PATIENT PROSTHESIS MISMATCH AND ITS IMPACT ON LEFT VENTRICULAR MASS REGRESSION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT FOR AORTIC STENOSIS

Thesis Submitted By

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Declaration

I **Dr Abid Iqbal VT**, hereby declare that this thesis titled *"Patient prosthesis mismatch and its impact on left ventricular mass regression in patients undergoing aortic valve replacement for aortic stenosis"* has been prepared by me under the capable supervision and guidance of **Prof. Jayakumar K**, Professor and Head of the department and **Dr.Varghese.T.Panicker**, Additional Professor, Department of Cardiothoracic and Vascular Surgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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We hereby certify that this thesis titled

"Patient prosthesis mismatch and its impact on left ventricular mass regression in patients undergoing aortic valve replacement for aortic stenosis"

Is the bonafide work of **Dr Abid Iqbal VT**, MCh CVTS resident, done under our guidance at Department of cardiovascular and thoracic surgery at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

He has shown keen interest in preparing this project.

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6-10-2017

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Dr Abid Iqbal VT

CONTENTS

ABBREVIATIONS AND EXPANSIONS	
AV	AORTIC VALVE
AS	AORTIC STENOSIS
AVR	AORTIC VALVE REPALCEMENT
LV	LEFT VENTRICLE
LVIDD	LV INTERNAL DIAMETER IN DIASTOLE
LVIDS	LV INTERNAL DIAMETER IN SYSTOLE
IVSD	INTERVENTRICULAR SEPTAL THICKNESS IN DIASTOLE
PWD	POSTERIOR WALL THICKNESS IN DIASTOLE
RWT	RELATIVE WALL THICKNESS
LVM	LEFT VENTRICULAR MASS
LVMI	INDEXED LEFT VENTRICULAR MASS
LVH	LEFT VENTRICULAR HYPERTROPHY
ACE	ANGIOTENSIN CONVERTING ENZYME
Vmax	MAXIMAL VELOCITY
Δ P	PRESSURE DIFFERENCE
LVEF	LEFT VENTRICULAR EJECTION FRACTION
AVA	AORTIC VALVE AREA
AVAi	INDEXED AORTIC VALVE AREA
BP	BLOOD PRESSURE
PPM	PATIENT PROSTHESIS MISMATCH
EOA	EFFECTIVE ORIFICE AREA
iEOA	INDEXED EFFECTIVE ORIFICE AREA
BSA	BODY SURFACE AREA
CHVP	TTK CHITRA HEART VALVE PROSTHESIS
PM	CARPENTIER EDWARDS PERIMOUNT VALVE
SJM	ST JUDE MASTERS PROSTHESIS
SJR	ST JUDE REGENT PROSTHESIS

TITLE

Patient Prosthesis Mismatch And Its Impact On Left Ventricular Mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

INTRODUCTION

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

INTRODUCTION

Aortic stenosis is the third commonest cardiovascular disease after hypertension and coronary artery disease and the commonest valvular heart disease in developed world.[1] In India,presently it is the third commonest valvular heart disease after Mitral Stenosis and Mitral Incompetence.[2] Aortic Stenosis causes development of cardiac hypertrophy, predominantly hypertrophy of left ventricle which in turn is associated with sudden death, congestive heart failure and stroke.[1,3,4,5]

Extend and pattern of cardiac hypertrophy depend on different factors. Relief of mechanical obstruction by Aortic Valve Replacement leads to hemodynamic improvement and subsequently, a substantial reversal of left ventricular hypertrophy.[6] This can be quantified as a decrease of Left Ventricular Mass. Regression of Left Ventricular Mass occurs early after Aortic Valve Replacement and continues up to 10 years after surgery. The early and late follow-up period has been studied in detail, but very few studies analyzed the intermediate time course of regression.

One of the factors that determine regression of Left ventricular hypertrophy is Relative size of prosthetic valve. Rahimtoola first proposed that a smaller than expected effective orifice area (EOA) in relation to the patient's body surface area (BSA) will result in higher transprosthetic gradients and thus affect clinical outcome. [7] Incidence of Patient Prosthesis mismatch varies between 20-70%. [8]

AIM OF THE STUDY

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

AIM OF THE STUDY

To assess regression of left ventricular mass in patients undergoing aortic valve replacement for severe aortic stenosis and to compare outcome based on patient prosthesis mismatch at two years after surgery.

To suggest a cut off value for indexed effective orifice area below which LV regression is impaired in study population.

REVIEW OF LITERATURE

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

REVIEW OF LITERATURE

Aortic stenosis is a common condition associated with major morbidity, mortality, and health economic costs.[1] There is no medical intervention till now capable of delaying or halting its progression. Aortic stenosis is characterized by progressive narrowing of aortic valve and subsequent left ventricular hypertrophy. This results the development of symptoms and adverse events that characterize the latter stages of the disease.

Anatomy of Normal Valve

Normal aortic valves are comprised of 3 cusps (Fig. 1). This tricuspid arrangement results in even distribution of mechanical stress to the valve ring and the aorta.[8] Each cusp is <1 mm thick and appears smooth, thin, and opalescent, with very few cells. Cusps are composed of 4 well defined tissue layers: the endothelium, fibrosa, spongiosa, and ventricularis. At their base, the valve leaflets are attached to a dense collagenous network, called the annulus, which facilitates their attachment to the aortic root and the dissipation of mechanical force.

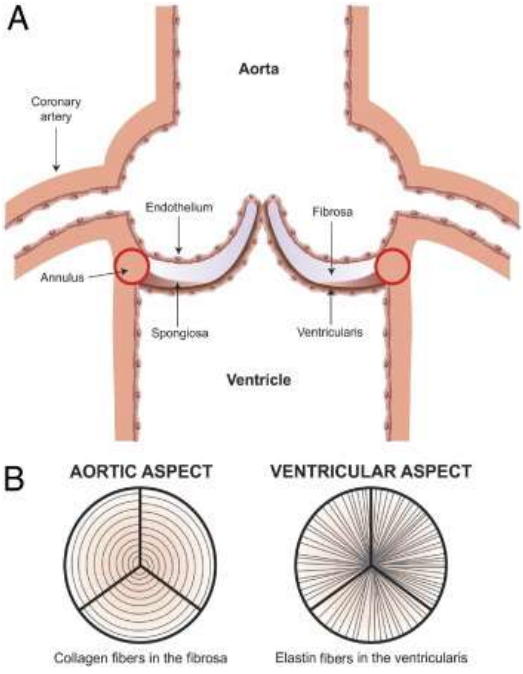


Fig 1 **Normal Aortic Valve**
(A) The valve cusps have a 4-layers. Superficial leaflet endothelium. Fibrosa, which consists of fibroblasts and collagen fibers. Spongiosa, predominantly found at the base of the leaflets is a layer of loose connective tissue containing mucopolysaccharides, mesenchymal cells, and fibroblasts, which resist compressive forces within the cusps. Ventricularis found on the ventricular aspect of the valve which contains elastin fibers orientated perpendicularly to the collagen. **(B)** Short-axis views of the aortic valve. Aortic aspect of the valve displays the concentric arrangement of collagen fibers in the fibrosa. Ventricular aspect showing the radial arrangement of elastin fibers in the ventricularis.

Pathology

Major causes of Aortic stenosis are degenerative, rheumatic and congenital pathology. Underlying pathological process remains same in all these conditions even though inciting trigger event may be different.

Calcific Aortic Stenosis

In calcific AS, the valve cusps become progressively thickened, fibrosed, and calcified. This results in increased valve stiffness, reduced cusp excursion, and progressive valve orifice narrowing. Previously, calcific AS has been attributed to prolonged “wear and tear” and age-associated valvular degeneration. However, recent evidence suggests that it is instead the result of active inflammatory processes involving biochemical, humoral, and genetic factors. (Fig 2) [9]

Rheumatic Aortic Stenosis

Rheumatic aortic stenosis follows Rheumatic Carditis. It typically involves the leaflets, free edges, and commissures, with fibrosis and little calcification. Pathophysiology is like other forms of calcific AS. [10]

Mechanical Stress and Endothelial Damage

The early stages of AS are like those of atherosclerosis. As with atherosclerosis, the initiating event is believed to be endothelial damage resulting from increased mechanical stress and

reduced shear stress. This results in a characteristic distribution of lesions within the stenotic valve. Shear stress is highest in the cusps adjacent to the coronary ostia due to the influence of coronary artery flow. As a result, the noncoronary cusp has lowest shear stress among three and is most frequently involved in AS. Mechanical tissue stress is highest around the flexion areas of the cusps near their attachment to the aortic root, and 50% of lesions can also be observed in this region.[11]

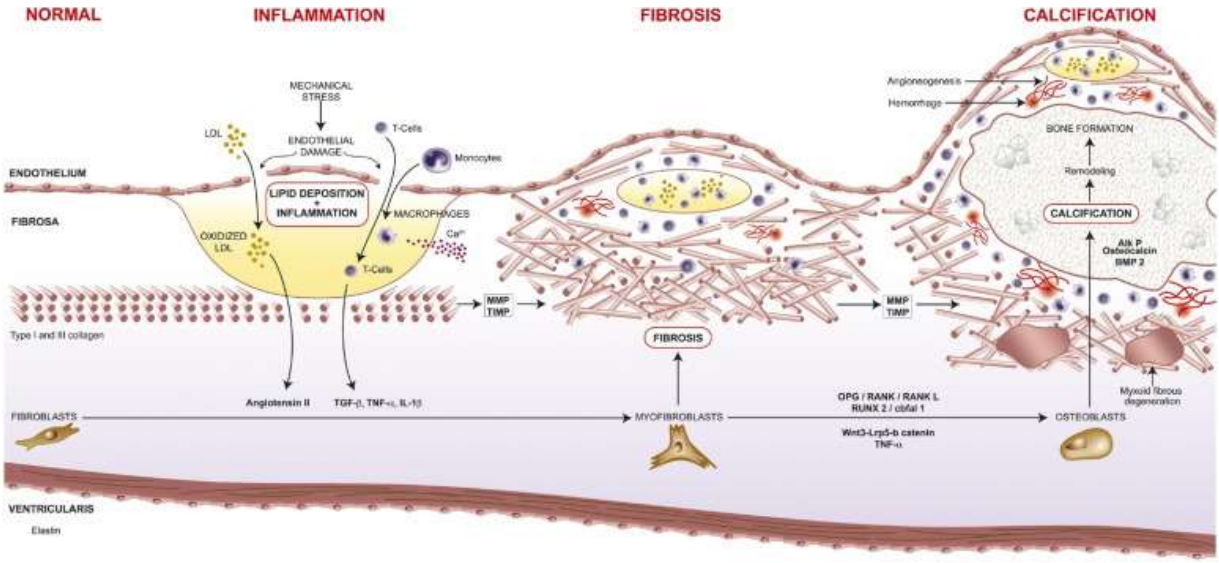


Fig 2. **Pathology Calcific AS.** Mechanical stress results in endothelial damage that allows infiltration of lipid and inflammatory cells into the valve. Lipid oxidization further increases inflammatory activity within these lesions and the secretion of proinflammatory and profibrotic cytokines. The latter drives the differentiation of fibroblasts into myofibroblasts that secrete increased collagen under the influence of angiotensin. In combination with the action of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), disorganized fibrous tissue accumulates within the valve. This leads to thickening and increased stiffness of the valve and in the later stages, the development of myxoid fibrous degeneration. Microcalcification begins early. Calcification accelerates in a proportion of patients because of the differentiation of myofibroblasts into osteoblasts under the influence of several procalcific pathways including osteoprotegerin (OPG)/receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL), Runx 2-cbfal 2, Wnt3-Lrp5-b catenin, and tumor necrosis factor (TNF)-α. Osteoblasts subsequently coordinate calcification of the valve similar to skeletal bone formation, with expression of many of the same mediators, such as osteocalcin, alkaline phosphatase (Alk P), and bone morphogenic protein (BMP)-2. With time, maturation of valvular calcification occurs so that by the end stages of the disease, lamellar bone, microfractures, and hemopoeitic tissue can all be observed within the valve. These pathogenic processes are sustained by angioneogenesis, with new vessels growing particularly in regions of inflammation surrounding calcific deposits. Hemorrhage in relation to these vessels has also been demonstrated in severe disease and may have a role in accelerating disease progression. IL-1β = interleukin-1–beta; LDL = low-density lipoprotein; TGF = transforming growth factor.

Bicuspid Aortic Valve

Bicuspid aortic valve perhaps best illustrates the role of mechanical stress in the pathogenesis of AS. This common congenital abnormality is characterized by a 2-cusp structure that results in a less efficient distribution and concentration of mechanical forces within the valve. AS develops almost invariably and on average two decades earlier in bicuspid patients than in patients with tricuspid valves.[12]

Role of Inflammation

Endothelial injury or disruption allow lipids to penetrate the valvular endothelium and accumulate in areas of inflammation. The lipoproteins implicated in atherogenesis, including low-density lipoprotein and lipoprotein(a), have been detected in early aortic valve lesions. [13] They undergo oxidative modification and these oxidized lipoproteins are highly cytotoxic which can stimulate intense inflammatory activity and subsequent mineralization (Fig. 2).[1415]

Concomitant endothelial damage and lipid deposition triggers inflammation within the valve tissue. Multiple inflammatory cells and cytokines ultimately help stimulate and establish the subsequent fibrotic and calcific processes that cause increasing valve stiffness (Fig. 2).[16] An inflammatory basis for AS is supported by studies demonstrating increased systemic C-reactive protein concentrations in patients with AS and increased temperature in stenotic aortic valve cusps.[17]

More recently noninvasive imaging studies using combined positron emission tomography and computed tomography has also given same conclusion.[18,19] Fluorine-18

labelled fluoro deoxy glucose is a positron emission tomographic ligand that serves as a marker of macrophage activity and has become an established means of measuring inflammation in aortic as well as carotid atheroma.[20] 18-Fluorine labelled fluoro deoxy glucose levels have been shown to be increased in patients with AS compared with controls, displaying a progressive rise in activity with increasing severity of valve stenosis.

