Volume-6, Issue-1, January - 2017 • ISSN No 2277 - 8160 IF : 3.62 | IC Value 80.26

Original Research Paper Medicine

ETIOLOGY AND CLINICAL PRESENTATION OF ATRIAL FIBRILLATION, ITS RELATION WITH

Sathyan E Junior resident, Department of General Medicine, Meenakshi medical college and research institute, kanchipuram.

Anbazhagan Professor, Department of General Medicine,Meenakshi medical college and research institute, kanchipuram

Gandhi srinivasarao Senior resident,Department of General Medicine,visakha institute of medical scineces, vizag.

ABSTRACT

BACKGROUND

Atrial fibrillation is the most common cardiac arrhythmias encountered in clinical practice, which is caused by various etiologies and it leads to morbidity and mortality.

AIM

1. To know various clinical presentation of atrial fibrillation.
2. To know various etiologies of atrial fibrillation.
3. To know the relation between atrial fibrillation and left atrial size.

METHODS AND MATERIAL: The material of this study was patients attending the department of general medicine in collaboration with cardiology department, MMCH &RI ,Kanchipuram. The study group consists of 50 cases of atrial fibrillation. A set of investigations were done to detect underlying causes and to know the left atrial size. Similar etiologies of AF and left atrial size is calculated. **RESULTS** Most commonclinical presentation was dyspnoea, chronic rheumatic heart disease was the most common underlying cause, left atrial size most commonly associated with AF was between 4 to 5.

KEYWORDS : AF-atrial fibrillation, MR- mitral regurgitation, MS-mitral stenosis, TR-tricuspid regurgitation, MI-myocardial infarction, LVH-left ventricular hypertrophy, CHF-congestive cardiac failure

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice[33].In atrial fibrillation, most symptoms are caused by a poorly controlled or irregular ventricular rate, and the associated risk of death is doubled in patients who have a history of atrial fibrillation,[19,8,2,44,6,34,35,43].The prevalence of AF is 1% in the general population[11]; the prevalence of AF increases markedly with age.Approximately 1% of patients with AF are <60 years of age, whereas up to 12% of patients are 75 to 84 years of age. More than one third of patients with AF are ≥80 years of age[7,9,25,27].The mechanisms causing and sustaining AF are multifactorial, and AF can be complex and difficult for clinicians to manage. AF symptoms range from non-existent to severe. Frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events related to AF result in significant morbidity and mortality [41]including congestive heart failure[26] and death.AF is associated with a 5- fold increased risk of stroke[17] and stroke risk increases with age [42].Key risk factors for AF include increasing age[6,30],cardiac valvular disease[2,16,30] hypertension[2,16],congestive heart failure(CHF),diabetes, myocardial infarction (MI),obesity, and structural abnormalities such as left ventricular hypertrophy(LVH)[17,37]which are constituting the economic burden also[5].AF is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction.The most common symptom of AF is fatigue. The appearance of AF is often associated with exacerbation of underlying heart disease, either because AF is a cause or consequence of deterioration, or because it contributes directly to deterioration.AF also confers an increased risk of stroke and/or peripheral thromboembolism owing to the formation of atrial thrombi, usually in the left atrial appendage (LAA).

EPIDEMIOLOGY

AF affects 1–2% of the population, and this is likely to increase in the next 50 years.In acute stroke patients, systematic electrocardiographic (ECG) monitoring would identify AF in 1 in 20 subjects, a far greater number detected than by standard 12-lead ECG recordings. AF may long remain undiagnosed (silent AF)[18], and many patients with AF will never present to hospital[22]. Hence, the 'true' prevalence of AF is probably closer to 2% of the population. The prevalence of AF increases with age, from 0.5% at 40–50 years, to 5–15% at 80years[13,27].Men are more often affected than women.

