

ORIGINAL ARTICLE**Thromboembolic events in Sudanese patients
with rheumatic mitral stenosis**Suliman FAE^{1,*}, Taifour KA², Abdoalraheem SA³¹Department of Medicine, Faculty of Medicine, University of Khartoum, ²Department of Medicine, Alzaiem Alazhari University. ^{1,2,3}Adult Cardiology Department, Ahmed Gasim Cardiac Surgery & Renal Transplant Centre, Khartoum, Sudan. Email: faisalae@yahoo.com**Abstract:****Background**

Rheumatic mitral stenosis (MS) is a common problem in the Sudanese community, usually affecting the younger population. It can be a crippling condition with many complications, thromboembolism being one of the most serious.

Objective

The aim of this study is to quantify the prevalence of thromboembolism and to identify its risk factors in Sudanese patients with MS at Ahmed Gasim Cardiac Centre.

Methodology

Records of patients admitted from Jan 1999-Jan 2003, were retrospectively reviewed and data from various clinical and echocardiographic variables were recorded.

Results

A total of 412 patients were studied, 142 (34.5%) were males, 270 (65.5%) were females. There were no significant differences in the gender ($P = 0.606$) or severity of symptoms between patients with and without thromboembolism. Patients with thromboembolism were older ($P < 0.016$), had more frequent atrial fibrillation ($P = 0.017$), smaller mitral valve area ($P = 0.021$) and higher pulmonary artery pressure ($P = 0.012$) compared to patients without thromboembolism. Dilated left atrial (LA) size was significantly associated with thromboembolism ($P = 0.034$), spontaneous echo contrast ($P = 0.048$) and the presence of LA or left atrial appendage (LAA) thrombus ($P = 0.029$). The presence of LA/LAA thrombus was significantly associated with both thromboembolism ($P = 0.05$) and spontaneous echo contrast ($P < 0.0001$). Transoesophageal echocardiography was more sensitive in detecting both spontaneous echo contrast ($P < 0.0001$) and LA/LAA thrombus ($P < 0.0001$) than transthoracic echocardiography.

Conclusion

These results highlight the clinical and echocardiographic risk factors for thromboembolism, the sensitivity of transoesophageal echo for assessment of those patients, and the need for early referral for percutaneous transvenous mitral commissurotomy (PTMC)

Key words Thromboembolism, Mitral Stenosis, Transoesophageal Echo, Spontaneous Echo Contrast, Left Atrial Appendage

Introduction:

Mitral Stenosis (MS) is usually due to rheumatic heart disease^{1, 2}. It is associated with thromboembolism, and before the advent of surgical treatment, this complication occurred in at least 20% of the patients in the course of the disease^{3, 4}. Embolism can affect any organ, and approximately 50% of clinically apparent emboli are found in the cerebral vessels³. Peripheral emboli can cause acute limb ischemia. Thromboembolism can lead to devastating medical and surgical sequel especially in young females. Emboli can be recurrent and multiple in up to a quarter of patients³. A pro-thrombotic state exists in the left atrium (LA) in patients with MS even with appropriate anticoagulation therapy^{5, 6}. The left atrial appendage (LAA) is the commonest site of thrombus formation^{7, 8}. The size of the LAA^{9, 10, 11, 12} and the presence of spontaneous echo contrast^{13, 14, 15, 16, 17} are considered positive predictors of LA thrombus. Mitral valve area (MVA) is inversely related to the presence of spontaneous echo contrast (SEC)^{6, 18, 19, 20, 21, 22}.

Atrial fibrillation (AF) which occurs in more than 40% of patients with MS later in the course of the disease carries a 17-fold increased risk of thromboembolism^{23, 24}. The presence of other valvular lesions in rheumatic heart disease may further affect the development of thromboembolism^{13, 19, 24}. Various clinical and echocardiographic parameters are considered to be predictors of systemic embolism in patients with MS. The LAA is the site most commonly associated with thrombus formation. There has been controversy over whether the LAA size determines thrombo-embolic risk^{4, 9, 25}. SEC, or smoke-like echo, has been defined as an amorphous, swirling, light grey haze inside the cardiac chambers, great arteries and veins. It arises in conditions of stasis, has been

attributed to rouleaux formation and is strongly associated with LAA thrombus formation. LA SEC was found to be a positive predictor of LA thrombus and systemic embolization^{13, 14, 15, 16, 17}.