Angioneogenesis And Valve Hemorrhage

Histological studies have suggested that these inflammatory processes are sustained by neo angiogenesis in the valve. Thin new vessels are commonly observed in regions of intense inflammation surrounding calcific deposits. Intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression is increased in these vessels, suggesting that they act as a portal of entry for inflammatory cells.[21] Hemorrhage related to these vessels also appears to be important, being present in 78% of patients with severe AS and associated with augmented neovascularization, macrophage infiltration, and accelerated disease progression (Fig. 2). [22]

Onset of Fibrosis

The stenotic aortic valve is characterized by significant cusp thickening due to the accumulation of fibrous tissue and remodeling of the extracellular matrix. In all 3 layers of the valve cusps, abundant fibroblast-like cells are found. They contain vimentin and are commonly referred to as valve interstitial cells.[23] A subpopulation of these cells become activated by the inflammatory activity within the valve and differentiate into myofibroblasts, which are believed to be responsible for the accelerated fibrosis leading to AS. In addition, MMPs (matrix

metalloproteinases) secreted by myofibroblasts and inflammatory cells also have an important and complex role in the restructuring of the valve leaflet matrix (Fig. 2).[24]

The renin-angiotensin system is thought to modify this fibrotic process. Tissue angiotensin-converting enzyme (ACE) and angiotensin II are both up-regulated in stenotic aortic valves, and angiotensin receptors have been identified on valve myofibroblasts.[25]

Calcification

Valve calcification plays a key role in the development of AS. The degree of valvular calcification correlates with valve severity, disease progression, and the development of symptoms and adverse events.[26] [27]

Microscopic areas of calcification can be observed in the early stages of aortic sclerosis at the areas of lipid deposition. In one-sixth of patients with sclerosis, the calcification process accelerates, hemodynamic obstruction ensues, and the valve becomes stenotic.[28] This progression is thought to be driven by the differentiation of myofibroblasts into osteoblasts under the influence of the Wnt3-Lrp5-β catenin signaling pathway [29]

In the early stages of AS, leaflet calcification is composed of nodules containing hydroxyapatite deposited on a bonelike matrix of collagen, osteopontin and other bone matrix proteins. Remodeling of this calcification occurs as AS progresses and by the later stages of disease, lamellar bone, microfractures, and hemopoeitic tissue can all be identified within the valve.[30]

Left Ventricular Hypertrophy

The ventricle responds to the pressure overload due to aortic stenosis by triggering a hypertrophic response, leading to an increase in myocyte size, left ventricular wall thickness and mass.[31,32,33] Initially this response restores wall stress but ultimately proves maladaptive and predicts an adverse prognosis.[34]

The degree of left ventricular hypertrophy is only weakly related to the severity of valve obstruction. [35] This was first established with echocardiography studies but has recently been confirmed using cardiac magnetic resonance, with which no correlation between peak aortic valve velocity and indexed left ventricular mass was observed.[36] The magnitude of the hypertrophic response appears to be more closely associated with other factors, such as advanced age, male sex, and obesity. Genetic factors modulate the degree of hypertrophy in response to a wide range of physiological and pathological triggers, and in AS, polymorphisms of the *ACE 1/D* gene have been associated with variation in left ventricular mass.[3738]

Hypertension is common in this patient group, and the results of SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial showed that coexistent hypertension was associated with increased left ventricular mass and a higher prevalence of hypertrophy.[39] Increased arterial stiffness is also frequently observed because of a combination of advanced age, coexistent atherosclerosis, diabetes, and high blood pressure. This results in increased afterload and contributes to the development of left ventricular dysfunction in AS. [40] Cioffi et al. has demonstrated that subjects with inappropriately high left ventricular mass have increased mortality compared with patients with comparable valve narrowing but more moderate hypertrophy. This may be due to premature decompensation of the hypertrophic process.[41] LV

hypertrophy is quantified by Indexed LV mass, which is the ratio of estimated LV mass to Body surface area.

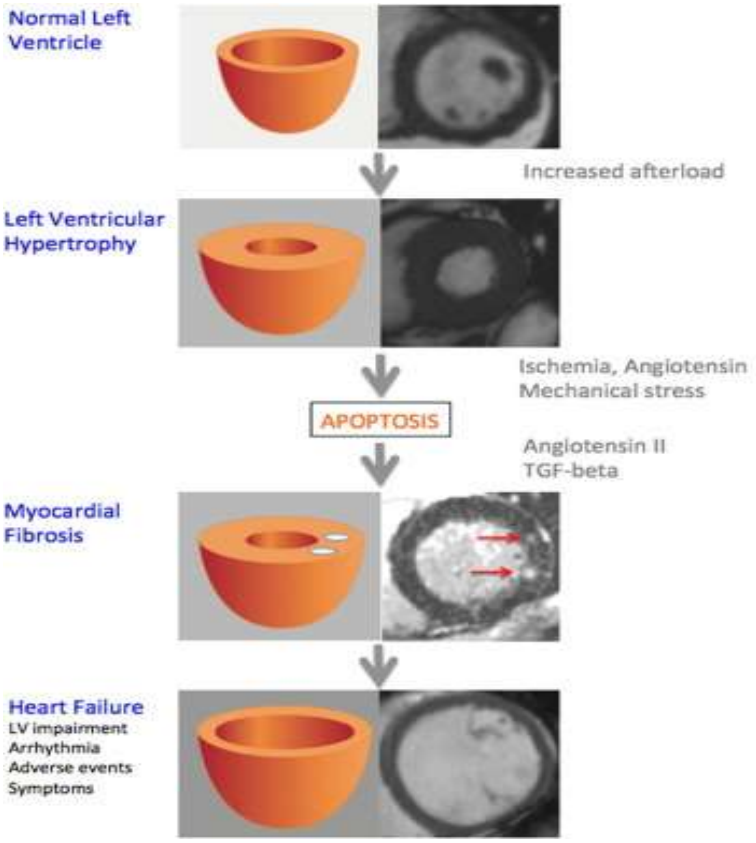
Development of Heart Failure

The transition from hypertrophy to heart failure is point at which the left ventricle fails in the face of an increased pressure afterload and is no longer able to maintain forward flow through the valve. This is followed by the onset of symptoms, adverse events, and associated with a poor prognosis. Hein et al. established that this key progression is associated with myocyte apoptosis and fibrosis and postulated that these two processes were responsible for the transition.[42]Apoptosis occurs at a rate of 5-10% myocytes per year, but is usually balanced by regeneration.[43]Mechanical stress, ACE receptors all influence apoptosis.[44] This is augmented by relative hypoxia due to dense myocardium and relative paucity of neo capillary network. [45]

Apoptotic foci are gradually infiltrated by myofibroblasts and fibrosis and scaring occur. [46]

Fig 3. **Developmet of Left Ventricular Hypertrophy**.

The Development and Subsequent Decompensation of LV Hypertrophy in Response to Aortic Stenosis. Aortic valve narrowing imposes increased afterload and wall stress on the left ventricle. This stimulates a hypertrophic response, which initially restores wall stress and maintains cardiac performance. However, this process ultimately becomes decompensated. Myocyte apoptosis is triggered by a combination of myocardial ischemia, direct mechanical forces, and the actions of angiotensin. This triggers a fibrotic response in the myocardium under the influence of profibrotic mediators such as angiotensin and transforming growth factor (TGF)–beta, which can be visualized using the late gadolinium enhancement technique (**red arrows** show regions of mid wall fibrosis on short-axis views of the left ventricle). Increasing myocardial fibrosis leads to progressive systolic and diastolic impairment and the progression to heart failure. Symptoms and adverse events ensue perhaps in part because of an increased tendency to arrhythmia.



Gadolinium enhanced cardiac magnetic resonance imaging using allows the noninvasive visualization of replacement fibrosis within the myocardium. A mid wall pattern of fibrosis has been observed in the myocardium of up to 38% of patients with moderate or severe AS and has been associated with a more advanced hypertrophic response as well as 8 fold increase in mortality.[47](Fig 3) Fibrosis leads to progressive systolic and diastolic dysfunction resulting in both reduced ventricular compliance and ejection fraction.[48,49] Fibrosis also results in creation of reentry circuits predisposing heart to arrhythmias. [50]

LV Remodeling After AVR

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

Valve replacement surgery relieves the aortic obstruction and prolongs the life of many patients. Favorable or adverse left ventricular remodeling is affected by many factors whose specific roles are still a subject of debate. Age, gender, hemodynamic factors, prosthetic valve types, myocyte alterations, interstitial structures, blood pressure control and ethnicity can all influence the process of LV regression. Myocardial metabolism and coronary artery circulation are also involved in the changes occurring after aortic valve replacement.[51]

Quantification of LV Regression

Left ventricular regression is quantified by the change in indexed LV Mass(LVMI). A ratio of difference in LVMI to original LVMI, Relative regression can be also be used to compare extend of LV regression.[4]

CLINICAL CLASSIFICATION OF AORTIC STENOSIS

According to AHA gudelines 2014, Aortic stenosis is classified as follows.[52]

Table 1

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequence	Symptoms
A	At risk of AS	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis	Aortic Vmax <2m/s	None	None

B	Progressive AS	Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or Rheumatic valve changes with commissural fusion	Mild AS: Aortic Vmax 2.0–2.9 m/s or mean ΔP<20mm Hg Moderate AS: Aortic Vmax 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C	Asymptomatic Severe				
C1	Asymptomatic Severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax>=4m/s mean ΔP >=40 mm Hg AVA typically is ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2) Very severe AS is an aortic Vmax ≥5 m/s or mean ΔP ≥60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None confirmed with Exercise testing
C2	Asymptomatic Severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax>=4m/s mean ΔP >=40 mm Hg AVA typically is ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2)	LVEF <50%	None
D - Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax>=4m/s mean ΔP >=40 mm Hg AVA typically is ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2) but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea or decreased exercise tolerance Exertional angina

					Exertional syncope or presyncope
D2	Symptomatic severe low-flow/low gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1.0 cm2 with resting aortic Vmax <4mm Hg 4 m/s or mean ΔP<40 mm Hg. Dobutamine stress echocardiography shows AVA ≤1.0 cm2 with Vmax ≥4 m/s at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient. AS with normal LVEF or paradoxical low-flow severe AS		AVA ≤1.0 cm2 with resting aortic Vmax<4mm Hg 4 m/s or mean ΔP<40 mm Hg Indexed AVA ≤0.6 cm2/m2 and Stroke volume index <35ml/m^2 Measured when patient is normotensive (systolic BP <140)	Increased relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	HF Angina Syncope or presyncope

MANAGEMENT GUIDELINES FOR AORTIC STENOSIS

Diagnosis and Follow-Up

Class I

Trans Thoracic Echo is indicated in patients with signs or symptoms of AS or a bicuspid aortic valve for accurate diagnosis of the cause of AS, hemodynamic severity, LV size and systolic function, and for determining prognosis and timing of valve intervention. (Level of Evidence: B)

Class IIa

1. Low-dose dobutamine stress testing using echocardiographic or invasive hemodynamic measurements is reasonable in patients with stage D2 AS with all of the following, (Level of Evidence: B):

a. Calcified aortic valve with reduced systolic opening;

b. LVEF less than 50%;

c. Calculated valve area 1.0 cm2 or less; and

d. Aortic velocity less than 4.0 m per second or mean pressure gradient less than 40 mm Hg.

2. Exercise testing is reasonable to assess physiological changes with exercise and to confirm the absence of symptoms in asymptomatic patients with a calcified aortic valve and an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher (stage C). (Level of Evidence: B)

Class III: Harm

1. Exercise testing should not be performed in symptomatic patients with AS when the aortic velocity is 4.0 m per second or greater or mean pressure gradient is 40 mm Hg or higher (stage D). (Level of Evidence: B)

Medical Therapy

Class I

1. Hypertension in patients at risk for developing AS (stage A) and in patients with asymptomatic AS (stages B and C) should be treated according to standard guidelines, started at a low dose, and gradually titrated upward as needed with frequent clinical monitoring . (Level of Evidence: B)

Class IIb

1. Vasodilator therapy may be reasonable if used with invasive hemodynamic monitoring in the acute management of patients with severe decompensated AS (stage D) with New York Heart Association (NYHA) class IV heart failure (HF) symptoms. (Level of Evidence: C)

Class III: No Benefit

1. Statin therapy is not indicated for prevention of hemodynamic progression of AS in patients with mild-to-moderate calcific valve disease (stages B to D). (Level of Evidence: A)

Indications for AVR

Class I

1. AVR is recommended in symptomatic patients with severe AS (stage D1) with (Level of Evidence: B):

    a. Decreased systolic opening of a calcified or congenitally stenotic aortic valve;

b. An aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher;

c. Symptoms of HF, syncope, exertional dyspnea, angina, or presyncope by history or on exercise testing.

2. AVR is recommended for asymptomatic patients with severe AS (stage C2) and an LVEF less than 50% with decreased systolic opening of a calcified aortic valve with an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher. (Level of Evidence: B)

3. AVR is indicated for patients with severe AS (stage C or D) when undergoing cardiac surgery for other indications when there is decreased systolic opening of a calcified aortic valve and an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher. (Level of Evidence:

Class IIa

1. AVR is reasonable for asymptomatic patients with very severe AS (stage C1) with (Level of Evidence: B):

a. Decreased systolic opening of a calcified valve;

b. An aortic velocity 5.0 m per second or greater or mean pressure gradient 60 mm Hg or higher; and

c. A low surgical risk.

2. AVR is reasonable in apparently asymptomatic patients with severe AS (stage C1) with, (Level of Evidence: B)

a. A calcified aortic valve;

b. An aortic velocity of 4.0 m per second to 4.9 m per second or mean pressure gradient of 40 mm Hg to 59 mm Hg; and

c. An exercise test demonstrating decreased exercise tolerance or a fall in systolic blood pressure (BP).

3. AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a (Level of Evidence: B):

a. Calcified aortic valve with reduced systolic opening;

b. Resting valve area 1.0 cm2 or less;

c. Aortic velocity less than 4.0 m per second or mean pressure gradient less than 40 mm Hg;

d. LVEF less than 50%; and

e. A low-dose dobutamine stress study that shows an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher with a valve area 1.0 cm2 or less at any dobutamine dose.

4. AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS (stage D3) with an LVEF 50% or greater, a calcified aortic valve with significantly reduced leaflet motion,

and a valve area 1.0 cm2 or less only if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms and data recorded when the patient is normotensive (systolic BP< 140 mm Hg) indicate (Level of Evidence: C):

a. An aortic velocity less than 4.0 m per second or mean pressure gradient less than 40 mm Hg; and

b. A stroke volume index less than 35 mL/m2 ; and

c. An indexed valve area 0.6 cm2 /m2 or less.

5. AVR is reasonable for patients with moderate AS (stage B) with an aortic velocity between 3.0 m per second and 3.9 m per second or mean pressure gradient between 20 mm Hg and 39 mm Hg who are undergoing cardiac surgery for other indications. (Level of Evidence: C)

Class IIb

1. AVR may be considered for asymptomatic patients with severe AS (stage C1) with an aortic velocity 4.0 m per second or greater or mean pressure gradient 40 mm Hg or higher if the patient is at low surgical risk and serial testing shows an increase in aortic velocity 0.3 m/s or greater per year. (Level of Evidence: C)

CONCEPT OF PATIENT PROSTHESIS MISMATCH (PPM)

Initial AVRs resulted in high trans prosthetic gradients. Trans prosthetic Gradient is determined by the geometric orifice area of prosthetic valve and trans valvar blood flow. Trans valvar blood flow is essentially the cardiac output. Expected cardiac output is a function of body

surface area. Thus, if we divide Effective Orifice Area (EOA) by Body Surface Area (BSA), the resulting value called indexed effective orifice area (iEOA) will determine transprosthetic pressure gradient. [53,54]

Ex vivo studies has documented an exponential relation between transprosthetic pressure gradients and prosthesis effective orifice areas indexed for body surface area.[55] These experiments were done assuming a normal resting cardiac index of 3.0 l/min m^2 and 10-50% increases in stroke volume such as may occur during maximal upright exercise. The exponential relations between these two parameters show that a small decrease in indexed effective orifice area produces a large increase in pressure gradient, and that the indexed effective orifice area should ideally be not less than 0.9-1.0 cm2/m2 for aortic prostheses to minimize postoperative gradients.

