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

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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.

KEY WORDS: aortic stenosis, echocardiography, hemodynamics

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 subspeciality 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.

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 cm² 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 (inter-quartile 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 1. Selected clinical characteristics of patients with high versus low trans-aortic pressure gradient

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

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

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

![Figure 1](image-url)  

*nts = patients
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-

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High PG (n=32)</th>
<th>Low PG (n=40)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak pressure gradient (mmHg)</td>
<td>80 ± 21</td>
<td>42 ± 11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean pressure gradient (mmHg)</td>
<td>49 ± 14</td>
<td>24 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>0.63 ± 0.15</td>
<td>0.75 ± 0.16</td>
<td>0.003</td>
</tr>
<tr>
<td>Severe valve calcification (%)*</td>
<td>100</td>
<td>100</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Aortic regurgitation (%)**</td>
<td>9</td>
<td>3</td>
<td>0.32</td>
</tr>
<tr>
<td>Aorta/outflow tract dimensions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular outflow tract diameter (cm)</td>
<td>2.2 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Aortic root diameter (cm)</td>
<td>3.2 ± 0.4</td>
<td>3.2 ± 0.4</td>
<td>0.48</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>26 ± 5</td>
<td>22 ± 5</td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>61 ± 13</td>
<td>53 ± 20</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.1 ± 1.4</td>
<td>4.2 ± 1.2</td>
<td>0.003</td>
</tr>
<tr>
<td>End-diastolic diameter (cm)</td>
<td>5.8 ± 0.6</td>
<td>5.9 ± 0.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Average wall thickness (cm)</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Mass (g)</td>
<td>269 ± 102</td>
<td>249 ± 67</td>
<td>0.91</td>
</tr>
<tr>
<td>Relative wall thickness §§</td>
<td>0.34 ± 0.09</td>
<td>0.32 ± 0.07</td>
<td>0.35</td>
</tr>
<tr>
<td>Segmental wall motion abnormalities (%)</td>
<td>69</td>
<td>80</td>
<td>0.29</td>
</tr>
<tr>
<td>Right ventricular dysfunction (%)**</td>
<td>0</td>
<td>13</td>
<td>0.06</td>
</tr>
<tr>
<td>Mitral regurgitation (%)</td>
<td>16</td>
<td>13</td>
<td>0.74</td>
</tr>
<tr>
<td>Tricuspid regurgitation (%)**</td>
<td>9</td>
<td>10</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mmHg)</td>
<td>60 ± 13</td>
<td>54 ± 15</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Defined in Methods section

**Severe

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

AVR = aortic valve replacement, PG = pressure gradient
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].

References
2. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report of 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.


**Capsule**

**Killer cells help protect from autoimmune diseases**

The primary job of natural killer (NK) cells, a type of immune cell, is to destroy host tissue infected by pathogens. The cells are also thought to boost autoimmunity under certain circumstances by acting on other immune cells in the lymph nodes. Shi et al. report that NK cells have a stronger effect on autoimmunity in the central nervous system. Studying a mouse model of multiple sclerosis they found that NK cells limit inflammation and the immune response against myelin antigens. Increasing the number of NK cells in the central nervous system protected the animals from disease, whereas limiting the cells’ numbers made symptoms worse. The researchers speculate that drugs used to treat multiple sclerosis may exert their positive effect by increasing NK cell numbers. *J Exp Med* doi:10.1084/jem.20092749 (2010) Eitan Israeli

**Capsule**

**Measuring single myosins at work**

In the past 15 years, the molecular mechanism of muscle contraction has been investigated at the single-molecule level; however, results have varied between laboratories because of the non-processive properties of skeletal myosin. Now, Kaya and Higuchi measured the non-linear elasticity and working stroke size of single skeletal myosins by combining optical trapping and fluorescence imaging with sub-nanometer accuracy. The data suggest that it is important to relate myosin’s internal structural changes to physiologic force generation and filament sliding. *Science* 2010; 329: 686 Eitan Israeli

**Capsule**

**Antidepressant action of ketamine**

In contrast to the weeks or months of treatment required for standard antidepressant medication, ketamine administration produces an antidepressant response within 4 to 6 hours in depressed patients. What lies behind the rapid actions of ketamine? Li and team found that ketamine administration resulted in fast activation of mammalian target of rapamycin (mTOR) signaling and increased levels of synaptic proteins in the rat prefrontal cortex. Ketamine rapidly increased the density and function of the dendritic spines of layer V pyramidal neurons in the prefrontal cortex. Thus, the behavioral actions of ketamine in models of depression and antidepressant response are dependent on mTOR signaling. *Science* 2010; 329: 959 Eitan Israeli

“Ring the bells that still can ring
Forget your perfect offering,
There is a crack in everything,
That’s how the light gets in

Leonard Cohen (born 1934), Canadian singer-songwriter, musician, poet and novelist. His work often deals with the exploration of religion, isolation, sexuality and interpersonal relationships. Famously reclusive, he once spent several years in a Zen Buddhist monastery. In the last year he gave several concerts in Europe and Israel, which were hugely successful.