ORIGINAL ARTICLE

Impact of Smoking on Cardiac Electrophysiological Parameters of Symptomatic Sinus Node patients in Iraq

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ABSTRACT

Background: Dysfunction of sinoatrial node is a set of abnormal rhythms which are resulted from the sinoatrial node malfunction of the sinus node, the chief natural cardiac pacemaker. The common, and occasionally, the single method for treatment of heart arrhythmias was implantation of pacemaker, which reduce symptoms exactly occurs after implantation.
Aim: To detect the role of smoking on cardiac electrophysiology parameters in sinus node dysfunction in Iraqi patients such as SNRT and AH.
Methods: A cross sectional study, was conducted on 59 patient ranging between 20-50 years old and involving 35 female and 24 male patients, suffering from an unexplained symptoms of sinoatrial node dysfunction (SND). The enrolled participants were gathered from patients who visited the arrhythmia consultant clinic in the Najaf center for cardiac surgery and interventional catheterization at Al-Sadr Medical City in Najaf from all parts of Iraq. The duration of study extended from the beginning of July 2018 till the ending of July 2019. The patients were selected and investigated according to inclusion criteria and either referred to electrophysiological study, pacemaker implantation and/or implantable loop recorder accordingly.
Results: The basic procedure of the study was measurement of cardiac electrophysiological parameters such as SNRT and AH as well as other noninvasive investigations such as PR. Depending on sinus node recovery time (SNRT) measurement for all patients, new cutoff point (1150 milliseconds) for pacemaker implantation was detected. Statistically significant correlations were found between new SNRT cutoff of study and most of electrophysiological, anthropometric, demographic that achieved in current study (P-value < 0.05).
Conclusion: The principal conclusion of this study was that smoking has a significant effect on PR, SNRT, and AH parameters of patients with unexplained symptomatic SND in Iraq.
Keywords: Sinus Node Dysfunction, EPS, smoking, Sinus Node Recovery Time.

INTRODUCTION

Arrhythmias of heart are one of the largest troubles in recent cardiology. Individuals throughout the world suffer from several symptoms which are associated with arrhythmias like chest fluttering, dizziness, bradycardia or tachycardia, and the most progressed symptoms is a syncope (Dagres N *et al.*, 2018; Grisanti LA, 2018). As a response for the symptoms nature, all can adversely change the life quality, which has been recognized several times (Lopez-Villegas A. *et al.*, 2018; Pyngottu A *et al.*, 2019). There are two major kinds of cardiac arrhythmia; sinus node dysfunction and atrioventricular blocks types. Dysfunction of sinoatrial node is a set of abnormal rhythms which are result from the sinoatrial node malfunction of the sinus node, the chief cardiac pacemaker (Dobrzynski H *et al.*, 2007). The furthermost common, and occasionally, the single method for treatment of heart arrhythmias is cardiac implantation of pacemaker, which reduce the symptoms exactly occurs after the pacemaker implantation.

Hereditary disease or abnormalities leading to impairment of heart conducting system constituents task can result in intense arrhythmias which need medical (e.g. blockers of beta receptors) or invasive (e.g. implantation of pacemaker or ablation) treatment (Wolf CM and Berul CI, 2006). In spite of development has been done in analyzing and understanding the characteristics of electrophysiology of cardiac conducting system (CCS) components (Munshi NV, 2012), the mechanisms development of molecular controlling conducting system of heart are still understood inadequately.

Nevertheless, the current new advent of new examining technologies for mechanisms regulating for transcription and inherited linkages at. Recent understandings were focused on the transcriptional appliances fundamental for homeostasis and development of CCS, and debate the outcomes of a CCS transcriptional network as a response for hereditary variation and disturbances.

The atrial sinoatrial node is the key cardiac pacemaker which initiate and regulate heart rhythm (Keith A and Flack M, 1907; Chandler NJ *et al.,* 2009; Fedorov VV *et al.,* 2012). Sinoatrial node conduction and automaticity influenced by calcium ion holding proteins, special various spreading of ion channels inside myocyte and autonomic receptors within the atrial sinus node (Monfredi *et al.,* 2010; Dobrzynski *et al.,* 2013; Wu and Anderson, 2014)in addition to the exclusive complex structure of the sinoatrial node (Fedorov VV et al., 2012).

