SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

PROJECT REPORT

Submitted during the course of DM Cardiology

Dr. Amit Kumar Chaurasia

DM Trainee

DEPARTMENT OF CARDIOLOGY

Jan 2009 – Dec 2011

DECLARATION

I, **Dr. Amit Kumar Chaurasia**, hereby declare that the projects in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram
Date :

Dr. Amit Kumar Chaurasia
DM Trainee

Forwarded

The candidate, **Dr. Amit Kumar Chaurasia,** has carried out the minimum required projects.

Thiruvananthapuram
Date :

PROF. Dr. JAGAN MOHAN THARAKAN
Head of the Department of Cardiology

GENERAL CONTENTS

PROJECT I : FOLLOW UP OF PATIENTS POST BALLOON MITRAL VALVOTOMY AND ASSESSMENT OF FACTORS LEADING TO RESTENOSIS

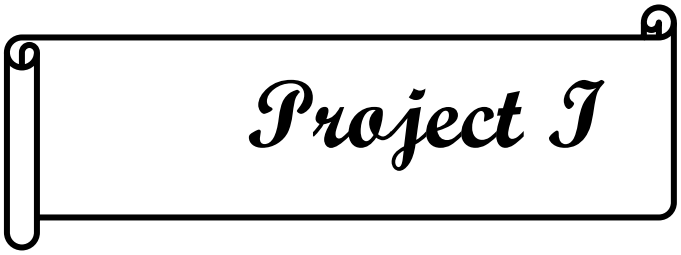
PROJECT II : EVALUATION AND MANAGEMENT OF PATIENTS WITH SYNCOPE: A SINGLE CENTRE STUDY

PROJECT-I

CONTENTS

PROJECT-II

CONTENTS



FOLLOW UP OF PATIENTS POST BALLOON MITRAL VALVOTOMY AND ASSESSMENT OF FACTORS LEADING TO RESTENOSIS

FOLLOW UP OF PATIENTS POST BALLOON MITRAL VALVOTOMY AND ASSESSMENT OF FACTORS LEADING TO RESTENOSIS

INTRODUCTION:

Mitral stenosis still continues to be a major problem in developing countries. Both surgical and percutaneous treatment provides excellent improvement to the patient. In the initial days surgery was thought to be curative and some argued that restenosis does not occur.[1-3] However soon a number of reports showed restenosis of the mitral valve does occur over a period of time. Restenosis today is well recognized following both surgical as well as percutaneous modality of treatment.

Post-PTMC mitral restenosis is defined as a valve area <1.5 cm^2 or a >50% loss of the initial gain in valve area.[4-7] Chen et al added reappearance of symptoms to this definition.[8] The development of restenosis is time-dependent[9-11] which is represented in the wide range of reported restenosis incidence (from 4 to 39%) according to the different follow-up durations.[5,12,13,9,14,15,16,17]

A number of studies have identified several factors that contribute to restenosis following treatment of patient by surgical valvotomy and balloon mitral valvotomy. Younger patients have a lesser chance of restenosis than older. [5,13,18,20,37] Atrial fibrillation also contribute to this.[5,35] Mitral valve area post procedure is probably the most important contributing factor[5,35,41]. Wilkins score is another strong factor that contributes to restenosis.[5,14,40-42]

There are few studies from India that have looked into predictors of restenosis after CMV [16]. The aim of this study is to evaluate the incidence and predictors of mitral restenosis in patients who have been treated with PTMC.

REVIEW OF LITERATURE:

The first successful attempt to relieve stenotic mitral valve through an incision in the left atrial appendage was done by Souttar in 1925.[26] However it took more than 20 years to be widely accepted. Dramatic improvement was evident immediately, but soon its limitation was also apparent. It was seen that the benefit was confined to pure mitral stenosis or those with minimal regurgitation. On follow up of these patients, it was seen that some patient would detoriate over a period of time. On surgical and pathological examination it was found that refusion had occurred.

In the early days it was thought that restenosis was due to incomplete split of the commissures during surgery. Therefore it was thought that mitral leaflets with good mobility offered the best target for conservative surgical approach. So pure commissural type of mitral stenosis would have better result and the effect at times would be permanent.[28] On the other side with cusps and chordae involvement in the stenotic process the relief would be temporary, with restenosis becoming only a matter of time. Also severe fibrocalcific disease of the valve cusps would make the relief of the obstruction impossible, as in these condition physiologic stenosis produced by inability of mitral leaflets to move under available filling pressure would come into play.

From the pathogenesis of mitral stenosis, restenosis would be inevitable.[28] But then what is the contribution of recurrent rheumatic activity in the pathogenesis of restenosis? Though rheumatic activity may be a contributing factor, it may not be the whole and sole cause as evidenced by scarcity of Aschoff bodies in excised atrial tissue from the patients undergoing reoperation.[28,29,30] So what would be the most probable explanation for this? The trauma theory would provide the best explanation. Deformed valve creates turbulent flow and this would encourage deposition of fibrin and thickening of the valve leaflets. The valve cusp that is thickened and deformed at the initial valvotomy would also allow microthrombi of platelets and fibrin deposition. All these factors cotribute to fibrosis over a period of time causing the valve to narrow over a period of time. Dystrophic calcification is a feature of aging, disorganized collagen and is seen in patients aged 45 or over. Attempts to correlate dystrophic calcification with age, cardiac rhythm, or previous operation have not been convincing, but there seems to be

an association with a raised mean diastolic pressure gradient, and its presence at initial valvotomy certainly predisposes to a need for a second operation.[31,32,33]

Extensive calcification at the first valvotomy suggests that the valve would be shrunken and deformed, and restenosis would be inevitable over a period of time. Operative result may also contribute to restenosis. If adequate split has not been obtained during the first valvotomy then likelihood of early restenosis is very high. With the development in echocardiography better visibility of size and mobility of the valve cusps, presence of calcification, and multiple valve dysfunctions can be delineated. This has enabled better management of the patient.

Post-PMV mitral restenosis is defined as a valve area <1.5 cm^2 or a >50% loss of the initial gain in valve area.[4-7] Chen et al added reappearance of symptoms to this definition.[8] The development of restenosis is time-dependent[9-11] which is represented in the wide range of reported restenosis incidence (from 4 to 39%) according to the different follow-up durations.[5,12,13,9,14,15,16,17]

A number of studies have identified a number of factors that contribute to restenosis following treatment of patient by surgical valvotomy and balloon mitral valvotomy. Younger patients have a lesser chance of restenosis than older.[18,19] Atrial fibrillation also contribute to this.[5,33] Mitral valve area post procedure is probably the most important contributing factor [18,19,25]. Wilkins score is another strong factor that contributes to restenosis.[21,22,23,24]

To conclude mitral restenosis in inevitable in long run and many factors contribute to this which may be the reason why in some it occurs early and some late. Knowing these factors may help in the management of the patients.

SOME STUDIES OF POST PTMC AND RESTENOSIS:

1. Palacios IF et al,[5] in 1989 reported clinical follow-up (13±1 months) of 100 consecutive patients who underwent percutaneous mitral balloon valvotomy (PMV). Echocardiographic (n=32) and cardiac catheterization (n=37) data from this group are also included. Patients were divided into two groups by an echocardiographic score. PMV resulted in a good hemodynamic result (post-PMV mitral valve area, .1.5 cm2) in 88% of patients with a score of 8 or less and 44% of patients with a score of more than 8. Eighty-eight percent of patients with a score of 8 or less (n =57) were New York Heart Association (NYHA) functional Classes III and IV before PMV; at follow-up, 81% were NYHA Class I and 12% were NYHA Class II. There were no deaths; three patients underwent mitral valve replacement (MVR). Ninety-eight percent of patients with a score of more than 8 (n =43) were NYHA Classes III and IV before PMV; at follow-up, 58% were NYHA Classes I and II. Seven patients who did not improve and were not surgical candidates died 3.8±1.2 months after PMV. Nine patients who were surgical candidates underwent elective MVR at 4+0.9 months after PMV. Repeat cardiac catheterization demonstrated restenosis in only one of 27 patients (4%) with a score of 8 or less. Mitral valve area after PMV was 1.9±0.1 cm2 and at follow-up was 2±0.1 cm2 (NS). In contrast, in patients with a score of more than 8 (n=10), mitral valve area decreased from 1.8±0.1 cm2 (after PMV) to 1.1±0.1 cm2 at follow-up ($p < 0.01$). Restenosis was demonstrated in seven of 10 patients (70%) with a score of more than 8. Multivariate analysis showed echocardiographic score and the presence of atrial fibrillation as predictors of restenosis. At ventriculography, the severity of mitral regurgitation after PMV decreased by one grade in 53% of patients. Thus, PMV produces excellent immediate and follow-up results in patients with a score of 8 or less; suboptimal results immediately after PMV, and hemodynamic restenosis are more likely to occur in patients with a score of more than 8.
2. Carlos E Ruiz et al[34], in 1994 reported outcome after attempted percutaneous balloon dilatation of the mitral valve in patients with severe mitral stenosis between February 1986 and June 1992. Mitral valve area as determined by the Gorlin formula, planimetry,

and Doppler methods was compared before and after dilatation and at follow up. 176 patients had serial clinical and Doppler echocardiographic follow up and 44 of them also underwent recatheterisation. At follow up 93% of patients were in New York Heart Association functional class I or class II. Mitral valve area (planimetry) increased from 0.97(0.24) cm^2 before to 1.86(0.39) cm2 after dilatation ($p = 0.0001$) and then decreased to 1.72(0-39) cm2 at follow up ($p < 0.001$); mitral valve area (Doppler) increased from 1.01 (0.24) to 1.89 (0.42) cm2 ($p = 0.0001$) and then decreased to 1.78(0.40) cm2 ($p <$ 005). The overall restenosis rate was 15% and over 90% of the patients were free from cardiovascular events. Age, valvar calcification, echocardiographic score, and mitral valve area after dilatation were found to be determinant predictors of restenosis. In patients who underwent recatheterisation, mitral valve area by the Gorlin method at follow up was comparable with that by planimetry and Doppler methods whereas a significant discrepancy between the three methods was noted immediately after dilatation. They concluded balloon dilatation of the mitral valve provided sustained anatomical and functional improvement in over 80% of patients at late follow up. Older age, heavy calcification, high echocardiographic score, and suboptimal immediate results are significant predictors of restenosis. Doppler echocardiographic examinaton is the procedure of choice for follow up evaluation.

3. Iung B. et al,[35] in 1999 reported late results of PTMC in 1024 patients whose mean age was 49±14 years. Echocardiography showed that 141 patients (14%) had pliable valves and mild subvalvular disease, 569 (55%) had extensive subvalvular disease, and 314 (31%) had calcified valves. A single balloon was used in 26 patients, a double balloon in 390, and the Inoue Balloon in 608. Good immediate results were defined as valve area ≥1.5 cm2 without regurgitation >2/4 (Sellers' grade) and were obtained in 912 patients. Median duration of follow-up was 49 months. The 10-year actuarial rate of good functional results (survival with no cardiovascular death and no need for surgery or repeat dilatation and in New York Heart Association [NYHA] class I or II) was 56±4% in the entire population. Follow-up echocardiography was available in 90% of the patients who experienced poor functional results after good immediate results and showed restenosis in 97% of these. In multivariate analysis, the predictors of poor functional results were old age (*P*=0.0008), unfavorable valve anatomy (*P*=0.003), high NYHA

class (*P*=0.0001), atrial fibrillation (*P*=0.0001), low valve area after PTMC (*P*=0.001), high gradient after PMC (*P*=0.0001), and grade 2 mitral regurgitation after PMC (*P*=0.04). They concluded PTMC can be performed with good late results in a variety of patient subsets. Prediction of late events is multifactorial. Knowledge of these predictors can improve patient selection and follow-up.

4. Langerveld J. et al[36], in 1999 reported results and follow up of PTMC attempted in 137 patients with severe mitral valve stenosis. In 127 patients follow-up was complete with a mean of 4·2±2·6 years. Events during follow-up were defined as death, mitral valve surgery or repeat percutaneous mitral balloon valvotomy. Restenosis was defined as a decrease in mitral valve area from ≥1·5 cm2 following percutaneous mitral balloon valvotomy to <1·5 cm2. There was 80±4% event-free survival 4 years after percutaneous mitral balloon valvotomy. Multivariate analysis showed chronic atrial fibrillation at baseline (*P*=0·039, relative risk (RR)=2·5) and a high residual maximal gradient after percutaneous mitral balloon valvotomy (*P*=0·004, RR=2·0 per 5 mmHg) to be independent predictors of an event during follow-up. The restenosis rate was 28·3% after 4 years. Chronic atrial fibrillation at baseline (*P*=0·0338, RR=2·2), a small mitral valve area after percutaneous mitral balloon valvotomy (*P*=0·0003, RR=0·8/0·1 cm2) and a high residual maximal transmitral gradient (*P*=0·0252, RR=1·6/5 mmHg) were all independent predictors of restenosis. They concluded patients with chronic atrial fibrillation and a high maximal transmitral gradient after percutaneous mitral balloon valvotomy have a higher risk for events during follow-up. Restenosis is related to the presence of chronic atrial fibrillation at baseline and a suboptimal percutaneous mitral balloon valvotomy result.
5. Mohamed Ben-Farhat et al[14], in 2001 reported result of PTMC done between December 1987 and December 1998. 654 patients were studied whose mean age was 33±13 years. Baseline and postprocedural variables were evaluated to identify predictors of event-free survival (survival without repeat PTMC or mitral valve replacement) and of freedom from restenosis defined as a mitral valve area (MVA) ≥1.5 cm2 after BMC and <1.5 cm2 at follow-up. The actuarial survival rates were 98%, 98%, and 97% at 5, 7, and 10 years, respectively. The 5, 7, and 10 year event-free survival rates were 85%, 81%, and 72%. Multivariate predictors of a higher 10-year event-free survival rate were lower

echocardiographic score (79% for a score ≤8, 61% for a score of 9 to 11, 62% for a score ≥12, $P < .001$) and sinus rhythm ($P = .04$) before BMC, lower mean left atrial pressure ($P < .001$), lower mitral valve gradient ($P < .001$), and less than or equal to grade 2 mitral regurgitation ($P = .036$) after BMC. Restenosis occurred in 16% of patients. The restenosis-free rates were 88%, 80%, and 66% at 5, 7, and 10 years, respectively. A higher freedom from restenosis at 10 years was associated with a lower score (77% for a score ≤8, 45% for a score of 9-11 and 50% for a score ≥12, $P = .03$) and a larger MVA before PTMC ($P = .03$), a larger MVA ($P < .001$), and a lower mitral valve gradient ($P = .04$) after PTMC. Conclusions PTMC produces excellent 10-year results in patients with pliable mitral stenosis and good results in patients with semi-pliable or calcified mitral stenosis. PTMC is the procedure of choice in patients with pliable valves and it is a reasonable treatment option in young patients with unfavorable mitral valve anatomy.

