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RESEARCH ARTICLE

Clinical Study for Oxidative Stress and Lipid Profile Levels in Patients with Cardiac Arrhythmias

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Abstract

Cardiac arrhythmia is a disturbance heart rhythm. Most types of arrhythmia are not serious, while there are some that types can be life threatening promptly because it impacts the pumping action of the heart substantially, enough to disrupt blood supply to the body, potentially leading to sudden cardiac death. The present study is designed to determine the levels of (MDA) (malondialdehyde) as a marker for lipid peroxidation , in addition, measurement the level of lipid profile (cholesterol TCH, triglyceride TG, high density lipoprotein HDL, low density lipoprotein LDL, very low density lipoprotein vLDL, in patients of cardiac arrhythmia. The study includes (110) subjects with average age (62.0±3.0) years and the average of BMI was (27.80 ± 3.0 kg/m^2) which were divided into five groups: (20) patients of (AF), (17) Patients of (SVT), (20) patients of (VT), (18) patients of (PVCs) and (35) clinically healthy subjects, who were attend blood bank to blood donation as control groups. The study aims to shed a light on the correlation between oxidants and lipid profile in patients with cardiac arrhythmia .The results show that there were a significant increases in serum concentrations of each of (MDA) ,(TCH), (TG), (LDL) and (vLDL) in all of patients groups in comparison with control group (P≤0.05), as for level of (HDL) there was a significant reduction (P≤0.05) In patients of AF in comparison with each one of study groups, also there was a significant increase in concentrations of MDA of patients of VT compared with each of AF, SVT, PVCs (P≤0.05) and non-significant increase in serum concentrations of MDA between SVT and AF ,while there was slightly significant increase between each of AF and SVT compared with PVCs(P≤0.05). On the other hand Pearson's correlation coefficient analysis showed a positive correlation between MDA level and each lipid profile parameter, except HDL which showed a negative correlation in all groups of cardiac arrhythmia.

Key words: *Arrhythmia, AF, SVT, PVCs, VT, Oxidative stress and MDA.*

Introduction

Cardiac arrhythmia is a disturbance heart rhythm result from abnormalities of impulse initiation, impulse conduction, or both [1]. Arrhythmias are classified by rate as either tachycardia (heart rate > 100/min) or bradycardias (heart rate < 60/min) [2]. In AL-Hussein Teaching Hospital in Thi Qar province, the number of patients cardiac arrhythmia who were hospitalized in 2017 about 700 patients, among them 450 patients with atrial fibrillation.

The increased level of ROS associated with all major clinical risk factors for arrhythmia is indirect evidence that oxidative stress may be important in the genesis of both a trial and ventricular arrhythmias [3].Despite the high prevalence and significance of arrhythmias; the mechanisms of Arrhythmogenesis are not fully understood. Some molecular mechanisms known to contribute to arrhythmias include genetic alterations of ion channels leading to electrophysiological dysregulations and structural remodeling of the left ventricle in hypertrophy and heart failure [4, 6]. Increasing evidence suggests that altered cardiac ion homeostasis and structural remodeling are highly associated with elevated reactive oxygen species (ROS) [7, 8].

Oxidative stress can be impair the ability of the endothelium, the inner layer of cells that line the blood vessels, to expand and dilate in response to blood flow, based on this scenario, an accumulation of reactive oxygen species has been linked to cardiac contractile dysfunction, potentially leading to

arrhythmia and heart attack[9]. Lipid per oxidation resulting from free radical activation results in the release of products, such as arachidonic acid, into the extracellular space. The involvement of free radicals here is represented by the free radical-induced release of arachidonic acid and subsequent formation of prostaglandins and end peroxides, may be further aggravate the injury process or generate arrhythmias [10].