ETIOLOGY& RISK FACTORS

Multiple clinical risk factors, electrocardiographic and echocardiographic features, and biochemical makers are associated with an increased risk of AF.One epidemiologic analysis found that 56% of the population attributable risk of AF could be explained by ≥1 common risk factor[14].Thus, it may be possible to prevent some cases of AF through risk factor modification such as blood pressure control or weight loss.Many potentially "reversible" causes of AF have been reported, including binge drinking, cardiothoracic and non-cardiac surgery, myocardial infarction (MI), pericarditis, myocarditis, hyperthyroidism, electrocution, pneumonia, and pulmonary embolism[24,32].AF that occurs in the setting of Wolff-Parkinson-White (WPW) syndrome, AV nodal re-entrant tachycardia, or atrial ectopic tachycardia may resolve after catheter ablation for these arrhythmias[38]. It is important to recognize that there are few data to support the notion that patients with AF that occurs in the setting of 1 of these potentially "reversible" conditions are, in fact, cured of AF after effective treatment or elimination of the condition. Since long-term follow-up data are not available in these clinical scenarios and AF may recur, these patients should receive careful follow-up.In the absence of an accessory AV pathway, the ventricular rate is determined by the conduction and refractory properties of the AV node and the sequence of wave fronts entering the AV node[20,36]. L-type calcium channels are responsible for the

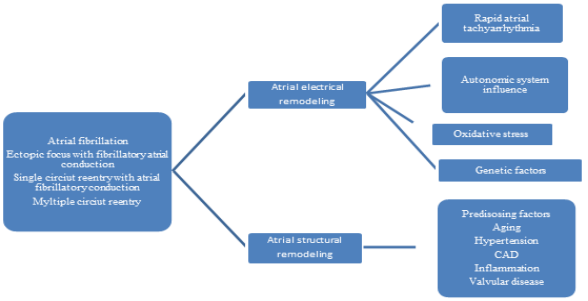
major depolarizing current in AV nodal cells. Beta-adrenergic receptor stimulation enhances AV nodal conduction, whereas vagal stimulation (muscarinic receptor activation by acetylcholine) impedes AV nodal conduction[36]. Sympathetic activation and vagal withdrawal such as with exertion or illness, accelerates the ventricular rate. Each atrial excitation wave front that depolarizes AV nodal tissue renders those cells refractory for a period of time, preventing successive impulses from propagating in the node—an effect called concealed conduction. This effect of concealed conduction into the AV node explains why the ventricular rate can be faster and more difficult to slow when fewer atrial wave fronts are entering the AV node, as in atrial flutter, compared to AF[10].Loss of atrial contraction may markedly decrease cardiac output, particularly when diastolic ventricular filling is impaired by mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy[1,40]. After restoration of sinus rhythm, atrial mechanical function fails to recover in some patients, likely as a consequence of remodelling or underlying atrial disease and duration of AF[39]. Ventricular contractility is not constant during AF because of variable diastolic filling time and changes in the force-interval relationship[3,4]. Overall, cardiac output may decrease and filling pressures may increase compared to a regular rhythm at the same mean rate .The two commonly recognized pathophysiologic processes underlying AF include

1) Enhanced automaticity in 1 or more rapidly depolarizing foci, typically in the superior pulmonary veins, and

2) Re-entry involving 1 or more circuits (known as the multiple wavelet hypotheses.
3) Two processes are not mutually exclusive and may coexist.

In the first scenario, a single focal discharge in the pulmonary veins, or short bursts of multiple focal discharges, may initiate AF[12]. In addition, AF may begin as a rapid atrial tachycardia from the pulmonary veins, but result 4 in electrical remodelling that promotes multiple circuit re-entry Af[28].

The following diagram depicts the multiple factors involved in the pathogenesis of AF:



Factors involved in the pathogenesis of atrial fibrillation. Adapted fromLeonardi, M &Bissett, J. CurrOpinCardiol. 2005; 20:417
The mechanisms involved in AF are summarized in the figure below:

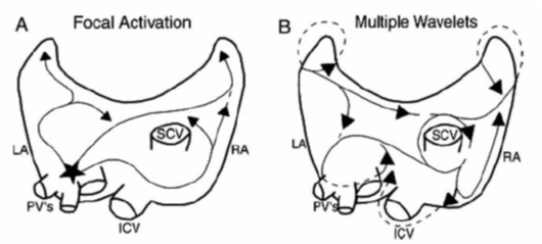


Figure - 5

Posterior view of electrophysiological mechanisms in atrial fibrillation.A)Focal activation: the initiating focus (indicated by the star) often lies within the pulmonary veins. B) Multiple wavelet re-entry: wavelets (indicated by the arrows) randomly re-enter tissue previously activated by the same or another wavelet. From Fuster, V et al. J Am CollCardiol. 2006;48:854-906.Regardless of the mechanism initiating the arrhythmia, atrial electrical properties are modified in a way that promotes the occurrence and maintenance of Af[23]

MATERIALS

The material for this study was patients attending the department of General medicine in collaboration with Cardiology department, MMCH & RI, Kanchipuram, from Sep 2014-Sep-2016.The study group consists of 50 cases of atrial fibrillation.Percentages of patients presented with various clinical manifestations were calculated.Similarly percentages for various etiologies of AF and left atrial size were also calculated.

