Gender differences in patients with severe aortic stenosis: impact on preoperative left ventricular geometry and function, as well as early postoperative morbidity and mortality

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Abstract

Objective: In patients with severe aortic stenosis, we studied the impact of gender on preoperative left ventricular geometry and function, as well as on early postoperative mortality and morbidity. Methods: Prospective Doppler echocardiographic evaluation was performed in 99 female patients and 96 males. Results: The patients had severe aortic stenosis and the mean pressure gradients were similar in females and males. Left ventricular diastolic volume adjusted for body surface area (BSA) was larger in males, \(55 - 17.4 \text{ml/m}^2\) versus \(43 - 13.1 \text{ml/m}^2\) (mean \pm standard deviation; \(P = 0.0001\)). The ejection fraction was similar in females (55–14%) and males (55–13%), and patients of both sexes had significantly lower stroke volume and cardiac index than healthy controls. The relative wall thickness (wall thickness/diastolic diameter ratio) was higher \((P = 0.03)\) in females \((0.47 - 0.10)\) than in males \((0.43 - 0.10)\). Consequently, the diastolic diameter/wall thickness ratio (a substitute for wall tension) was higher \((P = 0.02)\) in males \((4.2 - 0.99)\) than in females \((3.9 - 0.80)\). Compared with survivors, patients who died within 30 days of the operation \((n = 17, 11 \text{ females})\) had a smaller body surface area \((1.70 - 0.19 \text{ vs. } 1.82 - 0.19 \text{ m}^2, P = 0.012)\), smaller left ventricular outflow tract \((20.8 - 0.21 \text{ vs. } 22.0 - 0.22 \text{ mm}, P = 0.023)\), higher incidence of abnormal intraventricular flow velocity \((33 \text{ vs. } 8\%, P = 0.018)\) and increased relative wall thickness \((0.52 - 0.17 \text{ vs. } 0.45 - 0.09 P = 0.039)\). Gender was of no independent importance for early mortality when age and left ventricular outflow tract diameter were accounted for. Conclusions: Cardiac adaptation to aortic stenosis seems to be influenced by gender, males presenting larger left ventricular volumes and higher wall tension. The echocardiographic findings of a narrow left ventricular outflow tract, abnormally increased intraventricular velocity and increased relative wall thickness identified patients with increased risk of early postoperative mortality. However gender had no independent impact on early postoperative outcome. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Gender; Aortic stenosis; Doppler; Echocardiography

1. Introduction

In aortic valve stenosis with an increased left ventricular pressure burden and increased wall stress, concentric hypertrophy develops in the heart [1]. Increased pressure is counterbalanced by increased wall thickness, which tends to normalize wall tension. Whether this adaptation process is altogether beneficial has been questioned [2]. An exaggerated response to pressure overload with increased relative wall thickness and with a female preponderance has been claimed to identify a subgroup of patients with increased early mortality and morbidity [3–5]. In some cases the hypertrophic left ventricle with relatively small diastolic and systolic volumes is associated with a supernormal ejection fraction. Patients with small chamber volumes run the risk of developing a low cardiac output syndrome postoperatively, when the afterload reduction...
further decreases chamber volume [4]. The situation may be worsened by inotropic and chronotropic agents, as well as by hypovolemia.

Gender differences in the left ventricular response to systolic pressure overload have previously been described [6–9]. However, these reports conflict and it is unclear whether systolic function is reduced and the left ventricle is dilated in males, or whether females have more pronounced hypertension and supernormal systolic function. The patient populations which have been studied are either small [2,6,9], retrospectively selected or prone to gender-based selection bias [8]. There is only one report on gender aspects and diastolic function in aortic stenosis [9] and we are unaware of any study reporting the influence of gender on early mortality and morbidity.

The aims of the present Doppler echocardiographic study were to describe gender differences in left ventricular geometry, as well as systolic and diastolic function, and to evaluate the impact of such differences on early mortality and morbidity in aortic valve replacement.

2. Materials and methods

2.1. Patient population and control subjects

The total patient population that was admitted for aortic valve replacement between January 1991 and December 1993 comprised 648 patients from Western Sweden. From the 648 patients, we selected for closer analysis all those who died within 30 days of operation (n=29) and a previously described representative subpopulation (n=232) [10]. We excluded from both groups those who had severe aortic (n=48) or mitral (n=7) regurgitation and those with peak gradient <60 mmHg or an effective orifice area >1 cm² (n=11). The study population then comprised 195 patients. Informed consent was obtained from all patients and the study was approved by the human ethics committee of Sahlgrenska University Hospital.

