosis and left ventricular systolic dysfunction is typically low but occasionally high.

Objectives: To examine the distribution of trans-aortic PG in patients with severe AS and severe LV dysfunction and compare the clinical and echocardiographic characteristics and outcome of patients with high versus low PG.

Methods: Using the echocardiographic laboratory database at our institution, 72 patients with severe AS (aortic valve area ≤ 1.0 cm²) and severe LV dysfunction (LV ejection fraction ≤ 30%) were identified. The characteristics and outcome of these patients were compared.

Results: PG was high (mean PG ≥ 35 mmHg) in 32 patients (44.4%) and low (< 35 mmHg) in 40 (55.6%). Aortic valve area was slightly smaller in patients with high PG (0.63 ± 0.15 vs. 0.75 ± 0.16 cm² in patients with low PG, $P = 0.003$), and LV ejection fraction was slightly higher in patients with high PG (26 ± 5 vs. 22 ± 5% in patients with low PG, $P = 0.005$). During a median follow-up period of 9 months 14 patients (19%) underwent aortic valve replacement and 46 patients (64%) died. Aortic valve replacement was associated with lower mortality (age and gender-adjusted hazard ratio 0.19, 95% confidence interval 0.05–0.82), whereas trans-aortic PG was not ($P = 0.41$).

Conclusions: A large proportion of patients with severe AS have relatively high trans-aortic PG despite severe LV dysfunction, a finding partially related to more severe AS and better LV function. Trans-aortic PG is not related to outcome in these patients.

IMAJ 2010; 12: 563–567

KEY WORDS: aortic stenosis, echocardiography, hemodynamics

*Presented, in part, at the European Association of Echocardiography 11th Annual Scientific Sessions, Lisbon, Portugal, 2007, and published in abstract form (*Eur J Echocardiogr* 2007; 8 (Suppl 1): S132)

PG = pressure gradient
AS = aortic stenosis
LV = left ventricular

Trans-aortic pressure gradient in patients with severe aortic stenosis and severe left ventricular systolic dysfunction is typically low, a condition termed "low-flow low-gradient AS" [1]. Nevertheless, in our clinical experience, PG is occasionally high despite significant LV dysfunction, but the frequency and characteristics of patients with AS, severe LV dysfunction, and high (versus low) PG are poorly defined.

The objectives of our study were: a) to assess the distribution of trans-aortic PG in patients with AS and LV dysfunction and to determine the relative frequency of high (versus low) PG; b) to compare the clinical and echocardiographic characteristics of patients with high PG with those of patients with low PG; and c) to examine the prognostic implications of trans-aortic PG in patients with AS and LV dysfunction.

PATIENTS AND METHODS

The computerized database of the echocardiography laboratory at our institution, a tertiary medical center, was reviewed to identify all patients who were examined between 2000 and 2006 and had a combination of severe AS (aortic valve area ≤ 1.0 cm²) and severe LV dysfunction (LV ejection fraction ≤ 30%). The echocardiographic reports of these patients were reviewed and the relevant findings collected. The study was approved by the Institutional Review Board.

All the echocardiographic examinations were performed as part of routine clinical practice by one of six senior cardiologists with subspecialty training and experience in echocardiography and valvular heart disease (the co-authors). Cardiac measurements and hemodynamic assessment were performed according to the guidelines of the American Society of Echocardiography [2,3]. Trans-aortic PG was measured by continuous-wave Doppler with sampling from multiple echocardiographic windows, using imaging and non-imaging Doppler probes. "High PG" and "low PG" aortic stenosis were defined as mean trans-aortic PG ≥ 35 mmHg and < 35 mmHg, respectively, a definition based on the average of definitions of low PG aortic stenosis in the American College of Cardiology/American Heart Association [4] and the European Society of Cardiology

[5] guidelines on valvular heart disease (PG < 30 and 40 mmHg, respectively) and the spectrum of definitions used in previous clinical studies [6-13]. Aortic valve area was calculated by the continuity equation [3]. The echocardiographic severity of aortic valve calcification was graded qualitatively, as previously proposed by Rosenhek et al. [14], and grades 3 (multiple large calcium deposits) or 4 (extensive calcification of all cusps) were considered "severe" valve calcification. LV dimensions were measured by two-dimensional guided M-mode [2]. LV ejection fraction was determined by a combination of the Teichholz formula [15] and visual assessment of LV function from multiple echocardiographic windows [16]. Severe LV dysfunction was defined as a LV ejection fraction ≤ 30% [2].

