Can restrictive filling pattern on dobutamine stress echocardiography predict recovery of left ventricular systolic function after valve replacement in patients with low flow-low gradient aortic stenosis?

Ahmed El Zayat a,*, Ali Refaat b, Ehab Sobhy b, Amir Farouk b

a Cardiology Department, Zagazig University Hospitals, Egypt
b Cardiothoracic Surgery Department, Zagazig University Hospitals, Egypt

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Restrictive filling pattern;
Systolic function recovery;
Viability test

Abstract  Background: Low flow/low gradient severe aortic stenosis continues to be a common medical problem with spontaneous dismal prognosis if left untreated. Relationship between improvement and persistence of restrictive filling pattern (that is present on baseline echocardiography) on DSE (dobutamine stress echocardiography) and recovery of LV systolic function after AVR has not been studied before.

Objective: We sought to clarify the relationship between improvement and persistence of restrictive filling pattern (that is present on baseline echocardiography) on DSE and recovery of LV systolic function after AVR.

Patients and methods: Thirty patients with LF/LG severe AS and restrictive filling pattern on baseline echocardiogram were divided into two groups. Group I included 17 patients with improved diastolic functional class during DSE, and group II included 13 patients with persistent restrictive pattern on DSE study. All patients had a contractile reserve and had AVR afterward.

Results: All patients had restrictive filling pattern. No significant difference was found between both groups regarding AVA, mean transaortic gradient, SV, LVEF, E/A ratio, IVRT, DT, S/D ratio, LV septal thickness or LVEDD (p > 0.05). On DSE, group I patients had a significantly more rise in both EF and SV (49.2 ± 5.4% in group I compared to 42.5 ± 6.9% and 66 ± 9 compared to 58 ± 9 ml respectively, p < 0.05). In group I, five patients had improve-
1. Introduction

Thousands of aortic valve replacements are performed annually worldwide and this number will continue to increase with the aging population. Over the last two decades, the operative mortality rate has steadily declined from 10% to 4% with improvement in surgical and anesthetic techniques. Aortic valve replacement (in severe AS), is the only effective corrective treatment that prolongs survival and greatly alleviates symptoms.

Current ACC/AHA guidelines for valvular heart disease state that dobutamine stress echocardiography is reasonable to evaluate patients with low flow/low gradient AS and LV dysfunction (class IIa). Patients without contractile reserve (<20% increase in stroke volume on DSE) were found to have a very poor prognosis with either medical or surgical therapy.

On the other hand, patients with contractile reserve were found to do well/get benefit from surgery. Along with age, New York heart association (NYHA) functional class, coexistent coronary artery disease and a low transvalvular gradient, LV systolic function appears to be an important operative and postoperative prognostic factor in patients with severe AS.

Restrictive filling pattern of LV has been studied in patients with LV systolic dysfunction due to a variety of etiologies as ischemic and dilated cardiomyopathy. It was concluded from these studies that restrictive filling pattern implies a striking rise in left atrial pressure, greatly attenuated LV inotropic response and markedly reduced survival with poor overall prognosis. The aim of this study was to clarify the relationship between restrictive filling pattern on dobutamine stress echocardiography in patients with low flow low gradient (LF/LG) aortic stenosis who showed viability, and the recovery of LV systolic function after valve replacement (AVR).

2. Patients and methods

This study was carried out in Zagazig University Hospitals on the period from November 2010 to July 2013. This study included 30 patients with LF/LG severe AS, as evidenced by aortic valve area (AVA) < 1 cm². Aortic valve area was obtained using the continuity equation.

All patients had LF/LGAS that was defined as low mean gradient across AV of ≤ 30 mmHg. LV systolic dysfunction was defined as an ejection fraction < 50%. Ejection fraction was calculated using the biplane Simpson’s rule. Stroke volume was also calculated by the standard formulae (product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral).

All patients showed presence of contractile reserve on dobutamine stress echocardiography. Presence of contractile reserve was defined as increase of stroke volume by ≥ 20% from baseline value on DSE. All patients had fixed AS, which was defined as an increase in valve area by < 0.3 cm² with a maximal valve area of ≤ 1 cm² on DSE.