6. Jae-Kwan Song et al[4], in 2009 analysed echocardiographic (median 74 months) and clinical (median 109 months) follow-up data of 329 patients who achieved procedural success, defined as mitral valve area (MVA)≥1.5 cm^2 and mitral regurgitation (MR) ≤2/4, between 1995 and 2000. Clinical events included cardiovascular death, mitral valve surgery, and repeat PMV. The 1, 3, 5, 7, and 9 year rates of restenosis-free survival were 99+1%, 97+1%, 95+1%, 86+3%, and 72+4%, respectively. The 1, 3, 5, 7, and 9 year rates of event-free survival were 99.7+0.3%, 96.4+1.0%, 94.5+1.3%, 90.8+1.6%, and 90.0+1.7%, respectively. Immediate post-PTMC MVA and commissural MR or splitting, indicators of procedural adequacy, were independent predictors of both restenosis and clinical events. The best immediate post-PTMC MVA cut-off value for predicting both restenosis and clinical events within 5 years after successful PMV were 1.8 cm2 [95% confidence interval (CI) = 1.7–1.9] and 1.9 cm^2 (95% CI = 1.7–2.0), respectively. Patients with immediate post-PTMC MVA,1.8 cm^2 showed significantly lower event-free survival rate than those with post-PTMC MVA <1.8 cm^2 (P , 0.001). They concluded immediate post-PTMC MVA≥1.8 cm^2 was an important predictor of both restenosis- and clinical event-free survival and this value should be considered as a component of optimal result.
7. Arora R et al[19], in 2002 performed PTMC in a total of 4,850 patients using double balloon in 320 (6.6%), flow-guided Inoue balloon technique in 4,374 (90.2%), and

metallic valvulotomy in 156 (3.2%) patients. Their age range was 6.5-72 years (mean, 27.2 +/- 11.2 years) and 1,552 (32%) patients were under 20 years of age. Atrial fibrillation was present in 702 (14.5%) patients. No patient was rejected on the basis of echocardiographic score using the Wilkins criteria. Echocardiographic score of > or = 8 was present in 1,632 (33.6%) patients, of which 103 (2.1%) had densely calcified (Wilkins score 4+) valve. A detailed clinical and echocardiographic (two-dimensional, continuous-wave Doppler and color-flow imaging) assessment was done at every 3 months for the first year and at 6-month interval thereafter. The procedure was technically successful in 4,838 (99.8%) patients but optimal result was achieved in 4,408 (90.9%) patients with an increase in mitral valve area (MVA) from 0.7 +/- 0.2 to 1.9 +/- 0.3 cm^2 ($P < 0.001$) and a reduction in mean transmitral gradient from 29.5 +/- 7.0 to 5.9 +/- 2.1 mm Hg ($P < 0.001$). The mean left atrial pressure decreased from 32.1 +/- 9.8 to 13.1 +/- 6.2 mm Hg ($P < 0.001$). Although there was no statistically significant difference in the MVA achieved between de novo and restenosed valves (1.9 +/- 0.3 and 1.8 +/- 0.2 cm^2, respectively; $P > 0.05$), or between noncalcific and calcific valves (2.0 +/- 0.3 and 1.8 +/- 0.2 cm^2, respectively; $P > 0.05$), on the whole MVA obtained after percutaneous transvenous mitral commissurotomy was less in restenosed and calcific valves. Ten (0.20%) patients had cardiac tamponade during the procedure. Mitral regurgitation appeared or worsened in 2,038 (42%) patients, of which 68 (1.4%) developed severe mitral regurgitation. Urgent mitral valve replacement was carried out in 52 (1.1%) of these patients. Data of 3,500 patients followed over a period of 94 +/- 41 months (range, 12-166 months) revealed MVA of 1.7 +/- 0.3 cm(2). Elective mitral valve replacement was done in 34 (0.97%) patients. Mitral restenosis was seen in 168 (4.8%) patients, of which 133 (3.8%) were having recurrence of class III or more symptoms. Thus, they concluded that percutaneous transvenous mitral commissurotomy is an effective and safe procedure with gratifying results in high percentage of patients. The benefits are sustained in a majority of these patients on long-term follow-up. It should be considered as the treatment of choice in patients with rheumatic mitral stenosis of all age groups.

AIMS AND OBJECTIVES:

1. To study the incidence of mitral valve restenosis in patients who have undergone successful PTMC.
2. To study the predictors of restenosis in patients who have undergone successful PTMC.

MATERIALS AND METHODS:

This was retrospective single centre study conducted at SCTIMST, Trivandrum, Kerala. Consecutive patients who had undergone PTMC from 1995 to 2009 and who satisfied the inclusion and exclusion criteria were included in this study.

DEFINITION OF MITRAL RESTENOSIS:

Mitral restenosis was defined as reduction of mitral valve area to less than 1·5 cm^2 during follow up[19] or loss of more than 50% of the gained mitral valve area [20] or both or the appearance of symptoms.

INCLUSION CRITERIA:

Patient who have undergone successful PTMC during the specified period of study.

EXCLUSION CRITERIA:

a) Patients who required mitral valve replacement (MVR).
b) Patients who had unsuccessful PTMC

PATIENTS CHARACTERISTICS:

The details of patients such as age, sex, height, weight, body surface area (BSA), NYHA functional class were noted.

BLOOD INVESTIGATIONS:

All patients had undergone relevant blood investigation prior to the procedure. The details of haemoglobin level, total leucocyte count, differential leucocyte count, erythrocyte sedimentation rate (ESR).

ECG:

The presence or absence of atrial fibrillation pre procedure and post procedure was noted.

ECHOCARDIOGRAPHY:

Transthoraxic echocardiography was performed in all patients one day prior to PTMC, during the procedure, and one day after the procedure. Prior to the procedure all patients underwent transesophageal echocardiography to exclude presence of left atrial/left atrial appendage clot. Hence forth echocardiography was performed 3 months after the procedure and yearly thereafter. Details of echocardiography findings pre and post procedure and also at each visit were noted. The following measurements were noted:

Measurements

i. Mitral valve area
ii. Mitral valve gradient
iii. The degree of mitral Regurgitaiton (if any)
iv. The extent of the commissurotomy or separation of the commissures, primarily at the parasternal short axis and the apical 2-chamber view
v. The degree of pulmonary artery hypertension (PAH) as recorded by right ventricular systolic pressure (RVSP)
vi. Left ventricular ejection fraction (LVEF).
vii. Left atrial dimension in parasternal long axis view by echocardiography.
viii. The presence of calcification on the valve apparatus prior to the procedure.
ix. The presence of subvalvular pathology by echocardiography prior to the procedure.

The Wilkins Echocardiography score was calculated and recorded for each patient.

Wilkins echocardiography Score Used to Predict Outcome of Mitral Balloon Valvuloplasty

GRADE	MOBILITY	SUBVALVULAR THICKENING	THICKENING	CALCIFICATION
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets nearly normal in thickness (4-5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one third of the chordal length	Mid leaflets normal, considerable thickening of margins (5-8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5-8 mm)	Brightness extending into the midportion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8-10 mm)	Extensive brightness throughout much of the leaflet tissue

The total echocardiography score was derived from an analysis of mitral leaflet mobility, valvular and subvalvular thickening, and calcification, which were graded from 0 (normal) to 4 according to the above criteria. This gives a total score of 0 to 16.

CARDIAC CATHETERIZATION DATA:

Informed consent was obtained from the patient or his/her relatives. Patients underwent right and left heart catheterization pre and post PTMC. The mitral valve area was calculated using Gorlin and Gorlin formula. All cardiac catheterization details of the patient were recorded.

OBSERVATIONS AND RESULTS:

From the year 1995-2009, 729 patients who underwent PTMC satisfied the inclusion and exclusion criteria. The mean age of the patients was 30.53±10.57yrs. 22.1% of the patients were males. The mean height of the patients was 153.44±10.10cm. The average functional class of the patients was 2.37±0.48 and 13% of the patients had atrial fibrillation at presentation.

BASELINE CHARACTERISTICS:

TABLE 1:

VARIABLE	N=729
AGE (YRS)	30.53±10.57
MALES (%)	22.1
HEIGHT (cm)	153.44±10.10
BSA (m^2)	1.58±4.66
FUNCTIONAL CLASS	2.37±0.48
ATRIAL FIBRILLATION (%)	13

Table 1: To show the baseline patients characteristic. (BSA=body surface area)

BASELINE DATA - ECHOCARDIOGRAPHY:

The mean LA size was 43.44±6.35mm. All patients at presentation had severe mitral stenosis with average mitral valve area of 0.83±0.14cm^2. The peak mitral valve gradient was 26.72±9.54mm Hg and the mean mitral valve gradient was 16.08±6.89mm Hg. The mean right ventricle systolic pressure (RVSP) was 58.39±20.72mm Hg. The mean Wilkins echocardiography score of the patient was 7.63±1.36.

TABLE2:

VARIABLE	**N=729**
LA SIZE (mm)	**43.44±6.35**
MVA (cm^2)	**0.83±0.14**
PEAK MS GRADIENT (mm Hg)	**26.72±9.54**
MEAN MS GRADIENT (mm Hg)	**16.08±6.89**
RVSP (mm Hg)	**58.39±20.72**
ECHO SCORE	**7.63±1.36**

Table 2: Baseline echocardiography data of the patients. (LA= left atrium, MVA=mitral valve area, MS= mitral stenosis, RVSP= right ventricle systolic pressure, ECHO SCORE=Wilkins echocardiography score)

BASELINE DATA - CARDIAC CATHETERIZATION:

All patients had elevated left atrial pressure and the mean left atrial pressure was 23.55±8.19mm Hg. The mean pulmonary artery systolic pressure was 59.01±2.38mm Hg and the mean pulmonary artery diastolic pressure was 25.87±11.28mm Hg. The mean pulmonary artery pressure was 35.97±14.47mm Hg. The mean left ventricle diastolic pressure of the patients was 9.46±3.55mm Hg. The calculated mean transmitral gradient across the mitral valve was 15.47±5.89mm Hg and the calculated mean mitral valve area of the patient was 0.80±0.98cm^2.

TABLE 3:

VARIABLE	**N=729**
LA MEAN (mm Hg)	**23.55±8.19**
PASP (mm Hg)	**59.01±2.38**
PADP (mm Hg)	**25.87±11.28**
PA MEAN (mm Hg)	**35.97±14.47**
LVED (mm Hg)	**9.46±3.55**
TMG (mm Hg)	**15.47±5.89**
MVA (cm^2)	**0.80±0.98**

Table 3: To show the baseline catheterization data of the patient. (LA=left atrium, PASP=pulmonary artery systolic pressure, PADP=pulmonary artery diastolic pressure, PA= pulmonary artery, LVEDP= left ventricle diastolic pressure, TMG= transmitral gradient, MVA= mitral valve gradient)

CHARACTERISTICS OF THE BALLOON USED FOR PTMC:

PTMC was done using ACCURA balloon in 57.1% of the patients and in rest of the patients INOUE balloon was used. The average balloon size was 25.66±1.10mm. The balloon was dilated to mean of 24.64±1.09mm during PTMC.

TABLE 4:

VARIABLE	N=729
ACCURA BALLOON (%)	**57.1%**
BALLOON SIZE (mm)	**25.66±1.10**
MAXIMUM DILATATION (mm)	**24.64±1.09**

Table 4: Table to show the characteristics of balloon used during the study.

BLOOD INVESTIGATION:

The mean total leucocyte count of the patient was 9638.57±4309.51 per mm^3 and the mean neutrophil count was 66.09±21.52%. The mean erythrocyte sedimentation rate (ESR) was 19.61±14.91mm in first hour.

TABLE 5:

VARIABLE	N=729
TOTAL LEUCOCYTE COUNT (per mm^3)	**9638.57±4309.51**
NEUTROPHILS (%)	**66.09±21.52**
ESR (mm in 1^{ST} Hr)	**19.61±14.91**

Table 5: To show the details of blood investigation of the patient. (ESR= erythrocyte sedimentation rate)

POST PTMC ECHOCARDIOGRAPHY DATA:

Post PTMC mean left atrial size was 41.91±5.90mm. The mean mitral valve area increased to 1.61±0.26 cm^2. The mean peak mitral valve gradient decreased to 12.63±4.87mm Hg and the mean mitral valve gradient decreased to 6.09±3.47mm Hg. Also the mean right ventricle systolic pressure decreased to 45.79±13.95mm Hg.