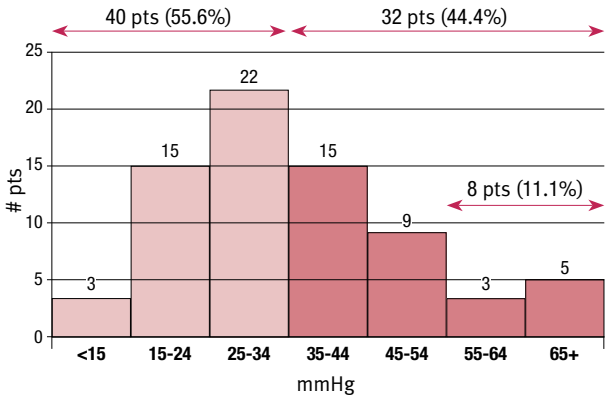
Clinical data at baseline and during follow-up, including data on aortic valve surgery during follow-up, were collected via the computerized clinical databases at our institution and the inter-institutional database of the largest health fund in the country. Mortality data were collected via the Ministry of Interior database.

Continuous variables were compared by the Wilcoxon rank sum test and categorical variables by the Fisher exact test. Survival curves were constructed according to trans-aortic PG (high versus low PG) and treatment strategy (aortic valve replacement versus conservative therapy) using the Kaplan-Meier method, and comparisons were made using the log rank test. Multivariate Cox proportional hazards modeling was used to determine the relationship between trans-aortic PG, treatment strategy, and mortality, adjusting for age and gender.

RESULTS

During a 7 year period 72 patients with severe LV dysfunction and severe AS were examined at our institution. The distribution of trans-aortic PG is presented in Figure 1. Trans-aortic PG was high (mean PG ≥ 35 mmHg) in 32 patients (44.4%) and low (< 35 mmHg) in 40 (55.6%). Trans-aortic PG was very high (≥ 55 mmHg) in 8 patients (11.1%). The clinical characteristics of patients with high versus low PG are presented in Table 1. Age, gender, the frequency of cardiovascular risk factors, and clinical cardiac disease were similar in the two groups, except for a higher frequency of diabetes in patients with low PG.

Figure 1. Distribution of mean trans-aortic pressure gradient in the study population.



pts = patients

Table 1. Selected clinical characteristics of patients with high versus low trans-aortic pressure gradient

	High PG (n=32)	Low PG (n=40)	*P*
Age (yrs)	75 ± 10	77 ± 9	0.33
Male (%)	66	60	0.81
Heart rate (beats/min)	84 ± 16	80 ± 16	0.16
Atrial fibrillation (%)	13	8	0.69
History of hypertension (%)	59	73	0.31
Blood pressure (mmHg)			
Systolic	121 ± 19	126 ± 18	0.36
Diastolic	73 ± 14	74 ± 11	0.74
Diabetes mellitus (%)	19	46	0.02
Coronary artery disease (%)*	59	73	0.31
Previous myocardial infarction (%)	56	49	0.63

*Coronary artery disease defined as previous myocardial infarction, coronary revascularization, or typical angina pectoris.

