Original Article / Orijinal Araştırma

Cardiac arrhythmias in adults with hypertension in a resource-constraint setting
Hipertansiyonu Olan Erişkinlerde Kaynak Kısıtlı Ortamda Kardiyak Aritmiler

Olusegun Adesola Busari[1], Timothy Olusegun Olarewaju[2], Rotimi Oluyombo[1], Emmanuel Olaleye Olalekan[1]

[1]Federal Medical Centre, Ido-Ekiti, Nigeria
[2]University of Ilorin Teaching Hospital, Ilorin, Nigeria;

Corresponding Author:

Dr Olusegun Adesola Busari

Federal Medical Centre, Ido-Ekiti, Nigeria

Email:

olubusari@yahoo.com

ÖZET

Amaç: Hipertansiyon, tüm dünyada toplum sağlığı önemi olan yaygın bir hastalıktır. Amaç kaynak kısıtlı ortamda, üçüncü basamak hastanede sistemik hipertansiyonu olan erişkinlerde aritmi prevelansı, paternleri ve ilişkili faktörleri belirlemektir.

Materyal ve metod: Nijerya, Ido-Ekiti'de Federal Tıp Merkezinin Kardiyloji ünitesine hipertansiyon ile başvuran 18 yaş ve üzeri erişkin hastalarda 12 derivasyonlu istirahat elektrokrdiyogramını kapsayan kesitsel bir araştıradır.

Sonuçlar: Altıyüziki (602) erişkin Nijeryalının istirahat elektrokardiyogramı çalışıldı. 340'ı erkek (%56.5) ve 262'i (%43.5) kadındı. Hastalaron ortalama yaşları 58.3±10.7 yıldı. Doksansekiz hastada (%16.3) aritmi mevcuttu. Aritmisi olmayanlar ile karşılaştırıldığında, aritmisi olan hastalar daha yaşlıydı (62.3±12.8 vs. 56.1±13.2, p =0.03), QTc uzaması (14.3% vs. 6.0%, p = 0.041), sol ventriküler hipertrofisi (24.5% vs 12.7%, p = 0.026) prevelansı daha yüksekti ve kalp yetmezliğinde olmaya yatkındı (32.7% vs. 8.5%, p < 0.001).

Tartışma: Bu araştırma hipertansiyonu olan erişkin Nijeryalılardaaritmi prevelansının %16.3 olduğunu göstermiştir. Erken ventriküler kompleks ve atrial fibrilasyon en sık aritmilerdir. Daha yaşlı olma, yüksek sistolik ve diastolik kan basıncı ve sol ventriküler hipertrofi ve QTc uzaması aritmi ile ilişkilidir.

Anahtar sözcükler: hipertansiyon, aritmi, istirahat elektrokardiyogramı, kaynak kıstılı ortam

ABSTRACT

Purpose: Hypertension is a common disease globally and it is of public health significance. The objective was to determine the prevalence and pattern of arrhythmias and the associated factors in adults with systemic hypertension in a tertiary hospital in a resource-constraint setting.

Materials and Methods: It was a cross-sectional study which included the resting 12-lead electrocardiograms of adult patients aged 18 years and above with hypertension attending the Cardiology Unit of the Federal Medical Centre, Ido-Ekiti, Nigeria.

Results: Resting electrocardiogram of 602 adult Nigerians with hypertension were studied. 340 (56.5%) were males and 262 (43.5%) females. The mean age of the patients was 58.3±10.7 years. Ninety eight (16.3%) patients had arrhythmia. Compared with those without arrhythmia, patients with arrhythmia were older (62.3±12.8 vs. 56.1±13.2, p =0.03), had a higher prevalence of QTc prolongation (14.3% vs. 6.0%, p = 0.041) and left ventricular hypertrophy (24.5% vs 12.7%, p = 0.026), and more likely to be in heart failure (32.7% vs. 8.5%, p < 0.001).

Conclusion: The study shows a prevalence of 16.3% of arrhythmia among adult Nigerians with hypertension. Premature ventricular complex and atrial fibrillation are the most frequent arrhythmias. Older age, higher systolic and diastolic blood pressure and left ventricular hypertrophy and QTc prolongation are associated with arrhythmia.

