Effect of persistence of left ventricular hypertrophy and left atrial dilatation after aortic valve replacement on early outcomes and survival: a prospective study

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ABSTRACT

Background: The objective of the study was to evaluate the early outcomes and survival in patients with severe aortic stenosis associated with concentric left ventricular hypertrophy following aortic valve replacement.

Methods: This is a prospective study done at SVIMS, Tirupati, from June 2014 to September 2015 evaluating outcomes and survival in patients undergoing primary isolated aortic valve replacement (AVR) for severe aortic stenosis, severe aortic stenosis with mild aortic regurgitation and severe aortic stenosis with moderate aortic regurgitation.

Results: A total of 40 cases 26 males and 14 females aged 18 to 60 years (mean age, 48.5±13.4 years) underwent elective AVR. Left ventricular end diastolic diameter (p=0.008) at 6 months, a statistically highly significant difference in left ventricular mass preoperatively, at discharge, at 3rd and 6th month follow up. The difference in mean left ventricular mass index (LVMI) had declined from 244.425 to 141.100 at 6 months, showing a statistically highly significant difference in LVMI preop, at discharge, at 3rd month and at 6th month follow up.

Conclusions: Patients with preoperative increase in LVMI, with large left atrial diameter carries a strong predictor of postoperative mortality for patients undergoing aortic valve surgery. We also conclude that there will be significant regression of LVMI following successful AVR. But, the decrease in LVMI is maximum during early three months and it is minimal though significant in the later course of follow up.

Keywords: Aortic stenosis, Aortic valve replacement, Aortic regurgitation

INTRODUCTION

Aortic valvular stenosis face a risk of sudden death that has been reported to be ~1% per year. Aortic valve replacement (AVR) has been the treatment of choice in significant symptomatic aortic stenosis (AS). Valvular aortic stenosis results in chronic left ventricular pressure overload resulting in concentric left ventricular (LV) hypertrophy and, more notably, diastolic dysfunction with onset of congestive symptoms or myocardial oxygen need in excess to the supply resulting in angina, whereas some patients may experience exertional syncope possibility reflecting the inability to increase the cardiac output and maintain blood pressure in response to the vasodilation, are the consequences of long-standing aortic stenosis and are powerful predictors of outcomes and survival after AVR. Patients can have advanced changes in the absence of symptoms, underscoring the inadequacy of symptom presence as the sole guideline for the timing of AVR. This indicates that the condition of the heart at surgery powerfully influences patient outcomes. The clinical challenge in asymptomatic patients with severe aortic stenosis has been to detect deleterious effects of left heart remodelling at the subclinical stage to perform
AVR before the occurrence of irreversible changes that diminish the long-term benefit of surgery.

The main aim of the study is to evaluate the early outcomes and survival in patients with severe aortic stenosis associated with concentric left ventricular hypertrophy (LVH) following aortic valve replacement. Other objectives of the study have been to observe the LV reverse remodeling time course predicted by LV MRI, to study the favorable outcomes of left ventricular reverse remodeling and to understand the relationship between preoperative symptoms (functional class preoperatively compared to postoperatively) and modulators of left ventricular remodeling and their influence on outcome and survival in the short term (3-6 months).

METHODOLOGY

Study Place and Population

All patients submitted for primary isolated aortic valve replacement for severe aortic stenosis, severe aortic stenosis with mild aortic regurgitation (AR) and severe aortic stenosis (AS) with moderate AR from June 2014 at Department of General Surgery, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, were prospectively enrolled into the present follow up protocol. Until September 2015, a total of 40 cases 26 males and 14 females aged 18 to 60 years (mean age, 48.5±13.4 years) underwent elective AVR had been included in the present study.

Inclusion Criteria

Inclusion criteria were elective patients between 18-70 yrs; undergoing cardiac surgery and willing for study; severe aortic stenosis; severe aortic stenosis with mild to moderate aortic regurgitation; small aortic annulus with severe aortic stenosis.

