ORIGINAL ARTICLE

Relation of Red cell width diameter with some electrophysiological parameters of symptomatic sinus node patients in Iraq

HEIDER HEMEED ABBAS[1] , AMEEN ABDULHASAN AL-ALWANY[2], FOUAD SHAREEFDLEIKH[3]
Department of Basic Medical Sciences, College of Dentistry, University of Babylon[1]
Department of Medicine, College of Medicine, University of Baghdad [2]
Department of Medical Physiology, College of Medicine, University of Kufa[3]

ABSTRACT

Background: Dysfunction of sinoatrial node is a set of abnormal rhythms which are resulted from the sinoatrial node malfunctionof the sinus node, the chief natural cardiac pacemaker. The common, and occasionally, the single method for treatment of heart arrhythmias wasimplantation of pacemaker, which reduce symptoms exactly occurs after implantation.
Aim: To detect the association between red cell width diameter (RDW) and some 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.
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: RDW has a significant effecton PR, SNRT, and AH parameters of patients with unexplained symptomatic SND in Iraq.
Keywords: Sinus Node Dysfunction, EPS, RDW, 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 adverselychange the life quality, which has been recognizedseveral times (Lopez-Villegas A.*et al.*, 2018; Pyngottu A *et al.*, 2019). There are two major kinds of cardiacarrhythmia; sinus node dysfunction and atrioventricular blocks types. Dysfunction of sinoatrial nodeis a set of abnormal rhythms which are result from the sinoatrial node malfunctionof the sinus node, the chiefcardiac pacemaker(Dobrzynski H *et al.*, 2007).
Hereditarydisorders leading to impairment of heart conducting systemconstituentstask can result inintense arrhythmias which needmedical (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 understandingthe characteristics of electrophysiology of cardiac conducting system (CCS) components (Munshi NV,2012),the mechanisms development of molecular controlling conducting system of heart arestill understood inadequately.
The atrial sinoatrial node is the keycardiac pacemakerwhichinitiate and regulate heart rhythm. Sinoatrial node conduction and automaticityinfluenced by calcium ion holding proteins, specialvariousspreading of ion channels inside myocyteand autonomic receptors within the atrial sinus node (Monfredi *et al.,* 2010; Dobrzynski *et al.,* 2013; Wu and Anderson, 2014).
Several factors impacting the structure ofsinoatrial node might cause dysfunction of sinus node (Csepe et al., 2015),when the sinoatrial nodeinefficientlypace the atrial tissue, which may lead to a number of heart diseases and disorders like atrial arrhythmia (Jensen *et al.,* 2014). Generally, the tiny features of the sinoatrial node structure as sinoatrial node size, the correlation of age with excessive ratio of collagen (Alings AMW *et al.,* 1995), the distinctsinoatrial node artery, in addition to the banana like fashioned three dimension sinoatrial node composition, are mostly agreed and accepted upon (Alings AMW*et al.,* 1995).
The significance of the structural-functionalsinoatrial node to atria connection concentrates in its essentialimpact in atrial stimulation mechanism forpacemaking actionof sinoatrial node and the sinus rhythmkeeping of normal cardiac function of human (Fedorov, 2012; Csepe *et al.,* 2015).

PATIENTS AND METHODS

Study population: The current cross sectional study was conducted on patients suffering from an unexplained symptoms of sinoatrial node dysfunction (SND).

The study group (59 patients) were 20-50 years aged weregathered from the arrhythmia clinic visitors in the Najaf center for cardiac surgery and interventional catheterization from all parts of Iraqthe study has started from the July 2018 and ended in July 2019 (Dobson, 1984).The approach to the diagnosis of SND was depended on:

- 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: Medical history for all patients was taken from each patient includinghis 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).

Procedure: Electrocardiography, ambulatory ECG monitors, and Treadmill testwere done before procedure.Twenty four hours before; patients must presented an authorized notified agreement to subject for EPS and probableimplantation of pacemaker.Five French catheters of quadripolar electrodewere introducedvia the femoral vein to reach for the appendage of right atrium, another catheterintroduced within the tricuspid valve to document thepotential of His bundle, whereas the third catheter inserted to be positioned in theright 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.