Key Words: hypertension, arrhythmias, resting electrocardiogram, resource-constraint setting

Introduction

Hypertension (HT) is a common disease globally and a major public health problem (1,2). It is a major risk factor for sudden cardiac death (3). The prevalence has been increasing worldwide and it has been estimated to increase to 29.2% by 2025 (2). In Nigeria, studies have reported prevalence from 12% to 36.6% (4-8). Arrhythmias occur commonly in HT and their presence, type and complexity may influence morbidity, mortality and quality of life (9). These arrhythmias have a wide spectrum ranging from supraventricular premature beats to atrial fibrillation (AF) and from ventricular premature complexes (PVC) to ventricular tachycardia (VT) or sudden cardiac death (9). Underlying mechanisms are many and varied, including left atrial enlargement (LAE), left ventricular hypertrophy (LVH), myocardial ischemia, impaired left ventricular function and abnormal blood potassium levels (10-13).Others are circadian variations and sudden increases in blood pressure; and sympathetic irritability which commonly accompanies HT (14-16). Left atrial enlargementresults in stretching of the atrial fibers leading to the creation of arrhythmogenic foci. Left ventricular hypertrophy in HT is characterised not only by increased myocardial mass, but also by proliferation of fibrous tissue and decreased intercellular coupling, that may predispose to various arrhythmias (17). The risk of arrhythmia in hypertensive patients is also exacerbated by impaired left ventricular function (systolic or diastolic) as a result of electrical asynchronism (18). This study was conducted to evaluate the prevalence and pattern of arrhythmiasand associated factors in adults with HT in a tertiary hospital in a resource-constraint setting using resting electrocardiogram (ECG).

Materials and Methods

Design, Setting and Patients

This is a cross-sectional study of the resting 12-lead ECG of adult patients aged 18 years and above with HT who attended the Cardiology Unit of the Federal Medical Centre (FMC), Ido-Ekiti, Nigeria, between January 2005 and December 2008. Federal Medical Centre is a tertiary hospital situated in rural Ido-Ekiti, southwest Nigeria. Nigeria is situated in sub-Sahara Africa and has an estimated population of about 167 million with more than 70% living below one United States Dollar per day. The hospital serves the population of Ekiti state and four other adjoining states. The study protocol was reviewed and approved by the institutional review board of the hospital. The information on the ECG request and report form included age, sex, ethnicity, blood pressure, clinical diagnosis and the drugs the patient was currently on. Inclusion criteria were patients aged 18 years and above and diagnosed with HT. Excluded from the study were patients: with incomplete or lost data, diabetes mellitus (DM), previous myocardial infarction, hyper- and hypo-thyroidism, valvular heart disease, electrolytes abnormalities, uraemia and on drugs such as macrolides, quinineand halofantrine.

Measurement of blood pressure and definition of hypertension

A standardized protocol was followed in which systolic (SBP) and diastolic (DBP) blood pressures were measured on the left arm after participants had been seated for at least 5 minutes. The cuff was positioned at the heart level and deflated at 2 mm/s. The blood pressure was measured to the nearest 2mmHg. Three measurements were done after 5 minutes of rest and at least 5 minutes apart. The average of second and third measurements was recorded for the study. Hypertension was defined as SBP ≥ 140mmHg and/or DBP ≥ 90mmHg, or use of antihypertensive drugs (19, 20)

Electrocardiograms

Standard supine resting 12-lead ECG was recorded using Schiller Cardiovit-10 machine fulfilling the recommendations of the American Heart Association for technical specifications (21). Modern computer-based ECG machines can easily calculate a corrected QT (QTc), but this correction may not aid in the detection of patients at increased risk of arrhythmia. The Bazett's formula (22) was used to calculate the QTc. This is the most commonly used formula to calculate the QTc.Corrected QT (QTc) was derived using the Bazett's formula as follows: $QTc = QTo/$square root of the R-R interval (in seconds), where QTo is the observed QT (22,23).The ECG report was contained in the ECG request form for each patient. These records were screened for the following abnormal rhythms: atrial fibrillation; atrial flutter; atrial and ventricular premature complexes; supraventricular and ventricular tachyarrhythmias. Those with arrhythmias were confirmed and coded by a cardiologist.The criteria for arrhythmias were based on the standard ECG criteria (21).

Statistical Analysis

The data collected was doubly entry into SPSS 20.0 software (IBM, Chicago, Il, US) and analysed. Variables were described as means and standard

deviations, frequencies or proportions. Univariate analysis was done using Student *t* test and Fischer's exact test to compare groups with continuous variables and categorical variables respectively. P value < 0.05 (two-sided test) was considered statistical significant in the hypothesis testing.