TABLE 6:

VARIABLE	**N=729**
LA SIZE (mm)	**41.91±5.90**
MVA (cm^2)	**1.61±0.26**
PEAK MS GRADIENT (mm Hg)	**12.63±4.87**
MEAN MS GRADIENT (mm Hg)	**6.09±3.47**
RVSP (mm Hg)	**45.79±13.95**

TABLE 6: Table to show the echocardiography data of the patients post PTMC.

POST PTMC CARDIAC CATHETERIZATION DATA:

Post PTMC the mean LA mean pressure decreased to 14.08±5.38mm Hg. The mean peak pulmonary artery systolic pressure decreased to 40.51±16.10mm Hg the mean pulmonary artery diastolic pressure decreased to 17.84±8.36mm Hg. The mean pulmonary artery pressure was 26.06±11.08mm Hg. The mean left ventricle end diastolic pressure was 12.73±4.23mm Hg. The mean transmitral gradient decreased to 6.36±4.65mm Hg and the mean mitral valve area increased to 1.50±0.80 cm^2.

TABLE 7:

VARIABLE	**N=729**
LA MEAN (mm Hg)	**14.08±5.38**
PASP (mm Hg)	**40.51±16.10**
PADP (mm Hg)	**17.84±8.36**
PA MEAN (mm Hg)	**26.06±11.08**
LVED (mm Hg)	**12.73±4.23**
TMG (mm Hg)	**6.36±4.65**
MVA (cm^2)	**1.50±0.80**

Table 7: Showing the cardiac catheterization details of the patients post PTMC.

DURATION OF FOLLOW UP AND INCIDENCE OF RESTENOSIS:

The mean duration of follow up of patients was 6.89±3.49yrs (1-15yrs) and during this time 71 patients (9.7%) developed mitral valve restenosis.

BASELINE CHARACTERISTICS OF PATIENTS WITHOUT AND WITH RESTENOSIS PRE-PTMC:

Patients who developed restenosis were older than patients who did not develop restenosis (37.79±9.44 vs 30.57±10.67yrs; p<0.001). Patients with restenosis were taller than patients without restenosis (156.01±0.08 vs 153.16±10.26cm; p=0.024). Patients who developed restenosis had higher NYHA function class than patients who did not develop restenosis (2.52±0.50 vs 2.35±0.48; p=0.007). More patients with restenosis had atrial fibrillation prior to PTMC than those who did not develop restenosis (25.4% vs 11.7%; p<0.001). Patients who developed restenosis also had higher ESR than patients who did not develop restenosis (33.84±12.25 vs 18.08±14.36, p<0.001).

TABLE 8:

VARIABLE	**WITHOUT RESTENOSIS (N=658)**	**WITH RESTENOSIS (N=71)**	**P**
AGE (YRS)	**30.57±10.67**	**37.79±9.44**	**<0.001**
HEIGHT (cm)	**153.16±10.26**	**156.01±0.08**	**0.024**
BSA (m^2)	**1.59±4.90**	**1.41±0.15**	**0.754**
FUNCTIONCAL CLASS	**2.35±0.48**	**2.52±0.50**	**0.007**
ATRIAL FIBRILLATION (%)	**11.7**	**25.4**	**<0.001**
TLC (per mm^3)	**9667.53±4452.5**	**9354.05±2504.90**	**0.551**
NEUTROPHILS (%)	**67.04±22.19**	**56.82±11.81**	**0.693**
ESR (mm in 1^{ST} Hr)	**18.08±14.36**	**33.84±12.25**	**<0.001**

Table 8: Showing the baseline characteristics of patients without restenosis and with restenosis.

ECHOCARDIOGRAPHY DATA OF PATIENTS WITHOUT AND WITH RESTENOSIS PRE-PTMC:

Patients with mitral valve restenosis had higher peak (27.04±9.54 vs 23.78±9.07; p=0.006) and mean mitral valve gradients (16.28±6.87 vs 14.28±6.79; p= 0.02). The Wilkins echocardiography score was higher in patients with restenosis (9.22±1.17 vs 7.46±1.26; p=0.001). There was no significant difference in mean let atrial size, mean mitral valve area, right ventricle systolic pressure between the two groups.

TABLE 9:

VARIABLE	WITHOUT RESTENOSIS N=658	WITH RESTENOSIS N=71	P
LA SIZE (mm)	**42.01±7.03**	**43.59±6.26**	**0.47**
MVA (cm^2)	**0.85±0.14**	**0.83±0.14**	**0.188**
PEAK MS GRADIENT (mm Hg)	**23.78±9.07**	**27.04±9.54**	**0.006**
MEAN MS GRADIENT (mm Hg)	**14.28±6.79**	**16.28±6.87**	**0.020**
RVSP (mm Hg)	**58.59±22.98**	**58.36±20.48**	**0.931**
ECHO SCORE	**7.46±1.26**	**9.22±1.17**	**.001**

Table 9: Showing the baseline echocardiography data of patients without restenosis and with restenosis.

CARDIAC CATHETERISATION DATA OF PATIENTS WITHOUT AND WITH RESTENOSIS PRE-PTMC:

Though there was no difference in the size of the balloon used for PTMC, in patients who developed restenosis lower size balloon dilatation was given to the mitral valve (24.91±1.11 vs 24.61±1.09; p=0.027). No other cardiac catheterization data had significant difference between patients who did not have restenosis and those with restenosis. The details of cardiac catheterization data is given in table 10.

TABLE 10:

VARIABLE	WITHOUT RESTENOSIS N=658	WITH RESTENOSIS N=71	P
LA MEAN (mm Hg)	**21.93±6.93**	**23.73±8.30**	**0.079**
PASP (mm Hg)	**51.74±24.11**	**54.26±21.06**	**0.352**
PADP (mm Hg)	**23.10±10.14**	**26.10±11.38**	**0.092**
PA MEAN (mm Hg)	**34.39±16.06**	**36.114±14.29**	**0.340**
LVED (mm Hg)	**9.15±9.53**	**9.53±3.60**	**0.402**
TMG (mm Hg)	**14.98±6.03**	**15.52±5.58**	**0.470**
MVA (cm^2)	**0.81±0.12**	**0.78±0.26**	**0.838**
BALLOON SIZE (mm)	**25.88±1.16**	**25.63±1.09**	**0.067**
MAXIMUM DILATATION(mm)	**24.91±1.11**	**24.61±1.09**	**0.027**

Table 10: Showing cardiac catheterization data of patients without and with restenosis.

ECHOCARDIOGRAPHY DATA OF PATIENTS WITHOUT AND WITH RESTENOSIS POST-PTMC:

Post PTMC patients who did not develop restenosis had higher mitral valve area than those who developed restenosis (1.74.±0.26 vs 1.60±0.26; p<0.001). The peak mitral valve gradient (12.86±4.93 vs 10.45±3.58; p<0.001) and mean mitral valve gradient (6.23±3.56 vs 4.79±2.03; p=0.001) was higher in patients who developed restenosis than in those who did not develop restenosis. Patients who developed higher grade MR post PTMC had higher rate of restenosis (1.63±0.83 vs 1.35±0.72; p=0.006).

TABLE 11:

VARIABLE	WITHOUT RESTENOSIS N=658	WITH RESTENOSIS N=71	P
LA SIZE (mm)	**40.70±6.66**	**42.05±5.80**	**0.068**
MVA (cm^2)	**1.74.±0.26**	**1.60±0.26**	**<0.001**
PEAK MS GRADIENT (mm Hg)	**10.45±3.58**	**12.86±4.93**	**<0.001**
MEAN MS GRADIENT (mm Hg)	**4.79±2.03**	**6.23±3.56**	**0.001**
RVSP (mm Hg)	**44.14±15.31**	**45.97±13.80**	**0.323**
MR	**1.35±0.72**	**1.63±0.83**	**0.006**

Table 11: Showing post PTMC echocardiography details of patients with and without restenosis.

CARDIAC CATHETERISATION DATA OF PATIENTS WITHOUT AND WITH RESTENOSIS POST PTMC:

The calculated mitral valve area post PTMC by cardiac catheterization was higher in patients without restenosis than those with restenosis (1.74±1.81 vs 1.47±0.59; p=0.009). There was no significant difference in other cardiac catheterization data between patients with restenosis and those without restenosis. The details of cardiac catheterization between patients with restenosis and those without restenosis are given in table 12.

TABLE 12:

VARIABLE	WITHOUT RESTENOSIS N=658	WITH RESTENOSIS N=71	P
LA MEAN (mm Hg)	**13.22±4.39**	**14.17±5.47**	**0.160**
PASP (mm Hg)	**38.95±18.55**	**40.68±15.81**	**0.402**
PADP (mm Hg)	**16.61±8.48**	**17.98±8.33**	**0.203**
PA MEAN (mm Hg)	**24.91±11.67**	**17.98±8.33**	**0.203**
LVED (mm Hg)	**12.34±3.67**	**12.77±4.28**	**0.419**
TMG (mm Hg)	**6.31±4.29**	**6.80±4.45**	**0.371**
MVA (cm^2)	**1.74±1.81**	**1.47±0.59**	**0.009**

Table 12: Showing the details of cardiac catheterization data between patients who developed restenosis and those who did not develop restenosis.

UNIVARIATE CORRELATION BETWEEN PATIENTS WITH AND WITHOUT RESTENOSIS:

BASELINE:

On univariate analysis pre PTMC older patients, higher NYHA functional class, presence of atrial fibrillation, higher ESR, larger left atrial size, higher peak and mean mitral valve gradient by echocardiography, higher Wilkins echocardiography score and lower then appropriate balloon dilatation given to the mitral valve during PTMC were significant predictors of restenosis. The details of univariate analysis at baseline are given in table 13.

TABLE 13:

VARIABLE	CORRELATION	OR (95% CI)	P
AGE (YRS)	**0.20**	**7.21 (4.62-9.8)**	**<0.001**
BSA (m^2)	**0.012**	**0.182 (-0.960- -1.33)**	**0.754**
FUNCTIONCAL CLASS	**0.10**	**-0.164 (-0.282- -0.045)**	**0.007**
ATRIAL FIBRILLATION	**0.120**	**-0.136 (0.218- -0.054)**	**0.001**
ESR (mm in 1^{ST} Hr)	**0.314**	**15.76 (12.287-19.241)**	**<0.001**
LA SIZE (mm)	**0.074**	**1.576 (0.022-3.132)**	**0.047**
MVA (cm^2) by ECHO	**-0.049**	**-0.024 (-0.058-0.015)**	**0.188**
PEAK MS GRADIENT (mm Hg)	**0.101**	**3.252 (0.922-5.582)**	**0.006**
MEAN MS GRADIENT (mm Hg)	**0.086**	**2.00 (0.315-3.683)**	**0.02**
RVSP (mm Hg)	**0.003**	**-0.226 (-5.378-4.925)**	**0.931**
ECHO SCORE	**0.384**	**1.765 (1.456-2.074)**	**<0.001**

Table 13: Showing baseline univariate correlation between patients with and without restenosis

TABLE 13 (CONT):

VARIABLE	CORRELATION	OR (95% CI)	P
LA MEAN (mm Hg)	**0.065**	**1.80 (-0.208-3.805)**	**0.79**
PASP (mm Hg)	**0.035**	**2.522 (-2.80-7.843)**	**0.352**
PADP (mm Hg)	**0.063**	**2.407 (-0.397-5.210)**	**0.092**
PA MEAN (mm Hg)	**0.036**	**1.757 (-1.851-5.210)**	**0.340**
LVED (mm Hg)	**0.032**	**0.376 (-0.503-1.255)**	**0.402**
TMG (mm Hg)	**0.027**	**0.540 (-0.927-2.007)**	**0.470**
MVA (cm^2) by CATH	**-0.008**	**-0.025 (-0.271- -0.220)**	**0.838**
BALLOON SIZE (mm)	**-0.068**	**-0.252 (-0.523- -0.017)**	**0.067**
MAXIMUM DILATATION(mm)	**-0.082**	**-0.136 (-0.58- -0.034)**	**0.027**

Table 13: Showing baseline univariate correlation between patients with and without restenosis

POST PTMC:

On univariate analysis post PTMC lower mitral valve area by echocardiography, higher peak and mean mitral valve gradient, presence of more mild mitral regurgitation, and lower mitral valve area calculated by catheterization data were predictors of restenosis. The details of univariate analysis post PTMC are given in table 14.