Several factors impacting the structure of sinoatrial node might cause dysfunction of sinus node (Csepe et al., 2015), when the sinoatrial node inefficiently pace the atrial tissue, which may lead to a number of heart diseases and disorders like atrial fibrillation, cardiac failure, severe ventricular arrhythmias, and ultimately the cardiac arrest (Faggioni *et al.,* 2013; Jensen *et al.,* 2014).

Sinoatrial dysfunction is the significant prediction for electric pacemaker implantation, that is at present the lone existing therapy (Packer *et al.,* 2009; Greenspon AJ *et al.,* 2012).

Generally, the tiny features of the sinoatrial node structure as sinoatrial node size, the correlation of age with excessive ratio of collagen (Lev M, 1954; Alings AMW *et al.,* 1995), the distinct sinoatrial node artery, in addition to the banana like fashioned three dimension sinoatrial node composition, are mostly agreed and accepted upon (Lev, 1954; Truex RC et al., 1967; Shirairshi I *et al.,* 1992; Alings AMW *et al.,* 1995). Nonetheless, refer to the difficulties of this three dimension configuration, a number of microstructural characters persist unclear and/or vague. The significance of the structural-functional sinoatrial node to atria connection concentrates in its essential impact in atrial stimulation mechanism for pacemaking action of sinoatrial node (Fedorov, 2012; Csepe *et al.,* 2015) and the sinus rhythm keeping of normal cardiac function of human.

SND symptoms involve syncope, presyncope, or paroxysmal dizziness which are mostly associated with elongated sinus pauses. Syncope incidents are repeatedly unnoticed and can exhibit in elderlies as repetitive downfalls.

Chronotropic incompetence or sinus bradycardia patients frequently manifest with fatigue or diminished exercise capability; additional symptoms involve nocturnal wakefulness, irritability, lightheadedness, memory loss, and lethargy. Extra delicate symptoms compose of periodic oliguria or edema, mild digestive disturbances, and mild intermittent dyspnea.

PATIENTS AND METHODS

Study population: The current cross sectional study was conducted on patients suffering from an unexplained symptoms of sinoatrial node dysfunction (SND). Fifty nine consecutive patients (20-50 years age) were enrolled in this study (Dobson, 1984) and gathered from the subjects who visited the arrhythmia clinic in the Najaf center for cardiac surgery and interventional catheterization at Al-Sadr Medical City in Najaf city from all parts of Iraq; the study extended from the beginning of July 2018 to the end of July 2019. The approach to the diagnosis of SND was depended on:

- Perform a good history and physical examination.
- Carefully review the medical conditions and medication use as potential remediable causes for apparent SND.
- Obtaining a resting twelve-lead ECG.
- Ambulatory ECG monitoring for up to 3 days and repeated more than one time when resting twelve-lead ECG is negative.
- Consider exercise stress testing, for assessment of the intrinsic heart rate if not achieve 80% of predicted value.
- Referral for electrophysiological study assessment.

Inclusion criteria:

- Age from 18 – 50 years .
- Symptomatic patient with neither findings suggestive for sinus node dysfunction as (sinus brady-tachy)nor evident cause for the symptoms.
- Have no structural heart disease with good LV function by ECHO study.
- Unexplained syncope after palpitations without documentation.
- Awareness of tachycardia without documentation.
- Frequent non-significant pauses by Holter monitoring study clinically.
- Sinus bradycardia by resting ECG with negative treadmill test (TMT).

Exclusion criteria:

- Patient with medical history of ischemic heart disease (IHD).
- Patient with poor LV function by Echo study.
- Patients have documented pause more than three seconds.
- Patients have documented SND.
- Develop any arrhythmia during study even AF.

Medical history: All the patients were referred by senior cardiac electrophysiologist. Brief relevant medical history was taken from each patient including his name, chief complain, age, sex, duration of disease, used drugs, marital state, smoking, occupation and the kinds of treatments. A special attention was paid on the development of unexplained symptoms of SND which might include syncope, chest pain, presyncope, palpitation, shortness of breath, fatigue, lightheadedness and chest discomfort (Kantharia BK, 2018). In addition to documenting of past medical and surgical history, social and family history and drug allergy history specially that used in cardiovascular intervention for all patients of study population sample. This system used to determine the cardiac electrophysiological study invasively which are very important parameters. The type of Cardiac Electrophysiological system was (St. Jude medical system model Allura Xpar FD 10/10).