The clinical and echocardiographic variables related to LA SEC were evaluated in many studies. LA SEC was significantly associated with atrial fibrillation, increased LA dimension^{14, 15, 18-20, 24, 26, 27, 28} and a history of suspected embolism^{13, 29}. SEC is increased in cases of decreased LA flow velocity^{26, 30}. Controversy exists about the effect of MVA on SEC, some studies demonstrated an inverse relationship^{16, 18-22} while others found no significant correlation^{14, 31}. SEC was also found to directly correlate with the degree of trans-mitral gradient^{20, 21}. LA SEC was characterized more frequently by advanced NYHA class in some studies³² while others refuted this finding¹⁸. The severity of MS as graded by MVA is a positive predictor of the development of thrombo-embolic complications in MS^{20, 17}. The presence of significant mitral regurgitation correlates with a lower incidence of SEC, thrombi, and embolization^{13, 19, 24}. The aim of this study is to quantify the prevalence of thrombo-embolic events in Sudanese patients with MS seen at Ahmed Gasim Cardiac Centre and to define their risk factors. Risk factors for thromboembolism in MS have been studied extensively worldwide, but there is no study conducted in Sudanese population to compare their risk factors with the international literature. Ahmed Gasim Centre is a tertiary cardiac facility that provides services to patients from all parts of Sudan.

Patients and methods:

This is a retrospective analytical study. Records of Patients admitted to Ahmed Gasim Cardiac Centre with MS from

January 1999 to January 2003 were reviewed. A total of 412 patients were studied. All patients with a diagnosis of MS confirmed by echocardiography were included. Patients who developed stroke due to other causes (e.g. intracerebral haemorrhage or carotid stenosis) were excluded.

The data collected were as follows:

Personal Data: name, age, gender, residence, occupation, tribe, education level and socioeconomic status. **Clinical variables:** Symptoms: dyspnoea, cough, palpitations, dizziness, syncope, chest pain and its type, other symptoms if included. **Signs:** pulse rate, blood pressure, heart sounds, added sounds, murmurs and chest signs. **Rhythm:** sinus rhythm (SR) versus atrial fibrillation (AF).

Echocardiography (using GE Vingmed®): variable included: MVA (calculated by pressure half time). LA size (quantified by M-mode dimensions in the parasternal long axis view). Pulmonary artery pressure (detected by Tricuspid Regurgitation jet), Presence of other valvular lesions. The presence of LAA thrombus and SEC. Findings on Trans-Oesophageal Echocardiogram (TOE) were also included, when performed.

While planimetry of the mitral valve orifice is considered the reference method for determining MVA, its accuracy can however be influenced by poor acoustic windows, severe calcification of the leaflets tips, excessive gain settings, and inter-observer variability. Hence, the pressure half-time (PHT) method is a simpler approach to estimate the functional MVA using Doppler echocardiography. Therefore, due to the limitations of planimetry and the simplicity of (PHT), the authors chose the latter method for MVA assessment in this study.

MVA was defined using the guidelines of the European Society of Cardiology and degree of stenosis is graded as mild when $MVA > 1.5 \text{ cm}^2$, moderate $MVA = 1.5-1 \text{ cm}^2$ and severe when $MVA < 1.0 \text{ cm}^2$.

Thromboembolism is diagnosed when ischemic pain and or dysfunction of the affected site is present.

Statistical Methods:

SSPS was used to analyse the data. Chi Square test was used to analyse all the data except Age, MVA, LA diameter and pulmonary artery pressure where correlation was used.

Results

A total of 412 patients were included in the study, all of whom had a Trans-Thoracic Echocardiography (TTE), and 40 patients (9.7%) had TOE. Of those 142 (34.5%) were males, 270 (65.5%) were females. In patients who had thromboembolism, 3 were males and 23 were females. However, that was not statistically significant ($P=0.606$).

The prevalence of thromboembolism (TE) in the studied population was 26/412 (6.3%). The types of thromboembolism were as follows: 2/26 (7.7%) had renal emboli, while 24/26 (92.3%) had hemiplegia. 17/412 (4.1%) had intra-cardiac thrombus (ICT) while 25/412 (6.1%) had SEC.