There is also evidence indicating that arrhythmias of the spontaneously contracting atrium may arise during induction of lipid peroxidation. The decrease in resistance of the atria to the lipid peroxidation inducer associated with an increase in their developed tension can very probably be explained on the grounds that an increase in the oxygen demand of the contracting muscle leads to activation of lipid peroxidation in it.

In turn, activation of lipid peroxidation causes a marked arrhythmogenic effect [11]. There are data that suggest that sodium channel defect excited by lipid peroxidation is a candidate mechanism for ischemia-related conduction abnormalities and arrhythmias [12].Because cardiac ion channels are embedded in the membrane lipid bilayer, Fukuda et al hypothesized that lipid peroxidation may alter the function of these channel proteins.

They reasoned that this could occur either as a result of structural alterations of the lipid bilayer by oxidative modification of membrane lipids or by the abduction of channel proteins by electrophilic short chain aldehydes produced by lipid peroxidation [12]. In this regard, oxidative stress has been found to induce alterations in the function of a number of membrane proteins, including ion channels, enzymes and receptors [13, 15].

Lipids, Lipoproteins and Arrhythmia

Clinical and epidemiological studies have proven that individuals with elevated TCH, TG, LDL and low HDL show an increased risk for cardiovascular diseases [16]. Disorder of lipids and lipoproteins increasingly important in clinical practice, primarily because of their association with coronary heart disease, abnormal lipid profile was reported to be an important risk factor for ischemic heart disease and atherosclerosis [17].

It is clear (CHD) is the commonest cause that lead to ventricular arrhythmia in>80% of cases [18]. Hypercholesterolemia can directly trigger neural and electro physiologic remodeling, resulting in increased arrhythmogenesis [19].

Material and Methods

Design of Study

This study is conducted on a group of patients with arrhythmia at AL-Hussein Teaching Hospital in Thi-Qar, especially, in the coronary care unit (CCU), at the period between 6/10/2016 to 29/3/2017. They included (110) subjects, control (35) and patients of arrhythmia (75).

The study has been conducted on a total number of supposed healthy individuals and patients, who were divided as the fallowing groups:-

AF Groups

20 patients with a trial fibrillation (AF) [7 males and 13 females] with age range (42-70).

SVT Groups

17 patients with supraventricular tachycardia (SVT) [8 males and 9 females] with age range (35-65).

VT Groups

20 patients with ventricular tachycardia (VT) [9 males and 11 females] with age range (40-70).

PVCs Groups

18 patients with premature ventricular contraction (PVCs) [8 males and 10 females] with age range (40-70).

Control Groups

Control group, consist of 35 supposed healthy subjects [16 males and 19 females] with no history of systematic illness at age range (40 -65).

Biochemical Parameter Lipid peroxidation Marker (Serum MDA)

Determinations of serum MDA level that consider as a lipid peroxidation marker were performed according to the method of **Fong** [20]. MDA concentrations were calculated, using the molar extinction coefficient of MDA

(^{e}MDA) equal to 1.56 x105 mol-1.Cm-1 [21].MDA formed from breakdown of polyunsaturated fatty acid, serves as a convenient index of peroxidation reaction.

Statistical Analysis

Statistical analysis was done using Microsoft Excel 2010 the results were expressed as mean ± standard deviation (mean ± SD). One way ANOVA was used to compare parameters in different studied groups. P-values (P≤0.05) were considered statistically significant. Correlation analysis was calculated using Pearson's correlation coefficient.

Result and Discussion

General Comparison for Some Studied Parameters

Lipid Peroxidation Status (Malondialdehyde)

Table (1) show a significant increases in serum MDA levels for each of the (VT), (AF), (SVT) and (PVCs) patients groups' compared with control group (P≤0.05),also a significant increases in the mentioned parameter levels can be observed in (VT) patients group when they are compared to AF, SVT and PVCs groups (P≤0.05). Generally, in arrhythmia the level of MDA was significantly higher than those who had no history with arrhythmia. This hypothesis is comported with [22, 23]. It is well known that ischemic heart disease widely accompany with VT [24].