All patients had aortic valve replacement. Preoperatively, within 30 days of AVR, diastolic function was assessed during peak DSE and the following variables were measured, E wave maximal velocity, A wave maximal velocity, E/A ratio, E deceleration time (DT), Isovolumic relaxation time (IVRT), S/D ratio (where S is the systolic and D is the diastolic wave as recorded by the pulsed Doppler from the pulmonary venous flow) and a mean of 3 beats was calculated. All patients showed restrictive filling pattern of diastolic dysfunction.

According to the working group of the European Association of Echocardiography and the American Society of Echocardiography, LV diastolic function was graded into four classes: normal (E/A > 0.8, DT < 200 ms, and E/A > 1 or S/D of 1–1.5 (where S is the systolic and D is the diastolic wave as recorded by the pulsed Doppler from the pulmonary venous flow), impaired relaxation (E/A < 0.8, DT > 200 ms, IVRT > 100 ms and E/A’ < 1 or S/D > 1.5), pseudonormalization (E/A = 1–2, DT = 150–200 ms, and E/A’ < 1 or S/D < 1.2), and restrictive pattern (E/A > 2, DT < 150 ms and E/A’ < 1 or S/D < 0.8).

Study patients (30 patients) were divided into two groups according to presence or absence of restrictive pattern of diastolic dysfunction at peak DSE before AVR.

Group I (17 patients) with no-restrictive filling pattern at peak DSE before AVR and group II (13 patients) with persistent restrictive filling pattern at peak DSE before AVR. All patients gave an informed consent to participate in the study. Recovery of LV systolic function was defined as a postoperative increase of LVEF by > 10%. Echocardiography studies were done using SONOS 5500 machine (Philips technologies, Andover, Massachusetts).

Patients with poor echo-window, history of previous cardiac surgery, previous myocardial infarction, atrial fibrillation, paced rhythm, associated grade 3 or 4 mitral or aortic regurgitation or concomitant operations on other valves were...
excluded. Concomitant coronary artery bypass graft surgery during AVR was not an exclusion criterion.

2.1. Preoperative assessment

All patients had viability dobutamine stress echo-Doppler study that was evaluated by a single experienced echocardiographer. After baseline measurements, a dobutamine infusion was started at 5 μg/kg/min; dose was increased every 3 min until a maximum dose of 20 μg/kg/min. Absence of contractile reserve during DSE was classically defined as the absence of increase in stroke volume of ≥20% compared with the baseline value. Dobutamine infusion was stopped if either a maximal dose was reached or heart rate increased by ≥10b/min.

Preoperative investigations as chest X ray, echo-Doppler study, coronary angiography and routine biochemical tests were done.

Presence of Coronary artery disease was defined as ≥50% luminal diameter narrowing of the left main coronary artery or ≥70% narrowing one or more major epicardial vessels.

2.2. Operative and postoperative data

Size of the AV prosthesis, concomitant coronary artery bypass grafting, number of grafts, the aortic cross clamp and cardiopulmonary bypass durations were all recorded.

LVEF was measured by echocardiography before the patients' discharge from the hospital at a median of seven days (range 4–10 days) after AVR.

2.3. Six month-post operative echocardiography assessment

LVEF was assessed at 6 months post AVR for all patients using biplane Simpson’s rule.

2.4. Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are summarized with the use of percentages. Differences among the study groups were analyzed by student’s t-test to compare continuous data, while χ²-test or the Fisher exact test was used to compare categorical data. Multivariate linear (stepwise) regression analysis was used to identify significant predictors (that were judged to be clinically important) of post-AVR recovery of LV systolic function.

A probability value of p < 0.05 was considered significant.

Data were analyzed using SPSS version 16, software (SPSS Inc, Chicago, Illinois, USA).

3. Results

As shown in Table 1, no significant difference was found between both groups regarding age, sex, etiology of AS, NYHA functional class or use of diuretics or B-Blockers (p > 0.05).