There was a significant association between the presence of ICT and TE ($P=0.05$). There was also a significant association between the presence of SEC and the presence of ICT ($P < 0.0001$). There was no significant association between SEC and TE ($P= 0.624$) **Figure (1).**

Of the 17 patients who had LA/LAA thrombus, 11 patients (64.7%) had the thrombus shown by TOE, while 6 patients (35.3%) had it shown by the TTE. **Figure (2).** TOE was more sensitive in detecting LA/LAA thrombus than TTE with ($P = <$

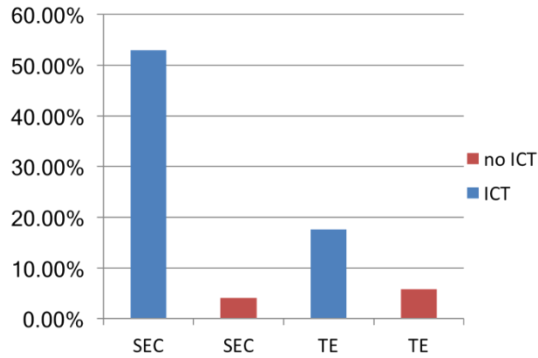


Figure 1: Association between ICT, SEC and TE
 TE = Thromboembolism. SEC= spontaneous Echo contrast. ICT = Intracardiac Thrombus

0.0001). 25 patients (100%) had the SEC shown by TOE while 6 patients (24%) had it shown by the TTE. Therefore, TOE was more sensitive in detecting SEC than TTE ($P = < 0.0001$).

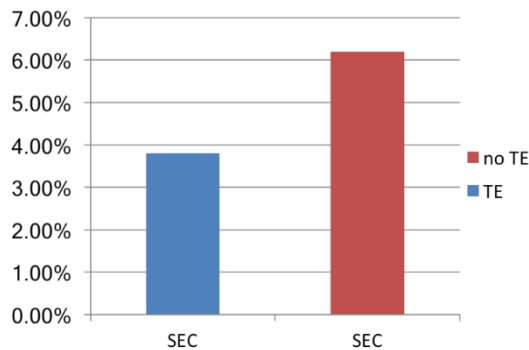


Figure 2: thromboembolism TE, versus spontaneous echo contrast SEC

TOE revealed the presence of SEC in 25 patients (62.5%) and the presence of LAA thrombus in 17 patients (42.5%). TOE was more sensitive in detecting LA/LAA thrombus than TTE ($P = < 0.0001$).

The age range of the study population was between 7 to 80 years with a mean age of (27.87 years). There was significant association between the increase in age and the occurrence of thromboembolism ($P = 0.016$).

302 (73.3%) had dyspnoea, 159 (38.6%) had cough, 243 (59.0%) had palpitations, 10 (2.4%) had dizziness, 20 (4.9%) had

syncope, 102 (24.8) had chest pain while 165 (40.0%) had additional symptoms. There was no significant association between dyspnoea and TE, SEC and the presence of intra-cardiac thrombus (ICT) ($P = 0.119, 0.168$ & 0.414 respectively). There was no significant association between palpitation and TE, SEC or ICT ($P = 0.523, 0.755$ & 0.989 respectively). 271 (67.4%) patients were in SR and 131 (32.6%) were in AF.

Figure (3) shows the relation between the heart rhythm and thrombo-embolism (TE), SEC and the presence of LA/LAA thrombus (ICT). There was a significant association between the presence of AF and TE ($P = 0.017$). Of the 26 patients having thrombo-embolism, 12 patients (41.7%) were in SR. The association between the cardiac rhythm, SEC and LA/LAA thrombus was not statistically significant ($P = 0.344, 0.193$) respectively.

