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Clinical Short-Term Outcome of Severe Untreated Aortic Stenosis

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ABSTRACT

Background: sclerocalcific aortic valve is a common condition. Risk stratification and decision making are particularly complex in adults with aortic stenosis (AS), because the disease mainly affects elderly patients who represent a heterogeneous population and require balanced and individualized analysis using a multidisciplinary collaboration. Further research is needed to provide better evidence in particular on spontaneous risk, earlier detection of LV dysfunction, and the results of transcatheter treatment and medical therapy.

Objectives: to study the clinical short term outcome of the severe untreated severe sclerocalcific aortic valve stenosis and also to evaluate the correlation between echocardiography assessment of aortic stenosis and clinical history and examination.

Methods: in our study of 50 patients with severe sclerocalcific aortic stenosis, were subjected to full history taking along with full clinical examination and transthoracic echocardiography at baseline and follow up. The TTE criteria for diagnosis of severe Sclerocalcific aortic stenosis are increased echogenicity and thickening of the aortic valve leaflets with mean gradient greater than 40 mm Hg, and maximum jet velocity greater than 4 m per second, valve area less than 1.0 cm^2.

Results: at short term follow up of our patients (2 years), there were significant increase in the number of patients who developed symptoms of angina and heart failure ($p<0.01$) but there was no statistically significant increase in those who develop syncope ($P=0.106$). There were very evident echocardiographic findings in the form of highly significant ($p<0.01$) decrease in the EF & valve area and increase in the MPG, PPG, Max. Jet velocity.

Conclusion: 41.2% of previously asymptomatic patient developed symptoms at follow up**.** There were very evident and significant changes in the echocardiographic findings related to significant decrease in the EF & vave area and increase in the MPG, PPG, Max. jet velocity and intracardiac dimensions that is reflected in the clinical symptoms progression throughout the follow up period.

Keywords: Sclerocalcific - Severe aortic stenosis - Aortic valve replacement - Ejection fraction – aortic valve area- Max. Jet velocity-mean pressure gradient.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular disease in older adults. Aortic stenosis can be congenital or degenerative, with the latter resulting from calcification of the aortic valve over time. Although congenitally bicuspid valve with calcification is the most common form of AS overall, degenerative calcific (sclerocalcific) AS of the trileaflet valve is the most common form observed in persons aged 60 years and older. Sclerocalcific AS is the most common form of AS among older adults in the United States [(1)].

Calcific AS is a chronic progressive disease. During a long latent period, patients remain asymptomatic. However, it should be emphasized that duration of the asymptomatic phase varies widely among individuals [(2,3)].

Patients may or may not have symptoms, but once symptoms manifest, AS has poor outcomes when left untreated [(2,3,4)].

In addition, patients may develop chest pain on exertion, effort dizziness or lightheadedness, easy fatigability, and progressive inability to exercise. Ultimately, the patient develops the classic triad of chest pain, heart failure, and syncope [(1,5)] .

Sudden cardiac death is a frequent cause of death in symptomatic patients but appears to be rare in the asymptomatic (1% per year) [(3,5)] .

As the severity of aortic stenosis worsens, the force the LV must generate to overcome the obstruction increases progressively. Although inotropic reserve and development of LV hypertrophy serve initially to compensate for this

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increase in demand, these double edged swords leads also to pathologic consequence, onset of symptoms, morbidity and mortality within 3 years of the onset of the angina, syncope, or the symptoms of the heart failure, meanwhile the mortality reaches 75% of symptomatic patients unless the outflow obstruction is relieved by aortic valve replacement (AVR). Thus before aortic valve replacement there is a striking mortality risk of 2% a month in symptomatic patients [6] .

Severe symptomatic calcific aortic valve stenosis (AS) is a proven indication for valve replacement according to the current guidelines. The therapeutic modality of choice is surgical aortic valve replacement (SAVR) [6,7] .

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative treatment for patients with severe AS considered at high surgical risk with promising early and mid-term results. In contrast to surgical replacement, this method forms a much less invasive approach, which therefore may be safely offered for high-risk surgical patients [7] .

Aim of the Work

1. To assess clinical progression of patient with severe untreated aortic stenosis.
2. To evaluate the correlation between echocardiography assessment of aortic stenosis and clinical history and examination.

METHODS

Study subjects:

This study is a prospective observational study that was done on 50 patients with severe sclerocalcific aortic stenosis presented to Ain Shams University Hospitals in the period between April 2014 and April 2016. Any patient diagnosed with sclerocalcific severe aortic stenosis are included the study.