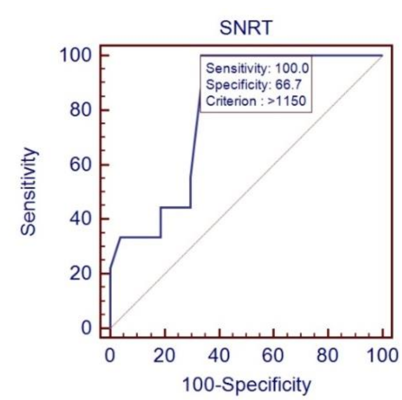
Sinus node refractory time (SNRT) assessment at various cycle lengths; patients were advised for implantation of pacemaker if there was sinoatrial node dysfunction (when SNRT more than 1400 milliseconds). EPS was involved calculation of AH interval at baseline and during application of stress condition via incremental atrialpacing. In addition to that CBC was done for all pts of study to calculate multiple parameters of blood the most significant parameter of CBC was calculation of RDW.

Statistical analysis: Two statistical Software installed on PC were used for analyzing data of this study, Med Calc 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 variablesrepresented 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: In 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 symptomssubsequent to pacemaker implantation and patients free of symptoms. ROC curve presentedthat the area under the curve for SNRT was 0.802, which mean that the level of threshold was 1150 milliseconds with 100% sensitivity and66.7% specificity as in Figure 1. The results were analyzed according to the outcomes of sinus node recovery time (SNRT) assessment via the electrophysiological study and 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 patients with SNRT equal or above the study cutoff (1150 ms).
Group2 (G2): included patients with SNRT below the study cutoff (1150 ms).
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.

Gender distribution and SNRT: According to (Table1 andFigure2), female's percentage was significantly higher than male's percentagein patients of G1 in comparison to patients of G2. (P < 0.05)

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 (Table1 and Figure3). (P < 0.001)

RDW and SNRT: The RDW valuein G1 patients was higher than the patients ofG2; these differences were a significant statistically as represented by (Table1 and Figures4, 5).(P < 0.01)

PR interval and sinus node recovery time(SNRT): The PR interval range of study patients was 156 – 300 ms. According to the (Table 2 and Figures 6, 7), there is highly significant positive correlation between PR interval length andSNRT. (P < 0.01)

AH interval and SNRT: According to (Table 2 and Figures 8, 9), there is a highly significant correlation between SNRT and AH interval l(P < 0.01). Considering AH interval, the patients of G1 recorded highly significant difference in comparison with patients of G2. (P < 0.01)

Table 1: Correlation of RDW, gender and marital status between two groups

Para-meters	Sub-domain	SNRT(ms) Group 1 (N=33)	SNRT(ms) Group 2 (N=26)	P-value
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%)	
RDW		14.85±0.64	13.80±0.18	< 0.01

Fisher's exact test.

Table 2: Electrophysiological parameters relation between two groups

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

Figure 2: Gender & SNRT cutoff relation.

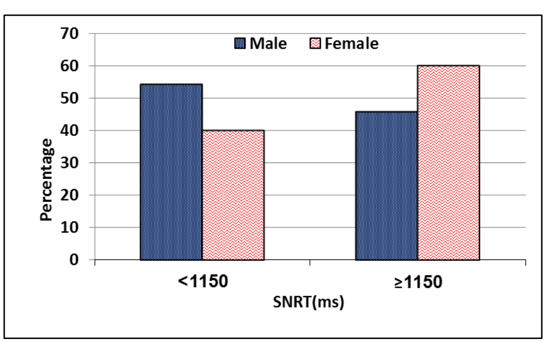


Figure 3: Marital status & SNRT cutoff link.