Rahimtoola first proposed the concept of Patient prosthesis mismatch.[7] Patient prosthesis is present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve. An indexed EOA 0.85 cm2/m2 is generally regarded as the threshold for PPM in the aortic position with values between 0.65–0.85 cm2/m2 being classified as moderate PPM and those, 0.65 cm2/m2 as severe PPM. [8]

Incidence of PPM is fairly common and varies between 20% to 70%. It is higher in female patients, older patients and those with higher BSA[56]

IMPACT OF PPM

Impact of PPM have been a matter of debate since its original description. Many authors have found that adversely affects early, intermediate as well as long term clinical course. [7]

Earlier studies showed a significant increase in mortality and morbidity in both long and short term in patients with PPM.[57,58,59,60,61]

Howell et all reported no increase in medium and long term mortality in patients with PPM.[62,63]Hong et al detected an increase in 12 year mortality only for patients with severe PPM.[64] Fuster et al has reported that PPM adversely impacts LV mass regression up to 1 year. This study also suggested that impaired LV mass regression occurs more in severely hypertrophied hearts. [65] Ruel et al observed that PPM affected outcome only in patients with severe LV dysfunction.[66]

Kaminishi et al observed that age, aortic valve stenosis, dyslipidemia, hypertension, old myocardial infarction, previous percutaneous coronary artery intervention, diabetes mellitus, cerebrovascular disease, and high body mass index were the risk factors for PPM. PPM was not an independent risk factor for short-term mortality[67]. Similar observations were made by Medalion and Lapar as well.[6869]

Sportelli et al reported an incidence of 53.8% of PPM. But there was no significant difference in mortality or clinical status in patients with PPM.[70] Guo et al reported that PPM is associated with increased 30day mortality in Chinese population.[71] Hernández-Vaquero D et al observed that PPM is not associated with early outcome in young and middle aged individuals.[72]

Kato et al and Hanayama et al observed that valve size and PPM is not an important factor determining clinical outcome in intermediate and long term respectively.[7374]

A meta-analysis in this subject showed an increased all cause and cardiac mortality in patients with PPM.[75] Another recently published meta-analysis by Chen et al noticed that moderate PPM is associated with poor prognosis only in younger and female patients with severe LV dysfunction. [76]

Only Indian study in this topic by Joshi et al showed no difference between early outcome in PPM patients.[77] Singh et al studied LV regression in rheumatic AS in Indian population and found out that LV regression was independent of the valve size.[78]

MATERIALS AND METHODS

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

MATERIALS AND METHODS

STUDY DESIGN

Single center non- randomized retrospective observational cohort study.

POPULATION

All Patients Who Underwent aortic valve replacement In SCTIMST Between July 1 2015 To December 31 2015.

A total of 91 patients underwent AVR in this period

INCLUSION CRITERIA

All Patients Undergoing Isolated Aortic Valve Replacement For Aortic Stenosis In Sree Chitra Institute For Medical Sciences And Technology From 1st July 2015 To 31st December 2015 Included.

EXCLUSION CRITERIA

All patients undergoing concomitant coronary artery revascularization or mitral or tricuspid valve surgery were excluded. Patients with aortic regurgitation more than 3+ were also excluded from study. All patients with other severe cardiac comorbidities like cardiomyopathy were also excluded. 54 for out of 91 met exclusion criteria and hence was excluded. 37 cases were selected for the study.

SURGICAL TECHNIQUE

All patients underwent Aortic valve replacement under cardiopulmonary bypass with moderate hypothermia. Cold blood cardioplegia using a blood cardioplegia delivery system was delivered through root cannula and augmented through coronary ostia every 30 minutes or earlier if electrical activity reappeared. Transverse aortotomy was done, Leaflets excised, annulus decalcified and annulus was sized with sizers. 4 types of valves were used. Carpentier Edwards Perimount Bioprosthetic valves were used in patients above 60 years.(Fig 4A). TTK Chitra monoleaflet (Fig 4B), StJude Masters bileaflet or StJude Regent bileaflet (Fig 4C) metallic prosthesis were used in other patients at surgeon's discretion and availability. Valves were fixed using pledgetted 2-0 ethibond ventriculo aortic sutures. Aorta was closed in 2 layers. Mediastinal drains were retained for 24 hours. Patients were kept on oral anticoagulation with a target INR between 2-3. Anticoagulation was discontinued in patients with bioprosthetic valves after 3 months.

A **B** **C**

Fig 4: **Prosthetic Valves** (A) Carpentier Edwards Perimount Valve , (B) St Jude Regent Valve , (C) TTK Chitra valve

DATA COLLECTED

Following data was collected from Case records.

- Age
- Sex
- Height and Weight at the time of surgery
- Clinical status
- Functional class of symptoms prior to surgery
- Functional class of symptoms at the time of follow up
- Type of valve
- Effective orifice area
- ECHO

  Pre operative values of
  - LV internal diameter in mm
  - Systolic and diastolic in mm
  - Posterior wall thickness in diastole in mm
  - Septal thickness in diastole in mm
  - Trans valvar gradient in mmHg
    - Peak
    - Mean
  - Aortic valve area in cm^2 by continuity equation
  - LV ejection fraction

  Immediate post op
  - Trans valvar gradient in mm Hg
    - Peak
    - Mean

1 year post surgery values of

- LV internal diameter in mm
- Systolic and diastolic in mm
- Posterior wall thickness in diastole in mm
- Septal thickness in diastole in mm
- Trans valvar gradient in mmHg
  - Peak
  - Mean
- LV ejection fraction

CALCULATED PARAMETERS

Following parameters were calculated using collected data.

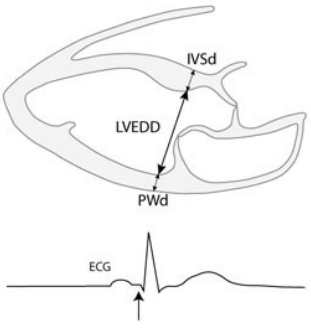
- **BODY SURFACE AREA**
- **LV MASS**

LV Mass was calculated using the equation[79]

$$\text{LV Mass (g)} = 0.8\{1.04[([\text{LVEDD} + \text{IVSD} + \text{PWD}]^3 - \text{LVEDD}^3)]\} + 0.6$$

Values were interpreted as per following chart suggested by Lang et al.[80]

	Female	Male
Reference Range	43-95	49-115
Mildly Abnormal	96-108	116-131
Moderately Abnormal	109-121	132-148
Severely Abnormal	≥122	≥149



- **RELATIVE WALL THICKNESS**

Relative wall thickness was calculated as per following equation.

RWT = 2 * PWd/LVEDD

RWT<0.06 was considered as eccentric hypertrophy

❑ INDEXED LV MASS

Indexed LV mass is the ratio of LV mass to body surface area calculated as

LVMI = LV MASS/ BSA

❑ ACTUAL LV MASS REGRESSION

Actual LV mass regression is the difference between pre operative and follow up LV mass in grams

ACTUAL LV MASS REGRESSION = PRE OP LV MASS – POST OP LV MASS

❑ LV MASS REGRESSION

LV mass regression is the difference between pre-operative and follow up indexed LV mass in grams/m^2

LV MASS REGRESSION = PRE OP LVMI – POST OP LVMI

❑ RELATIVE LV MASS REGRESSION

Relative LV mass regression is the ratio of Actual LV mass regression to pre-operative LV mass

RELATIVE LV MASS REGRESSION = ACTUAL LV MASS REGRESSION /PRE OP LV MASS

STATISTICAL ANALYSIS

All data were coded and entered in an excel sheet and analyzed using Statistics pack of MS Excel 2016 and statacalc online calculators. Quantitative data analysed with mean, standard deviation and Student T test. Qualitative data analysed with Chi square test. Regression analysis done with Pearson coefficient.

OBSERVATIONS AND RESULTS

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

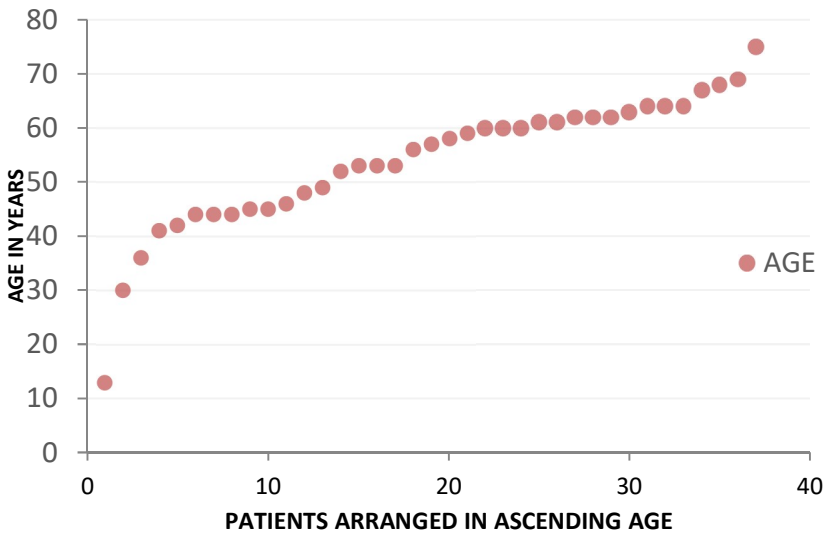
DEMOGRAPHY

Total number of AVR during study period = 91
Total number of cases after exclusion criteria (n) = 37

AGE

Median Age - 57 years
Youngest Patient- 16 years
Oldest Patient- 75 years

Graph 1. Age

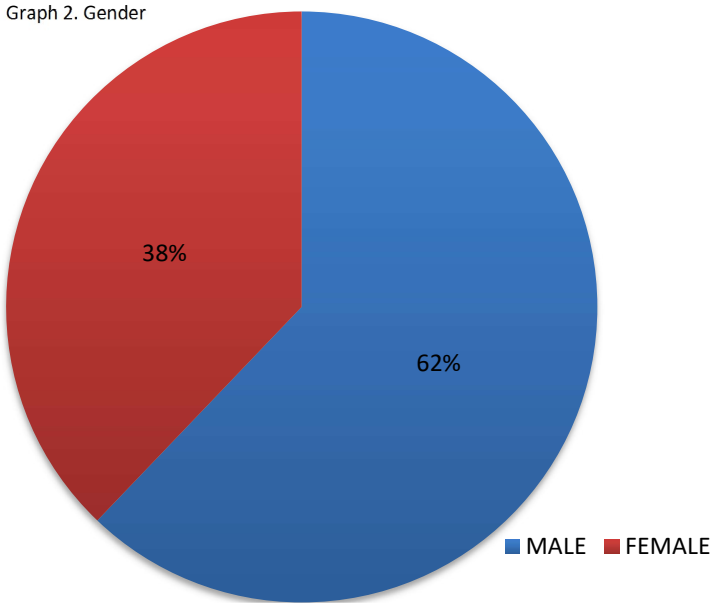


SEX

62% of the patients were males and 38% were females

Table 2. Gender	n
Male	23
Female	14

Graph 2. Gender



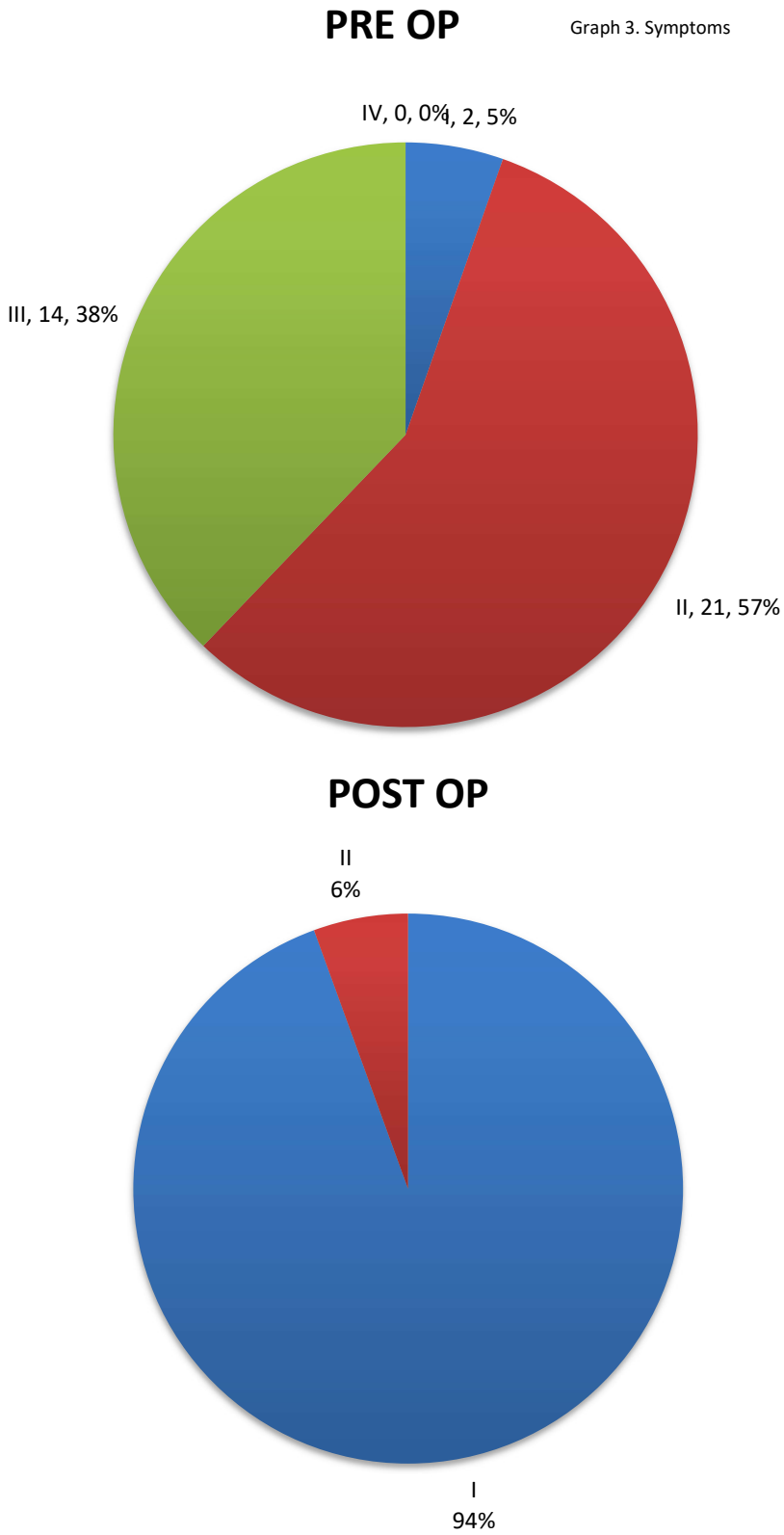
CLINICAL STATUS

Majority of our patients had NYHA Class II symptoms at initial presentation.