Patients were excluded from the study if they had: Rheumatic aortic stenosis, other significant valvular lesions, chronic renal failure, prosthetic aortic valve, poor echogenic patients, congenital bicuspid aortic valve, history of previous stroke and other co-morbidities that may affect symptoms or life expectancy (i.e. Liver cirrhosis, cancer etc…).

Study methods:

All patients were subjected to full medical history with emphasis on age, gender, diabetes mellitus, hypertension, cigarette smoking, dyslipidemia, time of diagnosis, method of diagnosis (accidental or presence of symptoms) and Symptoms of aortic stenosis (Angina, syncope and heart Failure symptoms). Full clinical examination both General examination and Local were done.

Transthoracic echocardiography (TTE): Echocardiographic Evaluation including 2D, M-mode and color flow mapping (CFM) from parasternal short/long axis and apical 4 – 5 chamber scans.

The following parameters were recorded at the time of diagnosis

M. Mode: Left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), ejection fraction (EF), interventricular septum diameter (IVSDd) and posterior wall diameter (PWDd)

Doppler: Peak and mean pressure gradient (PPG/MPG) across aortic valve, maximum jet velocity (V. Max.) and valve area using continuity equation across the aortic valve.

The TTE criteria for diagnosis of severe Sclero-calcific aortic stenosis are increased echogenicity and thickening of the aortic valve leaflets with mean gradient greater than 40 mm Hg, and maximum jet velocity greater than 4 m per second, valve area less than 1.0 cm^2**.**

Follow up for: Progression of symptoms, hospitalization and Echocardiography: For LV dimensions, wall thickness, EF, valve area & pressure gradient.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Also the following statistical tests were done: Independent-samples t-test of significance was used when comparing between two means. Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters. Binary logistic regression: was used to predict the outcome of categorical variable based on one or more predictor variables.

RESULTS

1. Demographic data of the studied patients:

Table (1): Distribution of gender, age and risk factors among studied patients.

Age	Mean ± SD Range	62.12 ± 7.27 50 – 76
Gender	Female Male	26 (52%) 24 (48%)
Smoking	Negative Positive	36 (72%) 14 (28%)
DM	Negative Positive	41 (82%) 9 (18%)
HTN	Negative Positive	26 (52%) 24 (48%)
Dyslipidemia	Negative Positive	28 (56%) 22 (44%)
CAD	Negative Positive	42 (84%) 8 (16%)

The mean age was 62.12 ± 7.27 years. 48% were males while 52% were females. 48% of patients were hypertensive while 44% were dyslipidemia (table 1).

2. Clinical Data:

A. Comparison between baseline and follow up

Table (2): Comparison between asymptomatic and symptomatic patients at baseline and follow up

Method	Baseline		Follow up		Chi-square test	
	No.	%	No.	%	X^2	P-value
Asymptomatic	34	68%	20	40%	7.890	0.005
Symptomatic	16	32%	30	60%		

16 patients had symptoms at the time of diagnosis, whereas 34 patients were accidentally discovered (asymptomatic). After the period of follow up, the number of symptomatic patents increased from 16 (32%) to 30 (60%) patients. There was highly significant increase in the number of patients who developed symptoms at follow up ($p<0.01$) (table 2).

B. Progression of symptoms:

Table (3): Comparison between the total numbers of the patient both accidentally and symptomatically diagnosed based on symptom developed at baseline and follow up.

Symptom	Presence	At baseline	After follow up	X2	P-value
Syncope	No Yes	41 (82%) 9 (18%)	34 (68%) 16 (32%)	2.613	0.106
Angina	No Yes	42 (84%) 8 (16%)	28 (56%) 22 (44%)	9.333	0.002
NYHA	0 1 2 3	35 (70%) 14 (28%) 1 (2%) 0 (0.0%)	23 (46%) 9 (18%) 14 (28%) 4 (8%)	18.836	0.001

There was significant increase in the total number of the patients suffering from angina and heart failure symptoms at follow up (P<0.01) (table 3).

3. Hospitalization

Table (4): Showing the relation between hospitalization and method of diagnosis.

		Not hospitalized	Hospitalized	Chi-square test	
		No. (%)	No. (%)	X^2/t*	P-value
Method	Accidental	20 (58.8%)	14 (41.2%)	7.034	0.008
	Symptoms	3 (18.75%)	13 (81.25%)		

The percentage of patients needed hospitalization among symptomatic patients at the time of diagnosis was significantly higher than those among accidentally discovered group (p<0.01) (table 4).