Procedure: Electrocardiography, ambulatory ECG monitors, and Treadmill test were done before procedure. Twenty four hours before; patients must presented an authorized notified agreement to subject for EPS and probable implantation of pacemaker. Five French catheters of quadripolar electrode, with a space of 4 millimeters space among them, were introduced via the femoral vein to reach for the appendage of right atrium, another catheter introduced within the tricuspid valve to document the potential of His bundle, whereas the third catheter inserted to be positioned in the right ventricle apex. Invasive electrograms inside heart and the leads I, II, V1 and V6 of surface ECG were seen on a multiple channels screen (EP WORK MET, SJM) at a greatest paper velocity (100 mm./sec.), and all Invasive cardiac electrograms gained (12 noninvasive and up to 64 invasive intracardiac channels or leads) were gathered on an particular optical disc drive. The passed package were positioned ranging from 30 to 500 Hertz. Automated pacing with two milliseconds duration of pace was achieved using internal accelerator. Also introducing of a full baseline electrophysiological study parameters was achieved by measuring of all interval AH (starting from A impulse in the catheter of upper right atrium to the His electrode potential. The identical automatic protocol of stimulation involved the subsequent points:

Sinus node refractory time (SNRT) assessment at various cycle lengths; patients were advised for implantation of pacemaker if there was sinoatrial node dysfunction (when SNRT more than 1400 milliseconds). EPS was involved calculation of AH interval at baseline and during application of stress condition via incremental atrial pacing.

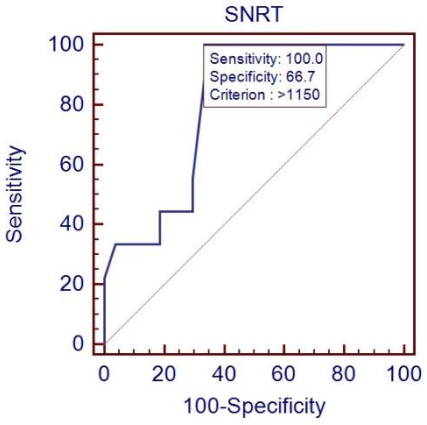
Statistical analysis: Two statistical Software installed on PC were used for analyzing data of this study, MedCalc software version 18.3 was used (MedCalc Software bvba, Ostend, Belgium), Receiver Operating characteristic (ROC) test was applied to determine optimal cutoff value of SNRT for pacemaker implantation; and SPSS version 21(SPSS, Chicago, IL, USA) was used to evaluate differences between continuous variables (expressed as Mean ± S.D.) via independent t-test. Ranking variables represented as frequency and percentage and their differences were inspected by Chi-squared test. Associations between variables were done by Pearson's correlation Coefficient. A P-value of 2-tailed <0.05 was set for significant difference statistically and P-value <0.01 for highly significance statistically.

RESULTS

Sinus node recovery time (SNRT) assessment: The receiver operating characteristic (ROC) curve was achieved on total patients of study, the zone under the curve for sinus node recovery time (SNRT) was assessed between patients with a remaining symptoms subsequent to pacemaker implantation and patients free of symptoms. ROC curve presented that the area under the curve for SNRT was 0.802, which mean that the level of threshold was 1150 milliseconds. The value of sensitivity was 100% whereas specificity was 66.7%. The elevated SNRT yielded more successful results, as illustrated below in (figure 1).

The results of this study were analyzed according to the outcomes of sinus node recovery time (SNRT) assessment via the electrophysiological study in addition to the evaluation of other electrophysiological parameters by using of special programmed stimulation compared with symptoms of patients.

Figure 1: ROC curve analysis demonstrate the predictive value of SNRT (1150 ms.) for pacemaker implantation.



According to the SNRT cutoff value, the patients were divided into two groups for testing the statistical correlation of parameters between them:

Group1 (G1): involved the patients who recorded SNRT equal or above the study cutoff (1150 ms) in EPS.