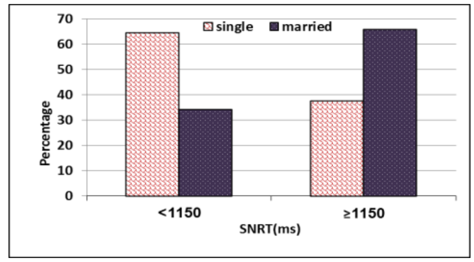


Figure 4: Association of RDW with SNRT.

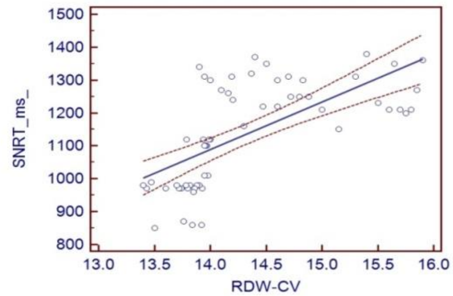


Figure 5: RDW and SNRT cutoff relation.

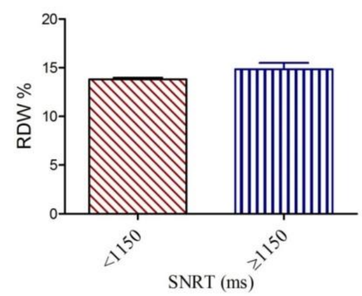


Figure 6: PR interval with SNRT correlation.

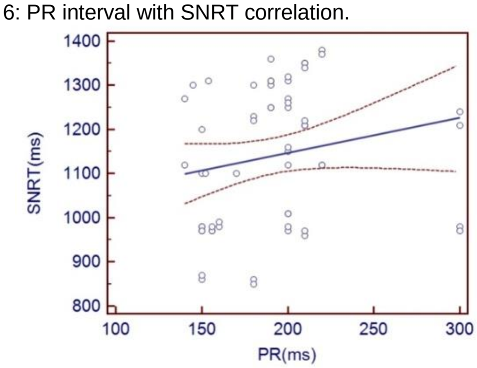


Figure 7: PR interval & SNRT cutoff linking.

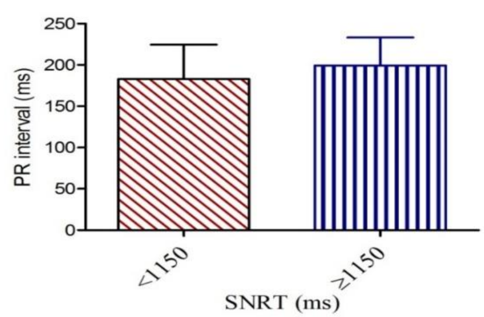


Figure 8: AH interval & SNRT relation.

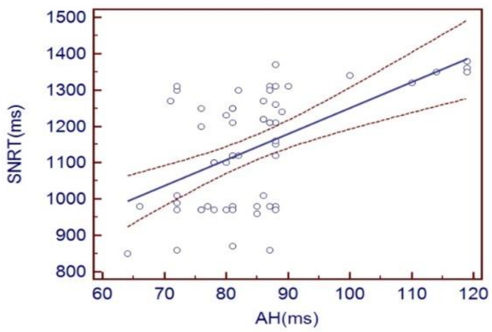
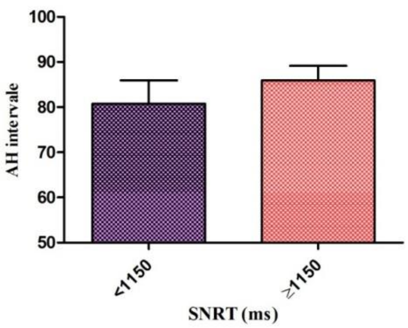


Figure 9: AH interval & SNRT cutoff correlation.



DISCUSSION

Sinus node recovery time (SNRT) assessment: The receiver operating characteristic (ROC) curve was done on all study patients with undocumented symptomatic sinus node dysfunction whichrevealed that SNRT cutoff point or threshold for pacemaker implantation was 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: 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 1150milliseconds that considered clinically sinus node dysfunction and markedly prolonged SNRT and syncope whichwas 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, G1PR versus G2 PR(199.3 ± 33.92 ms versus 182.90±41.67ms) and G1SNRT versus G2 SNRT (1271.61±61.64ms versus 995±80.76ms). 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 as in (Table 2, Figures 6, 7, 8, 9).