TABLE 14:

VARIABLE	CORELATION	OR (95% CI)	P
LA SIZE (mm)	**0.068**	**1.343 (-0.102-2.788)**	**0.068**
MVA (cm^2) by ECHO	**-0.164**	**-0.144 (-0.207- -0.808)**	**<0.001**
PEAK MS GRADIENT (mm Hg)	**0.147**	**2.4 (1.230-3.596)**	**<0.001**
MEAN MS GRADIENT (mm Hg)	**0.124**	**1.445 (0.601-2.291)**	**0.01**
RVSP (mm Hg)	**0.038**	**1.827 (-1.801-5.455)**	**0.323**
MR	**0.101**	**0.102 (0.787-0.480)**	**0.006**
LA MEAN (mm Hg)	**0.053**	**0.949 (-0.371-2.269)**	**0.158**
PASP (mm Hg)	**0.032**	**1.727 (-2.314-5.770)**	**0.402**
PADP (mm Hg)	**0.049**	**1.361 (-0.734-3.457)**	**0.203**
PA MEAN (mm Hg)	**0.034**	**1.279 (-1.521-4.080)**	**0.370**
LVED (mm Hg)	**0.030**	**0.430 (-0.615-1.476)**	**0.419**
TMG (mm Hg)	**0.034**	**0.528 (0.630-1.687)**	**0.371**
MVA (cm^2) by CATH	**-0.990**	**-0.266 (-0.466- -0.066)**	**0.009**

Table 14: Showing post PTMC univariate correalation between patients with and without restenosis

LINEAR REGRESSION BETWEEN PATIENTS WITH AND WITHOUR RESTENOSIS:

On linear regression presence of atrial fibrillation, pre PTMC left atrial size, pre PTMC pulmonary artery systolic pressure, higher Wilkins echocardiography score, presence of more than mild mitral regurgitation, post PTMC lower mitral valve area by echocardiography and by cardiac catheterization data, post PTMC right ventricle systolic pressure were the only predictors of restenosis. The details of linear regression are given in table 15.

TABLE 15:

VARIABLE	(SE)	OR (95%CI)	P
ATRIAL FIBRILLATION (%)	**0.118**	**0.147 (0.048-0.200)**	**0.001**
PRE PTMC LA SIZE (mm)	**0.079**	**0.017 (0.008-0.000)**	**0.033**
PRE PTMC PASP (mm Hg)	**0.107**	**0.049 (0.003-000)**	**0.016**
ECHO SCORE	**0.220**	**0.291 (0.039-0.075)**	**<0.001**
POST MR	**0.072**	**0.044 (0.001-0.060)**	**0.042**
POST PTMC MVA by ECHO (cm^2)	**-0.424**	**-0.485 (-0.473- -0.659)**	**<0.001**
POST PTMC MVA by CATH (mm Hg)	**-0.075**	**-0.153 (-0.002- -0.058)**	**0.035**
POST PTMC RVSP (mm Hg)	**0.195**	**0.182 (0.07-0.30)**	**0.042**

Table 15: Showing linear regression between patients with and without restenosis

DISCUSSION:

This was a retrospective study of 729 patients from the year 1995 to 2009.

The mean age of the patients was comparable to other studies from developing countries which is less than 40 years [12,14,17,19,21]. The age of the patients from developed countries is more than 40yrs[18,35,34]. This indicates that patients in developing country present with severe mitral stenosis early in life. Mitral stenosis was more common in females and this is similar to that reported in other studies.[12,18,34,35,19,14]

The incidence of atrial fibrillation was similar to study from Egypt and India,[19,21] however the incidence is higher in studies reported from western population[12,18,34,35]. This may be because patients present with severe mitral stenosis at older age in the western countries and older age is a risk factor for atrial fibrillation.

All patients had severe mitral stenosis and majority of the patients had pulmonary arterial hypertension. ACCURA balloon was commonly used to perform PTMC. The mean balloon size used was in accordance to the height of the patient (balloon size=height in centimeter+10).

Majority of the patients had successful PTMC. There was also decrease in right ventricle systolic pressure and pulmonary artery systolic pressure.

We compared patients who developed restenosis on follow up with patients who did not develop restenosis. The mean duration of follow up of patients was 6.89±3.49yrs and during this time 71 patients (9.7%) developed mitral valve restenosis. The incidence of restenosis is similar to other studies. The incidence of restenosis has been reported to range from 4 to 39% [5,12-17] and progressive decrease of MVA over time has been well documented.[5,9]

Patients with restenosis on follow up were older than patients without restenosis. This was similar to other studies.[5,13,18,20,37] Higher number of patients with restenosis had atrial fibrillation. Atrial fibrillation is a well recognized predictor for mitral restenosis.[5,33]

The patients with restenosis had significantly higher ESR than patients without restenosis. There are no studies that have looked into the correlation of ESR with restenosis. High ESR is likely to suggest that the patients have smoldering chronic rheumatic activity and this may be the reason why these patients have higher chance of restenosis on follow up.

Long-term outcome in patients undergoing PTMC is multifactorial, incorporating two important components: preprocedural risk factors and post-procedural variables reflecting the quality of the procedure. Among the pre-procedural risk factors are age,[5,35,40] echocardiographic score,[5,14,40-42] cardiac rhythm,[5,35] and New York Heart Association functional class,[5,35,42] whereas immediate post-PMV MVA and MR[5,35,41] are associated with long-term outcomes.

Baseline echocardiographic score, which represents mitral valve morphology, has been found to be the most important pre-procedural factor determining procedural success, as well as being an independent factor determining event-free survival. [5,14,40-42]

In a study with a follow-up duration of 39±23 months, procedural results (immediate post-PMV MVA and MR) were found to be the only independent predictor of major event-free survival after PMV.[9] In another study with a follow-up duration of 2.3±1.5years, echocardiographic score and immediate post-PMV MVA were independent predictors of event-free survival.[41]

In this study on univariate analysis pre PTMC older patients, higher NYHA functional class, presence of atrial fibrillation, higher ESR, larger left atrial size, higher peak and mean mitral valve gradient by echocardiography, higher Wilkins echocardiography score and lower then appropriate balloon dilatation given to the mitral valve during PTMC were significant predictors of restenosis; and post PTMC lower mitral valve area by echocardiography, higher peak and mean mitral valve gradient, presence of more mild mitral regurgitation, and lower mitral valve area calculated by catheterization data were predictors of restenosis.

However on linear regression presence of atrial fibrillation, pre PTMC left atrial size, pre PTMC pulmonary artery systolic pressure, higher Wilkins echocardiography score, presence of more than mild mitral regurgitation, post PTMC lower mitral valve area by echocardiography and by cardiac catheterization data, post PTMC right ventricle systolic pressure were the only predictors of restenosis.

In this study we also found patients with PAH who had residual PAH post PTMC were more likely to develop restenosis on follow up. Sinha et al had also found patients with severe pulmonary arterial hypertension (PAH) who had residual PAH post PTMC had higher rate of restenosis at 29 months of follow up.[39]

Larger pre PTMC left atrial size was also predictor of restenosis. Large left atrial size indicates more severe stenosis pre PTMC and burnt out rheumatic heart disease. There may also have occurred left atrial fibrosis and calcification. All these indicate unfavorable mitral valve anatomy and thus must have resulted in suboptimal result and higher chance of restenosis.

The presence more than mild mitral regurgitation was also found to be predictor of restenosis on multivariate analysis in this study. This has been documented in other studies too.[9,25] Commissural MR has be correlated with restenosis. In this study it may be seen that the height of the patients with restenosis was more than those without restenosis however the size of balloon dilatation given was lower. Lower size balloon dilatation might have been given due to development of more than mild MR. All this would have resulted in suboptimal PTMC result and this may also be the reason for higher restenosis in these patients.

STUDY LIMITATIONS:

This was a retrospective study and hence may have been subject to selection bias. This was also a single centre study and hence the result may have been influenced by the experience of the centre. An advantage is that the results are not influenced by individual centre variability. Most of our patients underwent percutaneous mitral balloon valvotomy by the ACCURA balloon technique, and therefore may be difficult to draw conclusion regarding other balloons. However it should be mentioned that in a significant number of patients INOUE balloon was used and this may bring down the discrepancy.

CONCLUSION:

1. Mitral restenosis can occur in the long run and many factors contribute to this
2. The incidence of mitral restenosis in this study was 9.7% at mean follow up of 6.89±3.49yrs
3. Predictors of mitral restenosis on univariate analysis were:
    a. Older patients
    b. Patients with larger left atrial size
    c. More symptomatic patients
    d. Patients with atrial fibrillation
    e. Higher mitral valve gradients pre PTMC and post PTMC
    f. Higher ESR level
    g. Higher Wilkins echocardiography score
    h. Lower mitral valve area pre PTMC and post PTMC
    i. Presence of more than mild MR post PTMC
4. Some important predictors of restenosis on multivariate linear regression analysis in this study were:
    a. Presence of pre PTMC atrial fibrillation
    b. Larger pre PTMC left atrial size
    c. Higher pre PTMC pulmonary artery systolic artery pressure
    d. Higher Wilkins echocardiography score
    e. Lower post PTMC mitral valve area
    f. Presence of moderate pulmonary arterial hypertension post PTMC
    g. Presence of at more than mild mitral regurgitation

REFERENCES:

1. Hudson Reb: Cardiovascular Pathology. Baltimore, Williams & Wilkins Co., 1965.
2. Magarey FR: Pathogenesis of mitral stenosis. Brit Med J 1951;1: 856.
3. Brock RC: The surgical and pathological anatomy of the mitral valve. Brit Heart J 1952;14: 489.
4. Song JK, Song JM, Kang DH, Yun SC, Park DW, Lee SW, Kim YH, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. Restenosis and adverse clinical events after successful percutaneous mitral valvuloplasty: Immediate post-procedural mitral valve area as an important prognosticator. Eur Heart J 2009;30:1254-62.
5. Palacios IF, Block PC, Wilkins GT, Weyman AE. Follow-up of patients undergoing percutaneous mitral balloon valvotomy. Analysis of factors determining restenosis. Circulation 1989;79:573-79.
6. Dubin AA, March HW, Cohn K, Selzer A. Longitudinal hemodynamic and clinical study of mitral stenosis. Circulation 1971;44:381-89.
7. Abascal VM, Wilkins GT, O'Shea JP, Choong CY, Palacios IF, Thomas JD, Rosas E, Newell JB, Block PC, Weyman AE. Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. Circulation 1990;82:448-56.
8. Chen CR, Cheng TO, Chen JY, Huang YG, Huang T, Zhang B. Long-term results of percutaneous balloon mitral valvuloplasty for mitral stenosis: A follow-up study to 11 years in 202 patients. Cathet Cardiovasc Diagn 1998;43:132-9.
9. Hernandez R, Banuelos C, Alfonso F, Goicolea J, Fernandez-Ortiz A, Escaned J, Azcona L, Almeria C, Macaya C. Long-term clinical and echocardiographic follow-up after percutaneous mitral valvuloplasty with the inoue balloon. Circulation 1999;99:1580-6.
10. Kang DH, Park SW, Song JK, Kim HS, Hong MK, Kim JJ, Park SJ. Long-term clinical and echocardiographic outcome of percutaneous mitral valvuloplasty: Randomized comparison of inoue and double-balloon techniques. J Am Coll Cardiol 2000;35:169-75.

11. Wang A, Krasuski RA, Warner JJ, Pieper K, Kisslo KB, Bashore TM, Harrison JK. Serial echocardiographic evaluation of restenosis after successful percutaneous mitral commissurotomy. J Am Coll Cardiol. 2002;39:328-34.

12. Ben Farhat M, Ayari M, Maatouk F, Betbout F, Gamra H, Jarra M, Tiss M, Hammami S, Thaalbi R, Addad F. Percutaneous balloon versus surgical closed and open mitral commissurotomy: Seven-year follow-up results of a randomized trial. Circulation 1998;97:245-50.

13. Herrmann HC, Ramaswamy K, Isner JM, Feldman TE, Carroll JD, Pichard AD, Bashore TM, Dorros G, Massumi GA, Sundram P, et al. Factors influencing immediate results, complications, and short-term follow-up status after inoue balloon mitral valvotomy: A north american multicenter study. Am Heart J 1992;124:160-6.

14. Ben-Farhat M, Betbout F, Gamra H, Maatouk F, Ben-Hamda K, Abdellaoui M, Hammami S, Jarrar M, Addad F, Dridi Z. Predictors of long-term event-free survival and of freedom from restenosis after percutaneous balloon mitral commissurotomy. Am Heart J 2001;142:1072-9.

15. Vahanian A, Michel PL, Cormier B, Vitoux B, Michel X, Slama M, Sarano LE, Trabelsi S, Ben Ismail M, Acar J. Results of percutaneous mitral commissurotomy in 200 patients. Am J Cardiol 1989;63:847-52.

16. Desideri A, Vanderperren O, Serra A, Barraud P, Petitclerc R, Lesperance J, Dyrda I, Crepeau J, Bonan R. Long-term (9 to 33 months) echocardiographic follow-up after successful percutaneous mitral commissurotomy. Am J Cardiol 1992;69:1602-6.

17. Lau KW, Ding ZP, Quek S, Kwok V, Hung JS. Long-term (36-63 month) clinical and echocardiographic follow-up after inoue balloon mitral commissurotomy. Cathet Cardiovasc Diagn 1998;43:33-8.

18. Iung B, Cormier B, Ducimetie`re P et al. Immediate results of percutaneous mitral commissurotomy: a predictive model on a series of 1514 patients. Circulation 1996; 94: 2124–30.

19. Arora R, Kalra GS, Singh S, et al. Percutaneous transvenous mitral commissurotomy: immediate and long-term follow-up results.Catheter Cardiovasc Interv 2002; **55:** 450–56.