4. Echocardiography data:

Table (5): Comparison between echocardiographic findings by M Mode at baseline and follow up.

Echocardiographic parameter		Before	After	Paired t-test	
				T	P-value
EF	Mean ± SD Range	58.04 ± 13.28 37.68 – 85.94	45.40 ± 7.23 31.3 – 63.56	6.829	0.001
LVESD	Mean ± SD Range	32.42 ± 4.65 25 – 42	38.14 ± 4.04 29 – 47	-9.565	0.001
LVEDD	Mean ± SD Range	44.10 ± 5.53 35 – 55	46.80 ± 4.94 33 – 60	-2.813	0.007
IVSDd	Mean ± SD Range	9.58 ± 1.57 7 – 13	10.74 ± 1.71 8 – 15	-5.315	0.001
PWDd	Mean ± SD Range	9.80 ± 1.34 7 – 12	11.44 ± 1.62 9 – 17	-6.872	0.001
PPG	Mean ± SD Range	68.18 ± 3.17 64 – 76.04	74.94 ± 8.12 56.85 – 103.63	-5.714	0.001
MPG	Mean ± SD Range	48.21 ± 2.18 45.33 – 53.6	52.84 ± 5.57 40.41 – 72.48	-5.714	0.001
Max. jet velocity	Mean ± SD Range	4.13 ± 0.10 4 – 4.36	4.32 ± 0.23 3.77 – 5.09	-5.716	0.001
Valve area	Mean ± SD Range	0.76 ± 0.18 0.4 – 1	0.59 ± 0.09 0.29 – 0.79	6.465	0.001

There was a significant decrease in the EF (p<0.01). There was a significant increase in internal LV dimensions (LVEDD and LVESD (P<0.01)). There was also a significant increase in the LV wall thickness (IVSDd and PWDd) (p<0.01). There was a significant increase in the PPG at follow up in comparison to baseline (p<0.01), MPG (p<0.01) and maximum jet velocity (p<0.01). There was a significant decrease in the Valve area (p<0.01) (table 5).

There is a highly significant inverse relation between occurrence of angina symptoms and valve area (p<0.01) (Figure 1) (table 6). There is a borderline statistical significance between development of heart failure symptoms and maximum jet velocity at follow up (p=0.057) (Figure 2) (table 7). There was significant direct relation between occurrence of syncope and DM at follow up (p=0.014) (Figure 3) (table 8).

Table (6): Relation between occurrence of angina symptoms and echocardiographic data at follow up:

		Negative angina	Angina	Independent t-test	
				t	P-value
PPG	Mean ± SD Range	73.03 ± 5.65 56.85 – 79.57	77.38 ± 10.09 61.78 – 103.63	1.929	0.060
MPG	Mean ± SD Range	51.53 ± 3.88 40.41 – 56.02	54.51 ± 6.91 43.81 – 72.48	1.928	0.060
Max. jet velocity	Mean ± SD Range	4.27 ± 0.17 3.77 – 4.46	4.39 ± 0.28 3.93 – 5.09	1.861	0.069
Valve area	Mean ± SD Range	0.63 ± 0.07 0.53 – 0.79	0.55 ± 0.11 0.29 – 0.71	-3.001	0.004
EF	Mean ± SD Range	43.72 ± 6.69 31.3 – 57.81	47.55 ± 7.47 31.85 – 63.56	1.906	0.063

Table (7): Relation between occurrence of heart failure symptoms and echocardiographic data at follow up:

		NYHA				One Way ANOVA test	
		0	1	2	3	F	P-value
PPG	Mean ± SD Range	76.64 ± 7.21 68.89 – 103.63	76.91 ± 5.94 70.9 – 87.98	73.39 ± 9.60 58.37 – 94.09	66.17 ± 7.40 56.85 – 74.65	2.435	0.077
MPG	Mean ± SD Range	54.01 ± 4.94 48.69 – 72.48	54.20 ± 4.07 50.07 – 61.78	51.78 ± 6.58 41.46 – 65.96	46.82 ± 5.09 40.41 – 52.65	2.442	0.076
Max. jet velocity	Mean ± SD Range	4.37 ± 0.20 4.15 – 5.09	4.38 ± 0.17 4.21 – 4.69	4.28 ± 0.28 3.82 – 4.85	4.06 ± 0.23 3.77 – 4.32	2.691	0.057
Valve area	Mean ± SD Range	0.58 ± 0.09 0.29 – 0.72	0.58 ± 0.09 0.39 – 0.68	0.61 ± 0.12 0.37 – 0.79	0.62 ± 0.06 0.59 – 0.71	0.403	0.752
EF	Mean ± SD Range	45.67 ± 5.34 34.9 – 54.73	48.62 ± 10.32 31.3 – 63.56	45.02 ± 7.36 31.85 – 54.2	38.00 ± 4.42 32.13 – 41.42	2.162	0.105