94% were asymptomatic at review.

Table 3.

NYHA	PRE OP	POST OP
1	2	34
2	21	2
3	14	0
4	0	0



Graph 3. Symptoms

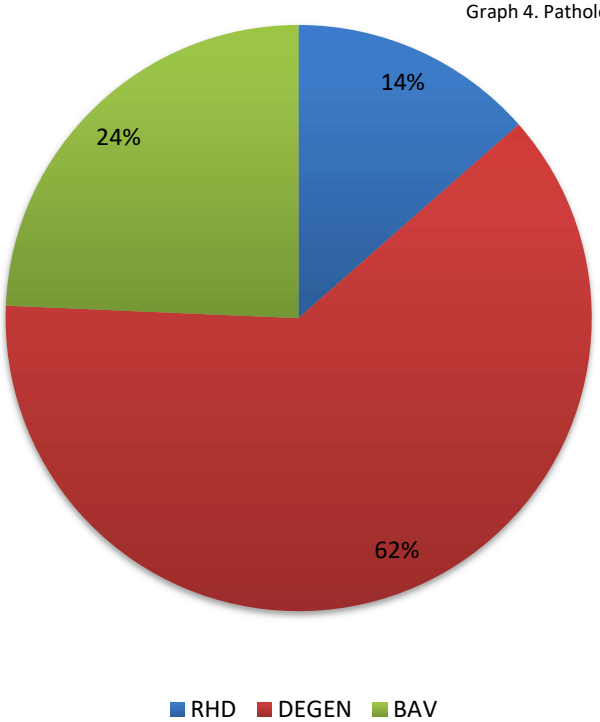
PATHOLOGY

Degenerative Valve diseases accounted for 62% , Bicuspid aortic Valve 24% and Rheumatic Heart Disease 14%.

Table 4.

PATHOLOGY	N
RHD	5
DEGENERATIVE	23
BAV	9

Graph 4. Pathology



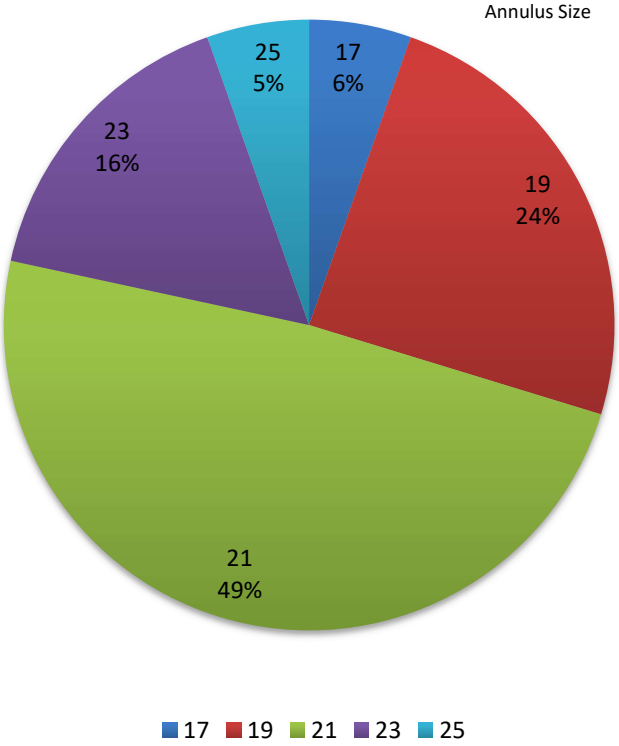
VALVE SIZES

21 sized valves were used in about half of the patients. 24% admitted 19 sized valves and 16%, 23 sized valves.

Table 5.

SIZE	NUMBER
17	2
19	9
21	18
23	6
25	2

Graph 5. Annulus Size



TYPE OF VALVES USED

Bioprosthetic valves were used in 16 patients. Metallic prosthesis of three different models were used in 21 patients

Carpentier Edwards Perimount valve was the commonest used one. TTK Chitra valves were second most commonly used model.

Graph 6. Valve type

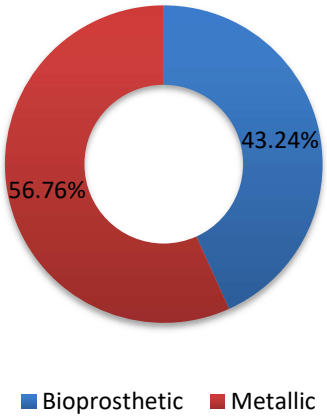
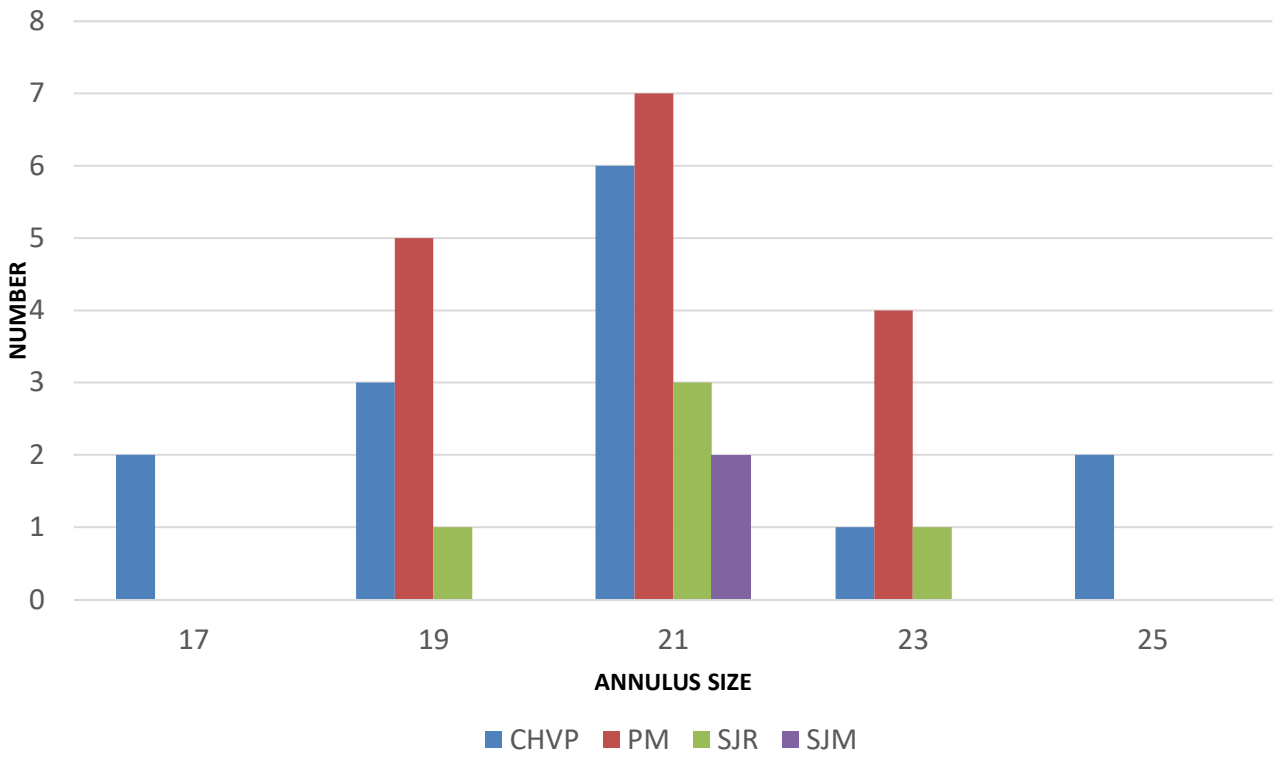


Table 6	CHVP	PM	SJR	SJM
17	2	0	0	0
19	3	5	1	0
21	6	7	3	2
23	1	4	1	0
25	2	0	0	0

Graph 7. Valve



PATIENT PROSTHESIS MISMATCH

Severe PPM was present in 11%, Moderate PPM in57% and no PPM in 32% of patients.

Graph 8. PPM

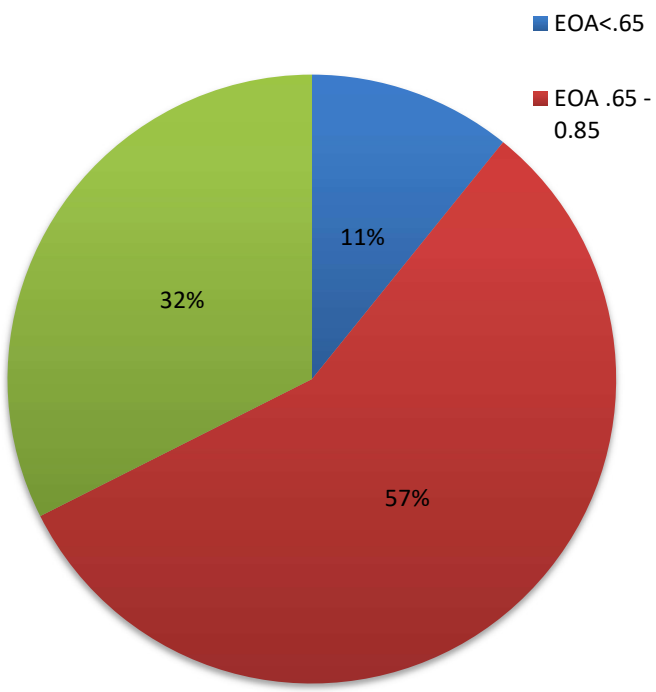


Table 7.

INDEXED EOA	N
<.65	4
0.65 - 0.85	21
>.85	12

PATIENT PROSTHESIS MISMATCH AGAINST VALVE TYPE

PPM was more common in Perimount valves (81.81%) and TTK Chitra valves (71.42%).

Graph 10. Age

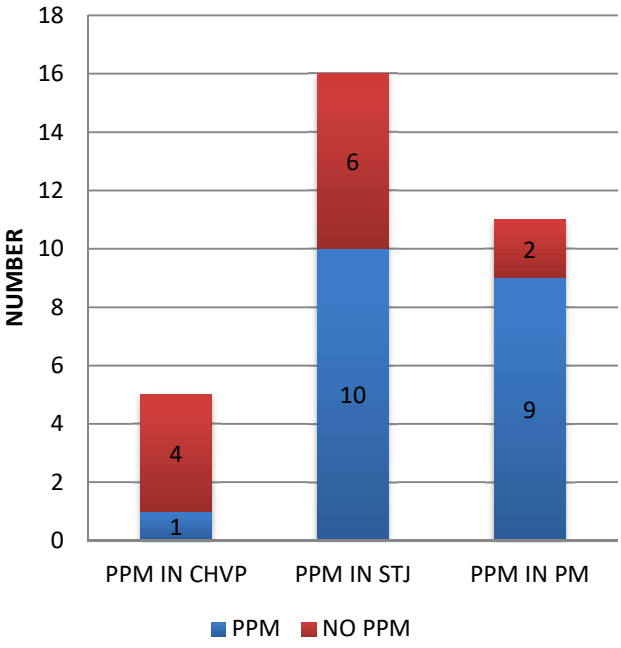
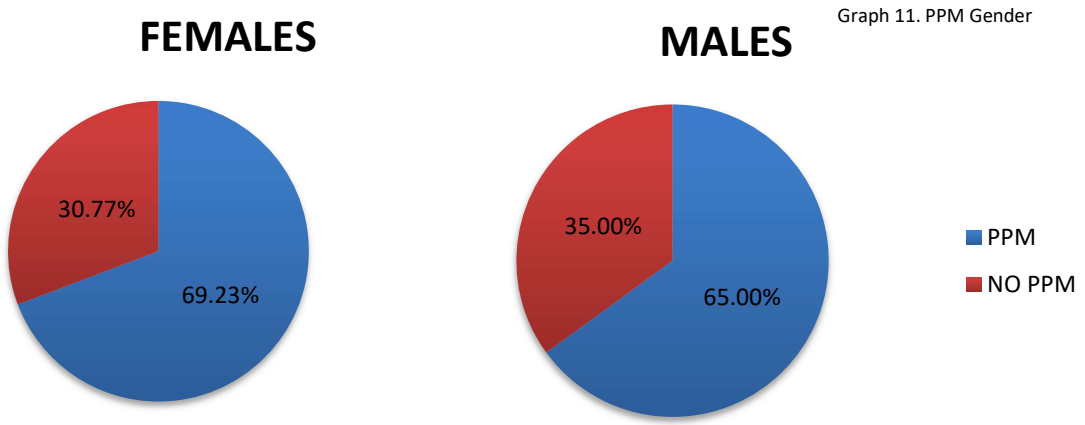


Table 8	PPM	NO PPM	PPM %
CHVP	10	4	71.42
ST JUDE	1	6	14.28
PERIMOUNT	9	2	81.81

VARIABLES FOR PPM

GENDER

Incidence of PPM was similar in both male and female patients. 69.23% of female patients and 65% male patients developed PPM.

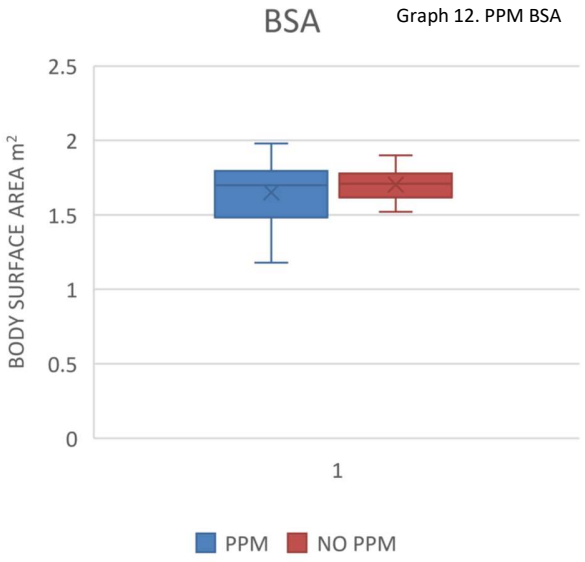


Graph 11. PPM Gender

BODY SURFACE AREA

There was no statistically significant difference in body surface area of both group of patients.

Table 9. BSA	MEAN	SD	P
PPM	1.65	0.19	0.39
NO PPM	1.70	0.12	



Graph 12. PPM BSA

AGE

There was no statistically significant difference in weight distribution of both group of patients.