20. Al Zaibag M, Ribeiro PA, Kasab SA et al. One-year follow- up after percutaneous double balloon mitral valvotomy. Am J Cardiol 1989;63:126-7.
21. Fawzy ME. Long-term results up to 19 years of mitral balloon valvuloplasty. Asian Cardiovasc Thorac Ann 2009;17:627-33.
22. Gaasch WH, Folland ED. Left ventricular function in rheumatic mitral stenosis. Eur Heart J 1991;12 (Suppl B):66-9.
23. Saeki F, Ishizaka Y, Tamura T. Long-term clinical and echocardiographic outcome in patients with mitral stenosis treated with percutaneous transvenous mitral commissurotomy. Jpn Circ J 1999;63:597-604.
24. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: An analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988;60:299-308.
25. Park SJ, Kim JJ, Park SW, Song JK, Doo YC, Lee SJ. Immediate and one-year results of percutaneous mitral balloon valvuloplasty using inoue and double-balloon techniques. Am J Cardiol 1993;71:938-43.
26. Souttar HS. The surgical treatment of mitral stenosis. Br Med J 1925;2:603.
27. Spencer FC. A plea for early, open mitral commissurotomy. Am Heart J 1978 ;95 :668-70.
28. Dekker A, Black H, von Lichtenberg F. Mitral valve restenosis. A pathological study. J Thorac Cardiovasc Surg 1968;55:434-46.
29. Roberts WC, Virmani R. Aschoff bodies at necropsy in valvular heart disease. Evidence from an analysis of 543 patients over 14 years of age that rheumatic heart disease, at least anatomically, is a disease of the mitral valve. Circulation 1978;57:803-07.
30. Patterson GCand Marshall JR. Mitral restenosis *Br Heart J* 1959 21: 174-76.
31. Kitchin A, Turner R. Calcification of the mitral valve. Results of valvotomy in 100 cases. Br HeartJ 1967;29:137-61.
32. Lachman AS, Roberts WC. Calcific deposits in stenotic mitral valves. Extent and relation to age, sex, degree of stenosis, cardiac rhythm, previous commissurotomy and left atrial body thrombus from study of 164 operatively-excised valves. Circulation 1978;57:808-15.

33. Smith GH, Belcher JR. Valvotomy in calcific mitral stenosis. Br Heart J 1970;32:198-202.
34. Carlos E Ruiz, He Ping Zhang, Habib Gamra et al Late clinical and echocardiographic follow up after percutaneous balloon dilatation of the mitral valve. Br Heart J7 1994;71:454-458
35. Iung B, Garbarz E, Michaud P et al Late Results of Percutaneous Mitral Commissurotomy in a Series of 1024 Patients. Analysis of Late Clinical Deterioration: Frequency, Anatomic Findings, and Predictive Factors. *Circulation*. 1999; 99:3272-3278.
36. J. Langerveld, H. W. Thijs Plokker, S. M. P. G. Ernst et al Predictors of clinical events or restenosis during follow-up after percutaneous mitral balloon Valvotomy. Eur Heart J 1999; 20: 519–526
37. The NHLBI balloon valvuloplasty registry participants. Multicenter experience with balloon mitral commissurotomy. Circulation 1992; 85: 448–61.
38. Thomas MR, Monaghan MJ, Michalis LK, et al. Echocardiographic restenosis after successful balloon dilatation of the mitral valve with the Inoue balloon: experience of a United Kingdom centre. Br Heart J 1993; 69: 418–23.
39. Sinha N, Kapoor A, Kumar AS, Shahi M et al Immediate and follow up results of Inoue balloon mitral valvotomy in juvenile rheumatic mitral stenosis. J Heart valve dis. 1997 Nov;6(6):599-603.
40. Meneveau N, Schiele F, Seronde MF et al. Predictors of event-free survival after percutaneous mitral commissurotomy. Heart 1998;80:359–364.
41. Pavlides GS, Nahhas GT, London J et al. Predictors of long-term event-free survival after percutaneous balloon mitral valvuloplasty. Am J Cardiol 1997;79:1370–1374.
42. Cohen DJ, Kuntz RE, Gordon SP et al. Predictors of long-term outcome after percutaneous balloon mitral valvuloplasty. N Engl J Med 1992;327:1329–1335.

EVALUATION AND MANAGEMENT OF PATIENTS WITH SYNCOPE: A SINGLE CENTRE STUDY

EVALUATION AND MANAGEMENT OF PATIENTS WITH SYNCOPE: A SINGLE CENTRE STUDY

INTRODUCTION:

Syncope is a clinical syndrome characterized by transient loss of consciousness and postural tone that is often due to temporary and spontaneously self-terminating global cerebral hypoperfusion.[1,2] It is a common presenting problem to the health care system and also one of the most challenging in terms of diagnosis and management. It is a multidisciplinary problem and evaluation requires good team work.

Three key questions should be answered during the initial evaluation of syncope.[1] Is loss of consciousness attributable to syncope or not?[2] Are there features in the history that suggest the diagnosis?[3] Is heart disease present or absent? The answer to these question helps to narrow down the diagnosis and evaluate the patient better.

According to the European cardiology society (ECS) task force on syncope; syncope according to pathophysiology has been divided into the following category:

(1) **Neurally-mediated (reflex) syncope**: A reflex response that, when triggered, gives rise to vasodilatation and/or bradycardia; however the contribution of each of these two factors to systemic hypotension and cerebral hypoperfusion may differ considerably. The triggering events might vary considerably in individual patients. The ‘‘classical vasovagal syncope’’ is mediated by emotional or orthostatic stress and can be diagnosed by history taking. ‘‘Carotid sinus syncope’’ is defined as syncope which, by history, seems to occur in close relationship to accidental mechanical manipulation of the carotid sinuses, and which can be reproduced by carotid sinus massage. ‘‘Situational syncope’’ refers to those forms of neurally-mediated syncope associated with specific scenarios (for example, micturition, coughing,

defaecating, etc). Often, however, neurally mediated reflex syncopes have ‘‘non-classical’’ presentations. These forms are diagnosed by exclusion of other causes for syncope (absence of structural heart disease) and positive response to tilt testing or carotid sinus massage. Examples of non-classical vasovagal syncope include episodes without clear triggering events or premonitory symptoms.

(2) Orthostatic hypotension: Syncope in which the upright position (most often the movement from sitting or lying to an upright position) causes arterial hypotension. This occurs when the autonomic nervous system is incapacitated and fails to respond to the challenges imposed by upright position. A second major cause is ‘‘volume depletion’’ in which the autonomic nervous system is itself not deranged, but is unable to maintain blood pressure due to decreased circulating volume.

(3) Cardiac arrhythmias: Can cause a decrease in cardiac output, which usually occurs irrespective of circulatory demands.

(4) Structural heart disease: Can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output.

(5) Steal syndromes: Rare, but can cause syncope when blood supply is diverted from the brain to another organ (the most common example is the so-called ‘‘subclavian steal syndrome’’).

Disorders without any impairment of consciousness such as falls, cataplexy, drop attacks, psychogenic pseudo-syncope, transient ischaemic attacks (TIA) of carotid origin and disorders with partial or complete loss of consciousness such as metabolic disorders, including hypoglycaemia, hypoxia, hyperventilation with hypocapnia, epilepsy, intoxications, vertebro-basilar TIA needs to be differentiated from syncope. Such a differentiation is crucial because the clinician is usually confronted with patients in whom sudden loss of consciousness has been

provoked by causes not associated with decreased cerebral blood flow such as seizure and/or conversion reaction.

The Framingham study reported an incidence of 6.2 per 1000 person-years; cumulative incidence during 10 years was 6%.[3] The prevalence of syncope varies from 15% in the pediatric population to 19% in an unselected adult population.[4] In selected populations, the prevalence of syncope can approximate 40%.[5] A common presenting problem in health care settings, syncope accounts for 1% of emergency department (ED) visits[6,7] and 1% to 3% of hospital admissions.[8-10]

Though there are several studies from the western population there is paucity of data regarding evaluation of syncope in the Indian scenario. This study was planned to study the evaluation of patients presenting with syncope in a tertiary care centre.

REVIEW OF LITERATURE:

Syncope is a clinical syndrome characterized by transient loss of consciousness and postural tone that is most often due to temporary and spontaneously self-terminating global cerebral hypoperfusion.[1,2] The Framingham study reported an incidence of 6.2 per 1000 person-years; cumulative incidence during 10 years was 6%.[3] The prevalence of syncope varies from 15% in the pediatric population 4 to 19% in an unselected adult population.[4] In selected populations, the prevalence of syncope can approximate 40%.[5] A common presenting problem in health care settings, syncope accounts for 1% of emergency department (ED) visits[6,7] and 1% to 3% of hospital admissions.[8-10]

The evaluation and management of syncope has dramatically changed over the past 15 years. In the early 1980s, several studies showed that the cause of syncope was often not established, and subgroups were identified with high mortality and sudden death rates.[8,9,11,12] Later a large number of studies on electrophysiology testing appeared, which led to a better understanding of the roles and limitations of tests in syncope. [13-15] Although tilt table testing started in 1980s, it assumed an important role in the evaluation of syncope in 1990s, showing that neurally mediated mechanism is a common etiology of unexplained syncope. [16-19] To evaluate syncope, sound clinical decisions are based on a carefully performed history with extreme attention to detail.

The history, with its proper interpretation and a directed physical examination, is the only appropriate way to guide further diagnostic evaluation. The history and physical alone can be diagnostic in 25%-35% of patients.[8,11,20] Of those for whom a cause is found, the history and physical alone are sufficient in 75%-85% of patients.[8]

Although ECG is often abnormal, causes of syncope are rarely assigned (<5% of patients) on the basis of ECG and rhythm strip.[8,9,11,12] An ECG is recommended in all patients with syncope because abnormalities found on ECG (such as bundle branch block) may guide further evaluation, or if a specific diagnosis is made the findings can be important in immediate decision making.

It has become clear that results of holter monitoring are often difficult to interpret in evaluating syncope because of the lack of a "gold standard" for diagnosis of arrhythmias and the rarity of symptoms during monitoring. The best way to assess the usefulness of holter monitoring is to use presence or absence of symptoms during monitoring.[21] Approximately 4% of patients have symptoms concurrently with arrhythmias, and 17% have symptoms but no arrhythmias, thus potentially excluding arrhythmias as a cause of symptoms. In approximately 79% of patients there are no symptoms, but brief arrhythmias are found in 13%. In the absence of symptoms during monitoring, finding brief or no arrhythmias does not exclude arrhythmic syncope. Brief arrhythmias are nonspecific and can be found in asymptomatic healthy individuals. Additionally, absence of arrhythmias on monitoring does not exclude arrhythmic syncope because arrhythmias are episodic and may not be captured during monitoring. In patients with high pretest probability of arrhythmias such as brief sudden loss of consciousness without prodrome, patients with abnormal ECG, or those with structural heart disease, arrhythmias are still of concern and further testing is needed. Holter monitoring for 72 hours rather than for 24 hours does not yield greater numbers of symptomatic periods.[22]

In patients with structural heart disease and/or abnormal ECG, the diagnostic yield of EPS is approximately 50%, whereas it is only 10% in patients without structural heart disease.[13-16] Bradyarrhythmias are much more likely to be diagnosed in patients with conduction disease on surface ECG, however, the sensitivity and specificity of EPS for detection of bradyarrhythmias is low. It is recommended that patients with structural heart disease or abnormal ECG undergo electrophysiological testing if clinical assessment is suggestive of arrhythmic syncope and if noninvasive testing with Holter or loop monitoring has been non-diagnostic.

Echocardiography in the absence of clinical evidence of organic heart disease generally does not reveal unexpected findings that lead to an etiology for syncope.[23] This test is not recommended for screening purpose in patients with syncope.

The yield of thread mill exercise testing (TMT) in the diagnosis of the etiology of syncope is very low (<1%). TMT is useful as an ancillary diagnostic test for evaluation of ischemic heart disease in patients with arrhythmic syncope, particularly ventricular tachycardia.

In these patients, in addition to the treatment of ventricular tachyarrhythmia, the management of underlying cardiac disease is critical. TMT is also recommended for the evaluation of symptoms with exercise and post exertional syncope.

The head up tilt table test (HUTT) has become a commonly performed test for the evaluation of syncope, particularly in young, otherwise healthy patients in whom the diagnosis of vasovagal or neurocardiogenic syncope is often entertained.[25,26] It is also useful in older persons with suspected neurally mediated syncope.[27] Maintaining the patient in an upright position for a brief duration on a tilt table has become a common means of testing for predisposition to vasovagal syncope. It is widely accepted that hypotension and /or bradycardia during upright tilt testing is equivalent to spontaneous vasovagal syncope. This is supported by the fact that the temporal sequence of blood pressure and heart rate changes during tilt testing is similar to spontaneous spells. In addition, catecholamine release immediately prior to tilt-induced syncope is similar to spontaneous vasovagal faint.

There are various positive response patterns seen during head-up tilt table testing. 1) Classical vasovagal (or neurocardiogenic), which is characterized by the sudden onset of hypotension with or without coexistent bradycardia. Vasovagal response can be cardioinhibitory, pure vasodepressor, or mixed type. 2) dysautonomic response, characterized by gradual parallel decline in systolic and diastolic blood pressure, leading to loss of consciousness.3) psychogenic or psychosomatic response, these patients experience syncope during tilt testing with no ascertainable alteration in heart rate, blood pressure, electroencephalographic, or transcranial blood flow patterns.4) Postural Orthostatic Tachycardia Syndrome (POTS), characterized by an increase in heart rate of at least 30 beats per minute (or a maximum heart rate of 120 bpm) within the first 10 minutes upright during the baseline tilt, this tachycardia is not associated with profound hypotension.