Table (8): Relation between occurrence of syncopal symptoms and demographic data at follow up:

		Negative syncope	Syncope	Independent test	
				t/X²*	P-value
Age	Mean ± SD Range	62.53 ± 7.046 50 – 76	61.25 ± 7.887 50 – 73	-0.577	0.567
Gender	Female Male	16 (47.1%) 18 (52.9%)	10 (62.5%) 6 (37.5%)	1.039	0.308*
Smoking	Negative Positive	24 (70.6%) 10 (29.4%)	12 (75.0%) 4 (25.0%)	0.105	0.746*
DM	Negative Positive	31 (91.2%) 3 (8.8%)	10 (62.5%) 6 (37.5%)	6.062	0.014*
HTN	Negative Positive	18 (52.9%) 16 (47.1%)	8 (50.0%) 8 (50.0%)	0.038	0.846*
Dyslipid	Negative Positive	22 (64.7%) 12 (35.3%)	6 (37.5%) 10 (62.5%)	3.268	0.071*

CAD	Negative Positive	30 (88.2%) 4 (11.8%)	12 (75.0%) 4 (25.0%)	1.418	0.234*

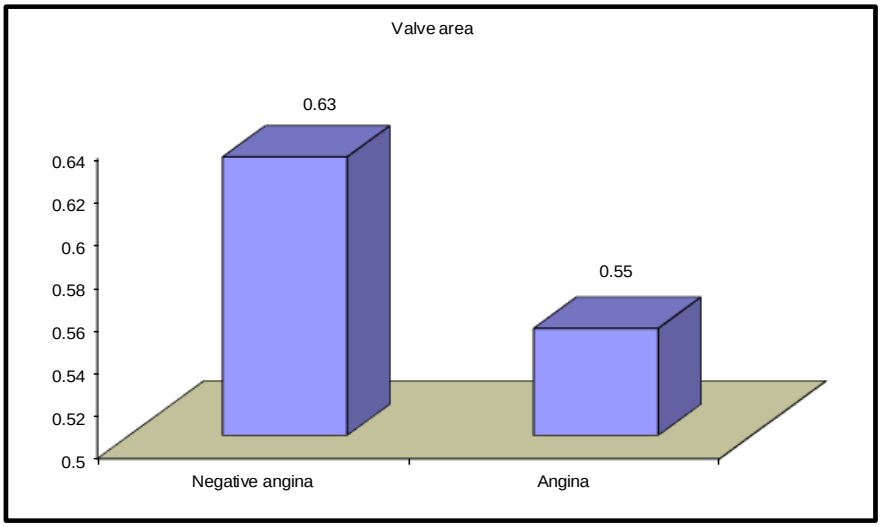

Figure (1): Relation between occurrence of angina symptoms and valve area at follow up

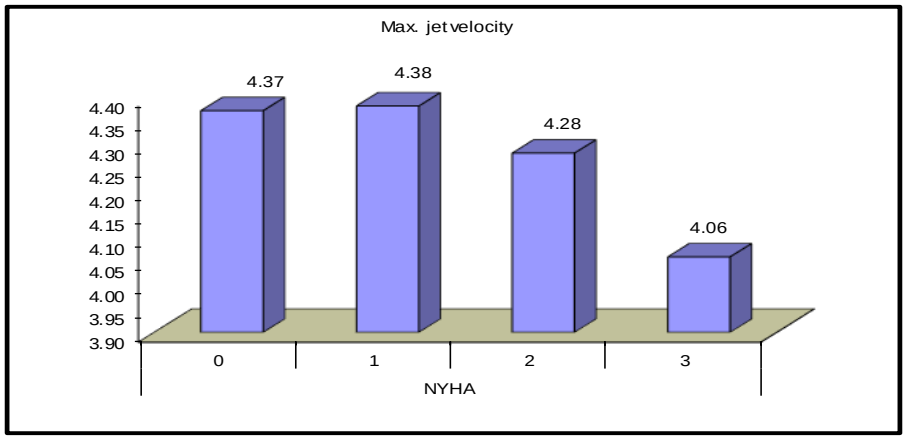

Figure (2**):** Relation between occurrence of heart failure symptoms and max. jet velocity at follow up.