The results were compared with those from a healthy control group of 33 male and 27 female individuals with normal resting ECG and without hypertension, diabetes mellitus or a history of heart disease.

2.2. Methods

2.2.1. M-mode and two-dimensional echocardiography

Preoperative (n=195) and postoperative (n=179) echocardiography was performed using an Acuson 128 or 128XP Computed Sonograph (Acuson, Mountain View, CA). Both M-mode registrations and off-line measurements were guided by the two-dimensional image. This was important to avoid incorrect measurements of septal and posterior wall thicknesses. M-mode measurements were made according to the recommendations of the American Society of Echocardiography [11]. Measurements of left ventricular end-diastolic diameter (LVd), thickness of the interventricular septum (IVS) and thickness of the posterior wall (LVPW) were made at the beginning of the QRS in the ECG. Relative wall thickness was defined as the ratio 2 × LVPW/LVd and the diastolic diameter and wall thickness ratio as 2 × LVd/IVS + LVPW. The ejection fraction according to Simpson’s rule was derived on-line from left ventricular volumes calculated from planimetry of two apical, orthogonal views of the left ventricular end-diastolic and end-systolic areas [12]. The image quality was regarded as acceptable for measurement when at least 75% of the endocardial border was visualized. Planimetry of the left atrium was performed on-line from a late systolic stop frame with the maximum atrial area.

Left ventricular mass was calculated according to the truncated ellipsoid model described by Byrd et al. [13].

2.2.2. Doppler measurements

All the patients were investigated by color Doppler, as well as by pulsed and continuous wave Doppler. The Doppler investigation was performed during quiet respiration. Blood flow velocity in the left ventricular outflow tract was estimated by pulsed wave duplex Doppler from an apical four-chamber view (sample size of 5 mm). Mitral flow was recorded at the tips of the mitral leaflets in the four-chamber view. From the mitral velocity tracings, early flow velocity (E), deceleration time of the early filling wave and peak velocity during atrial contraction (A) were measured. Pulmonary venous flow velocities were obtained by placing the sample volume at the orifice of the upper right pulmonary vein. Peak velocity during systole (S) and diastole (D) were measured. Continuous wave Doppler signals were recorded by a 2 MHz non-imaging probe to obtain an optimal signal-to-noise ratio and multiple windows were used.

Abnormal intraventricular flow velocity was defined as an intracavitary Doppler spectrum with a late peak systolic velocity of > 1.5 m/s.

The stroke volume was calculated as the product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral. Cardiac index was calculated as the product of heart rate and stroke volume divided by body surface area. Pressure gradients were calculated according to the simplified Bernoulli equation (pressure = 4 × (maximum velocity)²), Effective orifice area was calculated according to the continuity principle using the velocity integrals [14].

2.2.3. Postoperative morbidity

To describe postoperative morbidity, we report the days at the intensive care unit, the maximum aspartate aminotransferase level and classification according to the Therapeutic Intervention Scoring System [15]. In this system a point score number is given for different interventions in the critical care unit describing the severity of illness.

2.2.4. Inter- and intra-observer variability

In our laboratory the inter-observer/intra-observer varia-
bility defined as the mean value of difference/mean value of measurements in percent are as follows: for 2-dimensionally guided M-mode (left ventricular diameter in diastole) 1/1%; 2-dimensional echocardiography (ejection fraction according to Simpson’s rule) 2/8%; Doppler measurements (mitral early deceleration time) 5/12%; calculations based on Doppler (E/A ratio) 9/8% and calculations based on 2-dimensional and Doppler measurements (effective orifice area) 2/1%. In the intraobserver study, the patients were investigated on two different occasions (median 18 days apart) while in the interobserver study they were investigated on the same occasion [10].

2.3. Statistical analysis

The results are expressed as the mean ± standard deviation (SD). The mean of three M-mode and Doppler measurements were used in patients with sinus rhythm. Patients with atrial fibrillation were excluded from the Doppler assessment of diastolic function. We analysed primarily gender differences in this study, while comparisons between controls and patients were performed as secondary analyses. Unpaired Student’s t-tests were used to compare data with normal distribution, while the Mann-Whitney U-test was used for data with skewed distribution and the χ²-square test was used for proportions. A P-value of < 0.05 was considered significant. We performed a multiple logistic regression analysis with early mortality as the dependent variable and gender, age and left ventricular outflow diameter as independent variables.