3.1. Baseline echocardiography data

All patients had restrictive filling pattern. As shown in Table 1, no significant difference was found between both groups

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Preoperative characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Group I (no restrictive pattern on DSE) (N = 17)</td>
</tr>
<tr>
<td>Age</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>Male</td>
<td>9 (53%)</td>
</tr>
<tr>
<td>Rheumatic AV disease</td>
<td>13 (76.5%)</td>
</tr>
<tr>
<td>Bicuspid AV</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Degenerative AV disease</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>NYHA functional class III/IV</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>Mean trans-valvular gradient (mmHg)</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>LV EDD (mm)</td>
<td>60.8 ± 4.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37 ± 10</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>48.0 ± 5.5</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>48 ± 12</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>123 ± 17</td>
</tr>
<tr>
<td>S/D ratio</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>LV septal thickness (mm)</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>≥50% left main stenosis</td>
<td>0</td>
</tr>
<tr>
<td>≥70% epicardial coronary stenosis</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>B Blockers</td>
<td>6 (35.2%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6 (35.2%)</td>
</tr>
</tbody>
</table>

AV, aortic valve; NYHA, New York Heart Association; LV EDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; SV, stroke volume; IVRT, isovolumic relaxation time; DT, deceleration time.
regarding AVA, mean trans-aortic gradient, SV, LVEF, E/A ratio, IVRT, DT, S/D ratio, LV septal thickness or LVEDD ($p > 0.05$).

3.2. Preoperative coronary angiography

No patients in either group had a left main stenosis. Two patients (11.8%) in group I had $\geq 70\%$ epicardial coronary artery stenosis compared to one patient (6.5%) in group II ($p > 0.05$).

3.3. Preoperative DSE data at peak stress

At peak stress, both groups showed a contractile reserve with $>10\%$ rise in EF and $>20\%$ increase in SV as shown in Table 2. Group I patients had a significantly more rise in both EF and SV (49.2 ± 5.4% in group I compared to 42.5 ± 6.9% in group II and 66 ± 9 compared to 58 ± 9 ml respectively, $p < 0.05$). In group I, five patients had improvement in the restrictive pattern to impaired relaxation while 12 patients showed a pseudonormal pattern at peak stress. On the other hand, all group II patients showed a restrictive pattern at peak stress ($p < 0.001$).

3.4. Operative and postoperative data

As shown in Table 3, all patients had AVR using mechanical prosthesis with a diameter of 21 mm. There was no significant difference between both groups regarding duration of cardiopulmonary bypass or aortic cross clamping time ($p > 0.05$).

One patient in each group had a concomitant coronary revascularization with one graft, while there was one patient in group I who had $>1$ graft ($p > 0.05$).

As shown in Fig. 1, early post operative LVEF was improved in both groups, although it was statistically significant in group I compared to group II (53 ± 7% in group I compared to 45 ± 6% in group II ($p < 0.05$). The follow up echocardiography showed maintained improvement in LVEF (56 ± 6% in group I compared to 47 ± 6% in group II, $p < 0.05$).

A multivariate regression (stepwise) analysis was performed for predictors (that were judged clinically to be important) of LV systolic function recovery post-AVR. Assessed variables were baseline LVEDD, at-rest and peak-stress mean trans-aortic pressure gradient, at-rest and peak-stress EF, at-rest and peak-stress SV and LV diastolic filling pattern at peak stress (either restrictive or non-restrictive). As shown in Table 4, only LVEF at peak stress ($\beta$ coefficient 0.663, $p = 0.009$) and non-restrictive filling pattern of LV at peak stress ($\beta$ coefficient 10.084, $p < 0.0001$) were significant independent predictors of post-operative systolic function recovery.

4. Discussion

Restrictive filling pattern was studied in a variety of clinical conditions as dilated and ischemic cardiomyopathies and it was found that it imparts a poor prognosis in such patients. In this study, we sought to clarify if persistence or improvement of restrictive filling pattern during peak DSE study in patients with severe LF/LGAS (who have restrictive pattern on basal echocardiography study) would be translated into LV systolic function recovery after AVR.

Restrictive pattern on DSE may identify an important subset of patients with severe AS and LF/LG where LV systolic function might not well recover after AVR. Despite that, AVR remains the only viable option to avoid the sinister prognosis of this condition.