Graph 13.PPM Age

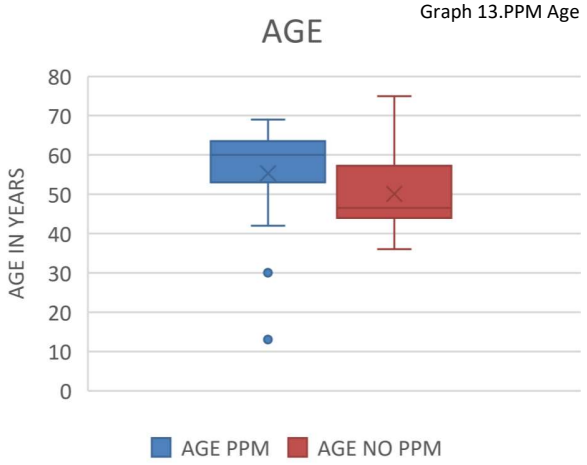
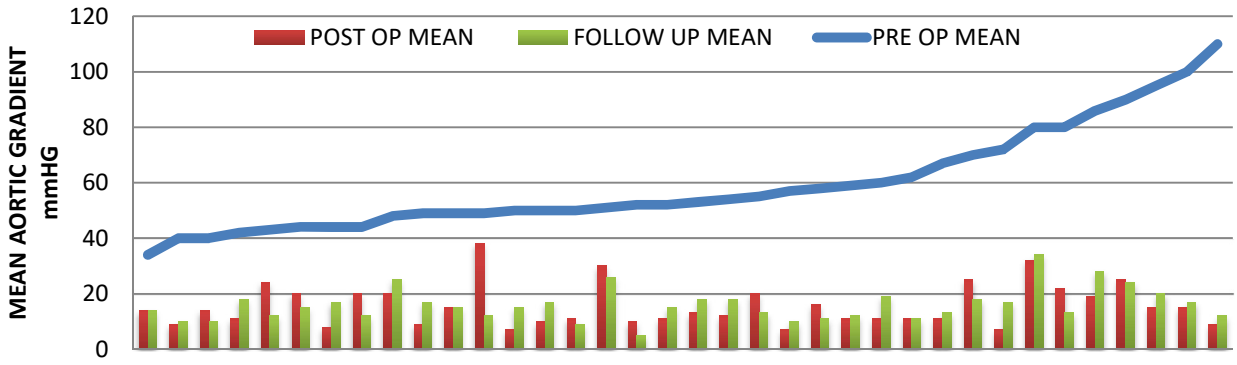


Table 10. AGE	MEAN	SD	P
PPM	54.77	13.29	0.41
NO PPM	50.91	10.92	

AORTIC VALVE GRADIENTS

Both mean and peak aortic valve gradients fell significantly following aortic valve replacement. There was no significant difference between aortic valve gradients in early and late echocardiograms. Average peak gradient reduced from 102.11+/- 30.93 mm Hg to 27.5+/-9.83 mm Hg following AVR. Average mean gradient fell from 59.30+/-18.26 mm Hg to 15.53+/-6.18 mmHg.

Graph 14. AV Gradient



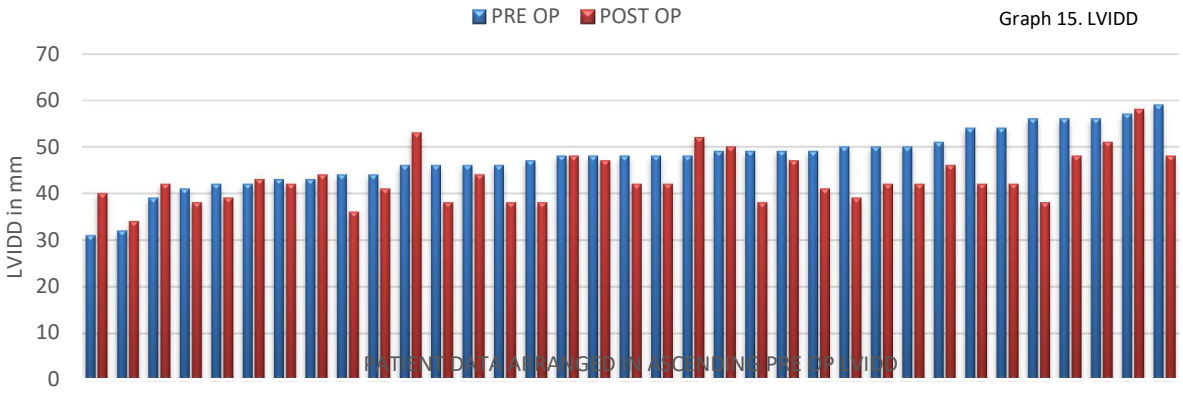
PATIENT DATA ARRANGED IN ASCENDING PRE OP MEAN GRADIENT

Table 11

	PRE OP MEAN	STD DEV	EARLY POST OP MEAN	STD DEV	P VALUE	LATE POST OP MEAN	STD DEV
PEAK GR	102.11	30.93	27.50	9.89	<0.01	29.76	11.48
MEAN GR	59.30	18.26	15.53	6.18	<0.01	15.46	7.52

LV INTERNAL DIAMETER

Mean Left ventricular internal diameter reduced from 47.81+/-6.26mm to 43.25+/-5.38. (p<0.01)

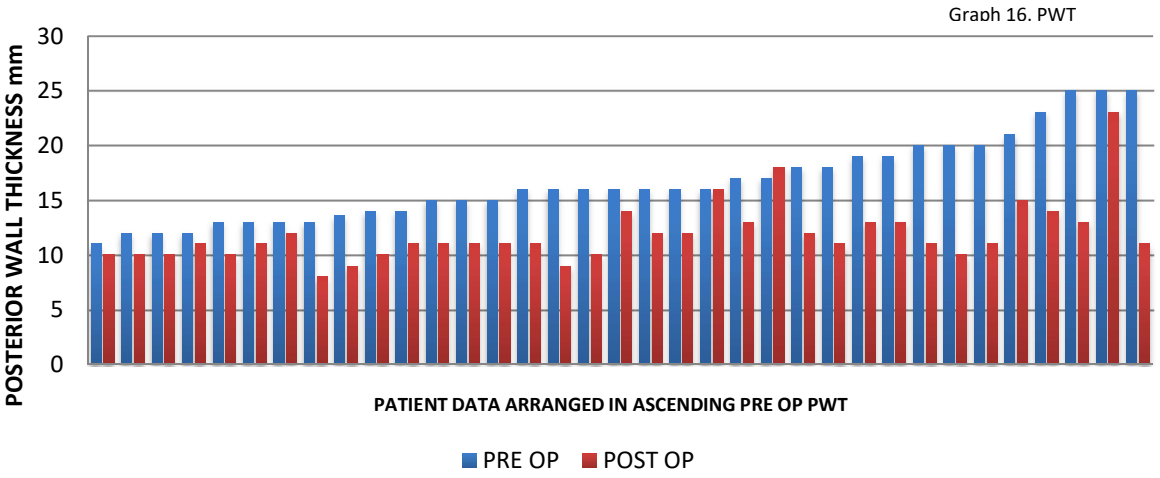


Graph 15. LVIDD

Table 12	PRE OP MEAN	STD DEV	POST OP MEAN	STD DEV	P VALUE
LVIDD	47.81	6.26	43.25	5.38	<0.01

LEFT VENTRICULAR WALL THICKNESS

LV wall thickness reduced significantly from 16.61+/-3.81 to 11.78+/-2.78 following AVR. Only one patient showed an increase in posterior wall thickness.



Graph 16. PWT

Table 13	MEAN	STD DEV	MEAN	STD DEV	p
WALL THICKNESS	16.61	3.81	11.78	2.78	<0.01

INTERVENTRICULAR SEPTAL THICKNESS

Inter ventricular septal thickness reduced from 15.68+/-2.98 to 11.65 +/-2.57. (p<0.05)

Graph 17. IVSD

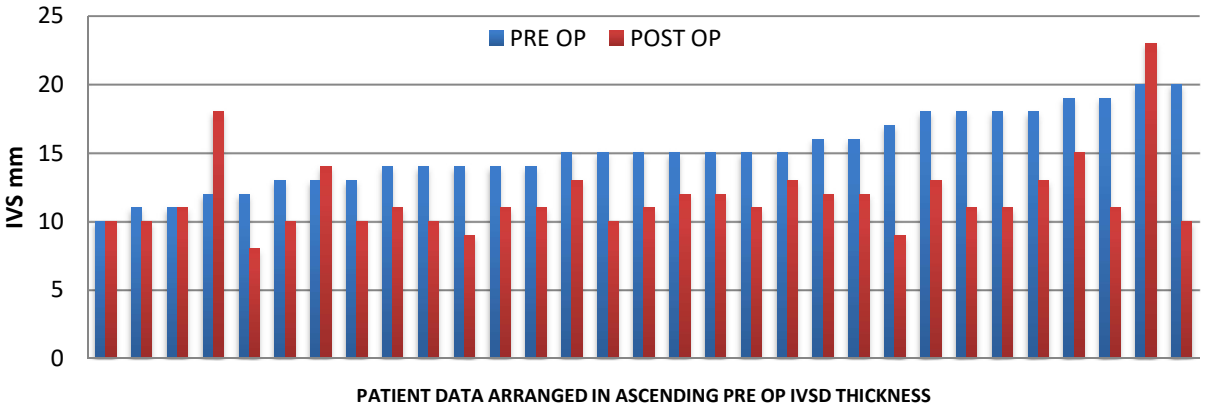


Table 14.	PRE OP	STD DEV	POST OP	STD DEV	T TEST
SEPTUM	15.68	2.98	11.65	2.57	<0.05

LEFT VENTRICULAR MASS

LV mass reduced from 335.86+/-108.65 g to 176.47+/-69.03g. (p<0.01) LV mass showed significant reduction in all patients.

Graph 18. LV MASS

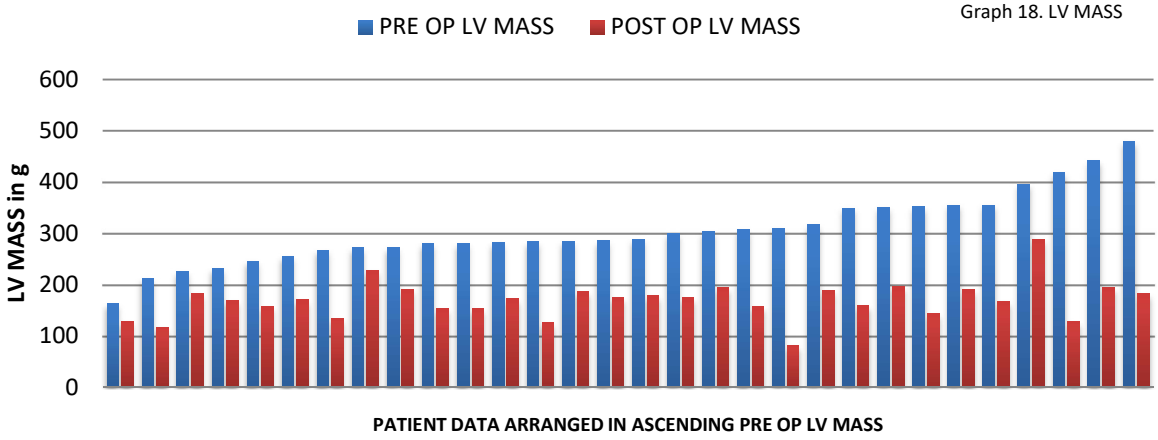
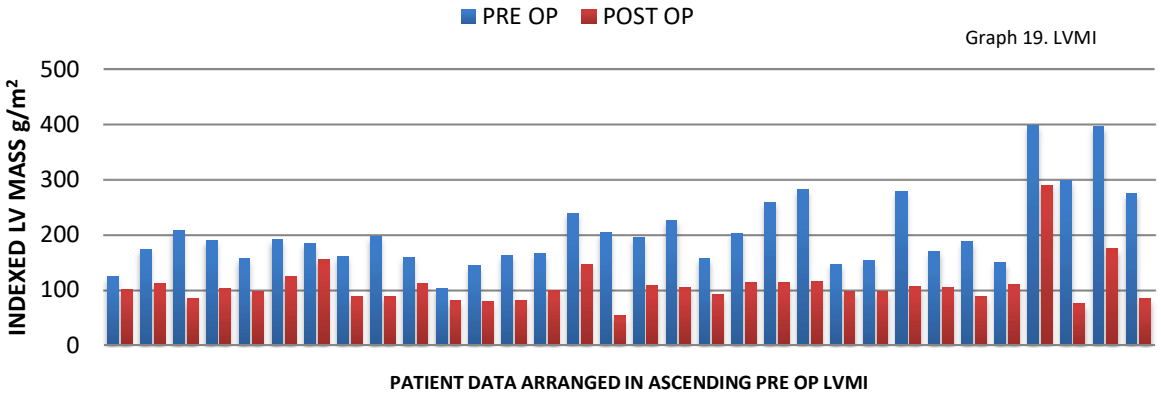


Table 15	PRE OP	STD DEV	POST OP	STD DEV	p
LV MASS (in g)	335.86	108.65	176.47	69.03	<0.01

INDEXED LV MASS

Indexed LV mass reduced from 206+/-67.44 g/m^2 to 105.88+/- 38.99m^2. (p<0.01)

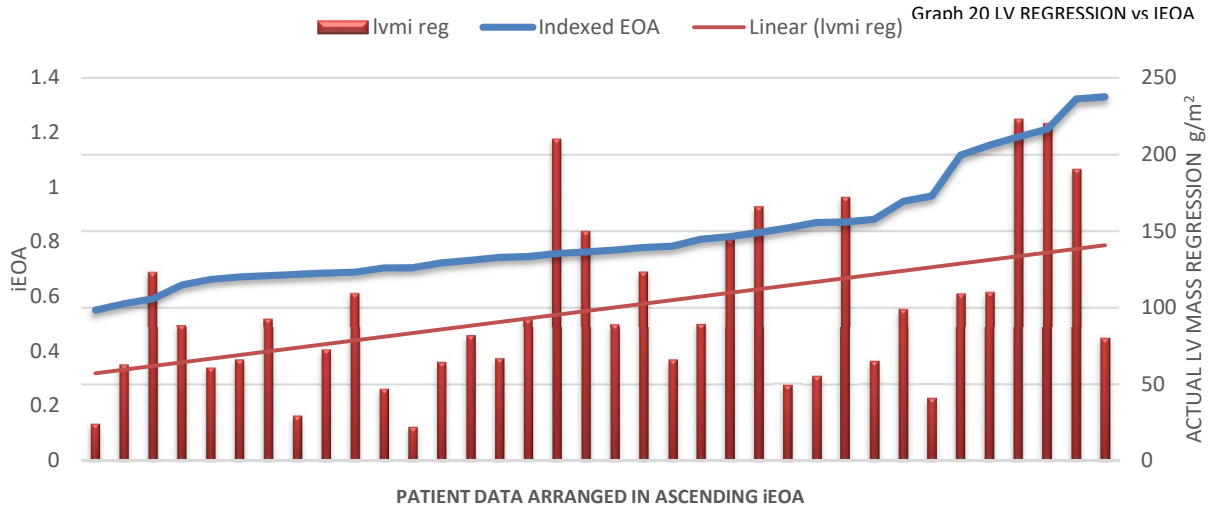


Graph 19. LVMI

Table 16.	PRE OP	STD DEV	POST OP	STD DEV	P
LV MASS INDEX	206	67.44	105.88	38.99	<0.01

LEFT VENTRICULAR MASS REGRESSION

Regression of Indexed LV Mass showed a positive correlation relation with indexed EOA with a correlation coefficient of +0.48. (95% CI 0.18-0.698)