Group2 (G2): involved the patients who recorded SNRT below the study cutoff (1150 ms) in EPS.

Fifty nine Iraqi patients with sinus node dysfunction were enrolled in this study whose age mean was 39.7 years composed of thirty five female patients (59.32%) and twenty four male patients (40.67%) as presented in (table 1).The variables of study in G1 and G2 were tested statistically as demonstrated in (tables 1, 2) consequently.

Table 1: Correlation of demographic parameters between two groups of study

Para-meters	Sub-domain	SNRT(ms)		P-value
		Group 1 (N=33)	Group 2 (N=26)	
Gender	Male	11(45.83%)	13(54.17%)	< 0.05
	Female	21(60%)	14(40%)	
Marital Status	Single	9(37.5%)	15(64.5%)	< 0.01
	Married	23(65.71%)	12(34.29%)	
Smoking	No	11(45.16%)	13(54.84%)	< 0.05
	Yes	24(62.39%)	11(37.71%)	

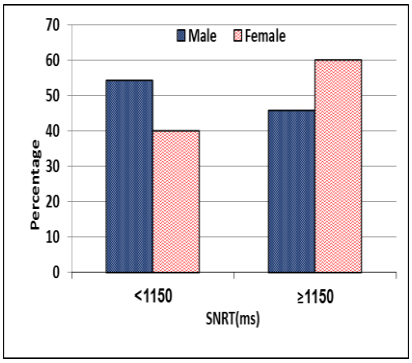
Fisher's exact test.

Table 2: Electrophysiological parameters relation between two groups of study.

Cardiac Parameters	Group 1 (N=33)	Group 2 (N=26)	P-value
SNRT (ms)	1271.61±61.64	995 ± 80.76	<0.01
PR interval (ms)	199.3±33.92	182.90 ± 41.67	<0.01
AH interval (ms)	86.26 ± 2.88	78.82 ± 5.09	<0.01

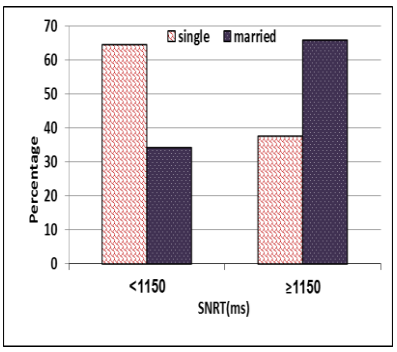
Gender distribution and SNRT: According to (table 1 and figure 2), female's percentage was significantly higher than male's percentage in patients of G1 in comparison to patients of G2. (P < 0.05)

Figure 2: Association of gender and SNRT cutoff.



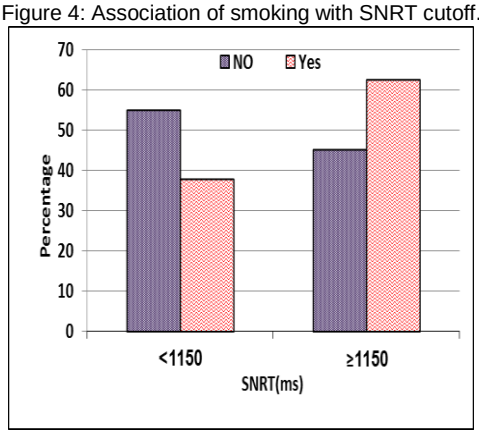
Marital status and SNRT: The percent of married patients in G1 was significantly higher than single patients as compared with G2 which demonstrated clearly by (table 1 and figure 3). (P < 0.001)

Figure 3: Association of marital status with SNRT cutoff.



Smoking and SNRT: The rate of smokers in G1 was higher than nonsmokers whereas the smoker's percentage of G2 was lower; these differences were a significant statistically as represented by (table 1 and figure 4). ($P < 0.05$)

Figure 4: Association of smoking with SNRT cutoff.



PR interval and sinus node recovery time (SNRT): The PR interval range of study patients was 156 – 300ms. According to the (table 2 and figures 5, 6), there is highly significant positive correlation between PR interval length and SNRT ($P<0.01$)

Figure 5: Correlation of PR interval with SNRT.