The echocardiographic findings in patients with high versus low PG are presented in Table 2. Aortic valve area was slightly smaller in patients with high PG, on average approximately 0.1 cm^2 smaller than in patients with low PG. Severe valve calcification was evident in all patients in both groups. There were no differences in LV outflow tract or aortic root dimensions. Left ventricular function was better in patients with high PG (slightly higher LV ejection fraction, higher stroke volume, and higher cardiac output), but there was no difference in the frequency of LV segmental wall motion abnormalities. There were no significant differences between the groups in various indices of LV remodeling (LV cavity size, mass, wall thickness, or relative wall thickness). Severe right ventricular dysfunction was noted only in patients with low PG. The frequency of severe aortic, mitral or tricuspid regurgitation was similar in the two groups. Pulmonary artery systolic pressure was slightly higher in patients with high PG.

During a median follow-up period of 9 months (interquartile range 2–22 months), 14 patients (19% of all patients) underwent aortic valve replacement: 10 patients (31%) with high PG and 4 patients (10%) with low PG. Forty-six patients (64% of all patients) died: 2 patients (14%) undergoing aortic valve replacement and 44 (76%) treated medically. Kaplan-Meier curves comparing the survival of patients according to trans-aortic PG and treatment strategy are shown in Figure 2.

Table 2. Echocardiographic parameters in patients with high versus low trans-aortic pressure gradient

	High PG (n=32)	Low PG (n=40)	*P*
Aortic valve			
Peak pressure gradient (mmHg)	80 ± 21	42 ± 11	‹ 0.001
Mean pressure gradient (mmHg)	49 ± 14	24 ± 6	‹ 0.001
Valve area (cm^2)	0.63 ± 0.15	0.75 ± 0.16	0.003
Severe valve calcification (%)*	100	100	› 0.99
Aortic regurgitation (%)**	9	3	0.32
Aorta/outflow tract dimensions			
Left ventricular outflow tract diameter (cm)	2.2 ± 0.2	2.1 ± 0.2	0.15
Aortic root diameter (cm)	3.2 ± 0.4	3.2 ± 0.4	0.48
Left ventricle			
Ejection fraction (%)	26 ± 5	22 ± 5	0.005
Stroke volume (ml)	61 ± 13	53 ± 20	0.008
Cardiac output (L/min)	5.1 ± 1.4	4.2 ± 1.2	0.003
End-diastolic diameter (cm)	5.8 ± 0.6	5.9 ± 0.7	0.86
Average wall thickness (cm) §	1.1 ± 0.2	1.0 ± 0.2	0.21
Mass (g)	269 ± 102	249 ± 67	0.91
Relative wall thickness §§	0.34 ± 0.09	0.32 ± 0.07	0.35
Segmental wall motion abnormalities (%)	69	80	0.29
Right ventricular dysfunction (%) **	0	13	0.06
Mitral regurgitation (%) **	16	13	0.74
Tricuspid regurgitation (%) **	9	10	› 0.99
Pulmonary artery systolic pressure (mmHg)	60 ± 13	54 ± 15	0.06

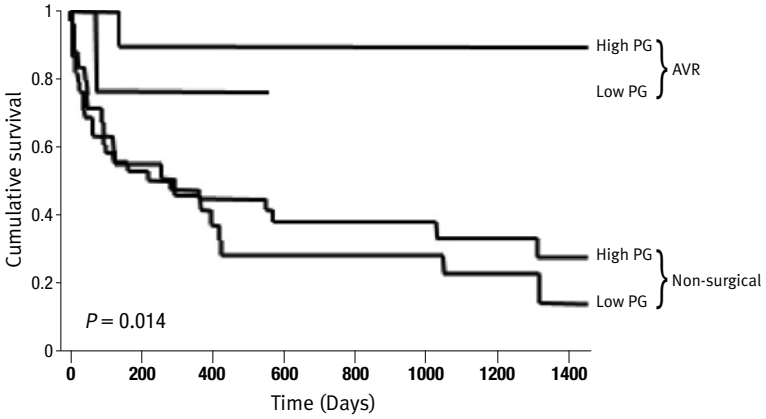
*Defined in Methods section

**Severe

§Average wall thickness = (septum thickness + posterior wall thickness)/2

§§Relative wall thickness = (posterior wall thickness * 2)/LV end-diastolic diameter.