This is clear also in this study**,** ischemia is characterized by ionic and biochemical alterations capable of initiating and sustaining arrhythmias, in turn VT increases myocardial oxygen demand, which may lead to aggravation of ischemia [25].

Moreover, probably the most important factor influencing the severity of reperfusion-induced arrhythmias is the duration of the previous period of ischemia whereas extending the duration of ischemia, lead to increased incidence of ventricular arrhythmia [26].Anyway the production of reactive oxygen species and lipid peroxidation plays a significant role in the progression chronic and acute events in atherosclerosis and coronary artery disease [27].Lipid peroxidation marker (MDA) is higher in patients with IHD, and this may due to the increasing of oxidative stress, may be the main reason to increase the levels of MDA in patients of (VT) compared with all groups of study. It is clear presence of significant increase in each of AF and SVT Compared with PVCs group (P≤0.05). On the other hand, there are no significant differences between (AF) and (SVT) (P≤0.05).

So far it is not clear whether oxidative stress is a primary pathogenic event or a consequence of AF. However, there is a possibility that both processes feeding each other leading to a vicious cycle [24].

Other putative pathogenesis mechanisms that may promote oxidative stress in AF include heart failure ,it is an important risk factor for AF, development of heart failure, AF can lead to HF and vice versa [28]. It seems logical that oxidative stress represents a common pathophysiologic link between the two conditions [29].

Accordingly, an increasing body of evidence indicates that oxidative stress is implicated in the pathophysiology of AF; the oxidative damage observed during AF may contribute to the remodeling process facilitating the perpetuation of the arrhythmia [24]. In patients of (SVT), as it is well known, they are not usually associated with structural heart disease [30].

Though there is an increase in the level of (MDA), remained significantly in persons without heart disease, this refers to other mechanisms than cardiac structural problems, Oxidative stress may also play critical roles in the initiation and perpetuation of SVT [31]. The presence of significant difference in the values of the MDA for patients of (PVCs) compared with the control group.

It is worth mentioning that chronic exposure of the heart to oxidative stress produces a variety of electrophysiological abnormalities, increased susceptibility to premature ventricular contraction [32]. The study suggests the involvement of oxidative stress in the occurrence and progress all type of arrhythmias, alike in presence or absence of heart disease.

Table 1: Serum Malondialdehyd Concentrations of (control), (AF), (SVT), (VT) and (PVCs) groups

Groups	No	MDA concentration (µmol/l)mean ± SD
CONT	35	**1.47^{d} ± 0.21**
AF	20	**3.27^{b} ± 0.48**
SVT	17	**3.22^{b} ± 0.39**
VT	20	**3.70^{a} ± 0.33**
PVCs	18	**2.91^{c} ± 0.23**
LSD		**0.16**

Note:-Each value represents mean ± S.D values with non-identical superscript (a, b or c …etc.), were considered significantly differences ($P \leq 0.05$).
-N**:** Number of subjects.
-SD: Standard deviation.
-LSD: Least Significant Difference.
-AF: Atrial fibrillation -SVT: Supraventricular tachycardia
-VT: Ventricular tachycardia -PVCs: Premature ventricular contraction

Serum Lipid Profile Concentrations

The results shown in Table (2) a significant increase in total cholesterol, triglyceride, LDL-c and vLDL levels, for patients of (AF),(SVT),(VT) and (PCVs) than healthy controls ($P \leq 0.05$),while there are no significant differences between each of VT, SVT and PVCs with control group($P \leq 0.05$) , regarding HDL- c. The results also appeared a significant decrease in HDL level in patients of AF compared with each of VT, PVCs, SVT and control groups, this result is similar to the result of a previous study of [33].

Reducing levels of HDL-c are associated with increased cardiac dysfunction, and the development of cardiac failure, which are risk factors for AF [34]. Therefore, abnormal HDL-c levels, through a structural alteration in the atrium may lead to AF. In other study in regards to (HDL-c), there was no significant difference between patients with AF than in those without AF [35].