AIMS & OBJECTIVES

1. To know various clinical presentations of atrial fibrillation.
2. To know various etiologies of atrial fibrillation.
3. To know the relation between atrial fibrillation and left atrial size.

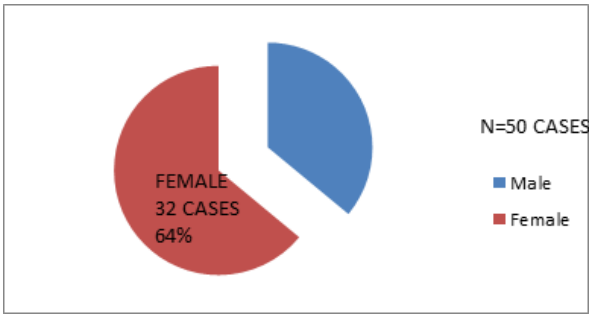
RESULTS:

In present study 64% were females and the rest 36% were males(Table:1). Majority of cases (30%) of AF were between ages 41-50 years. Among cases in the age group 41-50 years, females were predominant (80%) and in cases more than 51 years, males (55%) a slight preponderance is seen. Dyspnoea (90%) and palpitations (84%) were most common clinical presentations and four cases had presented with 8%stroke (Table:2).Majority (62.0%) of cases of atrial fibrillation were due to chronic rheumatic heart disease and other causes of AF were Hypertension (18%), CAD (8%) and Heart failure (6%)(Table:3). Majority of CRHD patients with AF were females (77.4%) while males were predominant with Hypertension (66.6%), alcohol (100%), COPD (100%) andpatients with Coronary artery diseases showed an equal incidence (50%)(Table:4). Valvular lesion in CRHD that was most commonly associated with atrial fibrillation was combined lesion of mitral stenosis, mitral regurgitation and tricuspid regurgitation (45%). In the present study 66.6% of mitral stenosis patients with AF had mitral valve area(MVA) of<1 sq.cm i.e., severe M S and 30% of cases had MVA of 1-1.5 sq.cm i.e., moderate MS(Table:5).Majority of atrial fibrillation cases (52%) had left atrial size of 4 to 5 cm and only 18% of cases had left atrial size of more 5 cm.(Table:6)

CLINICAL PRESENTATIONS	NO.OF PATIENTS
DYSPNOEA	45(90%)
PALPITATIONS	43(86%)
PEDAL EDEMA	24(48%)
CHEST PAIN	19(38%)
HAEMOPTYSIS	11(22%)
STROKE	4(8%)
ASYMTOMATIC	1(2%)

CLINICAL PRESENTATION IN AF (TABLE: 2)

SEX DISTRIBUTION OF AF (Table:1)



ETIOLOGY OF AF(Table : 3) N=50

AETIOLOGY	NO OF CASES (%)
RHEUMATIC HEART DISEASE	31(62.0)
HYPERTENSION	9(18.0)
CORONARY ARTERY DISEASE	4(8.0)
HEART FAILURE	3(6.0)
HYPERTHYROIDISM	1(2.0)
ALCOHOL	1(2.0)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1(2.0)

SEX DISTRIBUTION OF AETIOLOGY N=50 (Table:4)

AETIOLOGY	NO OF CASES	MALES	FEMALES
CRHD	31	7	24
HTN	9	6	3
CAD	4	2	2
CCF	3	1	2
HYPERTHYROIDISM	1	0	1
ALCOHOL	1	1	0
COPD	1	1	0

VALVULAR LESION	NO OF PATIENTS
MITRAL STENOSIS(MS)	4(12.9%)
MR	1(3.22%)
MS + MR	8(25.8%)
MS+MR+TR	14(45.1%)
MS+MR+AORTIC REGURGITATION(AR)	2(6.45%)
MS+MR+AORTIC STENOSIS(AS)	2(6.45%)
ISOLATED AR	0(0.00%)
ISOLATED AS	0(0.00%)

Table: 5 VALVULAR LESIONS IN CRHD

This table showed valvular lesions in CRHD that were most commonly associated with atrial fibrillation i.e. combined lesion of mitral stenosis, mitral regurgitation and tricuspid regurgitation (45.1%).