SND is suggested as thefirst electrophysiological manifestation in patients with the SCN5A mutation after controlling on the confounding variables involving genetics, hormones, aging, and uncertainfactors 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). Sinus node dysfunction was detected as sinus node bradycardia and tachycardia, that was concomitant with Cx45lossing (Lisewski*et al.,* 2008), a protein of gap junctionmainlydetected in the SAN (Coppen *et al.,* 2003).

Demographic and anthropometric parameters:

Gender distribution and SNRT: In (Table 1, 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).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 (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.

RDW and SNRT: Due to clarification of (Table 1 and Figures 4, 5). It had been concluded that there was a highly significant relation of RDWwith SNRT and SNRT cutoff (P < 0.01).

Sinus node dysfunction happens as an outcome of disturbances in conduction, automaticity of the sinoatrial node or both of them (Choudhury M et al., 2015). The main reasons for sinus node dysfunction initiation comprised of the inflammation, ischemia, fibrosis, genetic mutation, and hypoxia (Jabbour F. and Kanmanthareddy A., 2019).

Atherosclerosis is a multifactorial pathological course that happens as a consequence of several metabolic imbalances, which basically contain inflammation, dyslipidemia, and thrombosis (Lippi G et al., 2011). As it has been established that a positive, strong and independent correlation joined the traditional biomarkers of inflammation and RDW (Lippi G et al., 2009).

It was reasonable that multiplied anisocytosis can produce precisely from low degree inflammation which is common in atherosclerotic patients (Krintus M et al., 2014). Inflammation could, really, stimulate anisocytosis via response erythropoietin disruption with iron metabolism impairment, therefore weakening maturation of red blood cells and producing immature red blood cells to move in the blood stream (Weiss and Goodnough, 2005). It is also remarkable that RDW was discovered to be adversely related with HDL cholesterol, and proportionally related with the hypertriglyceridemia, atherogenic index of plasma, and the total to HDL cholesterol ratio, so that anisocytosis may also be regarded as a marker of dyslipidemia. Another possible determining factor of RDW rate is arterial blood pressure which contribute to the linkage of CVD and hypertensionwith RDW. (Lippi and Franchini, 2008; Tanindi A et al., 2012).

Some studies confirmed there was a very considerable association joining parameters of RDW and cardiac arrhythmias (Sarikana S et al., 2014; Danese E et al., 2015; Korantzopoulos P et al., 2015).The higher RDW is significantly linked with prolongation of SNRT; which may be attributed to several causes of SND and these finding is consistent with the current study (Danese E et al., 2015).

Another theory links high RDW values with oxidative stress, the latter stimulates erythropoiesis which leads to synthesis of large immature blood cells with poor oxygen transport properties leading to hypoxia (Friedman J et al., 2004; Lippi G. et al., 2019). Furthermore, some authors have suggested a relationship between elevated RDW and limited physiological reserve with a higher incidence of complication, such as atrial arrythmia (Hunziker S et al., 2012; Korantzopoulos et al., 2015).