Generally in this study there are association between increased risk of AF and HDL cholesterol levels, however, remained significantly in persons without heart disease, which refers to other mechanisms than cardiac structural problems. Oxidative stress or Inflammation may also play critical roles in the initiation and perpetuation of AF [36, 37] and low HDL-c levels may increase the risk of AF via these disturbances [33].

Hypertriglyceridemia and hypercholesterolemia were associated with oxidative modification of LDL, thus leading to excess production of lipid peroxidation products which may cause elevation of oxidative stress in higher lipid and hyperlipidemia subjects [38]. Our results, demonstrate that lipid peroxidation is associated with development of hyperlipidemia in patients of arrhythmia, in our correlation coefficient analysis study, appears a positive correlation between increased oxidative stress and abnormal lipid profile Parameters, except HDL-c which showed a significant negative correlation as follows. Positive correlation between MDA and TCH for each of AF (r=0.17), SVT (r=0.1),VT (r=0.24) and PVCs (r=0.02) Figure (1), also there are positive correlations between MDA and LDL-c for each of AF (r=0.39), SVT (r=0.15),VT (r=0.45) and PVCs (r=0.05) Figure (2), as regarding TG and MDA also positive correlation for each of AF (r=0.1), SVT(r=0.06), VT(r=0.16) and PVCs(r=0.03) Figure (3),while there are negative correlation between HDL-c and MDA for each of AF(r=-0.35),SVT(r=-0.11),VT(r=-0.10) and PVCs(r=-0.14) Figure (4).

The presence of high concentrations of lipids and lipoproteins compared with the control group, may be involved in incidence and develops of arrhythmia through several mechanisms such as alteration structural of the heart, inflammation and oxidative stress, each of these mechanisms lead to the increase lipid peroxidation and thus incidence of arrhythmia [33].in this study, Positive and negative correlations between MDA and lipid profile are non-linearity, This clearly suggests that both increased oxidative stress and abnormal lipid profile are two independent risk factors in arrhythmia.

Hypercholesterolemia is not only atherogenic, but is also associated, alteration of the contractile properties of the myocardium and ventricular electrophysiological remodeling [39] Myocardial electrical remodeling due to hypercholesterolemia caused prolonged action potential durations, conduction slowing [40]. In addition, LDL-c increases the cholesterol to phospholipid ratio in the cell membrane,

enhancing membrane rigidity and impairing functionality of the ion channels and ventricular repolarization [41].

Table 2: Serum Lipid Profile concentrations of (control), (AF), (SVT), (VT) and (PVCs)

Groups	No	TCH	TG	HDL-c	LDL-c	vLDL
CONT	35	$172.7^{b} \pm 9.4$	$102.47^{b} \pm 12.6$	$48.1^{a} \pm 4.6$	$102.2^{b} \pm 8.3$	$20.7^{b} \pm 2.8$
AF	20	$219^{a} \pm 16.9$	$153.3^{a} \pm 21.8$	$40.26^{b} \pm 5.5$	$146.6^{a} \pm 16.6$	$32.33^{a} \pm 7$
SVT	17	$218.6^{a} \pm 16.6$	$149.8^{a} \pm 15.9$	$47.82^{a} \pm 5.5$	$142.6^{a} \pm 20$	$30.5^{a} \pm 5.0$
VT	20	$224.2^{a} \pm 17.6$	$152.85^{a} \pm 23$	$47.7^{a} \pm 4.7$	$146.5^{a} \pm 16.7$	$30.6^{a} \pm 4.6$
PVCs	18	$218.5^{a} \pm 18$	$153.6^{a} \pm 18.9$	$46.3^{a} \pm 6.7$	$140.4^{a} \pm 16.8$	$30.78^{a} \pm 5.48$
LSD		6.3	7.45	2.2	6.5	2.05