Exclusion Criteria

Exclusion criteria were predominant aortic regurgitation, infective endocarditis; indications for AVR other than aortic stenosis; those who undergo concomitant mitral valve replacement with or without tricuspid valve annuloplasty; associated aortic operations as Bentall’s procedure or correction or repair of aortic aneurysm; those who undergo concomitant coronary artery bypass grafting; emergencies involving aortic valve replacement; re-do operations which would involve aortic valve replacement.

Patient clinical data were collected prospectively and entered into a database at the time of referral for AVR. In as much as 2 patients died, 38 patients were investigated at discharge, 3 months and 6 months follow up after the operation. At the late follow-up the patients received a questionnaire, they were interviewed about preoperative and late postoperative symptoms (dyspnea and angina), and their functional status was classified according to the New York Heart Association (NYHA). Informed consent was obtained from all patients. The Ethics Committee of Sri Venkateswara Institute of Medical sciences approved this study.

Echocardiographic Methods

All patients underwent preoperative transthoracic echocardiography, coronary angiography. 2D echocardiography is performed by the cardiologists within 15 days prior to the surgery of the subject. It includes routine assessment of all the cardiac valves with special focus on the aortic valve with respect to its morphology, the degree of stenosis as estimated by the valve area, trans valvular gradients, peak systolic velocity, the degree of aortic valve regurgitation. Severe aortic stenosis was defined as peak jet velocity of >4 m/s, Mean gradient across aortic valve of >40 mmHg or aortic valve area of <1 cm². Mild aortic regurgitation was defined as Angiographic grade 1+, color Doppler jet width < 25% of LVOT, Doppler vena contracta width <0.3 cm, regurgitant volume <30 ml/beat, regurgitant fraction <30% or regurgitant orifice area <0.10 cm². Moderate aortic regurgitation was defined as Angiographic grade 2+, Doppler vena contracta width 0.3-0.6 cm, regurgitant volume 30-59 ml/beat, regurgitant fraction 30-49% or regurgitant orifice area 0.10-0.29 cm². LV dimensions are taken in systole and diastole which include Posterior wall thickness, Interventricular septal diameter and internal diameter of left ventricle. LV systolic function is assessed by ejection fraction. Modified ASE (American Society of Echocardiography) formula is used to calculate LVM (left ventricular mass) in grams.

\[ \text{LVM} = 0.8 \times ( \frac{1.04 \times (IVSd+LVID+PWTd) - 3 \times LVID3)}{100} + 0.6 \]

Where IVSd is the end-diastolic interventricular septum thickness, LVID is the LV end-diastolic internal diameter, and PWTd is the LV end-diastolic posterior wall thickness.

LVMI is calculated with below formula described by Devereux and colleagues.

\[ \text{LVMI} = (1.04 \times (IVSd +LVID +PWTd) - 14g)/ \text{body surface area} \]

Follow-up 2D echocardiograms are repeated in these subjects between 8 months to 12 months post surgery. All the parameters assessed in the pre-op 2D Echo are taken again.

\[ \text{LVMR} = \frac{\text{pre op LVM} - \text{post op LVM} \times 100}{\text{preop LVM}} \]
Angiographic methods

Preoperative hemodynamic assessment of adult aortic stenosis included right and left heart cardiac catheterization and selective coronary angiography for patients aged above 40 years.

Surgical procedures

The subjects will undergo aortic valve replacement using a prosthetic valve either mechanical or bio-prosthetic as per the guidelines. Aortic root enlargement is done when the aortic root was small in comparison to BSA (body surface area) as per the surgeon’s discretion. The surgical procedure performed, along with cross -clamp and cardiopulmonary bypass times were included in the database for analysis.