Results

Resting ECG of 602 adult Nigerians with HT were studied. There were 340 (56.5%) males and 262 (43.5%) females with a male to female ratio of 1.3:1.The mean age of the patients was 58.3±10.7 years.Mean ages of patients with and without arrhythmia were 62.3±12.8 years and 56.1±13.2 years respectively(p = 0.03). The frequency of arrhythmias increased with age and was more in patients 60 years and older (Table 2).Ninety eight (16.3%) patients had arrhythmia,more in the females than males (17.1% vs 15.6%, p = 0.490).AF was more common in females than males (4.7% vs 3.2%, p = 0.840)though not statistically significant.Compared with those without arrhythmia, patients with arrhythmia were older (62.3±12.8 vs. 56.1±13.2, p <0.030), had a higher SBP (178.2±19.5 vs. 169.8±17.1, p < 0.0001) and DBP (102.4±11.6 vs 99.9±10.8, p = 0.039) , had a higher prevalence of QTc prolongation (14.3% vs. 6.0%, p = 0.041) and LVH (24.5% vs 12.7%, p = 0.026), and more likely to be in HF (32.7% vs. 8.5%, p < 0.001); Table 1.The patterns and proportions of arrhythmia are shown in Table 3.The most frequent arrhythmias were PVC and AF representing 42.9% and 23.5% respectively. Table 4 catalogs the relations between age of patients and pattern of arrhythmias.

Discussion

The study showed that PVC and AF were the commonest arrhythmias in adult patients with HT in our setting constituting 42.9% and 23.5% respectively. This is consistent with the findings in some previous studies (24-27). PVCis a common problem in clinical practice (28). The mechanism of the arrhythmia may be automatic, triggered activity, or re-entry (29-31)and increased sympathetic tone and QTc prolongation may play a role in progression to ventricular tachyarrhythmia particularly in the presence of LVH and ventricular dysfunction. (32).

Table 1. Characteristics of patients with and without arrhythmia

	Patients with arrhythmia (n = 98) Frequency (%)	Patients without arrhythmia (n = 504) Frequency (%)	P values
Mean age (year)	62.3±12.8	56.1±13.2	0.010
Sex			
Male 53	(55.1)	286 (56.7)	0.770
Female	45(44.9)	218 (43.3)	0.770
SBP (mmHg)	178.2± 19.5	169.8±17.1	<0.001
DBP (mmHg)	102.4±11.6	99.9±10.8	0.039
PP (mmHg)	75.4±10.8	69.6±11.3	<0.001
HF	28(32.7)	43 (8.5)	<0.001
QTC(sec)	0.438±0.012	0.392±0.018	0.060
QTc prolongation	14 (14.3)	30 (6.0)	0.041
ECG LVH	24 (24.5)	77 (12.7)	0.026

Table 2. Age distribution of patients with arrhythmia

Age (years)	Frequency (n) (%)
18-29	3 (3.1)
30-39	5 (5.1)
40-49	10 (10.2)
50-59	17 (17.3)
60-69	29 (29.6)
≥70	34 (34.7)

The study also revealed that arrhythmia was more common in older patients as 64.3% occurred in those who were 60 years and above. This finding also corroborates reports from other studies (33-35).The increased prevalence of arrhythmia and other ECG findings in the elderly are due to the increased prevalence of cardiovascular disease and the impact of physiologic ageing changes.

Table 3: Patterns and proportions of arrhythmia

	Male	Female	Total	P value
	(n = 55)	(n = 43)	(n = 98)	
	Frequency (%)	Frequency (%)	Frequency (%)	
PAC	12 (21.8%)	5(11.6%)	17(17.3%)	0.010
PVC	20(36.4%)	22 (51.2%)	42 (42.9%)	0.018
AF	11(20.0%)	12(27.9%)	23 (23.5%)	0.022
AFL	5 (9.1%)	2 (4.7%)	7(7.1%)	0.437
AT	3 (5.5%)	2(4.7%)	5 (5.1%)	0.460
VT	4(7.3%)	-----	4 (3.1%)	
VF	-----	-----	—	

PAC = Premature atrial complexes; PVC = Premature ventricular complexes; AF = Atrial fibrillation; AFL = Atrial flutter; AT = Atrial tachycardia; VT = Ventricular tachycardia; VF = Ventricular fibrillation