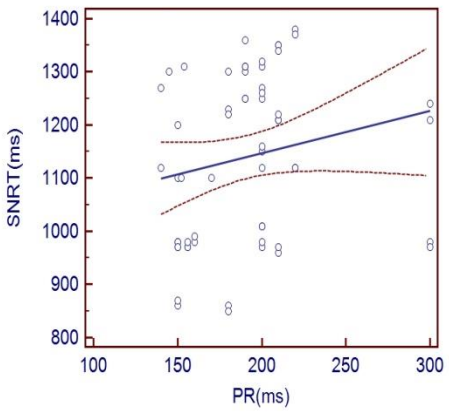
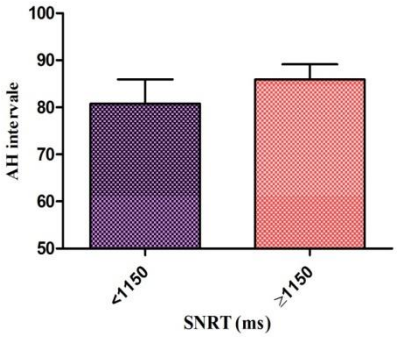


Figure 6: Association of PR interval with SNRT cutoff.



AH interval and SNRT: According to (tables 2 and figures 7, 8), there is a highly significant correlation between SNRT and AH interval ($P < 0.01$). Considering AH interval, the patients of G1 recorded highly significant difference in comparison with patients of G2. ($P < 0.01$)

Figure 7: Correlation between AH interval and SNRT.

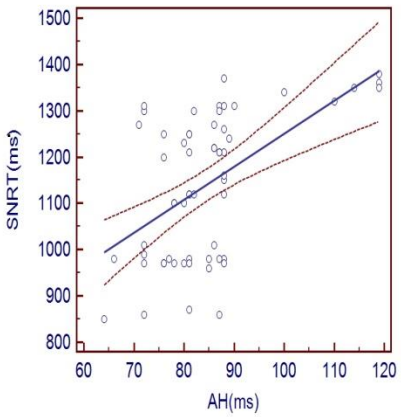
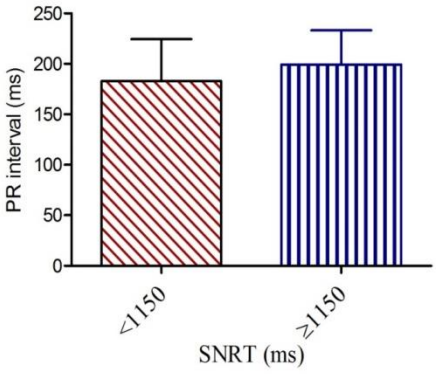


Figure 8: Relationship between AH interval and SNRT cutoff.



DISCUSSION

Sinus node recovery time (SNRT) assessment: The results of current study were analyzed according to the assessment of SNRT (sinus node recovery time) by the electrophysiological study. The receiver operating characteristic (ROC) curve was done on all study patients

with undocumented symptomatic sinus node dysfunction which revealed that SNRT cutoff point or threshold for pacemaker implantation was 1150 milliseconds. The value of sensitivity was 100% whereas specificity was 66.7%.

During the evaluation of sinus node dysfunction (SND), invasive electrophysiological studies (EPS) are still infrequently used since sensitivity still limited although the overdrive suppression test to assess the sinus node recovery time (SNRT) is significant in detecting sick sinus syndrome (SSS) but with inadequate sensitivity. In our study, as a mean SNRT in our study was 1150 milliseconds and according to its value we divided our patients into two groups:

Group One (G1): was involved patients with SNRT equal to or above the cutoff point (1150 milliseconds).

Group Two (G2): was included patients with SNRT below the cutoff point (1150 milliseconds).

According to the international guidelines for treatment of sinus node dysfunction (Kusumoto FM *et al.,* 2018),the SNRT cutoff for pacemaker implantation was 1400 milliseconds, so that the SNRT cutoff of this study was significantly different from that stated in international guidelines for treatment of sinus node dysfunction.