Median sternotomy was performed under general anesthesia and cardiopulmonary bypass was instituted with ascending aortic and two-stage single atrial cannulation. Moderate hemodilution and mild systemic hypothermia (>28°C) were used. A LV vent was inserted through the right superior pulmonary vein in selected patients. Myocardial protection was initiated with a dose of high-potassium blood cardioplegia through the ascending aortic root/through retrograde route to induce cardiac arrest. This was followed by continuous antegrade cardioplegia directly into each coronary ostium. A transverse aortotomy was performed above the aortic annulus. The native aortic valve was excised completely and the annulus, aorta, and anterior leaflet of the mitral valve were extensively debrided of calcium when it was present. All valves were implanted using interrupted mattress and pledgeted 2-0 ethibond stitches. All pledgets were placed in the subannular position. Aortotomy was closed with prolene stitches in 2 layers.

All patients underwent transthoracic echocardiography 10-15 days before operation and before discharge and at 3 months, 6months follow up after AVR.

Follow-up

Patients were systematically followed up for 6 months. Transthoracic echocardiography was performed at each follow up visit.

End point

Study end point was all cause mortality, including in-hospital mortality. In-hospital death was defined as death before hospital discharge. After discharge, death were classified as either cardiac or non-cardiac.

Statistical analysis

Categorical variables were given in frequencies and percentages. Continuous variables were given in mean±SD and medians with ranges. Cumulative incidence rates of individual and composite, survival outcomes will be estimated using the Kaplan-Meier survival analysis and compared with the log-rank test. Nonlinear mixed-model regression analysis was used to characterize the time course of the postoperative LVMI from the repeated measures data using a multiphase parametric model. This same approach was used to characterize the time courses of the postoperative LA diameter, LVEF, and peak trans prosthesis gradient. The associations between the New York Heart Association functional class and preoperative LVMI, LA diameter, and LVEF was determined using Pearson's correlation coefficient. Comparisons of these variables among the New York Heart Association groups were done using the Kruskal-Wallis nonparametric test. All analyses were performed using Epi info7.1.02 statistical software/IBM SPSS version 20 is used to perform the calculations.

RESULTS

A total of 40 patients (n= 40) were included in this study who were the cases of severe as with or without mild-moderate AR operated between September 2013 and September 2015 (period of 24 months). Among them 14 were females and 26 were males.

Table 1: Preoperative baseline characteristics of study patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value±1SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.5±13.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>26 (65%)</td>
</tr>
<tr>
<td>Females</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>BSA</td>
<td>1.54±0.15</td>
</tr>
<tr>
<td>Aortic valve pathology</td>
<td></td>
</tr>
<tr>
<td>Bicuspid</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>Other cardiac comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.89±0.23</td>
</tr>
<tr>
<td>Smoking</td>
<td>24 (60%)</td>
</tr>
</tbody>
</table>

Patient and aortic valve replacement characteristics (total n=40).

In this study mean age of the patients was 48.5±13.4 years with a range of 18-80 years. Fourteen patients (35%) were females and 26(65%) patients were males. the common comorbid conditions associated with the disease includes hypertension 12 (30%), COPD 8 (20%), and diabetes constitutes 8 (20%).

In this study 75% of patients had severe aortic stenosis (AS), 12.5% had severe AS with mild AR and 12.5% had severe AS with moderate AR (Table 2).

In this study preoperatively 6 patients (15%) were with NYHA functional class II, 34 (85%) patients were NYHA functional class III (Table 3).
septal wall thickness is 11.6 and mean EF was 54.6, mean LVM was 244.43 with minimum of 110 gms and maximum of 360 gms (with SD of 54.82). Comparison of means using one sample t-test showed a statistically highly significant difference in LVM preop, at discharge, at 3rd month and at 6th month follow up, mean LVMI 160.65 respectively.

Prosthetic, Medtronic, Saint Jude (St. Jude) mechanical, bio prosthetic valves were used for replacement. Out of forty patients, one patient (2.5%) received 16 mm, one patient 17 mm (2.5%) eight patients (20%) received 18 mm, four patients (10%) received 19 mm, eleven patients (27.5%) received 20 mm, seven patients (17.5%) received 21 mm, five patients (12.5%) received 22 mm while three patients (7.5%) received 29 mm valve.