Table 4: Age of patients and pattern of arrhythmia Age (years) Pattern of arrhythmia

	PAC	PVC	AF	AFL	AT	VT	VF
	n=17	n=42	n=23	n=7	n=5	n=4	
18-29	1	1	-	-	1	-	-
30-39	1	2	-	-	2	-	-
40-49	2	3	1	2	2	-	-
50-59	3	8	4	2	-	-	-
60-69	6	12	6	3	-	-	-
>70	4	16	12	-	-	-	-

Aging is associated with extensive and pervasive changes in cardiovascular structure and function which may result in electrocardiographic alterations (36). Thus, aging might be an important factor in abnormal findings and appearance of arrhythmias in conventional surface 12 lead ECG (37).

In our study, although the overall prevalence of AF was 3.8%; 4.3%, 43.5% and 52.2% of the cases occurred in patients <50 years, 50-69 years and 70 years and older respectively. The prevalence of atrial fibrillation was strongly associated with increasing age. This is similar to findings reported by Alan et al (38) and other authors (34-37). AF is one of the most common arrhythmias in elderly persons and it is a potent risk factor for ischaemic stroke, increasing the risk of stroke five fold and accounting for about 15% of all strokes in the United States (38). Symptomatic AF may also reduce quality of life, functional status and cardiac performance, and it is associated with higher medical costs as well as an increased risk of death (39,40). In our study, although not statistically significant, females were more likely to have arrhythmia, including AF, than males except in those at and above 70 years. This is consistent with the findings of the study by Yamaguchi et al(37) which showed that PAC, PVC and AF were more frequent in men than in women, but only in the older age stratum.This study also showed that hypertensive patients with arrhythmia were significantly more likely to be in heart failure (HF) than those without HF. There is a two way relationship between arrhythmia and HF (41). While arrhythmia imparts a significant burden in all forms of HF and some even perpetuate it, structural substrates for arrhythmia are common in HF, regardless of the underlying cause, and these include myocardial hypertrophy, myocardial fibrosis and ventricular dilatation. In HF at the cellular level, myocytes may be exposed to increased stretch and wall tension, excessive catecholamines, ischaemia and electrolyte imbalance (42-44). The complex interplay of these factors contributes to increased incidence of arrhythmogenic sudden cardiac death in patients with HF. In our study, patients with arrhythmia also had significantly higher SBP and DBP and were more likely to have LVH. While elevated SBP causes increased wall tension, increases in DBP lead to increased myocardial energy expenditure, remodeling of the ventricle, increased myocardial oxygen demand, myocardial ischemia, and eventual progression of the maladaptive mechanisms of the heart that lead to decompensated HF and/ or breakdown of normal conduction patternswith increased propensity for

abnormal automaticity or activation of reentrant pathways in the myocardium which may generate arrhythmia(45).

Patients with arrhythmia had longer QTc and more frequent QTc prolongation with statistical significance for the latter when compared with their counterparts without arrhythmia. The association between QTc and arrhythmia, particularly ventricular, has long been established (46-48). The QT interval represents the duration of depolarization and repolarization of the ventricular myocardium (49). Prolonged repolarization increases the likelihood of dispersing refractoriness across the three layers of the myocardium with maximum refractoriness in the mid-myocardium. Prolonged QTc increases the transmural dispersion of repolarization creating a functional substrate for arrhythmogenesis and transmural reentry (50,51).In the study, arrhythmias were more likely to be found in patients who were older, in HF, have higher blood pressures, LVH and QTc prolongation.

In summary, the study shows that the prevalence of arrhythmia among adult Nigerians with systemic HT in our hospital, a resource-constraint setting, is 16.3% and frequently more in females than males. Premature ventricular complex is the most frequent arrhythmia followed by AF and the arrhythmias are more likely to be found in patients who are older, in HF, have higher blood pressures, LVH and QTc prolongation.

Limitations

Although this study was done in a resource-constraint setting, we consider not using Holter ECG monitor as a limitation.

References

1.   Kearney PM, Whelton M, Reynolds K, et al. Worldwide prevalence of hypertension: a systematic review. J Hypertens 2004; 22(1):11–9.

2.   Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365(9455):217–23.