- Combined lesion of MS and MR was common in 25.8%.
- Isolated MS and MR lesions formed 12.9% and 3.2% respectively.

Table: 6 LEFT ATRIAL SIZE IN AF

LEFT ATRIAL SIZE	NO.OF CASES
<4cms	15
4-5cms	26
>5cms	9

DISCUSSIONS:

COMPARISION OF THE PRESENT STUDY RESULTS WITH PREVIOUS STUDIES

CLINICAL PRESENTATIONS	PRESENT STUDY (%)	Le´vy et al(%)[21]
DYSPNEA	90	44.4
PALPITATIONS	84	54.1
CHEST PAIN	38	10.1
PARALYSIS	6.0	-
ASYMPTOMATIC	2.0	11.4

The various clinical presentations of AF in the present study are less prevalent when compared with the ALFA (Etude en Activite´ Libe´raledela Fibrillation Auriculaire) STUDY byLe´vyet al21. The main reasons for this variation are Patients in present study presented late after developing complications. Most common cause of AF in present study is CRHD patients and these patients

develop more complications with AF and therefore more symptomatic.

AETIOLOGY	PRESENT STUDY (%)	MANITOBA STUDY (%)	ATRIA STUDY (%)	RAMAN T K et al[15] (%)
CRHD	62	8.3	4.9	58
HYPERTENSION	18	53	49.3	3
CORONARY ARTERY DISEASE	8	36.5	34.6	33
CONGESTIVE CARDIAC FAILURE	6	14.7	29.2	-
OTHERS	4	4.7	-	6

The present study results regarding etiology of AF were different from Minotoba31 and ATRIA studies because there is high prevalence of Rheumatic fever and rheumatic heart disease in India. According to Kalmanet al15, in recent years, there has been a decline in the frequency of both RHD and the resultant AF in western countries. Currently, the most common underlying abnormalities associated with chronic AF are hypertensive heart disease and congestive heart failure.

COMPARISION OF PREVALENCE OF VARIOUS LA SIZES OF PRESENT STUDY WITH PREVIOUS STUDIES

LA SIZE	PRESENT STUDY (%)	PETER PROBST et al[29](%)
<4 cm	30	36.0
>4 cm	70	64.0

- Findings in present study were similar with that of Peter probstet al29.-The normal left atrial dimension in adults is less than 4.0 cm (or <2.0 cm/m2 body surface area). Left atrial enlargement is common in AF, particularly in patients with mitral valve disease, left ventricular dilation, annular calcification, or hypertension. In addition, sustained AF itself can lead to a further increase in left atrial size, an effect that is reversible after cardioversion and maintenance of sinus rhythm. Regardless of the mechanism, left atrial enlargement is important prognostically. Compared to a normal left atrial diameter of less than 4.0 cm, the relative risk of recurrent AF was 1.6 with a left atrial diameter between 4.1 and 5.0 cm and 4.5 above 5.0 cm.As neither atrial fibrillation nor marked atrial enlargement can consistently be related to the severity of mitral stenosis as determined by valve area size or to any other measurable hemodynamic variable affected by mitral valve obstruction, the question of whether left atrial enlargement is the cause or the effect of the arrhythmia remains unresolved.

CONCLUSION:

- Most common clinical presentation was dyspnoea
- Chronic rheumatic heart disease was the most common underlying cause
- Left atrial size most commonly associated with AF was between 4 to 5 cm

REFERENCES :