The test is usually performed in an electrophysiology laboratory using a special tilt table; isoproterenol is often infused if the initial tilt test is negative.[28] Occasional patients have a pronounced cardioinhibitory response to this test characterized by symptomatic hypotension, bradycardia, or both . In one series, 77 of 179 patients (43 percent) with unexplained syncope

had a positive tilt test; 10 of these patients developed asystole, often associated with seizures, requiring a brief period of cardiopulmonary resuscitation.[29]

The false negative rate of the upright tilt table test is as high as 14 percent and up to 30 percent when isoproterenol is infused[30,31] and is less specific in the elderly.[32] The mechanism for syncope during tilt table testing is different in normal and patients with a history of neurocardiogenic syncope. One study compared 8 normal with and 8 normal without a positive tilt table test and 15 patients with neurocardiogenic syncope.[33] Patients with neurocardiogenic syncope had a shorter time to syncope than normal subjects with a false positive study; an immediate and persistent drop in mean blood pressure, suggesting impaired vascular resistance response; more rapid peripheral pooling of blood, as determined by left ventricular end-diastolic dimension on echocardiography; and higher peak epinephrine levels.

Tilt table testing should not be performed in a patient who is orthostatic at baseline or who has had near-syncope without overt loss of consciousness. The utility of the tilt table test depends upon the study population. One report evaluated the role of this test in 145 patients with a history of presyncope or syncope.[34] The following findings were noted:

1. Patients with recurrent syncope were more likely to have a positive test compared to those with a single episode or with recurrent presyncope (41 versus 17 percent, $p<0.005$).
2. Patients with structural heart disease or with a noncardiovascular cause for syncope were less likely to have a positive test (16 versus 42 percent, $p<0.0001$).
3. When multiple factors were combined, the yield ranged from 0 percent in patients under 50 without recurrent syncope who had structural heart disease or a noncardiovascular cause to 73 percent in those over 50 with recurrent syncope who did not have structural heart disease or a noncardiovascular cause.
4. The additional yield of positive tests with the use of isoproterenol or edrophonium was 10 percent.

Another study evaluated the role of the tilt study in patients with bifascicular block who had unexplained syncope. When compared to those with bifascicular block and no syncope, no difference in the incidence of a positive tilt test was observed, suggesting that test specificity in

this population is of concern.[35] Tilt testing is also of limited value for patients with situational vagal syncope, i.e. syncope due to situations associated with enhanced vagal tone such as micturition, defecation, cough, or vomiting.[36]

Various pharmacologic provocation test are used if the initial tilt test is negative like isoproterenol, nitrates, adenosine, clomipramine. Most investigators use isoproterenol and at our Institute too we use the same. One study found that a single-stage isoproterenol tilt table test more frequently induced syncope than a standard passive tilt study (56 versus 32 percent) and reduced the time necessary for the procedure. There was, however, a lower specificity (83 versus 91 percent for standard tilt testing).[37]

In order to reduce the time necessary for the tilt test, another study of 109 patients reported that a heart rate change $\leq$ 18 beats per minute during the first six minutes of the test prospectively predicted a negative tilt table study with a 96.4 percent specificity, 98.4 percent positive predictive accuracy and 87.3 percent sensitivity, even with the subsequent use of isoproterenol.[38]

Generally, skull films, lumbar puncture, radionuclide brain scan, carotid Doppler's, and cerebral angiography do not yield diagnostic information for a cause of syncope in the absence of clinical findings that are suggestive of a specific neurological process.[11] Studies of EEG in syncope have shown that an epileptiform abnormality was found in 1% of patients; almost all of these were suspected clinically.[39] Head CT scans are rarely useful to assign an etiology, but are needed if subdural bleed due to head injury is suspected or in patients suspected to have seizures as a cause of loss of consciousness.[11]

Psychiatric illnesses must be considered as a cause of syncope, especially in young patients and those with multiple syncopal episodes who also have other nonspecific symptoms.[40] The disorders that may cause syncope include generalized anxiety and panic disorders, major depression, somatization disorder, and alcohol/substance abuse. Screening instruments for these disorders are available and recommended.

To summarize, syncope is a common manifestation of many disease processes. In a minority of cases, the problem is recurrent and handicapping. Patient with syncope and heart disease, particularly when there is impaired left ventricular function, bundle branch block, evidence of congestive heart failure, or a positive family history of syncope and heart disease, appear to be at high risk for death and require an aggressive initial approach. Patients who benefit most from hospitalization include those with suspected cardiac disease, the elderly, those with serious injuries, and those with new neurological findings.

Diagnostic test should be used sparingly, directed by a carefully performed history and physical examination. No series of test is universally applicable.

AIMS AND OBJECTIVES:

- To indentify management strategies and prognosis in patients with benign syncope in a tertiary cardiac centre.

MATERIALS AND METHODS:

Study duration: From 2000-2009

Type of study: Retrospective observation study

Inclusion criteria:

Consecutive patients presenting to cardiology OPD for evaluation of the cause of syncope or referred from other Departments like Neurology for the evaluation of the cause of syncope were included in the study.

Exclusion criteria:

The following patients will be excluded from the study:

1. Patients with documented arrhythmias like ventricular arrhythmias, supraventricular arrhythmias, complete heart block.
2. Possible arrhythmic cause strongly suspected by ECG, ECHO.
3. Referred with diagnosis of seizure confirmed by neurologist after evaluation.

The details of the patients included in the study were retrospectively collected from the available patient hospital record. Patient basic information was collected which included age, sex, total number of loss of consciousness, whether warning symptoms were present prior to the incident, details of the history to know if any cause could be ascertained like hypoglycemia, drop attack or psychogenic cause. Also the details of clinical examination were noted.

The details of the investigations like electrocardiogram (ECG), echocardiogram, holter, HUTT, electrophysiology study (EPS), electroencephalography study (EEG), thread mill exercise testing (TMT), coronary angiography, carotid Doppler if done were recorded.

Evaluation of the patient:

At our institute we follow a structured evaluation for all patients presenting with syncope. A case record is made for all patients that are preserved in medical record department of our

institute. The case record consists of detail history of problem with clinical examination at initial visit. It also consists of provisional diagnosis made and all investigations done for the patients. The following investigation are mandatorily done for all patients

1. Chest X ray
2. ECG
3. Echocardiogram

Further investigations were done as and when indicated. All the details of any further investigation done are also recorded in the same case record. The details of the follow up at each visit are also recorded in the same case record of the patient at each visit. This enabled a good data collection for each patient.

Follow up data:

The patients follow up data was obtained either from the patient case record or by telephonic interview or by postal communication.

The following investigations were done as and when indicated:

1. Holter: 24 hour Holter ECG monitoring was done for all patients.

In hospital 24 h ECG telemetry was done when a patient was hospitalized due to syncope which was likely to be arrhythmic (history of arrhythmia, organic heart disease, and abnormal baseline ECG).

2. HUTT: HUTT was done for all patients whose ECG, echocardiogram, HOLTER was non diagnostic or when the suspicion of vasovagal syncope was very high.
3. TMT: TMT was done when syncope was associated with exercise (during or after) or was a part of a diagnostic work-up towards possible coronary artery disease (CAD). It was also done when certain form of ventricular tachycardia like catecholenergic polymorphic ventricular tachycardia was suspected or when arrhythmia due to WPW syndrome was suspected.

4. EPS: EPS was done when all the above investigations were negative and still the chance of arrhythmic cause was very high historically.
5. NEUROLOGICAL EVALUATION: As a part of departmental policy all patients presenting with syncope underwent neurological evaluation to rule out any neurological cause.

HUTT:

The test was performed in cardiac intensive care unit with minimal distractions for the patient. The patient was placed on a hydraulic lift or swinging bed capable of moving the patient passively from a supine position to a head-up position between 60° and 80°. The table had a footboard and safety restraints for patient. Continuous ECG and noninvasive blood pressure monitoring was employed throughout the test. Patients were encouraged to identify symptoms that may develop. An infusion pump and intravenous catheter for administration of fluids and isoproterenol if indicated was kept ready. Patients were kept in a semi fasting state without orthostatic blood pressure changes at baseline. The patient was monitored in the supine position for 5 minutes to obtain baseline heart rate and blood pressure measurements. The patient was then positioned in a head-up tilt position. Blood pressure, heart rate, and symptoms are recorded every 5 minutes and the ECG was recorded continuously. If the patient experienced loss of consciousness or was unable to maintain posture in association with a significant fall in blood pressure or heart rate, he or she was returned to a supine position, and the test was considered positive. If, after a period of 30 minutes, no symptoms developed, the patient was returned to the supine position.

If the patient remained asymptomatic infusion of isoproterenol was done in gradual increasing dose every 5 minutes to a maximum dose 3μgm/min.

Types of response to HUTT:

1. Type 1 or mixed response: The heart rate dropped at the time of syncope but not less than 40 bpm and if it dropped it lasted for less than ten seconds. The blood pressure drops before heart rate.

2. Type 2A or cardioinhibitory without asystole: The heart rate drops below 40 bpm for more than ten seconds. The BP drops before the heart rate.
3. Type 2B or cardioinhibitory with systole: There is asystole that lasts for more than 3 seconds. The decrease in blood pressure precedes or coincides with the drop in heart rate.
4. Type 3 or mixed response: heart does not drop more than 10% compared to the peak at the time of syncope.
5. Exception 1 (Chronotropic incompetence): There is no significant increase in heart rate during the tilt (i.e less than 10% of the heart rate before the tilt)
6. Exception 2 (postural orthostatic tachycardia syndrome-POTS): Excessive increase in heart rate (i.e greater than 130bpm) both initially and throughout the tilt before the syncope.

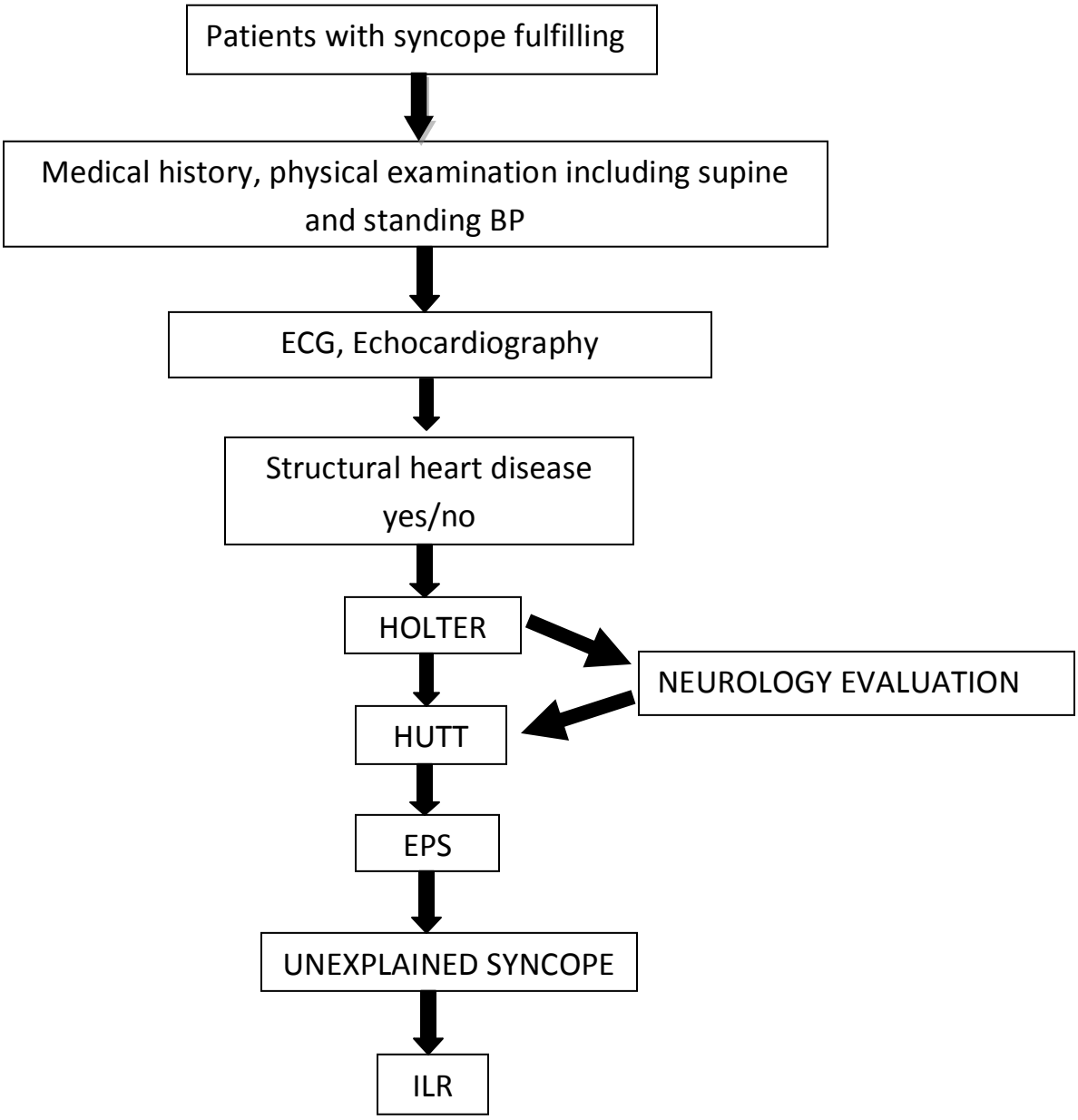
MANAGEMENT OF THE PATIENTS:

All patients were reassured and explained about the disease conditions and why it happens. The following lifestyle modifications were advised to the patients:

1. Avoid prolong standing
2. Avoid dehydration
3. Early recognition of prodrome symptoms and method to avoid it
4. Triggers of situations inducing syncope must be avoided as much as possible
5. Isometric physical counterpressure maneuvers with prodrome like repeated opening and closing of the fist, leg crossing
6. Drugs like antihypertensives were modified

Patients with cardioinhibitory response were started on beta-blockers. Some patients were put on paroxetine. The patients were reassessed for response after 3 months.