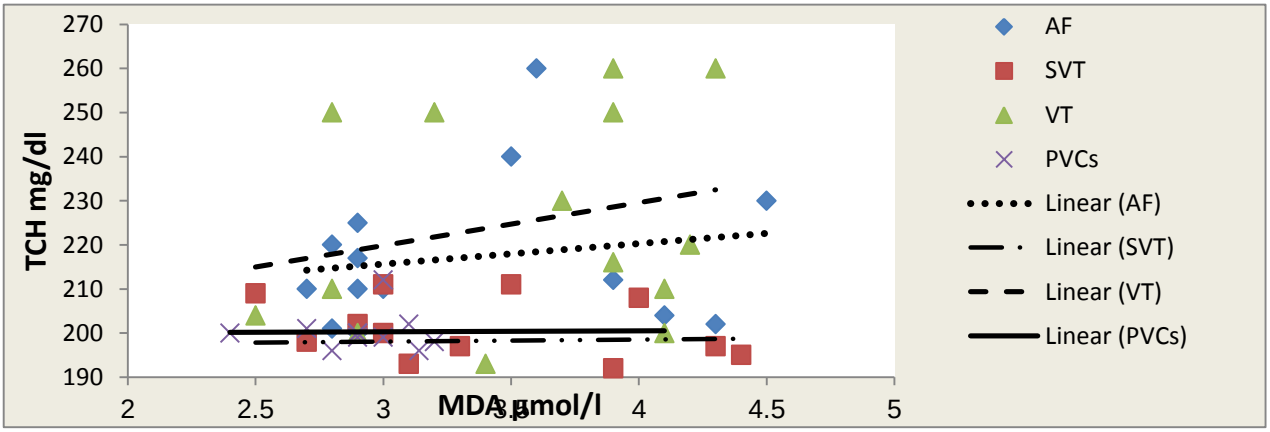

Figure 1: Correlation relationship between MDA and TCH

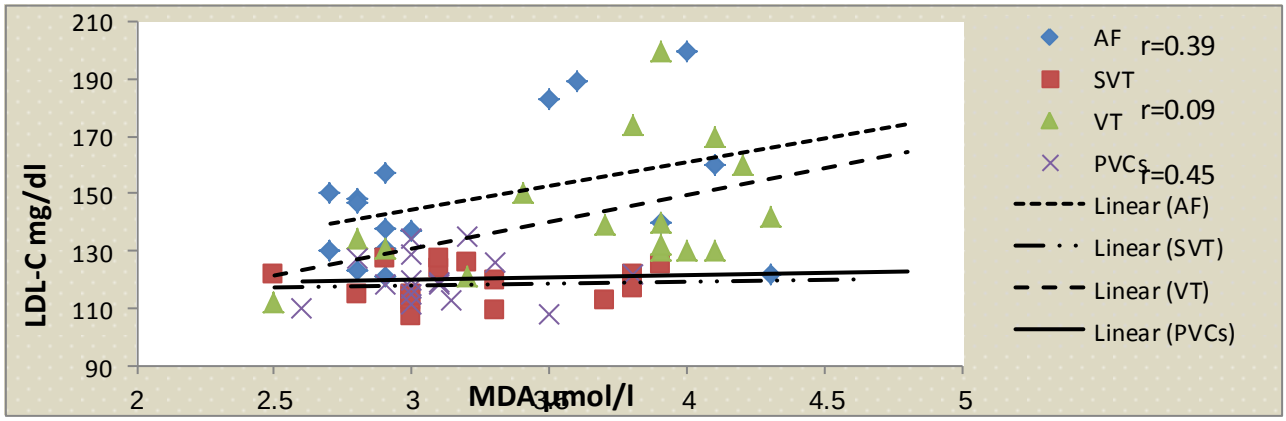

Figure 2: Correlation relationship between MDA and LDL cholesterol

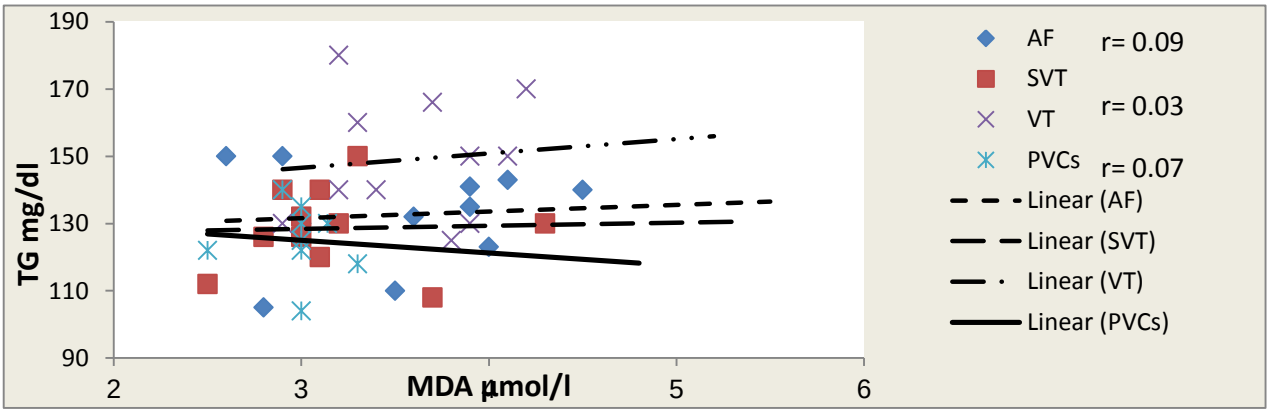

Figure 3: Correlation relationship between MDA and TG

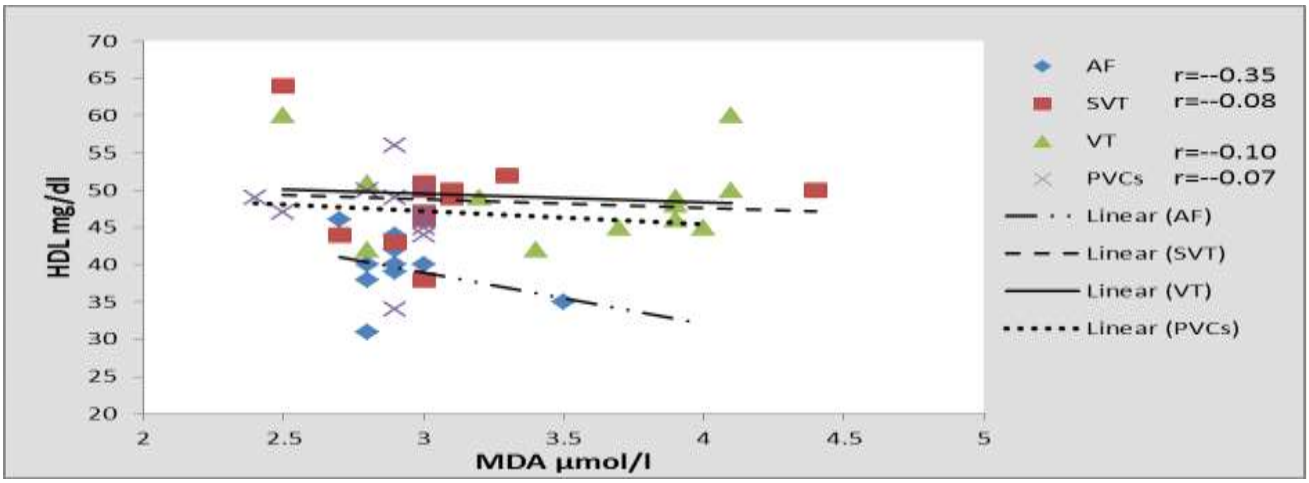

Figure 4: Correlation relationship between MDA and HDL cholesterol

References

1. Cranefield Paul F, Andrew L Wtt, Brian F Hoffman (1973) Genesis of Cardiac Arrhythmias, Circulation., 47: 190-204.
2. Alastair Innes J (2016) Davidson's Essentials of Medicine, E book ISBN 13 978-0-7020-5595-9.
3. Jeong EM, et al (2012) Metabolic stress, reactive oxygen species and arrhythmia. Journal, 52(2): 454-463.
4. Gao G, Dudley Jr SC (2009) Redox regulation, NF-κB and atrial fibrillation. Antioxid Redox Signal, 11: 2265-77.
5. Akar FG, Spragg DD, Tunin RS, Kass DA, Tomaselli GF (2004) Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. Circ Res., 95: 717-25. 14.
6. Shah M, Akar FG, Tomaselli GF (2005) Molecular basis of arrhythmias. Circulation, 112: 2517-29.