Since the prevalence of coronary artery disease differs between female and male patients, we compared also female (n = 59) and male patients (n = 53) known not to have coronary artery disease. We selected variables likely to be influenced by coronary artery disease: those expressing left ventricular volume, ejection fraction and diastolic function.

3. Results

3.1. Clinical data

Concomitant coronary artery bypass grafting was more common in male patients than in females (Table 1). Male patients had more severe coronary artery disease with 2.8 ± 1.4 bypass grafts compared with 1.9 ± 1.0 grafts for female patients (P = 0.027). The female patients were older than the males and had comparable blood pressure as well as prevalence of atrial fibrillation. Dyspnea was the dominant symptom in both females and males with no differences according to the New York Heart Association symptom classification.

3.2. Aortic valve variables

Neither maximum nor mean pressure gradients differed between female and male patients (Table 2). The valve areas and valve area indices were significantly smaller in females than in male patients. There was no significant difference in the prevalence or severity of aortic regurgitation between the two sexes.

3.3. Left ventricular dimensions and systolic function

Female and male body surface areas differed markedly (Table 1). The left ventricular diameters and volumes were therefore adjusted for body surface area (Table 3). Male patients had increased diastolic and systolic diameters when normalized to body surface area, compared with healthy controls. Female patients had larger systolic volume index compared with controls. There was no gender difference between left ventricular diameters normalized to body surface area. However, both diastolic and systolic volume indices were larger in male patients compared with the

| Table 1 | Patient and control subject characteristics |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Control subjects | Patients        |                |                |                |
|                | Female (n = 27)  | Male (n = 33)   | Female (n = 99)| Male (n = 96)  | P               |
| Age (years)    | 54 ± 9.7        | 56 ± 14.4       | 72 ± 7.5         | 69 ± 9.2       | 0.040           |
| BSA (m²)       | 1.67 ± 0.09     | 1.96 ± 0.13     | 1.7 ± 0.15       | 1.93 ± 0.15    | <0.0011         |
| SBP (mmHg)     | 125 ± 28.2      | 127 ± 18.7      | 146 ± 26.6       | 140 ± 21.5     | 0.105           |
| DBP (mmHg)     | 74 ± 9.8        | 75 ± 10.9       | 81 ± 12.4        | 81 ± 12.0      | >0.40           |
| HR (beats/min) | 68 ± 9.3        | 68 ± 8.7        | 73 ± 14.0        | 68 ± 12.8      | 0.008           |
| Sinus rhythm (%) | 100             | 100             | 90               | 87             | >0.40           |
| Atrial fibrillation (%) | –   | –   | 10               | 11             | >0.40           |
| Pacemaker (%)  | –               | –               | 0                | 0              | >0.40           |
| CABG (%)       | –               | –               | 24               | 46             | 0.002           |
| NYHA III and IV|                 |                 | 58 (74)          | 54 (70)        | >0.40           |
| Dyspnea (%)    | –               | –               | 30 (74)          | 37 (70)        | 0.35            |
| Angina (%)     | –               | –               | –                | –              | –               |

Mean ± SD. Comparison between controls and patients with aortic stenosis; *P < 0.05; **P < 0.01; ***P < 0.001. Numbers in parentheses indicate sample size when smaller than 90% of total number. BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association.
females (Fig. 1). Also in patients without coronary artery disease, the diastolic volume was significantly larger in males, 51 ± 15.9 ml/m² vs. 43 ± 12.9 ml/m² (P = 0.006). We found a reduced ejection fraction (<45%) in 20% of the study population, without gender differences. Systolic function assessed by two-dimensional echocardiography (ejection fraction ad modum Simpson) and cardiac index was similar in female and male patients (Fig. 1), as well as in patients without coronary artery disease. The ejection fraction, stroke volume and cardiac index were significantly lower in patients of both sexes compared with healthy controls.

3.4. Left ventricular geometry and mass

There were no significant differences between females and males in terms of septal and posterior wall thicknesses (Table 4). The relative wall thickness was higher in female patient; compared with males. The ratio between left ventricular and wall thickness was lower in female patients, compared with males. The ratio between left ventricular mass and mass in males, an effect of left ventricular dilatation in males. The stenosis, the ratio was significantly lower in females than compared with normal controls. For patients with aortic stenosis, the ratio was significantly lower in females than in males, an effect of left ventricular dilatation in males. The males had significantly larger left ventricular mass and mass index compared with the females. However, the proportion with a left ventricular mass index above the upper normal limits did not differ between male and female patients.