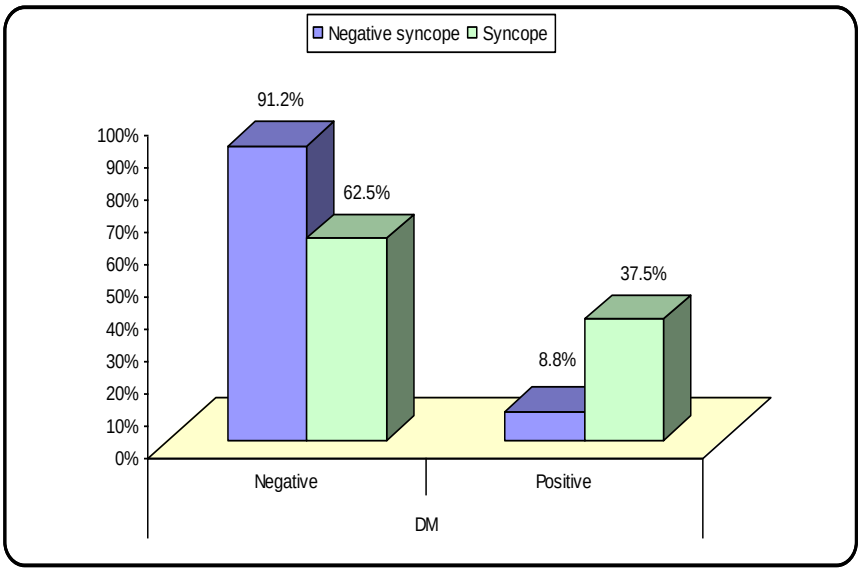

Figure (3): Relation between occurrence of syncopal symptoms and demographic data at follow up.

DISCUSSION

In our study the mean age was 62.12 ± 7.27 years. Worldwide, Aortic sclerosis prevalence is 25% of adults over 65 years of age; however, only about 10% of those patients progress to hemodynamically significant AS. It may occur in middle-aged patients (e.g. 8% among African-Americans) [8,9].

Any difference in the mean age in other studies demographic data when compared to our study most probably would be due to our study small sample size and also may be due to other local factors that contribute to early development of calcification and metabolic syndrome among our population, which could be justified by The results of Multi-Ethnic Study of Atherosclerosis (MESA) and another recent prospective trial suggests that Metabolic Syndrome is independently associated with progression of AS, particularly in younger individuals[10,11].

In our study 24 patients (48%) were males while 26 (52%) were females, almost similarly to a study of 408 consecutive patients (215 women (52.7%) and 193 men (47.3%)) analyzed [12].

In our study, 14 (28%) patients gave history of smoking, 9(18%) were diabetic patients, 24 (48%) were hypertensive patients, 22 (44%) had abnormal lipid profile and 8 (16%) patent gave history of coronary artery disease symptoms. basically, Sclerocalcific aortic valve disease has been correlated with clinical risk factors for atherosclerosis, including smoking, hypertension, dyslipidemia and diabetes.[9,13,14] Hypertension is not uncommon in patients with AS and approximately 40 percent of patients have hypertension [15].

In our study of 50 patients with severe sclerocalcific aortic stenosis, 16 patients (32%) had symptoms at the time of diagnosis (8 patients of them (16%) had symptoms of angina, 9 patients (18%) had symptoms of syncope and 15 patients (30%) had symptoms of heart failure) at presentation.

The number of patients developed symptoms increased from 16 (32%) to 30 (60%) after the follow up period (P<0.01) (22 patient (44%) had symptoms of angina, 16 patients (32%) had symptoms of syncope, and 27 patients (54%) had symptoms of heart failure), this findings was consistent with the results of other study done by ***Rosenhek et al.*** [16] on a larger sample size and Over 2 years of follow-up, showing progression to symptoms requiring valve replacement occurs in ~80% of adults with an AS velocity >4 m/s, compared with about 35% of those with a velocity between 3 and 4 m/s and only 15% of adults with a velocity <3 m/s.

And also this study can be compared with another recent study during a median follow-up of 3.5 years, where Syncope occurred in only 18 (4%) patients, while heart failure requiring admission occurred in 188 (43%) patients as the most frequent event[17].