We chose patients who survived the first 6 months post AVR and hence who had better prognosis. Further studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (no restrictive pattern on DSE)</th>
<th>Group II (restrictive pattern on DSE)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine peak dose (µg/kg/min)</td>
<td>13 ± 2</td>
<td>11 ± 3</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart rate change (b/min)</td>
<td>9 ± 3</td>
<td>8 ± 2</td>
<td>0.37</td>
</tr>
<tr>
<td>Peak-stress systolic blood pressure (mmHg)</td>
<td>113 ± 15</td>
<td>122 ± 10</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak-stress SV (ml)</td>
<td>66 ± 9</td>
<td>58 ± 9</td>
<td>0.02*</td>
</tr>
<tr>
<td>Peak LVEF (%)</td>
<td>49.2 ± 5.4</td>
<td>42.5 ± 6.9</td>
<td>0.005*</td>
</tr>
<tr>
<td>Peak AVA (cm²)</td>
<td>0.8 ± 0.3</td>
<td>0.8 ± 0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Peak-stress mean transaortic PG (mmHg)</td>
<td>40 ± 4</td>
<td>42 ± 5</td>
<td>0.24</td>
</tr>
<tr>
<td>Restrictive pattern (n, %)</td>
<td>0</td>
<td>13 (100%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Impaired relaxation pattern (n, %)</td>
<td>5 (29.4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pseudo-normal pattern (n, %)</td>
<td>12 (70.6%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

AVA, aortic valve area; LVEF, left ventricular ejection fraction; PG, pressure gradient; SV, stroke volume.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (no restrictive pattern on DSE)</th>
<th>Group II (restrictive pattern on DSE)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of CPB (min)</td>
<td>52 ± 14</td>
<td>51 ± 16</td>
<td>0.85</td>
</tr>
<tr>
<td>Duration of aortic cross clamp (min)</td>
<td>38 ± 9</td>
<td>37 ± 10</td>
<td>0.77</td>
</tr>
<tr>
<td>Coronary revascularization 1 graft</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Coronary revascularization &gt;1 graft</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Early post operative EF (%)</td>
<td>53 ± 7</td>
<td>45 ± 6</td>
<td>0.003*</td>
</tr>
<tr>
<td>6 m postoperative EF (%)</td>
<td>56 ± 6</td>
<td>47 ± 6</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; min, minutes; EF, ejection fraction; 6 m, 6 months; DSE, dobutamine stress echocardiography.
should include operative outcome, early operative complications and mortalities.

Although all included patients had a contractile reserve on DSE study, we found a significant difference between both groups regarding peak SV and EF on DSE with more contractile reserve in group I (patients with no restrictive pattern during DSE).

Ding et al. studied the echocardiographic predictors of LV functional recovery following valve replacement for severe aortic stenosis in patients with systolic LV dysfunction. They found that among all echocardiographic variables, LV dimensions (LVEDD index, OR 0.70, CI 0.52–0.97, p < 0.05; LVESD index, OR 0.57, CI 0.40–0.85, p = 0.005) were the two independent predictors of post operative LV functional recovery on multivariable analysis. A cut off value of pre operative LVESD index of ≤27.5 mm²/m² was 85% sensitive and 72% specific in predicting intermediate term recovery of LV function after AVR (AUC, 0.72, p = 0.002). They concluded that a lower prevalence of LV functional recovery in patients with large pre-operative LV end systolic dimension index signifies loss of contractile reserve and thus predicts poor post operative functional recovery.19 We found no statistically significant difference between any of the assessed baseline echo-Doppler criteria. This disagreement between the results of last study and ours may be due to the fact that we basically enrolled patients with contractile reserve as proved by DSE.

A study done by Licker et al. concluded that preoperative diastolic function predicted the onset of left ventricular dysfunction following aortic valve replacement in high risk patients (expected operative mortality ≥9% with aortic stenosis).20 They found that besides advanced age and prolonged myocardial ischemic time, LV diastolic dysfunction characterized by Vp (transmitral flow propagation velocity) ≤40 cm/s identified patients who would require cardiovascular support following valve replacement for aortic stenosis. Last study recruited patients into two groups (group I with no LV dysfunction post-operatively n = 56 and group II with LV dysfunction post operatively n = 38).