7. Liu M, Liu H, Dudley SC Jr (2010) Reactive oxygen species originating from mitochondria regulates the cardiac sodium channel. Circ. Res., 15: 107(8): 967-74.
8. Barth AS, Tomaselli GF (2009) Cardiac Metabolism and Arrhythmias. Circulation: Arrhythmia and Electrophysiology, 2: 327 35.
9. Vincent HK, et al (1999) Obesity is Associated with Increased Myocardial Oxidative Stress. Int. J. Obes., 23: 67-74.
10. Coker SJ, Parra TT, Ledingham JR, IMcA Zeitlin IJ (1981) Thromboxane and prostacyclin release from ischaemic myocardium in relation to arrhythmias. Nature, 291: 323-324.
11. Didenko V (1985) Bulletin of Experimental Biology and Medicine, 687-690.
12. Fukuda, Koji, et al (2005) Oxidative Stress and Cardiac Sodium Channels, Circ Res., 97: 1262-1269.
13. Gill JS, McKenna WJ, Camm AJ (1995) Free radicals irreversibly decrease Ca2; Eur. J. Pharmacol., 292: 337-340.
14. Tokube K, Kiyosue T, Arita M (1996) Openings of cardiac KATP channel by oxygen free radicals produced by xanthine oxidase reaction. Am J. Physiol., 271: H478–H489.
15. Ueda K, Shinohara S, Yagami T, Asakura K, Kawasaki K (1997) Amyloid beta C.