Figure 2. Survival of patients according to trans-aortic PG (high or low PG) and treatment strategy (AVR or non-surgical treatment).



AVR = aortic valve replacement, PG = pressure gradient

The survival of patients undergoing aortic valve replacement was significantly better than that of patients treated medically, regardless of preoperative trans-aortic PG. By age- and gender-adjusted multivariate analysis, aortic valve replacement was associated with lower mortality (hazard ratio 0.19, 95% confidence interval 0.05–0.82, $P = 0.03$), whereas trans-aortic PG was not related to mortality (hazard ratio for high PG 1.35, 95% confidence interval 0.67–2.72, $P = 0.41$).

DISCUSSION

Our study demonstrates that, in contrast to the classic concept of low gradient aortic stenosis, a large proportion of patients with severe AS and severe LV dysfunction exhibit a relatively high trans-aortic PG. At times, PG may be very high.

Several differences between patients with high and low PG may at least partially explain the difference in PG between the two groups. Demographic and clinical characteristics were similar in the two groups except for a higher frequency of diabetes in patients with low PG, a finding of questionable significance. AS was more severe in the patients with high PG (valve area was smaller in these patients), although the difference between the two groups was relatively small and does not appear to fully explain the large difference in PG between the groups. LV function was better in patients with high PG. The difference in LV ejection fraction between the two groups was relatively minor (4% difference in average LV ejection fraction), but the difference in LV stroke volume, a major determinant of trans-aortic PG, was more prominent. There were no differences between the groups in the frequency of LV segmental wall motion abnormalities and clinical ischemic heart disease, suggesting that the etiology of LV dysfunction (i.e., ischemic versus non-ischemic LV dysfunction) is not an important determinant of PG. There were no differences between the groups in various indices of LV remodeling, a finding that does not support the hypothesis that differences in ventricular remodeling in response to AS is a cause of the variability in trans-aortic PG. Significant right ventricular dysfunction was evident only in the subgroup with low PG. Right ventricular dysfunction may decrease trans-aortic PG by further lowering LV stroke volume in patients with LV dysfunction. Concomitant valve regurgitation may increase (severe aortic regurgitation) or decrease (severe mitral and tricuspid regurgitation) trans-aortic PG, but the frequency of these pathologies was similar in the two groups. Thus, additional valve dysfunction does not appear to explain the differences in PG between patients.

Aortic valve replacement was performed more frequently in patients with high trans-aortic PG (~ a third of patients) than in patients with low PG (~ a tenth of patients). Our data sug-

gest that in patients with AS and LV dysfunction, aortic valve replacement was associated with better survival, whereas preoperative trans-aortic PG was not related to outcome. Although it is reasonable that valve surgery alone improves survival, it is highly likely that patient selection for surgery plays a role in the apparent survival benefit, an effect that is difficult to ascertain in a retrospective, non-randomized observational study. Nevertheless, our observations suggest that PG should not be a major factor in decision making in patients with AS and LV dysfunction, as survival was poor in conservatively treated patients with either high or low PG [Figure 2].

The following study limitations should be acknowledged. First, the study was conducted retrospectively, based on a prospectively collected computerized database. Second, the patients included in the study are representative of patients seen at our tertiary medical center and, therefore, selection bias was unavoidable. Third, aortic valve area was not indexed for body size since the relevant data for indexing (height and weight) were missing in a substantial proportion of patients in this retrospective analysis. Even so, other echocardiographic indices that are related to body size – namely, LV outflow tract and aortic root diameter [17] – were similar in the two groups, suggesting that a difference in body size was not a major determinant of the differences between patients with high versus low PG. Fourth, dobutamine stress echocardiography was not routinely performed in the group of patients with impaired LV function and low PG in order to differentiate between severe AS and pseudo-severe AS [1,18]. Thus, disease severity may have been overestimated and aortic valve area may have been underestimated to some extent in patients with low PG. Nevertheless, the uniform presence of severe aortic valve calcification in all patients supports the assumption that AS was indeed severe in all patients, including in the subgroup of patients with low PG. Moreover, the focus of our study was the subgroup of patients with high PG, a subgroup in whom overestimation of AS severity was unlikely. Finally, as noted above, the decision to treat patients surgically (aortic valve replacement) or medically was not randomized and, thus, the observational outcome data should be interpreted with caution.