In this study 10% of patients had arrhythmias with need of DC shock and drugs, one patient had intractable VT 5% of patients had immediate postoperative bleeding required re exploration and 2.5% had low cardiac output syndrome leading to death of patient, and 2.5% had multiorgan failure, and 2 patients (5%) died before discharge.

In this study the mean peak gradients were 97.38, mean posterior wall thickness is 11.98, mean intraventricular wall thickness was 11.69, mean EF was 54.6, mean LVM was 244.43 with minimum of 110 gms and maximum of 360 gms (with SD of 54.82). Comparison of means using one sample t-test showed a statistically highly significant difference in LVM preop, at discharge, at 3rd month and at 6th month follow up, mean LVMI 160.65 respectively.

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### Table 7: Mean LVM changes preoperative to 6th month follow up.

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th>Df</th>
<th>Sig.</th>
<th>Mean difference</th>
<th>95% confidence interval of the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre op LVM</td>
<td>28.195</td>
<td>39</td>
<td>0.000</td>
<td>244.425</td>
<td>(226.89-261.96)</td>
</tr>
<tr>
<td>LVM at discharge</td>
<td>27.826</td>
<td>39</td>
<td>0.000</td>
<td>189.400</td>
<td>(175.63-203.17)</td>
</tr>
<tr>
<td>LVM at 3rd month follow up</td>
<td>28.328</td>
<td>39</td>
<td>0.000</td>
<td>155.000</td>
<td>(143.93-166.07)</td>
</tr>
<tr>
<td>LVM at 6th month Follow-up</td>
<td>27.011</td>
<td>39</td>
<td>0.000</td>
<td>141.100</td>
<td>(130.53-151.67)</td>
</tr>
</tbody>
</table>

LVM: Left ventricular mass.

### Table 8: NYHA functional class distribution among patients pre-op, at discharge, 3rd month follow up and at 6th month follow up.

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>Pre-op</th>
<th>At discharge</th>
<th>Follow up 3rd month</th>
<th>Follow up 6th month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freq</td>
<td>%</td>
<td>Freq</td>
<td>%</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>36.84</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>15</td>
<td>22</td>
<td>57.89</td>
</tr>
<tr>
<td>III</td>
<td>34</td>
<td>85</td>
<td>2</td>
<td>5.26</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>100.0</td>
<td>38</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 9: Mean LVMI changes preoperative to 6th month follow up.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Count</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop LVMI gm²</td>
<td>161</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>At discharge LVMI gm²</td>
<td>164</td>
<td>38</td>
<td>196</td>
</tr>
<tr>
<td>Follow up 3rd month LVMI gm²</td>
<td>101</td>
<td>38</td>
<td>21</td>
</tr>
<tr>
<td>Follow up 6th month LVMI gm²</td>
<td>91</td>
<td>38</td>
<td>19</td>
</tr>
</tbody>
</table>

LVMI: Left ventricular mass index.

### Table 10: Mean LVMR changes preoperative to 6th month follow up.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMR at discharge</td>
<td>27.2</td>
<td>23.2</td>
</tr>
<tr>
<td>LVMR at 3rd month</td>
<td>36.08</td>
<td>11.70</td>
</tr>
<tr>
<td>LVMR at 6th month follow-up</td>
<td>47.06</td>
<td>37.70</td>
</tr>
</tbody>
</table>

LVMR: Laparoscopic ventral mesh rectopexy.

Comparison of means using one sample t-test showed a statistically highly significant difference in LVM preop, at discharge, at 3rd month and at 6th month follow up. The difference in means has declined from 244.425 to 141.100 at 6 months. This shows that the differences in LVM among the patients has regressed indicating the LV remodeling has taken effect and LVM changes are consistent post operatively.