The relationship linking the inflammation and the AF happening is well documented. Consequently, various inflammatory biomarkers have been involved in AF while the therapies of anti-inflammatory upstream may diminish the burden of AF (Liu T et al., 2007; Liu T et al., 2008). These studies have informed that higher levels of RDW as a potent independent predictor of augmented morbidity and mortality in cardiovascular diseases patients (Cavusoglu E et al., 2010; Lippi G., 2019).The processes between elevated levels of RDW and inadequate clinical results in cardiovascular diseases have not yet been interpretate precisely (Uyarel H et al., 2012). As a first, some studies suggest that elevated RDW levels can reveal a state of pro-inflammation (Emans ME et al., 2013; Ozcan F et al., 2013).Really, the discharge of proinflammatory cytokines can inhibit erythropoietin stimulated development of erythrocytes, and therefore, great ratio immature erythrocytes may generate greater levels of RDW (Pierce CN and Larson DF, 2005). Secondly, Patel et al. (2015) submitted that enhanced life span of red cells, beside higher RDW and Lower MCV, might be an essential reaction for happening of disease. Another potential justification could be that red cells which have been circulated for an elongated period (aged red cells are smaller sized causing RDW increment) has decline of enzymatic systems resulting in losing specific functions of their anti-oxidative ability. Multiple processes of pathophysiology, as pro-inflammatory environment and oxidative stress, could induce the levels of RDW levels via decreasing survival of erythrocytes, thus generating a further merged red cells population in blood. Moreover, an accumulative confirmation body proposes a linkage joining the oxidative stress and inflammation together with AF (Liu T et al., 2007; Liu T et al., 2008; Lippi G. et al., 2015). Hence, confirming correlation of RDW and atrial fibrillation, RDW is an indicator of red cells anisocytosis and is associated with inflammatory stress (Lippi G. et al., 2015).

REFERENCES

1. Alings, A. M. W., Abbas, R. F., &Bouman, L. N. (1995). Age-related changes in structure and relative collagen content of the human and feline sinoatrial node: a comparative study. European heart journal, .1667-1655 ,(11)16
2. Cavusoglu E, Chopra V, Gupta A, et al. (2010). Relation between red blood cell distribution width and all-cause mortality at two years in anunselected population referred for coronary angiography. Int J Cardiol.,;141:141-146.
3. Chandler, N. J., Greener, I. D., Tellez, J. O., Inada, S., Mussa, H., Molenaar, P.,… &Billeter, R. (2009). Molecular architecture of the human sinus node: insights into the function of the cardiac pacemaker. Circulation, 119(12), 1562-1575.
4. Choudhury, M., Boyett, M. R., & Morris, G. M. (2015). Biology of the sinus node and its disease. Arrhythmia & electrophysiology review, 4(1), 28.
5. Coppen SR, Kaba RA, Halliday D, Dupont E, Skepper JN, Elneil S, Severs NJ.(2003). Comparison of connexin expression patterns in the developing mouse heart and human foetal heart. Mol Cell Biochem ; 242:121–7.
6. Csepe TA, Kalyanasundaram A, Hansen BJ, et al. (2015). Fibrosis: a structural modulator of sinoatrial node physiology and dysfunction. Front Physiol.;6:37.
7. Dagres N, Chao TF, Fenelon G, et al. (2018). European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice? J Arrhythmia.,;34:99–123.