Also this study is consistent with our study follow up results where (54%) had symptoms of heart failure with highly significant relation between heart failure symptoms and hospitalization (p<0.01) at follow up

and inconsistent where (32%) had symptoms of syncope.

In our study 34 patients (68%) were complete asymptomatic discovered during routine examination. 41.2% of accidentally diagnosed patient developed symptom at follow up which is highly significant (p<0.01), of them 8 patients (23.5%) developed symptoms of angina, 4 patients (11.8%) developed symptoms of syncope and 11 patients (32.4%) developed symptoms of Heart failure at follow up.

In comparison to other study on a large sample on 622 patients with severe asymptomatic AS with a mean 72 years, done at Mayo Clinic.[18] Of these 622 patients, 166 (27%) developed symptoms and had AVR. Another 97 patients (16%) had AVR in the absence of symptoms. At 3-year follow-up, 52% of the 622 patients had developing symptoms, undergone AVR, or died. The most important risk factor for 10-year mortality was absence of AVR (hazard ratio=3.53, p<0.001).

Of 197 consecutive patients with asymptomatic severe AS, early AVR was performed in 102 patients (52%)[4] .

The estimated 6-year all-cause mortality rates were 2% for AVR and 32% for the conventional treatment group (p<0.001). Despite being asymptomatic, patients with very severe AS have a poor prognosis [19].

As regard the Doppler echocardiographic parameters, there was a significant increase in the maximum jet velocity across the decreased valve area. There was also a statistically significant increased estimated MPG and PPG across the more stenotic valve. These results are comparable to the study done by Palta ***et al.*** [20] which concluded an annual rate of reduction in AVA was 0.1 +/- 0.27 cm2 or 7 +/- 18% per year. The rate of progression is highly variable; however, it is difficult to predict in individual patients. In clinical studies, the factors associated with more rapid hemodynamic progression included older age, more severe leaflet calcification, renal insufficiency, hypertension, smoking, and hyperlipidemia [21,22], however in our study this wasn't obvious possibly related to relatively small sample size.

There was also an increase in the onset of syncope form 18% of the patient population to 32% of the patient population. This may be attributed to the worsening of the Aortic stenosis due to the progression of the pathological sclerosis and calcification or may be attributed to the decrease in the myocardial muscle contractility and decreased cardiac output, due to the presence of significantly lower EF at follow-up.

The prevalence of angina symptoms was 16% of the patient population at baseline which increased to 44% (P =0.002) at follow-up. The increased incidence of angina symptoms at follow-up maybe partly due to low coronary filling due to lower cardiac output, as being associated with lower valve area at follow-up and increased myocardial wall thickness, which will impair diastolic filling. Also, angina may be a predictive for associated coronary artery disease progression.[23] The study sample, being of the Egyptian population, where there is high prevalence of Coronary artery disease may be a confounding factor which may increase the incidence of angina symptoms.

As regard the onset of syncopal symptoms there was no associated echocardiographic parameters with the onset of syncopal attacks. This may be due to small sample size and fewer number of patients with syncopal symptoms, being a later symptom in the disease progression, which is not enough to prove the association between syncopal symptoms and different the echocardiographic parameters.

In our study, there was a statistical significance between development of heart failure symptoms and maximum jet velocity at follow up (p=0.057), which goes with current definitions of severe AS that based on prospective studies showing that the V_{max} is the strongest predictor of symptom onset and clinical outcomes. (In adults with calcific AS and an V_{max} >4 m/s, 70 to 80% develop symptoms requiring AVR within 2 years compared to symptom onset in 25-35% of those with a V_{max} between 3 and 4 m/s and only 15% of those with a V_{max} <3 m/s.[16]

Higher V_{max} values (>5 or 5.5 m/s) are associated with even higher rates of symptom onset[19].

From the demographic data, DM was statistically significantly associated with syncope, this may be due DM which aggravates the progression of aortic calcification [24] or may be as a confounder due to associated hypoglycemic attacks which may be mistaken as syncope due to low cardiac output.

Study Limitations

This study is a single center study. Relatively small numbers of patients were included in the study (only 50 patients) and Follow up was at 6 months only (short term). Results were not compared to those undergone AVR.

CONCLUSION

41.2% of previously asymptomatic patient developed symptoms at follow up**.** There were very evident and significant changes in the echocardiographic findings related to significant decrease in the EF & vave area and increase in the MPG, PPG, Max. jet velocity and intracardiac dimensions that is reflected in the clinical symptoms progression throughout the follow up peroid.

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