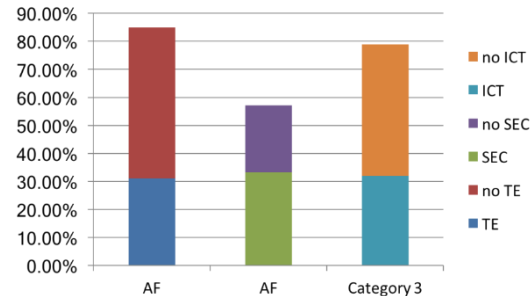


Figure 3: Cardiac rhythm versus other variables

The clinical diagnosis of heart failure was made in 258 (62.6%) of the patients, 144 (35.0%) were not in failure, it was unknown in 10 patients (2.4%). There was no statistically significant association between the clinical diagnosis of heart failure and TE, SEC and the presence of ICT with ($P = 0.681, 0.316, 0.357$) respectively.

Table (1) showed Mean and SD of MVA, LA size and PA pressure.

The MVA of 397 patients was determined; it ranged from 0.32 to 4.10 cm² with a mean value of 1.43 cm². There was a significant association between the MVA

and TE ($P = 0.021$), but there was no statistically significant association between the MVA and SEC or the presence of ICT ($P = 0.104$ & 0.021 respectively).

Variable	Mean	SD
MVA	1.43	0.81
LA size	5.78	7.56
PA pressure	47.9	38.16

Table 1: Mean values of MVA, LA size, PA pressure

The LA size of 322 patients was determined; it ranged from 1.30 to 7.25 cm² with a mean value of 5.78 cm². There was statistically significant association between the LA size and TE, the presence of SEC and ICT ($P = 0.034$, 0.048 & 0.029 respectively).

The pulmonary artery pressure of 216 patients was evaluated. It ranged from 29-160 mmHg with a mean of 47.98 mmHg. There was a statistically significant association between pulmonary artery pressure and TE ($P = 0.012$).

60/412 (14.6%) patients had Aortic Stenosis (AS), 190/412 (46.1%) had Tricuspid Regurgitation (TR), 194/412 (47.1%) had Mitral Regurgitation (MR) while 208/412 (50.5%) had Aortic Regurgitation (AR).

There was a significant correlation between the absence of MR and SEC ($P < 0.0001$), 94% of those with ICT had no mitral regurgitation; there was significant association between the absence of mitral regurgitation and ICT ($P = 0.001$). However, there was no significant association between the absence of MR and TE ($P = 0.18$).

There was a significant association between the absence of AR and TE ($P = 0.038$), but there was no significant association between AR and SEC, and the presence of ICT ($P = 0.135$ & 0.4335 respectively).

There was no significant association between AS and presence of TE, SEC and ICT with ($P = 0.651$, 0.122 , 0.300) respectively. There was no significant association between TR and presence of TE, SEC and ICT ($P = 0.224$, 0.543 & 0.564 respectively).

Discussion

One of the aims of the study was to determine the risk factors for TE in patients with MS. Many clinical and echocardiographic variables are studied in relation to TE. We attempted to identify any association between those variables, SEC and the presence LA/LAA thrombus as well.

412 patients with a diagnosis of MS were included in the study, 65.5% of them were females. In the studied population, there was no effect of gender on thromboembolism. A similar finding was demonstrated by Chiang *et al* in their study which revealed that the prevalence of left atrial thrombus and left atrial SEC was similar in male and female patients^{33,34}.

The majority of the studied population were below the age of 40 years (87.4%), signifying that MS tends to affect the productive age group, thereby negatively impacting on the community's economy and prosperity. There was a significant association between age and thromboembolism that was consistent with the findings of Chiang *et al* in a separate study theirs, which demonstrated that age was a significant predictor of thromboembolism for patients in SR³¹.

62.4% of our studied population were of low socio-economic status, again reflecting the

prevalence of rheumatic fever in this sector of the community.

There was no significant association between the dyspnoea grade and thromboembolism in this study ($P = 0.119$). No association was found between SEC and the grade of dyspnoea. However, Vigna *et al* studied concluded that patients with LA SEC, compared with those without LA SEC, tended to have more advanced NYHA class¹⁸. Although the majority of those with thromboembolism (57.7%) had palpitations, and the majority of those with SEC (56.0%) and LA/LAA thrombus (58.8%) had palpitations, we found no statistically significant association between those three variables and the presence or absence of palpitations. This could be attributed to the fact that many patients with AF may not complain of palpitations.