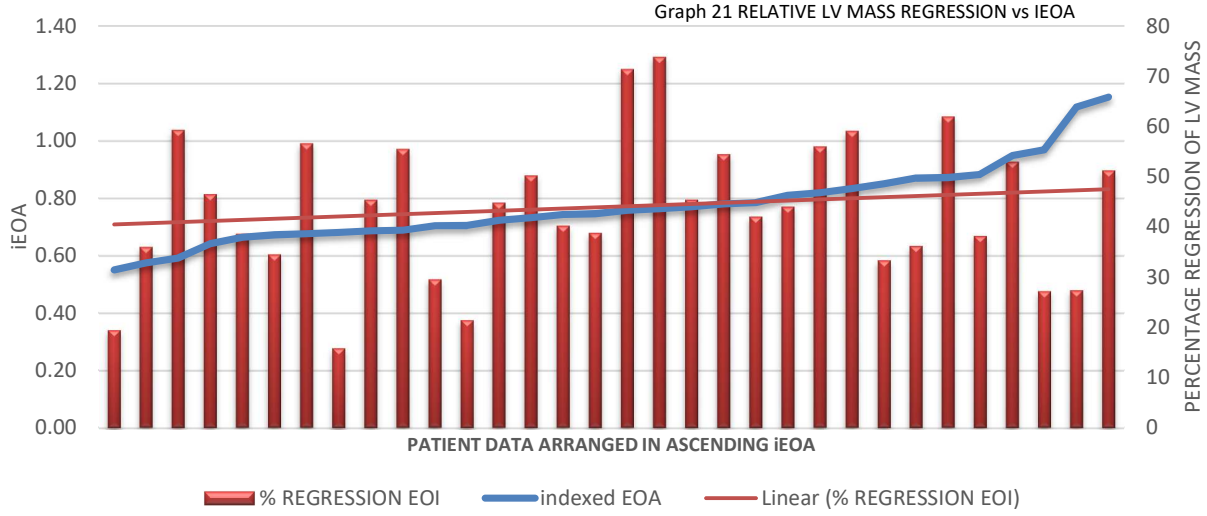
Graph 20 LV REGRESSION vs IEOA

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

RELATIVE REGRESSION OF LV MASS

Relative LV mass regression measured as reduction as ratio to original LV mass also showed a positive correlation, though correlation coefficient was only +0.19 (CI: -0.14- +0.19)

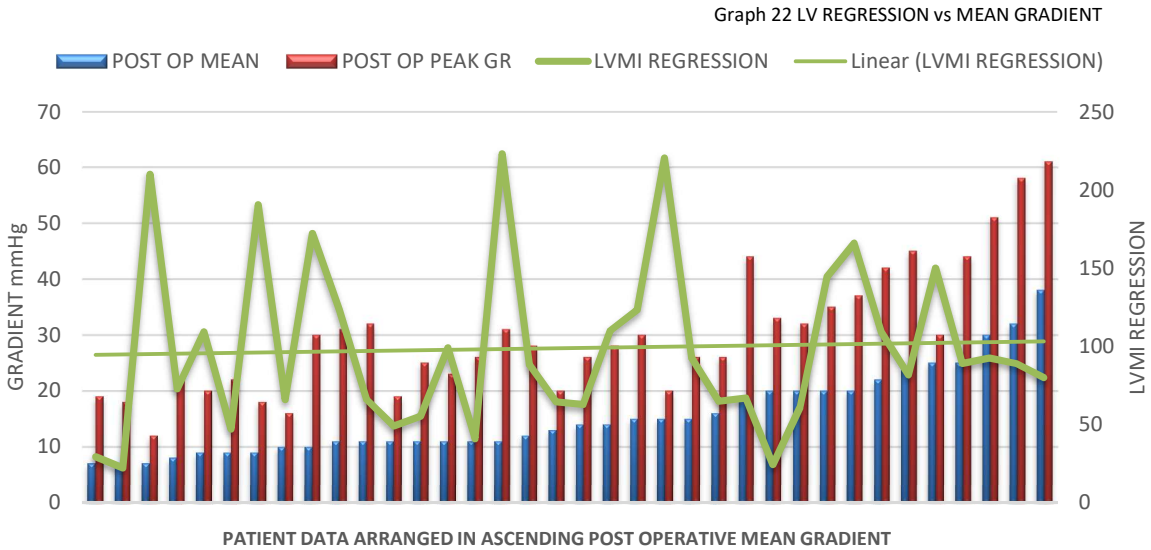
Graph 21 RELATIVE LV MASS REGRESSION vs IEOA



INDEXED LV MASS REGRESSION v/s POST OPERATIVE MEAN GRADIENT

There was no correlation between mean or peak trans valvar gradients achieved after surgery to relative LV mass regression. Correlation coefficient of mean and peak AV gradients to Relative LV Mass Regression was -0.02 and -0.05 respectively.

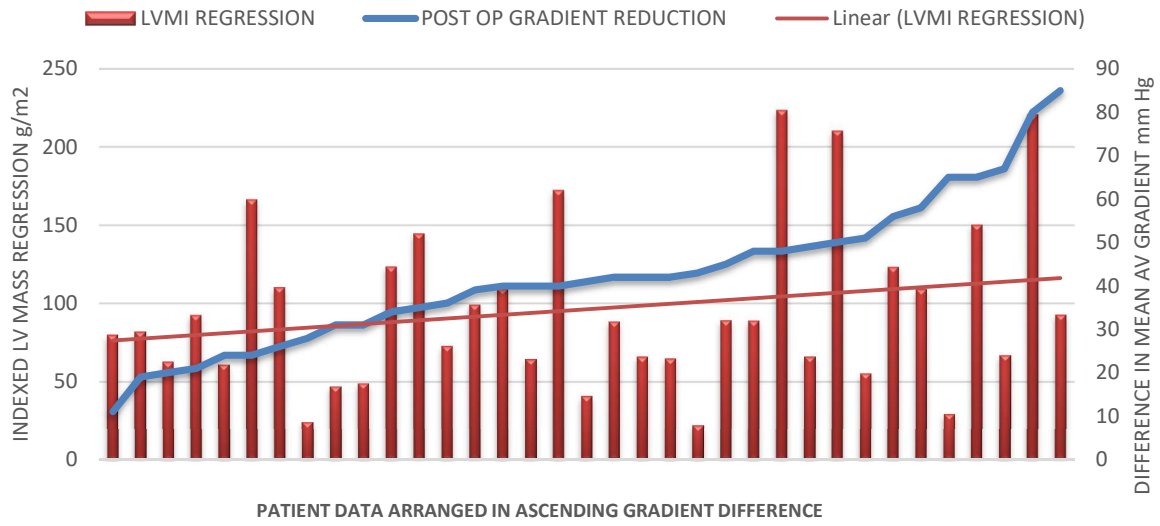
Graph 22 LV REGRESSION vs MEAN GRADIENT



LV MASS REGRESSION v/s REDUCTION IN MEAN GRADIENT ACHEIVED

A positive correlation was noticed between reduction achieved in mean aortic valve gradient and Indexed LV mass regression. Correlation coefficient was +0.35. (95% CI 0.03-0.605)

Graph 23 LV REGRESSION vs GRADIENT REDUCTION



MEAN AORTIC VALVE GRADIENT COMPARISON - PPM vs NO PPM

There was no statistically significant difference between PPM and no PPM patients in preoperative, immediate post operative and follow up period.

Graph 24 MEAN AV GRADIENT PPM vs NO PPM

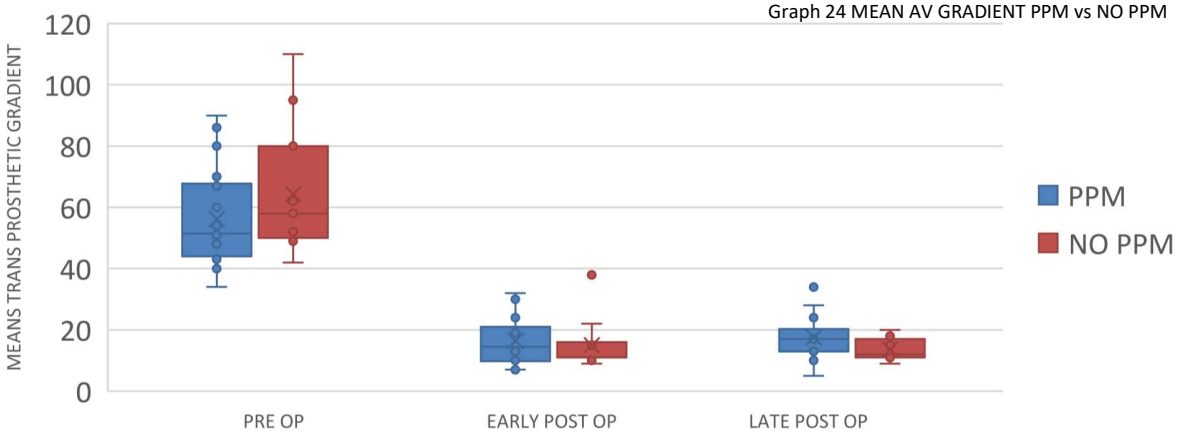


Table 17. AS GRADIENT	NO PPM MEAN	SD	PPM MEAN	SD	P
PRE OP	58	17.01	62.25	21.71	0.08
EARLY POST OP	15.96	7.44	14.92	8.09	0.17
LATE POST OP	16.62	6.98	13.33	3.42	0.10

INDEXED LV MASS COMPARISON - PPM vs NO PPM

Preoperative Indexed LV mass was significantly higher in No PPM group. There was no significant difference between both groups on follow up.

Graph 25 INDEXED LV MASS PPM vs NO PPM

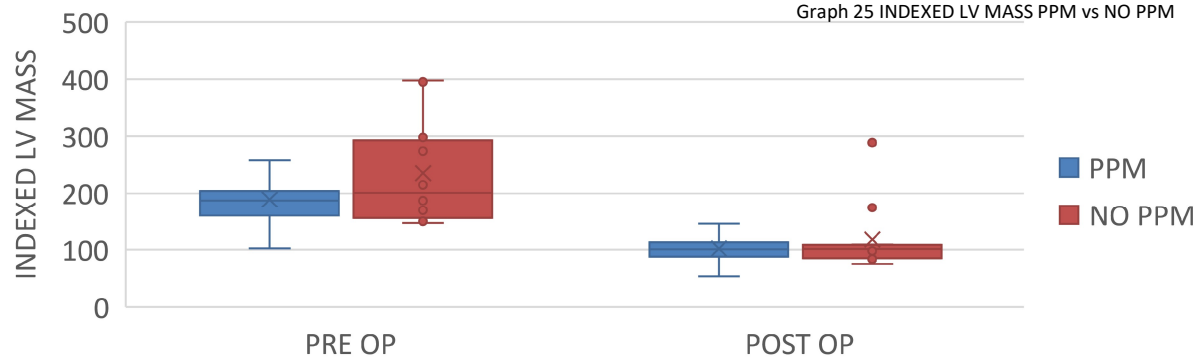


Table 18

INDEXED LV MASS	PPM	SD	No PPM	SD	P
PRE OP	189	45.99	236	92.18	0.007
POST OP	99.94	22.61	117.74	59.48	0.135

LV MASS REGRESSION COMPARISON- PPM vs NO PPM

LV mass regression following surgery was significantly higher in No PPM group.

Graph 26 LV REGRESSION. PPM vs NO PPM

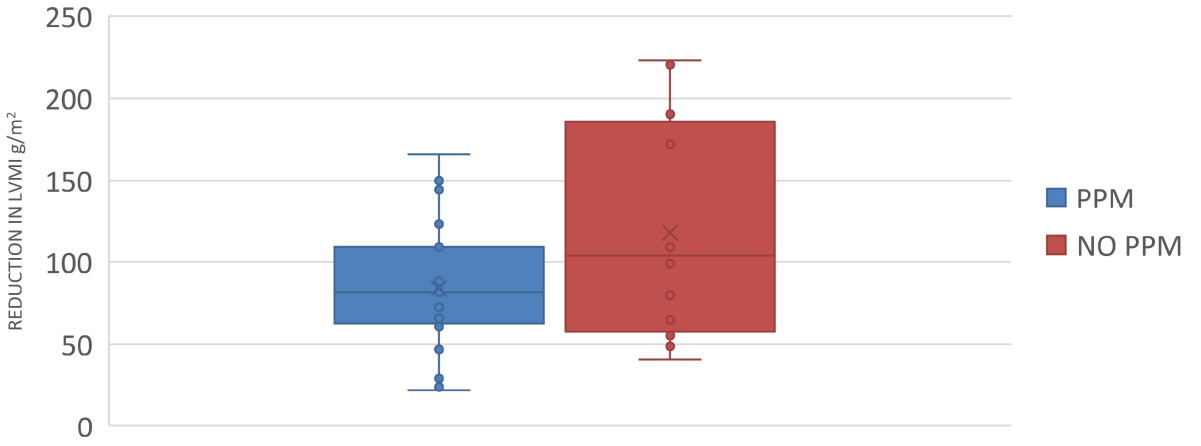


Table 19	PPM	SD	NO PPM	SD	P
LV MASS REGRESSION in g/m²	89.16	45.78	117.78	66.90	>0.01

INDEXED LV MASS REGRESSION BY IEOA

A statistically significant difference was noted between LV mass regression in patients with IEOA less than 0.65, 0.65 to 0.75, 0.75 to 0.85 and those more than 0.85.

Graph 27 LV REGRESSION vs IEOA

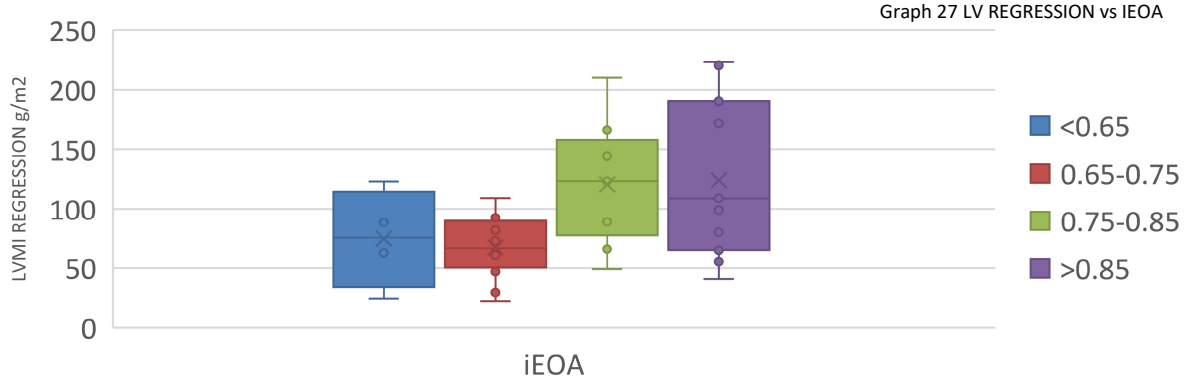


Table 20. IEOA	LVMI REGRESSION	SD	P
0.65 or less	74.51	41.73	0.02582
>0.65-0.75	67.01	25.63	
>0.75-0.85	120.72	52.05	
>0.85	124.04	66.37	

LV MASS RELATIVE REGRESSION COMPARISON

Relative reduction in LV mass was higher in patients with higher iEOA. But this difference was not significant statistically.