In conclusion, in contrast to common knowledge, a large proportion of patients with severe AS and severe LV dysfunction have relatively high trans-aortic PG. This finding is partially related to more severe AS and better LV function in patients with higher PG, although other currently undefined factors are also likely to play a role in determining PG. Aortic valve replacement in appropriately selected patients appears to be associated with better patient survival, regardless of preoperative PG, suggesting that trans-aortic PG should not be a major factor in clinical decision making in patients with severe AS and LV dysfunction. Additional studies are necessary to fully understand all the factors involved in determining trans-aortic PG and the clinical relevance of the PG in clinical practice, beyond other measures of severity of AS [1,19].

Corresponding author:
Dr. Y. Agmon
Dept. of Cardiology, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096, Israel
Phone: (972-4) 854-2342
Fax: (972-4) 854-3507
email: agmon@rambam.health.gov.il

References

1. Burwash IG. Low-flow, low-gradient aortic stenosis: from evaluation to treatment. *Curr Opin Cardiol* 2007; 22: 84-91.
2. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63.
3. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002; 15: 167-84.
4. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006; 48: e1-148.
5. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007; 28: 230-68.
6. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 2000; 101: 1940-6.
7. Pereira JJ, Lauer MS, Bashir M, et al. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol* 2002; 39: 1356-63.
8. Levy F, Laurent M, Monin JL, et al. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol* 2008; 51: 1466-72.
9. Schwammenthal E, Vered Z, Moshkowitz Y, et al. Dobutamine echocardiography in patients with aortic stenosis and left ventricular dysfunction: predicting outcome as a function of management strategy. *Chest* 2001; 119: 1766-77.
10. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR, Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation* 2002; 106: 809-13.
11. Monin JL, Quere JP, Monchi M, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 2003; 108: 319-24.
12. Kulik A, Burwash IG, Kapila V, Mesana TG, Ruel M. Long-term outcomes after valve replacement for low-gradient aortic stenosis: impact of prosthesis-patient mismatch. *Circulation* 2006; 114: I553-8.
13. Bergler-Klein J, Mundigler G, Pibarot P, et al. B-type natriuretic peptide in low-flow, low-gradient aortic stenosis: relationship to hemodynamics and clinical outcome: results from the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study. *Circulation* 2007; 115: 2848-55.
14. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000; 343: 611-17.
15. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations

in the presence of absence of asynergy. *Am J Cardiol* 1976; 37: 7-11.

16. Dabbah S, Reisner SA, Aronson D, Agmon Y. Left ventricular filling hemodynamics in patients with pulmonary edema and preserved versus reduced left ventricular ejection fraction: a prospective Doppler echocardiographic study. *J Am Soc Echocardiogr* 2006; 19: 733-43.
17. Agmon Y, Khandheria BK, Meissner I, et al. Is aortic dilatation an atherosclerosis-related process? Clinical, laboratory, and transesophageal echocardiographic correlates of thoracic aortic dimensions in the population with implications for thoracic aortic aneurysm formation. *J Am Coll Cardiol* 2003; 42: 1076-83.
18. Bermejo J, Yotti R. Low-gradient aortic valve stenosis: value and limitations of dobutamine stress testing. *Heart* 2007; 93: 298-302.
19. Bermejo J, Odreman R, Feijoo J, Moreno MM, Gomez-Moreno P, Garcia-Fernandez MA. Clinical efficacy of Doppler-echocardiographic indices of aortic valve stenosis: a comparative test-based analysis of outcome. *J Am Coll Cardiol* 2003; 41: 142-51.