3.   Le Heuzey JY, Guize L. Cardiac prognosis in hypertensive patients. Am J Med 1988; 84: 65–8.

4.   Akinkugbe OO. The epidemiology of hypertension in Africa. In: Akinkugbe, ed.Cardiovascular diseases in Africa. Ciba-Geigy, 1976: 91-100.

5.   Adedoyin RA, Mbada CE, Balogun MO, *et al.* Prevalence and pattern of hypertension in a semiurban community in Nigeria.Eur J Cardiovasc PrevRehabil 2008, 15(6)**:**683-7.

6.   Ofuya Z: The incidence of hypertension among a select population of adults in the Niger Delta region of Nigeria. *Southeast Asian J Trop Med Public Health*2007; **38**(5)**:** 947-9.

7.   Oladipo B, Akinkungbe. Current epidemiology of hypertension in Nigeria. Archives of Ibadan Medicine 2001; 1(1): 4- 8.

8.   Oladapo OO, Salako L, Sodiq O, et al. A prevalence of cardiometabolic risk factors among a rural Yoruba south-western

Nigerian population: a population-based survey. Cardiovasc J Afr. 2010 Jan-Feb; 21(1):26-31.

9.   Yildirir A, Batur MK, Oto A. Hypertension and arrhythmia: blood pressure control and beyond. Europace2002; 4:175–82.

10.   The AFFIRM Investigators. Baseline characteristics of patients with atrial fibrillation: the AFFIRM study. Am Heart J 2002; 143: 991-1001.

11.   Madu EC, Baugh DS, Gbadebo TD, et al. Effect of ethnicity and hypertension on atrial conduction: evaluation with high-resolution P wave signal averaging. ClinCardiol 2001; 24: 597-602.

12.   Levy D, Anderson KM, Savage DD, et al.Risk of ventricular arrhythmias in left ventricular hypertrophy: theFramingham heart study. Am J Cardiol 1987; 60: 560-5.

13.   Siegel D, Hulley S, Black D, et al. Diuretics, serum and intracellular electrolyte levels and ventricular arrhythmias in hypertensive men. JAMA 1992; 267: 1083–9.

14.   James MA, Jones JV. Systolic wall stress and ventricular arrhythmias: the role of acute changes in blood pressure in the isolated working rat heart. ClinSci 1990; 79: 499-504.

15.   Zehender M, Meinertz T, Hohnloser S, et al. Prevalence of circadian variations and spontaneous variability of cardiac disorders and ECG changes suggestive of myocardial ischemia in systemic arterial hypertension. Circulation 1992; 85: 1808–15.

16.   Schwartz P, Larovere MT, Vanoli E. Autonomic nervous system and sudden death. Experimental basis and clinical observations for post-myocardial risk stratification. Circulation 1992; 85: 177-191.

17.   Aidietis A, Laucevicius A, Marinskis G. Hypertension and cardiac arrhythmias. Curr Pharm Des 2007; 13:2545–55.

18.   Wolk R. Arrhythmogenic mechanisms in left ventricular hypertrophy. Europace 2000; 2(3):216–23.

19.   Chobaman AU, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: JNC 7 report. JAMA 2003; 289: 2560-2572

20.   2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; 1983-1992

21.   Kligfield P, Gettes LS, Bailey JJ, et al.Recommendations for the standardization and interpretations of electrocardiogram. Part I: The Electrocardiogram and Its Technology: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. Circulation 2007; 115:1306-24.

22.   Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; (7): 353–70.

23.   Busari O, Opadijo G, Olarewaju T,et al. Electrocardiographic correlates of microalbuminuria in adult Nigerians with essential hypertension. Cardiol J. 2010; 17(3):281-7.

24.   Kiatchoosakun S, Pachirat O, Chirawatkul A,et al. Prevalence of cardiac arrhythmias in Thai community. J Med Assoc Thai. 1999; 82(7):727-33.

25.   Krittayaphong R, Bhuripanyo K,Punlee K,et al.Effect of Atenolol on Symptomatic Ventricular Arrhythmia without Structural Heart Disease: A Randomized Placebo-Controlled Study. Am Heart J. 2002;144(6)

26.   Lok NS, Lau CP. Prevalence of palpitations, cardiac arrhythmias and their associated risk factors in ambulant elderly.Int JCardiol. 1996;54:3231-6.