Both scope and targets of last study were different from our study. Last study did not consider pre-operative DSE for AS patients (as patients’ LV systolic function was almost preserved (EF = 56 ± 8% for group I compared to 49 ± 11% in group II) and hence diastolic function was studied only on the pre-operative resting echocardiography. On the other hand, last study did not follow up patients in the intermediate term (only the need for LV support in the immediate post operative period was studied).

Preoperative LV diastolic dysfunction associated with myocardial hypertrophy and fibrosis could predispose patients to LV dysfunction during weaning from CPB for several reasons. Patients with larger LV mass and reduced capillary density are prone to develop ischemic lesions due to suboptimal delivery of the cardioplegic solution particularly after prolonged aortic cross clamping time.23,24 Accelerated apoptosis of hypertrophied cardiomyocytes may further decrease LV systolic function and has been linked to the increased release of troponin following aortic valve surgery.23,24

LV diastolic dysfunction often co-exists with latent alteration in systolic LV function. This subsequently corresponds to the clinical syndrome of congestive heart failure and the functional status of elevated LV end diastolic pressure which are considered strong predictors of LV dysfunction, cardiac complications and mortality after cardiac surgery.25,26,28

Diastolic dysfunction is supposed to react favorably and improve during dobutamine stress. A fall in left atrial pressure (and hence improvement of diastolic function) at constant or increased SV is likely to depend on the LV being able to mount a significant positive inotropic response to dobutamine.9

In contrast, patients in group II might have demonstrated features of further considerable rise in LA pressure at peak stress and hence failure of improvement of the diastolic functional class.

Mean age was significantly lower in our patients, as the etiology of AS was rheumatic in most cases (76.5% in group I and 84.6% in group II), contrary to that in developed countries where the main cause of AS is degenerative aortic valve disease. Aging process is physiologically associated with worsening of diastolic functional class besides more prevalence of diseases that may negatively affect LV diastolic function as hypertension and diabetes.
A study done by Gjertsson et al. found that moderate to severe diastolic dysfunction was an independent risk factor for late total mortality following AVR. They suggested that moderate to severe AS indicated non-reversible structural myocardial changes that negatively affect survival. Their findings agree with ours in that restrictive pattern of diastolic dysfunction in AS patients was not a mere benign finding.

Some variables that have been shown to impact outcome and/or LV systolic function recovery in patients with low flow/low gradient aortic stenosis as baseline and peak-stress mean trans-aortic gradient, baseline stroke volume were statistically non-significant on comparing both groups. The non-statistical significance (despite variables seemed to be clinically different in both groups) could be linked to the small number of patients in our study.

On multivariate analysis, significant independent predictors of post-operative LV systolic function recovery were peak-stress LVEF and non-restrictive pattern at peak stress. Our results match those of Clavel et al. who studied predictors of outcomes in low-flow/low-gradient aortic stenosis. They concluded that reduced peak stress LVEF was one of the most significant risk factors for poor outcome together with impaired functional capacity as measured by Duke Activity Status Index or 6-min walk test distance; and more severe valve stenosis as measured by projected aortic valve area at a normal transvalvular flow rate. Diastolic functional class on DSE was not addressed in that study.

We found that the initial improvement in LVEF early post-AVR was maintained (with maintained significance between both groups) in the follow up LVEF assessment after 6 months. This consolidates the finding that restrictive filling pattern is associated with less LV systolic function recovery after AVR.

To the best of our knowledge, this is the first study to address the relationship between preoperative diastolic function on DSE and recovery of LV systolic function after AVR in patients with LF/LGAS.

4.1. Study limitations and suggestions for further research

Small sample size could have affected our results. Larger caliber studies are recommended with longer follow up periods. Studying the relationship between recovery of both diastolic and systolic functions after AVR in patients with LF/LGAS is also an interesting area of research.

5. Conclusion

Persistence of LV restrictive filling pattern (that is present on baseline echocardiography) during DSE in patients with LF/LG severe AS could be associated with less LV systolic function recovery after AVR. On the other hand, improvement of diastolic functional class during DSE might be associated with better LV systolic function recovery in such patients.

Conflict of interest

All authors have no conflict of interest to declare.