Outline of evaluation of patients:



OBSERVATIONS AND RESULTS

Consecutive patients presenting to cardiology OPD for evaluation of the cause of syncope or referred from other departments like Neurology for the evaluation of the cause of syncope from the year 2000 to 2009 were retrospectively analyzed in this study.

During the above mentioned period 235 patients satisfied the inclusion and exclusion criteria. The mean age of the patients was 35.17±18.98yrs. 52.3% of the patients were females and their mean age was 40.78±19.25yrs where as 47.6% of the patients were males and their mean age was 29.19±16.67yrs.

FIGURE 1:

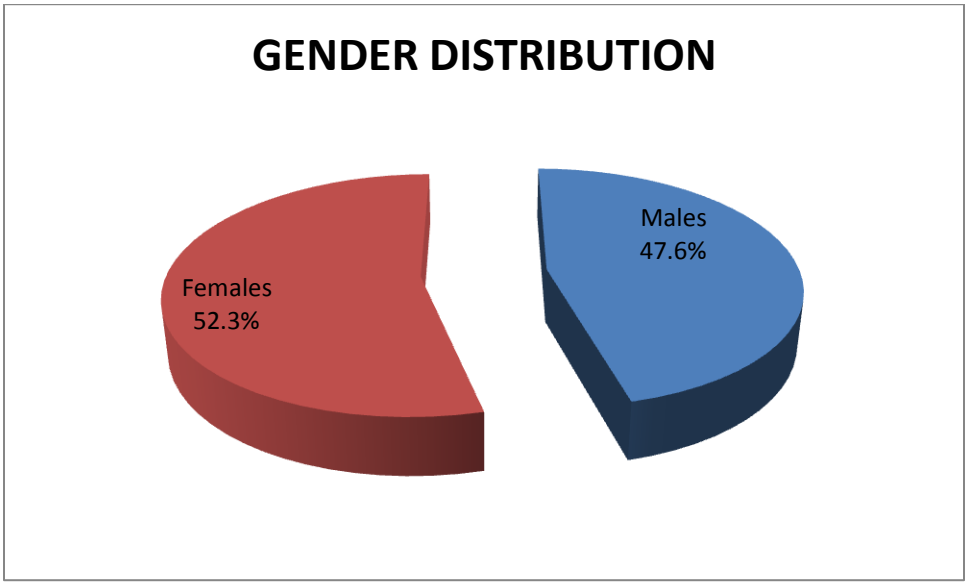


Figure 1: Pie chart to show age distribution of the patients

13.2% of the patients had single episode of syncope and the rest had two or more episodes (multiple episodes). The mean age of the patients with single episode of syncope was 41.71±21.18yrs and the mean age of the patients with multiple episodes of syncope was 33.52±18.97yrs (p=0.025).

FIGURE 2:

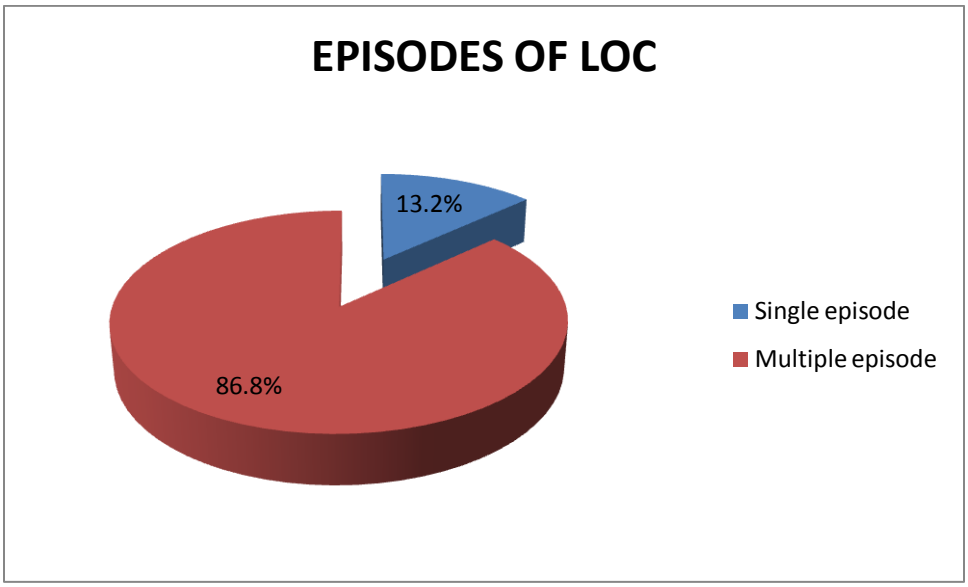


FIGURE 2: Pie chart to percentage of patients who had single episode and those who had multiple episodes.

ECG DATA:

175 (74.4%) patients had normal ECG, 20 (8.5%) had first degree atrioventricular block, 10 (4.3%) had atrial flutter, 10 (4.3%) had right bundle branch block (RBBB), 5 (2.1%) had atrial fibrillation, 5 (2.1%) had sinus bradycardia, 2 (0.9%) had bifascicular block, 2 (0.9%) had left bundle branch block and 1 (0.4%) had right ventricular outflow tract ventricular premature complex (RVOT VPC).

The patients with first degree atrioventricular block were advised to avoid atrioventricular conduction prolonging drugs apart from life style modifications and on follow up these patients had no further episodes of syncope. All patients with atrial flutter were started on oral anticoagulation and DC cardioverted successfully to sinus rhythm. 2 Patients with sinus bradycardia on HOLTER showed evidence of sick sinus syndrome and were advised for permanent pacemaker implantation (PPI). One patient had permanent pacemaker implanted and one patient underwent PPI elsewhere. The other 3 patients with sinus bradycardia on follow up

did not have symptoms. Both patients with LBBB were advised for life style modification and on follow up they had no adverse outcome. Both patients with bifascicular block underwent electrophysiology study (EPS) and were found to have significant HV prolongation and hence were advised for PPI and the same was done. On follow up both these patients were asymptomatic. One patient with RVOT VPC underwent EPS study and had successfully ablation of RVOT VT.

TABLE 2:

ECG FINDINGS	N (%)
NORMAL	175 (74.4)
AF	5 (2.1)
ATRIAL FLUTTER	10 (4.3)
RBBB	10 (4.3)
SINUS BRADYCARDIA	5 (2.1)
BIFASCICULAR BLOCK	2 (0.9)
LBBB	2 (0.9)
RVOT VPC	1 (0.4)
FIRST DEGREE AVB	20 (8.5)

Table 2: To show the ECG findings of the patients

ECHOCARDIOGRAPHY DATA:

All patients were evaluated with echocardiography. 8 (3.44%) patients had ASD, 2 (0.9%) had PDA, 1 (0.4%) had VSD, 2 (0.9%) had rheumatic heart disease (RHD), 1 (0.4%) had mitral valve prolapse (MVP), 1 (0.4%) had dilated cardiomyopathy (DCM), 11 (4.7%) had regional wall motion abnormality suggestive of coronary artery disease (CAD).

All patients who were diagnosed to have ASD and PDA were treated with device closure. One patient diagnosed to have VSD subsequently underwent surgical closure. On follow up these patients were asymptomatic. Eleven had CAD confirmed by coronary angiography. 10 patients

underwent PTCA (6 to LAD lesion, 2 to LCX and another to RCA) and the remaining 1 with three vessel disease underwent CABG.

TABLE 1:

SHD	N (%)
ASD	8 (3.44)
PDA	2 (0.9)
RHD	2 (0.9
VSD	1 (0.4)
MVP	1 (0.4)
DCM	1 (0.4)
CAD	11 (4.7)

Table 1: To show the no. of patients with structural heart disease (SHD)

HOLTER MONITORING:

All patients underwent Holter monitoring. 4 (2.2%) patients has sick sinus syndrome (SSS), 2 (1.1%) had non sustained ventricular tachycardia, 2 (1.1%) had ventricular tachycardia (VT), 2 (1.1%) had paroxysmal AF and one had rate dependent aberrancy.

All patients with SSS underwent PPI done and on follow up had no recurrence of symptoms. Both patients with NSVT underwent EPS study for VT induction but sustained VT could not be induced in both the patients and hence both these patients were kept on medical follow up with advice to take ECG if the symptoms recurred. Both these patients are on regular follow up and had not had symptoms. Both the patients with paroxysmal AF were started on oral anticoagulation and beta blocker was started in both the patients. The patients had no further symptoms on follow up. The patient with rate dependent aberrancy was lost to follow up.

TABLE 3:

HOLTER FINDINGS	N=175 (%)
SSS	4 (2.2)
NSVT	2 (1.1)
VT	2 (1.1)
Paroxysmal AF	2 (1.1)
RATE DEPANDENT ABBERANCY	1 (0.06)

Table 3: To show the findings of holter monitoring

HUTT:

All patients with normal ECG, HOLTER findings and in whom the suspicion of vasovagal syncope was high underwent HUTT. 23.6% patients had positive HUTT test and rest 76.4% of the patients had negative HUTT test. 13(26.5)% patients had type I response, 32(65.3%) patients had type II response and 4(8.2%) patients had type III response. Among patients with type II response 28(87.5%) had type IIa response and 4(12.5%) had type IIb response.

The patients with positive HUTT test (29.39±18.04yrs) were younger than those with negative HUTT (37.56±18.89yrs) and this difference was significant. There were 51% females in the HUTT positive group and 54.6% patients in the HUTT negative group. There were 14.5% and 16.1% patients with single episode of LOC in positive HUTT test and negative HUTT test group respectively. There was significant improvement in symptoms with lifestyle modification advice in both groups, 91.8% in positive HUTT test group and 87% in negative HUTT test group.

FIGURE 3:

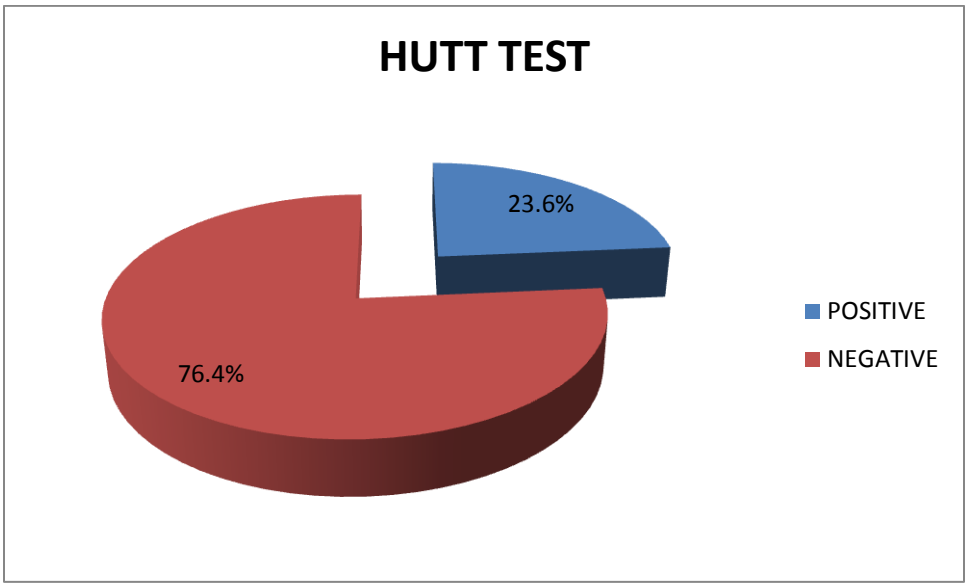


Figure 3: To show the response to HUTT test

TABLE 4:

TYPE OF RESPONSE	N=210
TYPE I (%)	13(26.5)
TYPE IIa (%)	28(57.1)
TYPE IIb (%)	4(8.2)
TYPE III (%)	4(8.2)

Table 4: to show the response to HUTT test

TABLE 5:

VARIABLES	HUTT POSITIVE (n=49)	HUTT NEGATIVE (n=161)	P
AGE (yrs)	29.39±18.04	37.56±18.89	O.OO3
FEMALES (%)	28 (51)	88 (54.6)	NS
SINGLE EPISODE OF LOC (%)	7 (14.5)	26 (16.1)	NS
IMPROVED SYMPTOMS ON FOLLOW UP (%)	45 (91.8)	140 (87)	NS

Table 5: To show the characteristics of patients with HUTT positive or negative

On follow up one patient developed sick sinus syndrome and was advised for permanent pacemaker implantation but the patient refused for the same. 2 patients developed complete heart block and underwent permanent pacemaker implantation. One another patient developed WPW syndrome and underwent successful ablation. All these patients had HUTT negative at their initial evaluation.

NEUROLOGY EVALUATION

EEG was done in 177 (75.3%) patients and was positive in 19.6% of the patients. Patients who were diagnosed to have EEG positive were treated by the Department of Neurology and were kept under their follow up. Apart from this 2 patients were diagnosed to have vertebral artery disease, 4 conversion disorder, and in another 2 patient psychogenic disorder were diagnosed. These patients were treated accordingly.

CAUSES OF SYNCOPE AND ITS RECURRENCES:

The most common cause for syncope was unexplained syncope, followed by neurocardiogenic. The recurrence rate was highest among patients with unexplained syncope, followed by the psychogenic group.