In this study preoperatively 6 patients (15%) were with NYHA functional class II, 34 (85%) patients were NYHA functional class III. At discharge 14 patients (36.84%) were with NYHA functional class I, 2 (5.26%) patients were NYHA functional class II, 22 patients (57.89%) were with NYHA functional class III, during follow up at 3rd month 22 patients (57.89%) were with NYHA functional class I, 16 (42.10%) patients were NYHA functional class II, and at 6th month follow up 28 patients (57.89%) were with NYHA functional class I, 10 (26.31%) patients were at NYHA functional class II. NYHA to 3rd month and 6th month LVM.

There is a decline in mean LVMI from 161 g/m² to 91 g/m² at 6 months follow up.

Mean LVMR at discharge was 27.2 and at discharge was 36.08 and at 6 months follow up it was 47.06, which shows that after AVR left ventricular remodelling has been occurred.

Analysis of variance showed that there has been a statistically significant difference in means of Left ventricular end diastolic diameter from preoperative level to at discharge, at third month follow up and 6th month Left ventricular end diastolic diameter.

In this study the difference of left atrial diameter within the group at discharge has been found to be statistically highly significant with a chi-square value of 221.526.
During follow up at 3rd month the difference of left atrial diameter (LAD) has been found to be statistically significant (p<0.01) with a chi-square of 140.11 and at 6th month follow up the difference of LAD within the group has been found to be statistically significant (p<0.05).

DISCUSSION

Aortic stenosis has been the most common form of valvular heart disease in elderly with approximately 2-3% of the patients being affected over 65 years of age. More than 12,000 patients annually undergo AVR in Germany. At least 70% of them have been over aged ≥60 years; 52% were men and 48% were women. The patients in our study group were mainly elderly with mean age of 48.5±13.4 reflecting the present epidemiological situation in aortic valve; with male preponderance 65% are men and 35% are women as in other studies.

Although sex differences in the pathophysiology and clinical expression of coronary artery disease were well appreciated, the impact of gender on valvular heart disease had not been extensively studied. In an article by Sofia Shames et.al it has been reported that although more women than men with severe AS have LV hypertrophy preoperatively, women more frequently experience reversal of hypertrophy shortly after aortic valve replacement. Lower collagen I and III, as well as matrix metalloproteinase 2 gene expression, in women versus men in the myocardial biopsy specimens performed at the time of surgery suggest that women had less fibrosis before surgery, leading to faster regression of LV hypertrophy postoperatively. In our study we had no statistically significant gender difference among the study group (p=0.278).

In most series, the LVM related to BSA was found to be similar in both sexes. However, if the LVM was expressed in percentage of sex-specific normal values, derived from large population-based cohorts, women had a greater prevalence of LVH than men.

In an article by Beach et al noted that across a wide range of LVMIs and LA diameters, the symptoms poorly reflected the degree of LV hypertrophy and diastolic dysfunction, with the distribution of values broadly overlapping. When the LVMI was 180 g/m² or greater, 14% of patients were asymptomatic and 50% mildly symptomatic. When the LA diameter was 5 cm or greater, 12% of patients were asymptomatic and 47% mildly symptomatic.

In our study majority of patients were in class III preoperatively. At discharge only 2 out of 34 remained in class III, rest 22 moved to NYHA II, 8 moved to NYHA I. During follow up at 3rd month 16 remained in NYHA class II and rest 22 in NYHA class I at 6-months follow up 10 patients were still in NYHA II.

Our study was in concordance with above study showing no statistically significant association with functional class and LVH (p=0.597).

In 1% to 2% of adults born with 2 aortic valve cusps, known as bicuspid aortic valve account for about half of all occurrences of aortic stenosis. Stenosis of a bicuspid aortic valve typically occurs at an earlier age (fifth to sixth decade) than does tricuspid valve stenosis (seventh to eighth decade) because 2 cusps, instead of 3, are forced to absorb the shearing stress of blood flow leaving the left ventricle. In our study the most common valve pathology seen was tricuspid valve type, (80%) and the rest were bicuspid aortic calcified valves.