Graph 28 LV RELATIVE REGRESSION vs IEOA

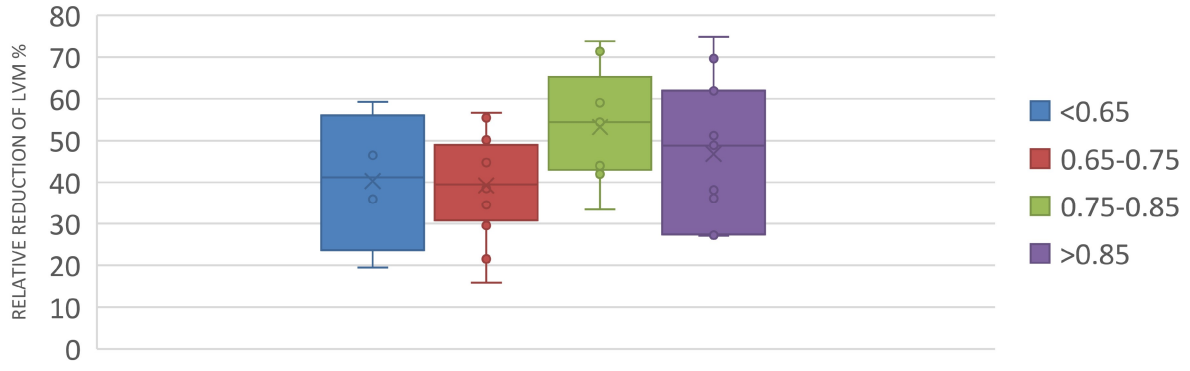


Table 21. IEOA	LVMI REGRESSION	SD	P
0.65 or less	40.29	16.84	0.182
>0.65-0.75	39.28	12.56	
>0.75-0.85	53.26	13.53	
>0.85	46.86	17.13	

LV MASS REGRESSION WITH IEOA BELOW 0.75

Regression of LVMI was compared in patients with iEOA more than and those with 0.75 and less. A statistically significant difference was noted between LVMI regression in both groups.

Graph 29. LV REGRESSION BELOW IEOA 0.75

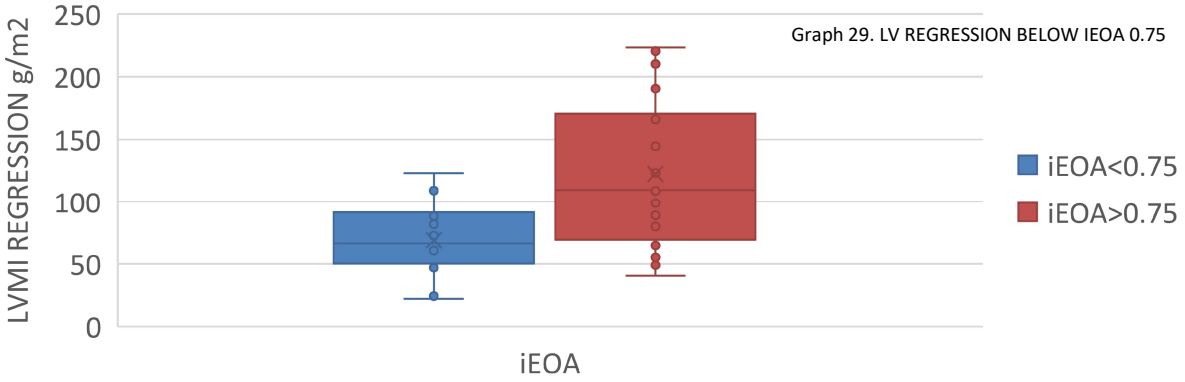


Table 22.	iEOA	LVMI REGRESSION	SD	P
	<0.75	68.8898	29.00235	0.028
	>0.75	122.5508	58.84326	

RELATIVE REGRESSION OF LV WITH IEOA BELOW 0.75

Relative Regression of LVMI was compared in patients with iEOA more than and those with 0.75 and less. A statistically significant difference was noted between in both groups.

Graph 30 LV RELATIVE REGRESSION BELOW IEOA 0.75

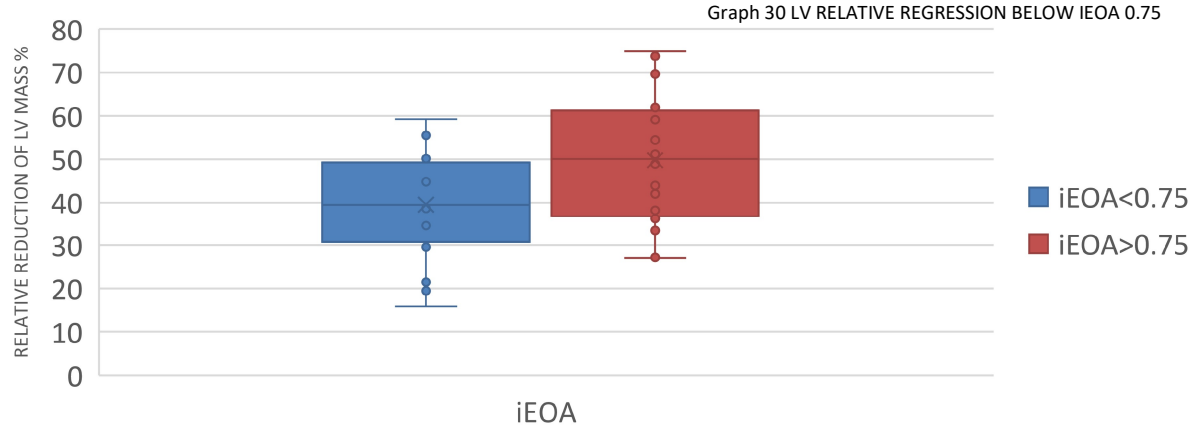


Table 23.	iEOA	LVMI REGRESSION	SD	P
	<0.75	39.53552	13.13372	0.022
	>0.75	49.73999	15.56461	

LV MASS REGRESSION BY VALVE TYPE

There was no statistically significant difference in LV Mass difference between different valve makes.

Graph 31. LV REGRESSION vs VALVE MODEL

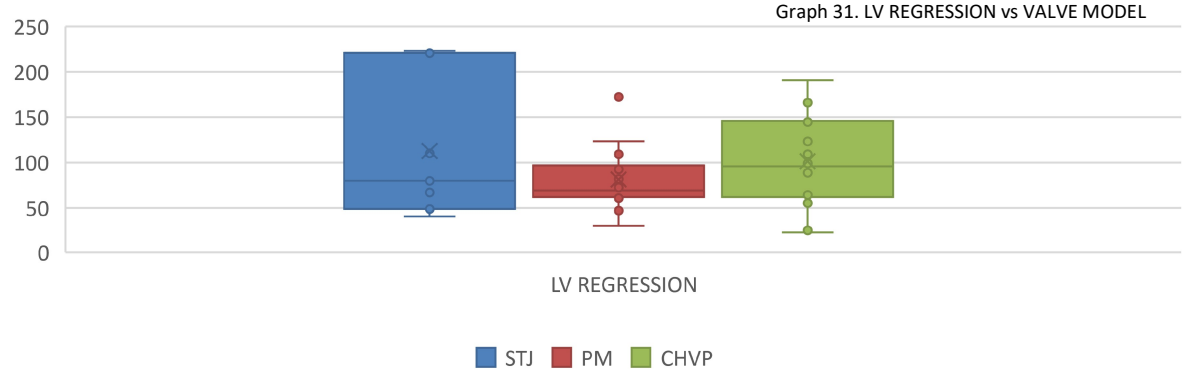


Table 24.	MEAN	SD	P
PERIMOUNT	112.85	89.8	0.594
CHVP	71.75	46.08	
ST JUDE	112.85	89.8	

All except two patients had good LV function prior to surgery.

DISCUSSION

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

DISCUSSION

Out of 37 patients included in study, one patient was lost to follow up. 62% of our patients were males and 38% were females. These were comparable with previous studies which showed an incidence in males varying from 41% to 77.8%.[6 77 81]

Median age at surgery was 57 with youngest patient being 16 year old and oldest 75 years old. Mean age of surgery in western literature varied between 58.1 to 71.1 years. Joshi et al in his study in Indian population reports that mean age at surgery was 43.2, much younger than that of western population.[77]

57% of patients had NYHA class II and 38% had class III symptoms at presentation. 5% were asymptomatic prior to surgery.

94% were asymptomatic on follow up. Of the 2 symptomatic patients, one had developed significant TR. One patient had developed prosthetic valve thrombosis due to noncompliance of anticoagulation. She was thrombolysed and symptoms regressed.

Degenerative valve disease was the pathology in 62% of patients, bicuspid aortic valve in 24% and rheumatic heart disease in 14%. Dare et al has also reported that predominant pathology in aortic stenosis was degenerative which accounts for 51%, 36% bicuspid aortic valve and 14% rheumatic. [82] Indian data published in 2006 shows rheumatic aetiology in 75.5% and degenerative in 24.5% patients. This disparity may be due to change in epidemiological pattern and reduction in incidence of rheumatic heart disease in India. [77]

Metallic valves were used in 56.76% patients while bioprosthetic valves were used in 43.24%. This higher incidence of use of metallic valve compared to international data may be due to lower age of patients and economic constraints. [76]

Age, higher BMI, use of bio prosthetic valve and female gender are classically considered to be associated with higher incidence of PPM. However, there was no gender predilection in our study. [56,67,68,69]. We could not find any difference between mean age and distribution of patients with or without PPM. Incidence of PPM was higher in Perimount bioprosthetic valves 81.81% against 71.42% in TTK Chitra and 14.48% in St Jude valves. This may be impacted by larger annulus size models of St Jude valves.

Both mean and peak aortic valve gradients fell significantly following aortic valve replacement. In all patients, trans valvar gradients subsided to normal. There was no significant difference between early and late post aortic valve gradients. Average peak gradient reduced from 102.11+/- 30.93 mm Hg to 27.5+/-9.83 mm Hg following AVR. Average mean gradient fell

from 59.30+/-18.26 mm Hg to 15.53+/-6.18 mmHg. On late follow up, peak gradient was 29.76+/-11.48 and mean gradient was 15.46+/-7.52.

LV internal Diameter, Posterior wall and septal thickness reduced significantly in our patients. LV Mass Index and Relative Regression of LVMI in our patients were higher than western data. Only literature from India shows comparable results.[83] Preop LVMI in our patients were 206+/- 67.44 and post operative LVMI was 105.88+/- 38.99. In a 3 month follow up study reported by Singh et al, mean preoperative LVMI was 199g±79.5 g/m2 . At three months post aortic valve replacement, the mean LVMI reduced to 130g±49.0 g/m2.

Regression of LVMI showed a positive correlation of with iEOA. Correlation coefficient is +0.48 (95% CI 0.18-0.698). Mean LVMI regression was significantly higher in patients with conventional definition of PPM. Data was further analyzed as 4 groups with iEOA <0.65, 0.65-0.75, 0.75-0.85 and >0.85. There was significant difference between LVMI regression in all 4 groups. Further evaluation showed that LVMI was significantly higher in patients with iEOA more than 0.75. Relative reduction of LV Mass was also higher in this group.

No significant relation was noticed between LVMI regression and early or late post operative gradients. This may be because normal gradients were achieved in all patients after surgery.

There is a positive correlation between reduction in mean gradient achieved by AVR. Correlation coefficient was +0.35. (95% CI 0.03-0.605)

CONCLUSION

Patient Prosthesis Mismatch And Its Impact On Left Ventricular mass Regression In Patients Undergoing Aortic Valve Replacement For Aortic Stenosis

CONCLUSION

Incidence of PPM in our patients were comparable with historical data. Age, gender or BSA did not influence occurrence of PPM.

Mean pre operative LV mass was higher in our patients compared to literature data. Pre operative LV mass was significantly higher in No PPM group though there was no significant difference on follow up.

AVR caused significant LV regression irrespective of PPM. But there is a positive correlation between LV regression and iEOA. LV mass regression was significantly higher in patients with iEOA more than 0.75. This can be considered as criteria for significant PPM in study population.

LV regression showed a positive correlation with reduction of mean aortic gradient achieved by AVR. There was no correlation between post-operative mean trans valvar gradients and LV regression.

Clinical implication of LV regression considering iEOA 0.75 as limit of PPM requires to be validated through further studies.

LIMITATIONS

Major Limitations include inter operator variability in Echo assessment of LV dimensions, differences in availability of valve models and small sample size.

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ANNEXURE i

Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

TAC Registration No: SCT-/S/2016/446 Date: 22.03.2016

Project title: PROSTHESIS PATIENT MISMATCH AND ITS IMPACT ON LEFT VENTRICULAR MASS REGRESSION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT FOR AORTIC STENOSIS

Principal Investigator:
Name: Dr. Abid Iqbal VT Degree: M.S. (General Surgery), M.B.B.S. Address: Senior Resident, Department of CVTS, SCTIMST, Trivandrum.
Co-Principal Investigator(s)
(1) Name: Dr. Varghese T Panicker Degree: MCh , CVTS, M.S. (General Surgery), M.B.B.S. Address: Associate Professor, Department of CVTS, SCTIMST, Trivandrum.
(2) Name: Dr Jayakumar K Degree: MCh , CVTS, M.S. (General Surgery), M.B.B.S. Address: Senior Professor and Head, Department of CVTS, SCTIMST, Trivandrum.

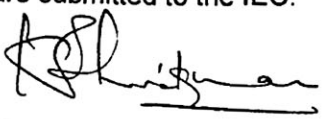
Members who participated in the TAC meeting on 05/03/2016
Dr. Rupa Sreedhar (Chairperson)
Dr. Thomas Koshy
Dr. Lissy K Krishnan
Dr. Sylaja P.N
Dr. Krishnamoorthy KM
Dr. Biju Soman
Dr. Bejoy Thomas
Dr. Syam. K
Dr. K. Shivakumar (Member Secretary)

Dr. Krishnamoorthy, Dr. Sylaja.P.N, Dr. Syam K and Dr. Bejoy Thomas stayed away from the proceedings when the projects in which they are involved (# 431, 435, 436, 442, 467, 447, 450, 452, 455) as investigators were discussed.