Cardiac symptoms and pacemaker implantation: After electrophysiological study for patients with unexplained symptoms; our data showed that clinically significant abnormalities of sinus node dysfunction in our patients occurred mainly with G1 patients for pacemaker implantation rather than with more than 1400ms as in indications of ACC/AHA/HRS (2018) for pacemaker implantation in management of dysfunction in sinoatrial node. And this is of important value since, may be our situation completely different with alter in EPS parameters and autonomic dysfunction.

According to this data and after deep discussion with patients and families with results and guideline value, we decided pacemaker implantation to those with highly symptomatic patient and SNRT equal or more than 1150 milliseconds that considered clinically sinus node dysfunction and markedly prolonged SNRT and syncope which was considered mainly due to prolonged bradycardia, for this reason and in the final analysis of our data in symptomatic patients with SNRT equal or above 1150ms (55.93%), pacemaker was implanted in 22 patients compare to other patients without pacemaker, and a short period of follow up we noticed symptoms completely resolved and no more symptoms, that proved pacemaker implantation had important role in the management of patients with clinically significant sinus node dysfunction.

The significant difference between two groups (G1 and G2) may be related to race, genetics, environment, ethnicity, nutrition, and geographical variation. Pacemaker implantation had significant positive effect on the symptoms of patients study; accordingly symptoms presence and absence were compared between patients without and with implantation of pacemaker; the outcomes expressed that the symptoms of patients had significantly disappeared with pacemaker implantation as compared with the patients without implantation of pacemaker (P-value < 0.05).

ECG parameters and Electrophysiological study: This study showed clear relationship between PR interval in the surface ECG and SNRT, as patient with prolonged PR interval near to maximum upper normal limit, seen to have more time and longer SNRT in comparison to those with short PR interval near the lower limit or normal PR interval, G1 PR versus G2 PR (199.3 ± 33.92 ms versus 182.90 ± 41.67ms) and G1 SNRT versus G2 SNRT (1271.61 ± 61.64 ms versus 995 ± 80.76 ms). Although statistically significant value (P< 0.05), this also considered of clinically importance for device implantation. At the same time we noticed in those patient the same relation in prolongation time from SA node to His (AH interval) seen to be more in those patients in G1 AH (86.26 ± 2.88 ms) with prolonged PR interval. While normal in G2, this indicated that most of time was suprahisian in SND, since there is no significant relation with HV interval and QRS duration in those patients with SND.

Metabolic syndrome is very risky to enhance the cardiovascular diseases developing (Assoumou N *et al.*, 2010) and the probability of supraventricular arrhythmias like in the abnormal P-wave and the Sick Sinus Syndrome; likewise, the atrial fibrillation rises in obese patients with metabolic syndrome that is related with an increased morbidity and mortality (Lin Y-K *et al.,* 2010).

SND is suggested as the first electrophysiological manifestation in patients with the SCN5A mutation after controlling on the confounding variables involving genetics, hormones, aging, and uncertain factors of environment (Delva *et al.,* 2009).

In desmosomes, some proteins forming a complex which having signaling and mechanical properties together functioning as a link between the filaments connecting between the two adjacent myocytes (Delva *et al.,* 2009). In cardiac conducting system, there is a certain confirmation for desmosomal structures presence, which has been achieved through:

1. Presence of desmosomal components in the SAN through electron microscopy (Saffitz *et al.,* 1997; Shimada *et al.,* 2004).
2. Immunological proof of particular structures of desmosome like the desmoplakin, a fundamental desmosomal constituent (Dobrzynski *et al.,* 2000) in addition to plakoglobin (Lim *et al.,* 2008) in the sinoatrial node. Gap junctions (nexus) establish a stage for exchanging of small molecule between each adjacent cells. Sinus node dysfunction was detected as sinus node bradycardia and tachycardia, that was concomitant with Cx45 lossing (Lisewski *et al.,* 2008), a protein of gap junction mainly detected in the SAN (Coppen *et al.,* 2003).

Demographic and anthropometric parameters:

Gender distribution and SNRT: In (table 3, figure 2) expressed that female's percentage of G1 patients was higher than male percentage whereas the females percentage of G2 was lower; these differences were a statistically significant (P < 0.05).