16. Keevil JG, Stein JH, Wiebe DA, Aeschlimann S, Folts JD (1999) Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. Circulation, 100: 1050-5.
17. Fox SI (2002) "Human Physiology", 7th edn. Eds. McGraw-Hill Higher Education. New York, 396-398 27.
18. Mehra, Rahul (2007) Global public health problem of sudden cardiac death, J of Electro cardiology, 40: S118-S122.
19. Yen-Bin Liu, Chau-Chung, Chii-Ming Lee, et al (2006)* Dyslipidemia is Associated with Ventricular Tachyarrhythmia in Patients with Acute ST-Segment Elevation Myocardial Infarction. J. Formos. Med. Assoc., 105(1):17-24.
20. Fong KL, McCay PB, Poyer JL (1973) Oxidative stress. Free Rad. J. Biol. Chem., 248(22): 7792-7797.

21. Wills E (1969) Role of fatty acid in the pathogenesis of insulin resistance and NIDDM. Biological Chemistry Journal, 113: 315.

22. Wu,Yongbo Kai Zhang1,2, Lin Zhao1,2, Jie Guo1,2, Xiaorong Hu1,3,4 and Zhiqiang Chen (2013) Increased serum HMGB1 is related to oxidative stress in patients with atrial fibrillation Journal of International Medical Research, 41(6): 1796-1802.