TABLE 6:

CAUSES	N=235	RECURRENCE
NEUROCARDIOGENIC (%)	49 (20.85)	4 (8.2)
ARRHYTHMIC CAUSES (%)	25 (10.64)	NIL
SHD (%)	26 (11.06)	NIL
NEUROLOGIC CAUSES (%)	46 (19.57)	1 (2.2)
VASCULAR CAUSE (%)	2 (0.85)	NIL
PSYCHOGENIC CAUSE (%)	6 (2.55)	3 (50)
UNEXPLAINED SYNCOPE (%)	92 (39.14)	13 (14.1)

Table 6: To show the causes of syncope and recurrences.

DISCUSSION:

This was a retrospective observation study with 235 consecutive patients presenting to cardiology OPD for evaluation of the cause of syncope or referred from other departments like Neurology for the evaluation of the cause of syncope. The study period was from the year 2000 to 2009.

During the pre-specified period 235 patients with syncope were indentified. The mean age of the patients was 35.17±18.98yrs. The mean age of the patients was much lower than most other studies.[7,41-46] The reason for this could be inclusion of higher incidence of patients with CAD in these studies. In our study the proportion of patients with CAD was 4.7% where as in the other studies it ranged from 26-37%. 52.3% of the patients were females which is comparable to those seen in other studies.[7,41-46] Mean age of females was more than that of males.

Multiple episodes of syncope were present in 86.8% of the patients. This was much higher in comparison to other studies.[7,41-46] In other studies it ranged from 32-76%. Since ours is a tertiary care centre and we receive patients only on referral basis, therefore, by the time patients reach us they would have visited many physicians causing delay in seeking proper medical advice. Younger patients tend to have recurrent symptoms than older patients.

All patients in our series were evaluated with echocardiography to look for any structural heart disease and 11% of the patients were detected to have structural heart disease. In contrast only one series had patients in whom echocardiography was done in 76% of the patients[46], otherwise in most other series echocardiography was performed in 11-18% of the patients.[7,41,42,44]

The incidence of structural heart disease was lower in our series in comparison to other series.[7,41-46] The higher incidence of patients with CAD in other series could have made this difference.

ECG abnormality was seen in 25.6% of the patients, this is in sharp contrast to Piotr K et al[46] who had 48% of patients with ECG abnormality. It would be difficult to assign the cause of syncope only on the basis of ECG. In other series the ECG abnormality has been assigned as the cause of syncope in less than 5% of the patients. [8,9,11,12]

Holter monitoring yielded additional diagnosis is 5.5% of the patients. This is lower than other series where in some it was as low as 8% [7] and as high as 49%[46]. It would be difficult to ascertain the percentage of patients with arrhythmias due to heterogeneity in the patient population in various series.

In our series 89.4% patients underwent HUTT evaluation, apart from one series which had HUTT done on 36% of patients[46], in rest of the series HUTT was done on 1-16% of the patients. [7,41,42,44] HUTT was positive in 23.6% of the patients which was lower than Piotr K et al [46] series where it was 36% and in aonther study where it was 45.3%[47] in pediatric population. In series by Lacroix HUTT positivity was 43%[29]. The reason for lower positivity could be because of inclusion of person with different age group in our series, also we had significant number of patients with neurological causes of syncope in our series. Other series had included patients with possible vasovagal syncope causing higher possibility for HUTT positivity. Type II response was seen more frequently in patients and this is similar to other series.[47,48] Older patients had higher HUTT positivity in our series, one Chinese series[48] showed similar result but in most other series the result have been variable. There was no significant difference in relation to gender, number of episodes of loss of consciousness with HUTT positivity, also both the group had similar response to treatment.

One patient on follow up developed SSS, 2 CHB, and 1 WPW syndrome which were managed appropriately. This shows that studies with longer follow up with larger no of patients, defining definite end points will be required to come to a definite conclusion. In our series there was a very good response to life style modification therapy with some patients being of beta blockers and SSRI. These have been shown to be effective in many studies.(49-54) Majority of our patients were on life style modification and for good response this requires high adherence to therapy. This may be due to better counseling for the patients that would have lead to better adherence to therapy. Also this may be because of high literacy rate of Kerala. Better literacy enables patients to have better understanding of their disease condition and hence this results in better adherence to therapy.

STUDY LIMITATIONS:

This was a retrospective study with a small sample size. Therefore selection bias may have occurred. Also since the sample size is small definite conclusion will be difficult.

CONCLUSION:

- Syncope is a complex problem and requires multidisciplinary investigation and management. Most investigations have a low yield in the etiological diagnosis of benign syncope. However, most patients have good prognosis and structured investigation and management plan yield good results.

References:

1. Brignole M, Alboni P, Benditt DG, et al; Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope—update 2004. Europace. 2004;6(6):467-537.
2. Thijs RD, Benditt DG, Mathias CJ, et al. Unconscious confusion—a literature search for definitions of syncope and related disorders. Clin Auton Res. 2005;15(1):35-39.
3. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. N Engl J Med. 2002;347(12):878-885
4. Chen LY, Shen W-K, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Prevalence of syncope in a population aged more than 45 years. Am J Med. 2006; 119(12):1088.e1-1088.e7. doi:10.1016/j.amjmed.2006.01.029.
5. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. Am J Cardiol.2003;91(8):1006-1008, A8. doi:10.1016/S0002-9149(03)00127-9.
6. Blanc JJ, L'Her C, Touiza A, Garo B, L'Her E, Mansourati J. Prospective evaluation and outcome of patients admitted for syncope over a 1 year period. Eur Heart J. 2002;23(10):815-820.
7. Brignole M, Disertori M, Menozzi C, et al; Evaluation of Guidelines in Syncope Study (EGSYS) group. Management of syncope referred urgently to general hospitals with and without syncope units. Europace. 2003;5(3):293- 298. doi:10.1016/S1099-5129(03)00047-3.
8. Day SC, Cook EF, Funkenstein H, Goldman L. Evaluation and outcome of emergency room patients with transient loss of consciousness. Am J Med. 1982;73(1):15-23.
9. Silverstein MD, Singer DE, Mulley AG, Thibault GE, Barnett GO. Patients with syncope admitted to medical intensive care units. JAMA. 1982;248(10):1185-1189.
10. Morichetti A, Astorino G. Epidemiological and clinical findings in 697 syncope events [in Italian]. Minerva Med. 1998;89(6):211-220.
11. Kapoor W. Evaluation and outcome of patients with syncope. Medicine 1990; 69: 160-175.
12. Martin GJ, Adams SL, Martin HG, et al: Prospective evaluation of syncope. Ann Emerg Med 1984; 13: 499- 504.
13. DiMarco JP, Garan H, Harthorne JW, Ruskin JN. Intracardiac electrophysiology techniques in recurrent syncope of unknown cause. Ann Intern Med 1981; 95: 542- 548.

14. Hess DS, Morady F, Scheinman MM. Electrophysiological testing in the evaluation of patients with syncope of undetermined origin. Am J Cardiol 1982; 50: 1309- 1315.
15. Akthar M, Shenasa M, Denker S, et al: Role of cardiac electrophysiologic studies in patients with unexplained recurrent syncope. Pacing Clin Electrophysiol 1983; 6: 192-201.
16. Olshansky B, Mazuz M, Martins JB. Significance of inducible tachycardia in patients with syncope of unknown origin: A long-term follow-up. J Am Coll Cardiol 1985; 5: 216- 233.
17. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: A useful test for investigating unexplained syncope. Lancet 1986;1:1352-1355.
18. Fitzpatrick AP, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. J Am Coll Cardiol 1991; 17:125-130.
19. Stransberg B, Rechavia E, Sagie A, et al. The head- up tilt table test in patients with syncope of unknown origin. Am Heart J 1989; 118: 923-927.
20. Raviele A, Gasparini G, DiPede F, et al. Usefulness of head- up tilt in evaluating patients with syncope of unknown origin and negative electrophysiologic study. Am J Cardiol 1990;65:1322-1327.
21. Kapoor WN, Karpf M, Maher Y, et al: Syncope of unknown origin: The need for more cost-effective approach to its diagnostic evaluation. JAMA 1982; 247: 2687- 2691.
22. DiMarco JP, Philbrick JT. Use of ambulatory electrocardiography (Holter) monitoring. Ann Intern Med 1990; 113: 53-68.
23. Bass EB, Curtiss EI, Arena VC, et al. The duration of Holter monitoring in patients with syncope: Is 24 hours enough? Arch Int Med 1990; 150: 1073- 1078.
24. Recchia D, Barzilai B. Echocardiography in the evaluation of patients with syncope. J Gen Intern Med 1995; 10: 649-655.
25. Stransberg B, Rechavia E, Sagie A, et al. The head- up tilt table test in patients with syncope of unknown origin. Am Heart J 1989; 118: 923-927.
26. Grubb, BP, Temsey-Armos, P, Hahn, H, et al. Utility of upright tilt-table testing in the evaluation and management of syncope of unknown origin. Am J Med 1991; 90:6.
27. Oribe, E, Caro, S, Perera, R, et al. Syncope: the diagnostic value of head-up tilt testing. Pacing Clin Electrophysiol 1997;20:874
28. Almquist, A, Goldenberg, IF, Milstein, S, et al. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. N Engl J Med 1989; 320:346

29. Lacroix, D, Kouakam, C, Klug, D, et al. Asystolic cardiac arrest during head-up tilt test: Incidence and therapeutic implications. Pacing Clin Electrophysiol 1997; 20:2746.
30. Sheldon, R, Rose, S, Koshman, ML, et al. Comparison of patients with syncope of unknown cause having negative or positive tilt-table tests. Am J Cardiol 1997; 80:581.
31. Kapoor, W, Brent, N. Evaluation of upright tilt testing with isoproterenol. Ann Intern Med 1992; 116:358.
32. Grubb, BP, Wolf, D, Samoil, D, et al. Recurrent unexplained syncope in the elderly: The use of head-upright tilt table testing in evaluation and management. J Am Geriatr Soc 1992; 40:1123.
33. Leonelli, FM, Wang, K, Evans, JM, et al. False positive head-up tilt: hemodynamic and neurohumoral profile. J Am Coll Cardiol 2000; 35:188.
34. Fitzpatrick, AP, Lee, RJ, Epstein, LM, et al. Effect of patient characteristics on the yield of prolonged baseline head-up tilt testing and the additional yield of drug provocation. Heart 1996; 76:406.
35. Englund, A, Fredrikson, M, Rosenqvist, M. Head-up tilt test. A nonspecific method of evaluating patients with bifascicular block. Circulation 1997; 95:951.
36. Sumiyoshi, M, Nakata, Y, Mineda, Y, et al. Response to head-up tilt testing in patients with situational syncope. Am J Cardiol 1998; 82:1117.
37. Shen, W-K, Jahangir, A, Beinborn, D, et al. Utility of a single-stage isoproterenol tilt table test in adults: A randomized comparison with passive head-up tilt. J Am Coll Cardiol 1999; 33:985.
38. Mallat, Z, Vicaut, E, Sangare, A, et al. Prediction of head-up tilt test result by analysis of early heart rate variations. Circulation 1997; 96:581.
39. Davis TL, Freemoon FR. Electroencephalography should not be routine in the evaluation of syncope in adults. Arch Intern Med 1990; 150: 2027- 2029.
40. Kapoor WN, Fortunato M, Hanusa BH, Schulberg HC. Psychiatric illnesses in patients with syncope. Am J Med 1995; 99:505- 512.
41. Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A et al. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. Eur Heart J 2006;27:76–82
42. Brignole M, Ungar A, Bartoletti A, Ponassi I, Lagi A, Mussi C et al. Standardizedcare pathway vs usual management of syncope patients presenting as emergencies at general hospitals. Europace 2006;8:644–50.

43. Ammirati F, Colivicchi F, Santini M. Diagnosing syncope in clinical practice. Implementation of a simplified diagnostic algorithm in a multicentre prospective trial—the OESIL 2 Study. Eur Heart J 2000;21:935–40.
44. Disertori M, Brignole M, Menozzi C, Raviele A, Rizzon P, Santini M et al. Management of patients with syncope referred urgently to general hospitals. Europace 2003;5:283–91.
45. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. Eur Heart J 2003;24:811–9.
46. Piotr K, Małgorzata L, Tomasz K et al. Prospective evaluation of diagnostic work-up in syncope patients: results of the PL-US registry. Europace (2010) 12, 230–239
47. Chaun W, Cheng W, Liw e et al. clinical analysis of vasovagal syncope children. Chn J Contemp pediatr, 2010, 12 (9): 723-725.
48. Zhang QY, Du JB, Li WZ et al. Association of clinical features with different hemodynamic patterns in head-up tilt test in children with unexplained syncope. Zhonghua Yi Xue Zazhi 2005 Jul 27;85(28):1962-5
49. Gaggioli G, Bottoni N, Mureddu R, Foglia-Manzillo G, Mascioli G, Bartoli P, Musso G, Menozzi C, Brignole M. Effects of chronic vasodilator therapy to enhance susceptibility to vasovagal syncope during upright tilt testing. Am J Cardiol 1997; 80: 1092-1094
50. El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. Heart 1996; 75: 134-140
51. Van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A, Wieling W. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). J Am Coll Cardiol 2006; 48: 1652-1657
52. Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Barsotti A. Usefulness of a tilt training program for the prevention of refractory neurocardiogenic syncope in adolescents: A controlled study. Circulation 1999; 100: 1798-1801
53. Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M, Del Rosso A, Santarone M, Raviele A, Brignole M. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. Europace 2004; 6: 199-204
54. Reybrouck T, Heidbüchel H, Van De Werf F, Ector H. Longterm follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. Pacing Clin Electrophysiol 2002; 25: 1441-1446