1. Ammash NM, Seward JB, Bailey KR, et al. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. Circulation. 2000;101:2490-6.\
2. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271(11):840-844.
3. Brookes CI, White PA, Staples M, et al. Myocardial contractility is not constant during spontaneous atrial fibrillation in patients. Circulation. 1998;98:1762-8.
4. Clark DM, Plumb VJ, Epstein AE, et al. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am CollCardiol. 1997;30:1039-45.
5. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. Value in Health. 2006;9(5):348-356.
6. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, StevensonLW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am CollCardiol 1998;32:695-703.
7. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications.Arch Intern Med. 1995;155(5):469-473.
8. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. Lancet 1987;1:526-9. [Erratum, Lancet 1987;1:878.]
9. Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:3442-53.
10. Gelzer AR, Moise NS, Vaidya D, et al. Temporal organization of atrial activity and irregular ventricular rhythm during spontaneous atrial fibrillation: an in vivo study in the horse. J CardiovascElectrophysiol. 2000;11:773-84.
11. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. JAMA.2001;285(18):2370-2375.
12. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by Ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659-666.
13. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949–953.
14. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011;123:1501-8.
15. Kalman JM, Tonkin AM. Atria1 fibrillation: epidemiology and the risk and prevention of stroke. PACE 1992;15: 1332-1346
16. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982;306(17):1018-1022.
17. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82:2N-9N
18. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, GoetteA,Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation: executive summary. Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). Eur Heart J 2007;28:2803–2817.
19. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995;98(5):476-484.
20. Kurian T, Ambrosi C, Hucker W, et al. Anatomy and electrophysiology of the human AV node. Pacing ClinElectrophysiol. 2010;33:754-62.
21. Levy, S, Maarek, M, Coumel, P, et al., for the College of French Cardiologists. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. Circulation 1999; 99:3028.
22. Lip GY, Golding DJ, Nazir M, Beevers DG, Child DL, Fletcher RI. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. Br J Gen Pract 1997;47:285–289.
23. Lu F, Sakaguchi S, Benditt DG. Cardiac arrhythmias and transcatheter ablation. In: laizzo PA, ed. Handbook of cardiac anatomy, physiology, and devices. Totowa, New Jersey: Humana Press, Inc.; 2005.
24. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004;291:1720-9.
25. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119–125.
26. Miyasaka Y, Barnes ME, Gersh BJ, et al. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. Eur Heart J. 2006;27(8):936-941
27. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol 2009;104:1534–1539. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, 8.D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk fordevelopment of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–1046
28. Ortiz J, Niwano S, Abe H, Rudy Y, Johnson NJ, Waldo AL. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. Circ Res. 1994;74(5):882-894.
29. Probst, P, Goldschlager, N, Selzer, A. Left atrial size and atrial fibrillation in mitral stenosis. Factors influencing their relationship. Circulation 1973; 48:1282
30. Psaty BM, Manolio TAMHS, Kuller LHDH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997;96(7):2455-2461.
31. Raman TK et al Indian heart journal no 2,3 1951
32. Rathore SS, Berger AK, Weinfurt KP, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. Circulation. 2000;101:969-74.
33. Rosamond W, Flegal K, Furie K, et al. Heart Disease and Stroke Statistics—2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117(4):e25-146
34. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. Am J Cardiol. 1999;84(9A):131R-138R.

35. Stewart S, MacIntyre K, Chalmers JW, et al. Trends in case-fatality in 22968 patients admitted for the first time with atrial fibrillation in Scotland, 1986-1995. Int J Cardiol 2002;82:229-36
36. Van Den Berg MP, Crijns HJ, Haaksma J, et al. Analysis of vagal effects on ventricular rhythm in patients with atrial fibrillation. ClinSci (Lond). 1994;86:531-5.
37. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994;89(2):724-730.
38. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. J Am CollCardiol. 2008;51:779-86.
39. Wang YC, Lin JL, Hwang JJ, et al. Left atrial dysfunction in patients with atrial fibrillation after successful rhythm control for > 3 months. Chest. 2005;128:2551-6.
40. Williams L, Frenneaux M. Syncope in hypertrophic cardiomyopathy: mechanisms and consequences for treatment. Europace. 2007;9:817-22
41. Wolf P, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor forstroke: the Framingham Study. Stroke. 1991;22(8):983-988.
42. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987;147:1561-4.
43. Wyse DG, Love JC, Yao Q, et al. Atrial fibrillation: a risk factor for increased mortality — an AVID registry analysis. J Interv Card Electrophysiol 2001;5:267-73.
44. Zaman AG, Kearney MT, Schecter C, et al. Angiotensin-converting enzyme inhibitors as adjunctive therapy in patients with persistent atrial fibrillation. Am Heart J. 2004;147:823-7.