Risk Classification of the project (Minimum/ Moderate/ High): Minimum
Requirement of DSMB: No
Recommended members of DSMB: Not applicable

Recommendations of TAC:
Recommended for consideration of IEC in the light of the responses received from the investigator

The PI may note that there can be no additions / alterations in the documents approved by TAC when they are submitted to the IEC.



Signature of the Member Secretary, TAC (Clinical Studies)

Note for IEC
Copy of the investigator's responses to questions/suggestions from TAC is attached (Appendix-1).

ANNEXURE ii

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/895/APRIL-2016 20.06.2016

Dr. Abid Iqbal V T
Senior Resident
Department of CVTS
SCTIMST, Thiruvananthapuram

Dear Dr. Abid Iqbal,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "PROSTHESIS PATIENT MISMATCH AND ITS IMPACT ON LEFT VENTRICULAR MASS REGRESSION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT FOR AORTIC STENOSIS" (IEC/895) on 16th April, 2016.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST, with check list*
2. *TAC Application Form*
3. *TAC Approval Letter*
4. *IEC Application Form*
5. *Project Proposal*
6. *Declaration Form*
7. *CV of Principal Investigator and Co- Investigators*

Revised submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 15.06.2016 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *CV of Principal investigator and Co- Investigators*

The following members of the Ethics Committee were present at the meeting held on 16th April, 2016 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Justice Gopinathan. P.S	BSc. LLB	Male	Legal Expert (Chairperson)	No
2.	Dr. Asha Kishore	MD, DM	Female	Clinician (Neurologist)	Yes
3.	Shri. O.S. Neelakantan Nair	BE	Male	Engineer	Yes
4.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro-Enterologist)	No
5	Dr. Rema M. N	MD	Female	Pharmacologist	No
6.	Dr. V. Raman Kutty	MPH(Harvard) MPhil, MD	Male	Public Health	Yes
7.	Dr. K R S Krishnan	ME, PhD	Male	Biomedical Scientist/Engineer	No
8.	Dr. Kala Kesavan. P	MD	Female	Pharmacologist	No
9.	Smt. Sathi Nair	MA	Female	Lay Person	No
10.	Dr. Christina George	MD	Female	Psychiatrist	No
11.	Dr. Mala Ramanathan	MSc, PhD, MA	Female	Ethicist/Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

ANNEXURE iii PROFORMA

PPM and its impact on LV mass in patients undergoing AVR for AS			
Patient ID	Age	Sex	M/F
Diagnosis	Height	Weight	
Valve Size	Valve Type	EOA	
	BSA	iEOA	
Date of Surgery	Date of Follow up		
Follow up			
	Pre Op	Follow up	Post Op
Clinical Status			
ECHO EF			
Mean AV Gradient			
Peak AV Gradient			
LVIDD			
IVSD			
PWT			
LV Mass			
RWT			
LVMI			
Aortic Valve area			

ANNEXURE v

ORIGINALITY ASSESSMENT

http://busywithseo.com/plagiarism-checker

Full Thesis

Observation, Discussion and Conclusion

ANNEXURE iv

PATIENT ID	SEX	AGE years	FOLLOW UP months	PATHOLOGY	SIZE	VALVE	EOA	NYHA CLASS	BSA m2	Indexed EOA	PEAK GRADIENT mm Hg	MEAN GRADIENT mm Hg	EF%	LVIDD mm	LV DS mm	PWT mm	IVSD mm	LV MASS g	LVMI g/m2	RWT	LVH	SVI	RV 5/6	SLV
1	M	60	19	DEGEN	21	C	1	3	1.82	0.55	92	48	74	49	31	11	13	226	124	0.53	MILD CO	6	13	19
2	F	62	11	DEGEN	19	M	1	2	1.742	0.57	75	34	65	48	24	16	14	303	174	0.58	SEV CONC	12	37	49
3	M	53	24	DEGEN	21	C	1	2	1.69	0.59	114	67	68	48	23	16	17	351	208	0.71	SEV CONC	11	26	37
4	M	64	17	DEGEN	21	P	1.2	2	1.87	0.64	84	54	70	50	30	17	15	355	190	0.60	SEV CONC	9	38	47
5	M	69	22	DEGEN	21	P	1.2	3	1.81	0.66	85	44	80	46	24	16	14	285	157	0.61	SEV CONC	12	23	57
6	F	64	23	BAV	19	P	1	3	1.489	0.67	100	60	65	32	20	21	19	284	191	1.31	SEV CONC	12	20	32
7	F	58	22	DEGEN	19	P	1	3	1.47	0.68	140	72	70	46	26	17	12	271	184	0.52	SEV CONC	6	16	22
8	M	60	16	DEGEN	21	P	1.2	3	1.75	0.69	80	44	65	54	34	14	11	280	160	0.41	SEV EC	17	37	54
9	F	68	17	BAV	19	P	0.99	2	1.438	0.69	82	49	75	49	28	13	15	283	197	0.61	SEV CONC	21	45	66
10	M	62	18	DEGEN	21	P	1.2	2	1.706	0.70	91	40	69	46	25	16	13	271	159	0.57	SEV CONC	29	68	97
11	F	46	18	RHD	19	C	1.12	2	1.59	0.70	83	50	60	43	24	12	10	163	103	0.56	MILD CO	13	10	23
12	F	42	15	RHD	19	C	1.07	3	1.48	0.72	82	53	66	47	29	13	11	212	143	0.47	SEV CONC	7	21	28
13	M	67	18	DEGEN	21	P	1.2	2	1.64	0.73	75	43	76	44	32	15	15	267	163	0.68	SEV CONC	12	35	47
14	M	56	11	DEGEN	21	R	1.41	1	1.9	0.74	136	86	80	39	29	19	18	316	166	0.92	SEV CONC	18	30	48
15	M	13	14	BAV	17	C	0.88	2	1.18	0.75	105	51	63	44	32	16	15	281	238	0.68	SEV CONC	10	19	29
16	F	53	19	DEGEN	19	C	1.16	2	1.52	0.76	160	90	67	56	37	20	18	309	203	0.97	SEV CONC	16	30	46
17	F	30	15	BAV	17	C	1.1	2	1.43	0.77	150	80	78	41	21	15	18	280	196	0.88	SEV CONC	15	20	35
18	M	64	21	DEGEN	21	P	1.2	3	1.54	0.78	80	49	62	42	30	19	18	349	227	0.86	SEV CONC	15	27	42
19	F	60	11	DEGEN	23	P	1.5	2	1.914	0.78	85	52	60	43	26	18	15	300	157	0.70	SEV CONC	16	11	27
20	M	53	22	DEGEN	21	C	1.4	2	1.73	0.81	120	70	55	57	46	13.6	14	350	202	0.48	SEV CONC	14	35	49
21	M	57	21	DEGEN	21	C	1.4	3	1.71	0.82	107	55	55	56	42	18	15	441	258	0.64	SEV CONC	13	37	50
22	M	44	19	DEGEN	21	C	1.45	1	1.74	0.83	71	44	83	49	28	25	15	489	281	0.61	SEV CONC	16	31	47
23	F	44	11	RHD	21	S	1.48	2	1.74	0.85	74	42	76	51	28	12	13	255	147	0.51	SEV CONC	11	35	46
24	M	59	13	DEGEN	21	C	1.4	2	1.61	0.87	94	62	68	48	29	12	14	246	153	0.50	SEV CONC	9	13	22
25	M	75	18	DEGEN	23	P	1.5	3	1.72	0.87	87	50	70	59	45	14	19	478	278	0.64	SEV CONC	9	23	32
26	M	63	11	DEGEN	23	P	1.5	2	1.7	0.88	100	58	71	48	28	13	16	288	169	0.67	SEV CONC	15	25	40
27	M	45	18	BAV	23	C	1.8	2	1.9	0.95	82	50	65	50	42	16	16	355	187	0.64	SEV CONC	12	19	31
28	F	52	17	DEGEN	19	R	1.5	2	1.55	0.97	87	52	60	48	29	13	12	232	150	0.50	SEV CONC	11	30	41
29	M	45	17	DEGEN	25	C	2	2	1.79	1.12	140	80	65	56	31	25	20	712	398	0.89	SEV CONC	20	31	51
30	F	44	9	RHD	21	S	1.94	3	1.64	1.18	107	59	68	49	33	20	20	489	298	0.82	SEV CONC	16	20	36
31	F	36	21	RHD	21	R	2	3	1.65	1.21	195	95	66	46	29	16	21	395	395	0.70	SEV CONC	20	49	69
32	M	49	17	BAV	25	C	2.01	3	1.52	1.32	156	110	75	31	20	20	20	418	274	1.29	SEV CONC	27	35	62
33	M	48	9	BAV	23	R	2.5	3	1.88	1.33	62	49	47	50	39	15	14	307	163	0.60	SEV CONC	14	23	37
34	F	62	21	DEGEN	19	P	1	2	1.48	0.68	150	100	55	42	22	23	22	242	164	0.60	SEV CONC	10	30	40
35	M	61	23	BAV	23	P	1.5	3	1.98	0.76	90	57	44	54	42	25	16	583	294	0.59	SEV CONC	20	27	47
36	M	41	6	BAV	21	R	2	2	1.736	1.15	71	40	60	55	37	12	18	373	215	0.65	SEV CONC	31	41	72
37	M	61		DEGEN	21	P	1.2	2	1.43	0.84	86	55	65	53	34	18	14	388	271	0.68	SEV CONC	17	53	70

ANNEXURE v

LVIDD LV INTERNAL DIAMETER IN DIASTOLE LVIDS- LV INTERNAL DIAMETER IN SYSTOLE

EOA - EFFECTIVE ORIFICE AREA EF-EJECTION FRACTION SLV- SOKLOV LYON VOLTAGE IVSD- SEPTAL DIASTOLIC THICKNESS PWT- POSTERIOR WALL THICKNESS

PATIENT ID	POST OP PEAK GR mm	POST OP MEAN GRADIENT	NYHA ON FOLLOW	PEAK GR ON FOLLOW	MEAN GRADIANT mm Hg	FOLLO W UP LVIDD	FOLLOW UP LVIDS mmHg	PWT mmHg	IVSDm m Hg	LV MASS g	INDEXED LV MASS g/m2	RWT	LVH	SVI	RV 5/6	SLV	LVMI REGRESSION %	LV MASS REGRESSION g	POST OP GR DIFFERENCE
1	33	20	1	44	25	50	32	10	10	182	100	0.4	N	5	13	18	19.47	126.00	28
2	26	14	2	29	14	48	39	11	11	194	111.366246	0.56	N	13	11	24	35.97	191.63	20
3	31	11	1	24	13	47	26	9	9	143	84.6153846	0.71	N			0	59.26	266.38	56
4	28	12	1	20	18	39	24	13	15	190	101.604278	0.67	N	8	24	32	46.48	253.40	42
5	32	20	1	31	15	53	25	10	8	175	96.6850829	0.3	N	12	15	27	38.60	188.31	24
6	32	11	1	38	19	34	18	15	16	186	124.916051	0.88	CON	8	19	27	34.51	159.08	49
7	19	7	1	26	17	38	19	18	13	228	155.102041	0.68	CON	6	13	19	15.87	115.90	65
8	22	8	1	26	17	42	22	10	11	153	87.4285714	0.51	N	12	11	23	45.36	192.57	36
9	20	9	1	21	17	38	23	10	11	126	87.6216968	0.58	N	14	18	32	55.48	195.38	40
10	22	9	1	21	10	44	19	14	10	191	111.957796	0.45	N	12	25	37	29.52	159.04	31
11	18	7	1	37	15	42	19	10	9	128	80.5031447	0.48	N	4	7	11	21.47	82.50	43
12	20	13	1	29	18	38	24	11	9	117	79.0540541	0.47	N	6	11	17	44.81	132.95	40
13	45	24	1	23	12	36	17	11	11	133	81.097561	0.67	N	9	10	19	50.19	185.90	19
14	44	19	1	41	28	42	24	13	12	189	99.4736842	0.57	N	13	27	40	40.19	216.53	67
15	51	30	1	45	26	41	25	12	12	172	145.762712	0.59	CON	9	15	24	38.79	135.24	21
16	30	25	1	39	24	38	19	11	17	81	53.2894737	1.16	N	12	12	24	73.79	255.71	65
17	58	32	1	50	34	38	27	11	13	153	106.993007	0.58	CON	9	12	21	45.36	173.01	48
18	30	15	1	30	15	39	25	13	11	159	103.246753	0.56	N	12	20	32	54.44	245.75	34
19	16	10	1	9	5	44	33	12	11	174	90.9090909	0.51	N	7	16	23	42.00	209.09	42
20	44	25	1	25	18	58	42	9	12	196	113.294798	0.41	N	13	29	42	44.00	236.71	45
21	35	20	1	25	13	48	31	11	11	194	113.450292	0.46	N	19	10	29	56.01	327.55	35
22	37	20	1	20	12	47	21	13	10	200	114.942529	0.43	N	10	14	24	59.10	374.06	24
23	19	11	1	26	18	46	28	10	11	170	97.7011494	0.48	N	18	9	27	33.33	157.30	31
24	25	11	1	29	11	42	28	11	11	157	97.515528	0.52	N	8	9	17	36.18	148.48	51
25	30	10	2	40	17	48	36	11	10	182	105.813953	0.42	CON	9	23	32	61.92	372.19	40
26	26	16	1	21	11	42	25	12	12	178	104.705882	0.49	N	13	23	36	38.19	183.29	42
27	23	11	1	17	9	42	29	12	11	167	87.8947368	0.52	N	9	12	21	52.96	267.11	39
28	26	11	1	37	15	52	31	8	10	169	109.032258	0.38	N	10	20	30	27.16	122.97	41
29	42	22	1	23	13	51	27	23	17	517	288.826816	0.9	CON	28	23	51	27.39	423.17	58
30	31	11	1	19	12	41	26	10	9	123	75	0.44	N	9	12	21	74.85	414.00	48
31	20	15	1	35	20	38	19	16	19	288	174.545455	0.7	CON	20	24	44	27.09	220.45	80
32	18	9	1	20	12	40	24	11	9	127	83.5526316	0.45	N	19	25	44	69.62	334.45	101
33	61	38	1	28	12	42	34	11	11	157	83.5106383	0.52	N	14	20	34	48.86	223.49	11
34	26	15	1	8	4	39	23	9	9	105	70.9459459	0.56	N	7	20	27	56.61	171.05	85
35	12	7	1	18	10	42	24	12	11	167	84.3434343	0.52	N	10	6	16	71.36	498.66	50
36	28	14	1	16	10	48	32	11	10	182	104.83871	0.46	N	12	18	30	51.21	268.16	26
37	21	10																LOST FU	45

VALVE C-TTK CHITRA, P-PERIMOUNT, R-STJUDE REGENT, S-ST JUDE