Sick sinus syndrome (SSS) is more liable in women as compared with men in contrast to occurrence of AV-block due to that Connexin (Cx-40) expression induction is more in women than men (Pfannmuller B. et al., 2013). Two human genders have different normal electrophysiology in their specified cardiac conduction system and functioning myocardial tissue. Sex electrophysiological and arrhythmic variations related to genders were more marked in different reports; further than

biological factors, differences in arrhythmia sex might be associated with genders regarding factors (Tadros R. et al., 2014).It had been displayed that pregnancy causes density increment of pacemaker current (I_f) which attributed to increasing expression of HCN2-subunit protein (El khoury N. et al., 2013).

Numerous models of animals reveal that the sex related differences include sex hormones effects, both via non-genomic effects (channel-function changes) and genomic effects (ion-channel subunits expression differences) (Burke JH et al., 1997) that could be attributed to female sided sex hormones prominence; these were resulted from great fluctuations in plasma levels of estrogen and progesterone through the cycle of ovary, which modify currents of ions via non-genomic influences (Kurokawa J et al., 2008; Nakamura H et al., 2007) that might be associated with increment of progesterone, whereas estrogen level reduces, repolarization of currents; therefore, enhanced ratios of estrogen/progesterone through the follicular phase reduces the currents of repolarization, extending action potential duration. Since the longer longevity of women and age advancement is the particular most significant risk factor, females compose around 50% of total atrial fibrillation patients. Progressing age, hypertension, diabetes, in addition to cardiac failure causes increment of atrial fibrillation occurrence is the same in two genders, although valvular disorders rises risk of AF in women more than men. (Feinberg WM et al., 1995; Michelena HI et al., 2010).

The elevated ratio of sex variances was associated with expression of Connexin-40 in females than males. It has been supposed that ion channel function and genomic expression in female gender cause weaker currents of repolarization, this might be linked to estrogen effect. Nevertheless, sex related differences in genomic expression of numerous ion chnnels makes advanced risk of AF in men and whether nongenomic changes additionally be existent persists for more researching which can be attributed to sex hormones prominence in females groups
(Pfannmuller B et al., 2013).

Marital status and SNRT:

The married patients percent of was higher than singles in G1 in comparison with G2 of study; these differences were a highly significant ($P < 0.001$) which demonstrated clearly by (table 1, figure 3).

This differences may be related to the sociodemographic criteria like alcoholism or bad habits as different types of smoking or may be related progressing aging in married as compared with unmarried patients. Also may be due to their hormonal activity which was more in married patients than unmarried patients.

Smoking and SNRT: The correlation of smokers percentage with SNRT of G1 was higher than G2 as compared with nonsmokers; these differences were a significant as represented by (table 1, figure 4) ($P < 0.05$).

Smoking of cigarettes stays one of the most significant regulateable risk factors for cardiovascular diseases (Benjamin EJ *et al.,* 2019).It was assumed that smoking changes levels of plasma catecholamine, oxidative stress induction, and triggers remodeling of atrial tissue by disordering fibroblasts, possibly as a total leading for AF occurrence (D'Alessandro A *et al.,* 2012).

Smoking involves every phase of atherosclerotic process from dysfunction of endothelium to clinically severe outcomes (Meissner and Bernhard, 2014). The indicative processes linking atrial arrhythmia and smoking comprising inflammation and oxidative stress, as showed by biomarkers of inflammation as C-reactive protein (Levitzky YS *et al.,* 2008), atrial fibrosis and electrical alterations (Goette A. , 2009). These harmful influences are possibly facilitated by carbon monoxide, nicotine, and polycyclic aromatic hydrocarbons (Heeringa J *et al.,* 2008). Metabolite of nicotine named Cotinine has a half-life of around 20 hours and chemically stable. Plasma concentration of cotinine was considerably related with atrial arrhythmia. Smoking is predisposing factor for atrial fibrillation in a dosage reaction pattern (Chamberlain AM *et al.,* 2011; Knuiman M *et al.,* 2014).Smoking also produces remodeling of the myocardial cells structure, that has a toxic effects on cardiac conduction system directly and can result in atrial dysrhythmia (Hayashi H *et al,* 2003; Schnabel RB *et al.,* 2009).