LVH prevalence increases in the elderly (33% of men and 49% of women over age 70 have hypertrophy). The most common pathologic conditions resulting in an increase in LV mass are obesity and hypertension. Other conditions associated with LVH include:

- Coronary artery disease (especially myocardial infarction)
- Valvular heart disease-mixed lesions
- Diabetes
- Alcohol abuse (in men)
- Insulin resistance and smoking.

These factors were excluded in our study. Nevertheless, much of the variance from normal in LV mass for a given individual could not be explained by underlying co-morbidities—suggesting that a likely, as yet unidentified, genetic component was also at work.

Our study also showed similar result with reduction in LVED diameters. Analysis of variance showed that there was a statistically significant difference in means of LVED diameter from preoperative level to at discharge, at three month follow up and 6th month LVED diameter (p=0.008) at 6 months, a statistically highly significant difference in LVM preoperatively, at discharge, at 3rd month and at 6th month follow up. The difference in mean LVM had declined from 244.425 to 141.100 at 6 months, showing a statistically highly significant difference in LVMi preop. at discharge, at 3rd month and at 6th month follow up.

Beach et al showed that LVH rapidly declined after surgery, from 137±42 g/m² preoperatively to 115±27 by 2 years and remained relatively constant reaching 119±18 g/m² by 10 years but greater than the upper limit of normal. Our study was in concordance with the above study in that there was a significant reduction in LVMi in early period which suggests that even successful AVR, in accordance with current guidelines, does not result in full recovery of the left ventricle.
Further Beach et al, quoted that various risk factors associated with residual LV hypertrophy, in decreasing level of importance, included preoperative LV hypertrophy, LA size, LV systolic dysfunction, and peak transvalvar gradient. The most important risk factor for residual LVH was greater preoperative LVH (p<0.0001) with similar result shown in our study (p<0.0001).

Elevated LVMI has also been considered as a risk factor for increased morbidity and mortality in several circumstances by investigators reported in the literature. In a study by Mehta et al, Youssef et al, and Fuster et al found that in patients with increased level of LVMI there was increased incidence of in hospital unfavorable clinical events, length of in hospital stay either in the ICU or post-operative in hospital stay. Our study also showed similar results with mean duration of in-hospital stay was 9.2±2.2 days.

In Mehta et al, they studied 473 consecutive patients undergoing elective AVR. The operative complications (respiratory failure, renal insufficiency, congestive heart failure and atrial and ventricular arrhythmias) were significantly increased in patients with increased LVMI. The need for inotropic support more than 24 hrs, the ICU stay and the post-operative hospital stay was significantly higher in group with increased LVMI which agreed with our results. We differed from Mehta et al, because we did not find post-operative respiratory failure, congestive heart failure, atrial arrhythmias or hepatic failure in our patients.

In our patients the mortality accounts for 2 cases (5%) both patients having increased LVMI and these findings are considered as a low mortality (may be explained by low risk characters of our patients) if compared with other studies like Mehta et al, where the mortality was 17% in patients with increased LVMI and Fuster et al, where the mortality was 11% in patients with increased LVMI. The major risk factors for mortality after AVR for AS include older age, greater functional class, greater preoperative LV hypertrophy. The same finding was collaborated by other studies like Beach et al where they also observed LA diameter was a significant predictor of mortality.

CONCLUSION

Hence, we conclude that patients with preoperative increase in LVMI, with large LA diameter carries a strong predictor of postoperative mortality for patients undergoing aortic valve surgery. We also conclude that there will be significant regression of LVMI following successful AVR. But, the decrease in LVMI is maximum during early three months and it is minimal though significant in the later course of follow up.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Hari KMP, Chandra A. Effect of persistence of left ventricular hypertrophy and left atrial dilatation after aortic valve replacement on early outcomes and survival: a prospective study. Int Surg J 2019;6:3786-93.