27.   Mbewu A, Mbanya JC, Cardiovascular disease. In: Jamison DT, Feachem RG, Makgoba MW, et al., editors. Disease and mortality in Sub-Sahara Africa. Washington (DC): World Bank; 2006. Chapter 21. Available from: http://www.ncbi.nlm.nih.gov/books/NBK2294. Accessed January 21, 2013.

28.   Barrett PA, Peter CT, Swan HJC, et al. The frequency and prognostic significance of electrocardiographic abnormalities in clinically normal individuals. Prog Cardiovasc Dis 1981;23:299-319.

29.   Buxton AE, Waxman HL, Marchlinski FE, et al. Right ventricular tachycardia: clinical and electrophysiologic characteristics. Circulation 1983;68:917-27.

30.   Sung RJ, Shen EN, Morady F, et al. Electrophysiologic mechanism of exercise induced sustained ventricular tachycardia. Am J Cardiol 1983;51:525-30.

31.   Lerman BB, Stein KM, Markowitz SM. Idiopathic right ventricular outflow tract tachycardia: a clinical approach. Pacing Clin Electrophysiol 1996;19:2120-37.

32.   Hayashi H, Fujiki A, Tani M, et al. Role of sympathovagal balance in the initiation of idiopathic ventricular tachycardia originating from right ventricular outflow tract. Pacing Clin Electrophysiol 1997;20:2371-7.

33.   Assantachai P, Panchavinnin P, Pisalsarakij D.An electrocardiographic survey of elderly Thai people in the rural community.J Med Assoc Thai. 2002;85(12):1273-9.

34.   Niwa K, Warita N, Sunami Y,et al. Prevalence of arrhythmias and conduction disturbances in large population-based samples of children. Cardiol Young. 2004; 14(1): 68-74.

35.   Wakida Y, Okamoto Y, Iwa T, et al. Arrhythmias in centenarians. Pacing Clin Electrophysiol. 1994; 17: 2217-21.

36.   Basile G, Cucinotta MD, Figliomeni P, et al. Electrocardiographic changes in centenarians: a study on 42 subjects and comparison with the literature.Gerontology2012;58(3):216-20..

37.   Yamaguchi I, Ito I. Electrocardiographic changes and arrhythmias in the elderly. J Cardiol Suppl. 1988; 19: 49-57.

38.   Alan S. G, Elaine M H, Kathleen A P 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) StudyFREE. JAMA 2001; 285 (18):2370-5.

39.   Lip GY, Tean KN, Dunn FG. Treatment of atrial fibrillation in a district general hospital. Br Heart J.1994; 71:92-95.

40.   Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation.1998; 98:946-52.

41.   Braunwald E. The pathogenesis of heart failure: Then and now. *Medicine.* 1991;70:68-9.

42.   Onwuanyi A, Taylor M. Acute decompensated heart failure: pathophysiology and treatment. *Am J Cardiol.* 2007;99(6B):25D-30D.

43.   Kajstura J, Leri A, Finato N, et al.Myocyte proliferation in end-stage cardiac failure in humans. *ProcNatlAcad Sci.* 1998; 95(15):8801-5.

44.   Cohn JN. Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition. *Circulation.* 1995;91 (10):2504-7.

45.   Marriot HJ, Conover MB. *Advanced Concepts in Arrhythmias.* 3rd ed. Philadelphia, Pa: Mosby Inc; 1998.

46.   Noda T, Shimizu W, Satomi K, et al. Classification and mechanism of Torsade de Pointes initiation in patients with congenital long QT syndrome. *Eur Heart J.*2004;25 (23):2149-54.

47.   Antzelevitch C, Sicouri S. Clinical relevance of cardiac arrhythmias generated by afterdepolarizations. Role of M cells in the generation of U waves, triggered activity and torsade de pointes. *J Am CollCardiol.* 1994; 23(1):259-77.

48.   Nguyen PT, Scheinman MM, Seger J. Polymorphous ventricular tachycardia: clinical characterization, therapy, and the QT interval. *Circulation.* 1986;74(2):340-9.

49.   Lankipalli RS, Zhu T, Guo D, et al. Mechanisms underlying arrhythmogenesis in long QT syndrome. *J Electrocardiol.* 2005;38:69-73.

50.   Roden DM. Long QT Syndrome. *N Engl J Med.*2008;358(2):169-76.

51.   Goldenberg I, Moss AJ. Long QT syndrome. *J Am CollCardiol.* Jun 17 2008;51(24):2291-300.