Abnormal intraventricular flow velocities defined as > 1.5 m/s were present in two females and one male patient at the preoperative investigation (2%, 3/195). At the early postoperative control, 11% (19/179) of the patients (15 females vs. 4 males, P = 0.01) had an abnormal intraventricular flow velocity.

3.5. Left ventricular diastolic function

Left atrial area was larger in males compared with females, but not when the area was normalized to body surface area (Table 5). The peak systolic velocity in the pulmonary vein was significantly higher in female patients, as was the mitral E/A ratio. However, in patients without coronary artery disease neither peak systolic velocity (56 ± 15.5 vs. 58 ± 14.4 cm/s; P = 0.530) nor E/A ratio (1.1 ± 0.61 vs. 1.02 ± 0.77, P = 0.312) differed significantly between males and females.

3.6. Morbidity and mortality

The number of days at the intensive care unit were the same for females and males (2.3 ± 1.18 vs. 2.7 ± 2.7 days, P = 0.370) as was the maximum aspartate aminotransferase level (1.9 ± 1.28 vs. 1.98 ± 1.1, P = 0.297). The complications classified according to the Therapeutic Intervention Scoring System were similar (74 ± 34.4 vs. 89 ± 118.5, P > 0.40), as was early mortality (n = 17, 11 females vs. 6 males, P = 0.229). Heart failure was the most common cause of death (11 patients, 65%), while 5 patients (29%) died of a myocardial infarction and one patient died as a result of bleeding. Patients who died within 30 days after operation were significantly older (76 ± 6.0 vs. 69 ± 8.5 years, P = 0.003) than those who survived longer. They also had a smaller body surface area (1.70 ± 0.19 vs. 1.82 ± 0.19 m²; P = 0.012), smaller left ventricular outflow tract (20.8 ± 0.21 vs. 22.0 ± 0.22 mm, P = 0.023), higher

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n = 27)</td>
<td>Male (n = 33)</td>
</tr>
<tr>
<td></td>
<td>Female (n = 99)</td>
<td>Male (n = 96)</td>
</tr>
<tr>
<td>LVd index (cm²/m²)</td>
<td>2.8 ± 0.19</td>
<td>2.7 ± 0.22</td>
</tr>
<tr>
<td>LVs index (cm³/m²)</td>
<td>1.8 ± 0.21</td>
<td>1.7 ± 0.17</td>
</tr>
<tr>
<td>LVd vol. index (mg/ml)</td>
<td>40 ± 5.7</td>
<td>45 ± 9.4</td>
</tr>
<tr>
<td>LVs vol. index (ml/m²)</td>
<td>14 ± 3.5</td>
<td>15 ± 4.2</td>
</tr>
<tr>
<td>EF (%)</td>
<td>65 ± 5.5 (22)</td>
<td>65 ± 6.2</td>
</tr>
<tr>
<td>EF &lt; 45% (%)</td>
<td>71 ± 10.7</td>
<td>85 ± 14.7</td>
</tr>
<tr>
<td>CI (L/min per m²)</td>
<td>2.7 ± 0.48</td>
<td>28 ± 0.59</td>
</tr>
</tbody>
</table>

LVd, left ventricular diameter in diastole; LVs, left ventricular diameter in systole; LVd vol., left ventricular volume in diastole; LVs vol., left ventricular volume in systole; SV, stroke volume; CI, cardiac index.
incidence of abnormal intraventricular flow velocity (33 vs. 8%, \( P = 0.018 \)) and increased relative wall thickness (0.52 ± 0.17 vs. 0.45 ± 0.09, \( P = 0.039 \)). In a multiple logistic regression analysis of gender, age and left ventricular outflow tract diameter, age \( (P = 0.0009) \) and outflow tract diameter \( (P = 0.048) \) were independently related to the observed early mortality. Gender was of no independent importance for early mortality \( (P = 0.63) \) when these other factors were accounted for.

4. Discussion

In this prospective Doppler echocardiographic study, we investigated a large sample of patients undergoing aortic valve surgery for aortic stenosis during the 3-year period from 1991 to 1993. The study population should be representative of patients with significant aortic stenosis undergoing aortic valve replacement in the 1990s.