In this study, a significant association was confirmed between AF and thromboembolism. This is consistent with what is mentioned in the literature and found in many previous studies^{14, 15, 18-20, 24, 26-28}.

Of the 26 patients having thromboembolism, 12 patients (46.1%) were in SR. This emphasizes the fact that thromboembolism, although significantly associated with AF, can still occur in SR, a finding that has previously been observed by Khatouri *et al*¹⁷. In our study however, the relationship between AF on one hand and SEC & LA/LAA thrombus on the other hand was found not to be statistically significant. Most patients without SEC (66.8%) and LA/LAA thrombus (68.1%) were in SR. This could be attributed to fact that SEC and LA/LAA thrombus were detected in a small number of patients 25 and 17 patients respectively in comparison to the large number of the study population (412) patients. Another possibility is that those very patients may have had paroxysmal AF.

The study found that TOE was more sensitive in detecting both SEC and

LA/LAA thrombus as compared to TTE. Unfortunately, it was only performed on 40 patients (9.7%) of the studied population, which could explain the detection of a small number of patients with SEC and LA/LAA thrombus and is a limitation of this study. Another identified significant association was between MVA and thromboembolism, which is consistent with the findings of Khatouri *et al* study¹⁷. However, CW Chiang *et al*³¹ suggested that the significance of MVA in patients with SR could be a false alarm as they noted that patients with a small MVA were more likely to undergo percutaneous balloon mitral commissurotomy (PTMC). When those patients were excluded, MVA become a non-significant predictor of thromboembolism. None of the patients in our study had PTMC.

In our study, the majority of patients with MVA $< 1.0\text{cm}^2$ had SEC (58.3%) and had LA/LAA thrombus (53.3%), while only 8.3% with MVA $> 1.6\text{cm}^2$ had SEC. None with MVA $> 1.6\text{cm}^2$ had LA/LAA thrombus. There was no statistically significant association between MVA and SEC or the presence of LA/LAA thrombus.

Many previous studies^{16, 18-22} have already established the existence of a significant association between MVA and SEC. However, Rittoo *et al* in particular found no significant association between MVA and SEC¹⁴.

The study demonstrated a significant association between SEC and LA size, a finding that is consistent with the results of many other previous studies^{14, 15, 18-20, 24, 26-28}.

A significant association was also identified between LA/LAA thrombus and LA size ($P = 0.029$), which is again consistent with the results of other previous studies^{10, 16, 28}. Furthermore, the study demonstrated a significant association between pulmonary hypertension and thromboembolism ($P = 0.012$). As

pulmonary hypertension correlates with the severity of MS, we can by extension conclude that patients with severe MS are more likely to have thromboembolism.

Other studies have shown that the presence of significant MR correlates with a lower incidence of SEC, thrombi and embolization^{13, 19, 24}. This study has shown the same finding in relation to SEC and thrombi but the relationship to thromboembolism did not reach statistical significance. Although the majority of those with thromboembolism (65.4%) had no MR, this is possibly because the degree of MR was not determined in most of the patients.

There was a significant association between the absence of AR and thromboembolism ($P = 0.038$), and between the presence of LA/LAA thrombus and thromboembolism. This seems logical and had been previously demonstrated³⁵. A significant association was also shown between the presence of intra-cardiac thrombus and SEC, which is consistent with the literature and the results of many previous trials^{14, 16, 29, 30}. Other studies have also established an association between LA SEC and thromboembolism^{13, 15, 17, 29}, a finding that was not demonstrated in our study. Like previous studies, our study has confirmed that TOE is more sensitive in detecting SEC than conventional TTE, yet still no association could be established between SEC and thromboembolism, probably due to the small number of patients who underwent TOE.

In the presence of LA SEC, Chiang *et al* identified some association between SEC and systemic embolism that did not reach statistical significance ($P = 0.056$). They concluded that LA SEC might confound or interact with other variables³¹. As there is a significant association between SEC and

ICT, and as there is a significant association between ICT and thromboembolism, it is reasonable to conclude that SEC correlates with thromboembolism. The majority of thrombo-embolic events (88.5%) were cerebral strokes, which is a higher percentage than the 50% that is described in the literature³.