Inhalation of nicotine as well as toxic materials facilitates to multiple numerous syndromes of atherosclerosis (Laniado-Laborín R. 2009; Saposnik G *et al.,* 2013) and is also connected with arrhythmia happening (Goette A *et al.,* 2002).Though, the smoking proarrhythmic effect appears to be dependent on the blood level of nicotine. Enhanced concentrations of nicotine elevate atrial susceptibility of atrium to arrhythmia (January CT *et al.,* 2014).These profibrillatory influences appear to be depended on the ion channels inhibition and slowing of properties of conduction (Heeringa J, 2008). However, the molecular and structural basis by which nicotine persistent exposure possibly will causes atrial fibrillation has still without full understanding. Several conclusions have evidently displayed that atrial fibrosis supplies established substrate that facilitates the atrial arrhythmias happening as a result to an activating occasion (Tuan TC *et al.,* 2008; Peters DC *et al.,* 2009). Fibrosis of atrial interstitial separates clusters of myocytes of atrium in addition to singular atrial myocytes. Furthermore, it weakens coupling of cell with cell, producing inconsistencies in conduction of inter and intra atrial tissue, which might worsens the function of atrial transfer and promote the probability of arrhythmia of atrium (Tuan TC *et al.,* 2008). Hence, the pathophysiological processes explanation controlling the atrial collagen accumulation give the impression of clinical importance. Nevertheless, the cigarettes smoking impact on fibrotic alterations in myocardium of atrium has yet not been discovered. The relationship between smoking of cigarettes and the amount of atrial fibrosis in patients with coronary artery bypass grafting (CABG).

In the CVS, prolonged nicotine exposure has been discovered to enhance stiffness of aorta, to increase ventricular interstitial fibrosis moderately which result in chamber stiffness increase (Lo LW et al., 2015) Additionally, cigarettes smoking is concomitant with enhanced markers of inflammation in AF patients such as C-reactive protein (Higa S et al., 2006).

However, cigarettes smoking is well identified to provoke ischaemia of heart due to vascular spasms and coronary arteries atherosclerosis, which can produce local

necrosis and substitution by fibrosis. In conflict with cardiac myocytes, atrial provision with oxygen basically dependent on diffusion of oxygen from chambers of atrium, therefore, atrial ischaemia of atrium provoked by effects of smoking on blood vessels appears doubtful to clarify the detected scattered forms of fibrosis in tissue of atrium. (January CT et al., 2014).Fibrosis of atrium detaches atrial cardiomyocytes clusters and singular cardiomyocytes, Thus, interstitial fibrosis may produce inconsistencies in inter and intra conduction of atrium (Santangeli P et al., 2016). Primarily, successive alterations in conduction of atrium can be hidden, and so that no noticeable on the surface electrocardiography (Hung Y et al., 2017).Analogous earlier researches have also discovered an relationship joining fibrosis of atrium, age, duration of surface P-wave and postoperative arrhythmia of atrium. Reactive cardiac fibrosis, maybe stimulated by endothelin, high concentration of angiotensin II, transforming growth factor b and so on, hypothesized (Chang HY et al., 2013).

Interstitial fibrosis separates clusters of myocytes in atrium in addition to singular myocytes. Also, it weakens cell to cell coupling, initiating inconsistencies in intra and interatrial conduction, which might cause impairment the transport function in atrium and enhance the AF possibility (Li D et al., 1999; Tuan TC et al., 2008).

Nicotine could be a chief reason for cardiac myocyte dysfunction induction and therefore cause precipitation of cardiac arrhythmia in the arterial coronary stenosis patients (Aronow WS et al., 1974). Studies on animals exhibited that increased concentration of nicotine in blood can be a probable elicit of cardiac arrhythmias. Next, multiple reports were documented around cases of nicotine and cardiac arrhythmia and nicotine in human (Choragudi NL et al., 2013).Nonetheless, Hayashi et al. (2003) had stated that nicotine administration might increase the frequent independent wave frontages, accordingly result in arrhythmia of conduction. Moreover, administration of nicotine also cause the automaticity induction (Hayashi H et al., 2003).Linking together these two mechanisms, probability of cardiac arrhythmia might be amplified and activated. The time for activation of RA completely was more in the smokers as compared with nonsmokers whereas such conclusion was not seen in the LA. Further, the voltage decrease of RA was smoking intensity duration connected in the smokers.

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