Table 4
Left ventricular mass and geometry

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female ((n = 27))</td>
<td>Male ((n = 33))</td>
</tr>
<tr>
<td>IVS (cm)</td>
<td>0.92 ± 0.12</td>
<td>1.01 ± 0.13</td>
</tr>
<tr>
<td>LVPW (cm)</td>
<td>0.86 ± 0.12</td>
<td>0.98 ± 0.08</td>
</tr>
<tr>
<td>RWT</td>
<td>0.37 ± 0.05</td>
<td>0.36 ± 0.04</td>
</tr>
<tr>
<td>LVd/t</td>
<td>5.3 ± 0.72</td>
<td>5.5 ± 0.69</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>62 ± 9.5</td>
<td>75 ± 14.7</td>
</tr>
<tr>
<td>LVMI &gt; normal (%)</td>
<td>88</td>
<td>72</td>
</tr>
</tbody>
</table>

IVS, inter-ventricular septum; LVPW, left ventricular posterior wall; RWT, relative wall thickness; LVd/t, ratio between left ventricular diameter in diastole and wall thickness; LVMI, left ventricular mass index calculated according to 2-D method.

According to Laplace’s law, the magnitude of wall stress is determined by the pressure burden and the left ventricular geometry (the left ventricular diameter/wall thickness ratio). In the present study, females and males had comparable systolic blood pressure and valvular pressure gradients. Therefore, the left ventricular diameter/wall thickness ratio represents a substitute for wall tension. Left ventricular geometry is closely correlated to ejection performance and some investigators claim that systolic dysfunction (reduced ejection fraction) in patients with aortic stenosis is due to inappropriate geometry (inadequate hypertrophy) rather than depression of intrinsic myocardial contractility \([1,7]\). We found a reduced ejection fraction (<45%) in approximately 20% of the study population, without gender differences. However, there was a significant but small gender difference in left ventricular volumes based on two-dimensional measurements corrected for body surface area. Our data therefore suggest that there is an inappropriate increase in left ventricular volume and consequently higher wall stress in male patients compared with females.

Our findings relating to systolic function differ from those in previous reports. We are therefore unable to confirm findings of a reduced ejection fraction in male patients compared with females \([2,6,8,9]\). The reasons for the detected differences and the proposed mechanisms vary. Aurigemma et al. and Douglas et al. found a supernormal ejection fraction in females \([2,8]\), while Carroll et al. and Villari et al. found a subnormal ejection fraction in male patients \([6,9]\). Possible causes of the differences in systolic function may include changes in chamber geometry \([2]\), excess hypertrophy in women, \([8]\) excess hypertrophy in men \([9]\) and afterload excess in male patients \([6]\). The different findings can probably be explained by small number of patients \([2,6,9]\) and selection bias \([8]\). Carroll et al. \((n = 63)\) and Aurigemma et al. \((n = 65)\) surveyed patients undergoing cardiac catheterization and echocardiography retrospectively over a period of 5 years. Douglas et al. retrospectively studied 232 patients selected for balloon dilatation of isolated aortic stenosis.

To our knowledge, no explanatory data are currently available.
4.3. Study limitations

The study population consists of a 35% subsample of patients with severe aortic stenosis operated upon with aortic valve replacement. Although, we cannot exclude influence of some selection bias on our results, it seems unlikely that the study population differs importantly from the total population.

The control subjects in the present study were younger than the patients. However, apart from the diastolic function, age did not influence other echocardiographic parameters. Therefore, we did not compare diastolic function between patients and control subjects.

4.4. Clinical implications

Gender-associated differences in left ventricular geometry and function characterized by increased relative wall thickness, small left ventricular systolic cavities with narrow outflow tracts and supernormal ejection performance in female patients have been claimed to increase early mortality and morbidity [3–5, 17]. However, it is important to recognize the problem of small hypertrophic left ventricles in the early postoperative period, irrespective of gender. In addition to describing the severity of aortic stenosis, the preoperative echocardiographic investigation can provide information of prognostic and possible therapeutic value about left ventricular function and geometry, including outflow tract diameter [18]. It is conceivable that postoperative care will benefit from greater use of Doppler echocardiographic investigations in patients with aortic stenosis and this could have a beneficial effect on mortality and morbidity by reducing the inappropriate use of inotropic drugs, avoiding hypovolemia and correcting tachyarrhythmias.

Acknowledgements

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References