Conclusion:

MS is more common in young females (65.5%) and in patients of low social classes (62.4%). There was a positive correlation between age and thromboembolism and significant association between MVA, LA size, pulmonary hypertension and thromboembolism. Thromboembolism is significantly associated with AF despite the fact that 46.1% of patient had thromboembolism while in SR. The presence of MR and AR were found to be protective against thromboembolism. The presence of LA/LAA thrombus was significantly associated with both thromboembolism and SEC. TOE is more sensitive in detecting both SEC and LA/LAA thrombus than TTE. Cerebral strokes accounted for the vast majority of thrombo-embolic events. Further prospective studies are needed to evaluate the benefit of anti-coagulating patients in SR who have more risk factors for thromboembolism. Older patients with severe MS, smaller MVA, dilated LA and elevated pulmonary artery pressure should undergo TOE in order to detect the presence of LA/LAA thrombus and/or SEC.

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References

- ¹ Wayne R, Alexander RC, Schlant VF, (Editorials). Mitral valve disease. Hurst's The Heart, ed. Philadelphia: McGraw Hill Company; 1998; 64: 1789-1799.
- ² Burge DJ, De Horatius RJ. Acute rheumatic fever. *CardiovascClin* 1993; 23: 3-23.
- ³ Libby Z. Valvular heart disease. In: Braunwald E, Zipes D, Libby P, (editors). *Braunwald Heart Disease*. 6th ed. Philadelphia: Saunders; 2001; 46
- ⁴ Neilson GH, Galea EG, Harsack KF. Thromboembolic complications of mitral valve disease. *Aus NZJ Med* 1978; 8 (4): 377-76.
- ⁵ Yamamoto K, Kazuyuki Shimada. A hypercoagulable state in the left atrium of patients with MS. *N Eng J Med* 1993; 328:1043-44.
- ⁶ Yamamoto K, Seino Y, Mito H, Fujikawa H. Coagulation activity is increased in the left atrium of patients with MS. *J Am CollCardiol* 1995; 25(1): 107-12.
- ⁷ Manning WJ, Siverman DI, Katz SE. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. *J Am CollCardiol* 1994; 23:1535-540
- ⁸ Leung DY, Black IW, Cranney GB. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J Am CollCardiol* 1994;24:755-62
- ⁹ Sommerville W, Chambers J. Systemic embolism in MS: relation to the size of the left atrial appendix. *BMJ* 1964; ii: 1167-169.
- ¹⁰ Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation* 1991; 84: 223-31.
- ¹¹ Rubin DN, Katz SE, Riley MF. Evaluation of left atrial appendage anatomy and function in recent-onset atrial fibrillation by transesophageal echocardiography. *Am J Cardiol* 1996; 78:744-78.
- ¹² Kato H, Nakanishi M, Maekawa N. Evaluation of left atrial appendage stasis in patients with atrial fibrillation using transesophageal echocardiography with an intravenous albumin-contrast agent. *Am J Cardiol* 1996;78:365-69
- ¹³ Black IW, Hopkins AP, Lee LC, Walsh WF. Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. *J Am CollCardiol* 1991; 18(2): 398-404.
- ¹⁴ Ritto D, Sutherland GR, Gurrie P, Starkey IR, and Show TR. "A prospective study of left atrial spontaneous echo contrast and thrombus in 100 consecutive patients referred for balloon dilation of mitral valve. *J Am SocEchocardiogr* 1994; 7 (5): 516-27
- ¹⁵ Vincelj V, Sokol I, Jaksico J. Prevalence of clinical significance of left atrial spontaneous echo contrast detected by transesophageal echocardiography. *Echocardiography* 2002; 19 (4):319-24.
- ¹⁶ Goswami KC, Yadaw R, Rao MB, Bahl VK, Talwar KK, et al. Clinical and echocardiographic predictors of left atrial clot and spontaneous echo contrast in patients with severe rheumatic MS: a prospective study in 200 patients by transoesophageal echocardiography. *Int J Cardiol* 2000; 73 (3): 273-79.
- ¹⁷ Khatour A, Kendoussi M, Elyounassi B, Nazzi M, Zbir E, et al. Predictive factors of thromboembolic complications in MS in sinus rhythm. *Ann CardiolAngeiol (Paris)* 1996; (10): 573-76.