23. Meerson FZ, Belkina LM, Sazontova TG, Saltykova VA, Yu V Arkhipenko (1987) The role of lipid peroxidation in pathogenesis of arrhythmias and prevention of cardiac fibrillation with antioxidants Basic Res Cardio., 182:123-137.

24. Pogwizd SM, Corr PB (1990) Mechanisms underlying the development of ventricular fibrillation during early myocardial ischemia. Circ. Res., 66(3):672-695.

25. Ghuran AV, Camm AJ (2001) Ischaemic heart disease presenting as Arrhythmias .Department of Cardiological Sciences, St George's Hospital Medical School, London, UK British Medical Bulletin, 59: 193-210

26. Corr PB, Witkowski EX (1983) Potential electro physiologic mechanisms responsible for dysrhythmias associated with reperfusion of ischaemic myocardium. Circulation, 68(1): 16-24.

27. Kostner K, Hornykewycz S, Yang P, Neunteufl T, Glogar D, Weidinger F, Maurer G, Huber K (1997) Cardiovascular Research, 36:30-33.

28. Roy Denis, Mario Talajic, Stanley Nattel et al (2008) Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure .N Engl. J. Med., 358:2667-2677.

29. Rocken C, Peters B, Juenemann G, et al (2002) Atrial amyloidosis. An arrhythmogenic substrate for persistent atrial fibrillation. Circulation, 106: 2091-7.

30. Delacretaz, Etienne MD (2006) Supraventricular Tachycardia, N. Engl. J. Med., 354:1039-51.

31. Boos CJ, Anderson RA, Lip GY (2006) Is a trial fibrillation an inflammatory disorder? Eur. Heart J., 27(2):136-149.

32. Sunagawa,Tadahiro, Takahiko Shimizu, Akio Matsumoto et al (2014) Cardiac Electrophysiological Alterations in Heart, Article ID 704291, 12: 1-12.

33. Hiroshi Watanabe, Naohito Tanabe, Nobue Yagihara, Toru Watanabe, Yoshifusa Aizawa, MD Makoto Kodama (2011) Association Between Lipid Profile and Risk of Atrial Fibrillation, Circ. J., 75: 2767-2774

34. Velagaleti RS, Massaro J, Vasan RS, Robins SJ, Kannel WB, Levy D (2009) Relations of lipid concentrations to heart failure incidence: The Framingham Heart Study. Circulation, 120: 2345-2351.

35. Iguchi Y, Kimura K, Aoki J, Kobayashi K, Terasawa Y, Sakai K et al (2008) Prevalence of a trial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: Analysis of 41,436 non-employee residents in Kurashiki-city. Circ. J., 72: 909-913.

36. Mihm MJ, Yu F, Carnes CA, Reiser PJ, McCarthy PM, Van Wagoner DR, et al (2001) Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. Circulation, 104(2):174

37. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al (2001) C-reactive protein elevation in patients with atrial arrhythmias: Inflammatory mechanisms and persistence of atrial fibrillation. Circulation, 104: 2886-2891.

38. Yang, Rui-Li, Yong-Hui Shi, Gang Hao, Wu Li, Guo-Wei L (2008) Increase oxidative stress with Progressive Hyperlipidemia in Human J. Clin. Biochem. Nutr., 43: 154-158.

39. Liu YB, Wu CC, Lu LS, et al (2003) Sympathetic Nerve Sprouting, electrical remodeling, and increased vulnerability to ventricular fibrillation in hypercholesterolemia rabbits. Circ. Res, 92: 1145-1152.

40. Liu YB, Lee YT, Pak HN, et al (2009) Effects of simvastatin on cardiac neural and electro physiologic remodeling in rabbits with hypercholesterolemia. Heart Rhythm

41. Szabo Z, Harangi M, Lörincz I, et al (2005) Effect of hyperlipidemia on QT dispersion in patients without ischemic heart disease. Can J. Cardiol., 21(10):847-850.