- ¹⁸ C Vigna G, deRito V, Criconia GM, Russo A, Testa M, et al. Left atrial thrombus and spontaneous echo-contrast in non-anticoagulated mitral stenosis, a transoesophageal echocardiographic study. *Chest*; 103: 348-52.
- ¹⁹ Karatasakis GT, Gotsis AC, Cokkinas DV. Influence of mitral regurgitation on left atrial thrombus and spontaneous echocardiographic contrast in patients with rheumatic mitral valve disease. *Am J Cardiol* 1995; 76(4): 279-81.
- ²⁰ Bernstein NE, Demopoulous LA, Tunick PA, Rosenzweig BP, Kronzan I. "Correlates of spontaneous echo contrast in patients with MS and normal sinus rhythm. *Am Heart J* 1994; 128 (2): 287-92.
- ²¹ Kaslival RR, Mittal S, Kanojia A, Singh RP. A study of spontaneous echo contrast in patients with rheumatic MS and normal sinus rhythm in an Indian perspective. *Br Heart J* 1995; 74 (3): 296-99.
- ²² Agarwal AK, Venugopalan P. Left atrial spontaneous echo contrast in patients in rheumatic mitral valve stenosis in sinus rhythm: relationship to mitral valve and left atrial measurements. *Int V Cardiol* 2001; 77(1): 63-8
- ²³ Wolf PA, Dawber TR, Thomas HE. Epidemiological assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology* 1978; 28: 973-77.
- ²⁴ Kranidis, A, Koulouris S, Anthopoulosl. Clinical implications of left atrial spontaneous echo contrast in mitral valve disease. *J Heart Valve Dis* 1993; 2 (3): 257-58.
- ²⁵ Fleming H, Bailey SM. Mitral valve disease, systemic embolism and anticoagulants. *Postgrad Med J* 1971;47:599-604
- ²⁶ Chen YT, Kan MN, Ghen JS, Lin WW, Hwang DS, et al. Contributing factors to formation of left atrial spontaneous echo contrast in mitral valvular disease. *J Ultrasound Med* 1990; 9(3):151-55.
- ²⁷ Vigna C, de Rito V, Criconia GM, Russo A, Testa M, et al. Left atrial thrombus and spontaneous echocontrast in nonanticoagulated MS. A transoesophageal echocardiographic study. *Chest* 1993; 103(2): 331-32
- ²⁸ Conradie C, Schall R, Marx JD. Echocardiographic study of left atrial thrombi in MS. *ClinCardiol* 1993;16 (10): 729-31
- ²⁹ Daniel WG, Nellessen U, Schroder E, Nomast N, Daniel B, et al. Left atrial spontaneous echo contrast in mitral valve disease, an indication for an increased thromboembolic risk. *J Am CollCardiol* 1988; 11(6); 1204-11.
- ³⁰ Gonzalez TE, Garcia-Fernandez MA, Perez-David E, Bermejo J, Moreno M, et al. Predictors of left atrial spontaneous echo contrast and thrombi in patients with MS and atrial fibrillation. *Am J cardiol* 2000; 86 (5): 529-34.
- ³¹ Chiang CW, Sing -kai Lo, Yu-ShienKo, Nye-Jan Cheng. Predictors of systemic embolism in patients with MS. *Annals Intern Med* 1998; 128:885-99.
- ³² Tsakinis AG, Gordon DA, Padiyar R, Frechette D. The role of displacement of the mitral annulus in left atrial filling and emptying in the intact dog. *C and J Physiol Pharmacol* 1978; 56(3): 447.
- ³³ Chiang CW, Kuo CT, Chen WJ, Lee CB, Hsu Ts. Comparison between female and male patients with MS. *Br Heart J* 1994; 72(6): 567-70.
- ³⁴ Chiang CW, Kuo CT, Chen WJ, Lee CB, Hsu Ts. Comparison between female and male patients with MS. *Br Heart J* 1994; 72(6): 567-70.
- ³⁵ Stollberger G, Chnupa P, Kronik G, Brainin M. Transoesophageal Echocardiography to Assess Embolic Risk in Patients with Atrial Fibrillation. *Ann Intern Med* 1998; 128: 630-38.