8. Danese E, Lippi G, Montagnana M. (2015). Red blood cell distribution width and cardiovascular diseases. J Thorac Dis,; 7:E402.
9. Delva E, Tucker DK, Kowalczyk AP. (2009). The desmosome. Cold Spring HarbPerspect Biol.;1: a002543.
10. Dobrzynski H, Boyett MR, Anderson RH. (2007). New insights into pacemaker activity: promoting understanding of sick sinus syndrome. .1932–**115**:1921; ,.Circulation
11. Dobrzynski H, Rothery SM, Marples DDR, Coppen SR, Takagishi Y, Honjo H, Tamkun MM, Henderson Z, Kodama I, Severs NJ, Boyett MR. (2013). Presence of the Kv1.5 K+ Channel in the Sinoatrial Node. Journal of Histochemistry&Cytochemistry. ; 48:769–780.
12. Dobrzynski, H., Anderson, R. H., Atkinson, A., Borbas, Z., D'Souza, A., Fraser, J. F., ... & Moorman, A. F. (2013). Structure, function and clinical relevance of the cardiac conduction system, including the atrioventricular ring and outflow tract tissues. *Pharmacology & .288-260 ,(2)**139** ,therapeutics*
13. Dobson AJ. (1984).Calculating sample size. Trans. Mezies Foundation; 7: 75-9.
14. Emans ME, Gaillard CA, Pfister R, et al. (2013). Red cell distribution width is associated with physical inactivity and heart failure, independent of established risk factors, inflammation or iron metabolism; the epicnor folk study. Int J Cardiol., ;168:3550-3555.
15. Ertaş, G., Aydin, C., Sönmez, O., Erdoğan, E., Turfan, M., Tasal, A., ... &Zeybek, R. (2013). Red cell distribution width predicts new-onset atrial fibrillation after coronary artery bypass grafting. *Scandinavian .135-132 ,(3)**47** ,Cardiovascular Journal*
16. Fedorov VV, Glukhov AV, Chang R. (2012). Conduction barriers and pathways of the sinoatrial pacemaker complex: their role in normal rhythm and atrial arrhythmias. Am J Physiol Heart Circ Physiol.;302:H1773–H1783.
17. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG.(1995). Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med; 155: 469-73.
18. Friedman JS, Lopez MF, Fleming MD, Rivera A, Martin FM, Welsh ML et al. (2004). SOD2-deficiency anemia: protein oxidation and altered protein expression reveal targets of damage, stress response, and antioxidant responsiveness. Blood,; 104:2565–2573.
19. Grisanti, L. A. (2018). Diabetes and arrhythmias: pathophysiology, mechanisms and therapeutic outcomes. ,**9** ,Frontiers in physiology ..1669
20. Hunziker S, Celi LA, Lee J, Howell MD. (2012). Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patient. Crit Care,; 16:89.
21. Jabbour F., Kanmanthareddy A. (2019).Sinus Node Dysfunction (https://www.ncbi.nlm.nih.gov/books/n/statpearls/article-29052).
22. Jensen PN, et al. (2014). Incidence of and risk factors for sick sinus syndrome in the general population. –**64**:531;.J Am Coll Cardiol .538
23. Kantharia, B., Shah, A., Chutani, S., Karnik, R., & Singh, A. (2018). P1828 Effects of interventricular pacing timings on the left ventricle activation and clinical outcome in patients treated with cardiac resynchronization therapy. European Heart Journal, 39(suppl_1), ehy565-P1828.
24. Korantzopoulos P, Sontis N, Liu T, Chlapoutakis S, Sismanidis S, Siminelakis S et al. (2015). Association between red blood cell distribution width and postoperative atrial fibrillation after cardiac surgery: a pilot observational study. Int J Cardiol, ; 185:19–21.
25. Krintus M, Kozinski M, Kubica J, Sypniewska G. (2014). Critical appraisal of inflammatory markers in cardiovascular risk stratification. Crit Rev Clin Lab Sci,;51:263–79.
26. Kusumoto FM, Schoenfeld MH, Barrett C, et al. (2018). ACC/AHA/HRS guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society;.
27. Lippi G, Cervellin G, Sanchis-Gomar F (2019). Red blood cell distribution width: A marker of anisocytosis potentially associated with atrial fibrillation. World J Cardiol.; 11(12):292-304.
28. Lippi G, Franchini M, Targher G. (2011). Arterial thrombus formation in cardiovascular disease. Nat Rev Cardiol,;8:502–12.
29. Lippi G, Franchini M. (2008). Pathogenesis of venous thromboembolism: when the cup runneth over. SeminThromb Hemost,;34: 747–61.
30. Lippi G, Targher G, Montagnana M, et al. (2009). Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med,; 133:628–32.
31. Lisewski U, Shi Y, Wrackmeyer U, Fischer R, Chen C, et al. (2008).The tight junction protein CAR regulates cardiac conduction and cell-cell communication. J Exp Med.; 205:2369–79.
32. Liu T, Li G, Li L, Korantzopoulos P. (2007). Association between c-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis.J Am CollCardiol., ;49:1642-1648.
33. Liu T, Li L, Korantzopoulos P, Goudevenos GA, Li G. (2008). Meta-analysis of association between c-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation. Am J Cardiol., ;101:1749-1752.
34. Lopez-Villegas A, Catalan-Matamoros D, Lopez-Liria R, et al. (2018). Health-related quality of life on tele-monitoring for users with pacemakers 6 months after implant: the NORDLAND study, a randomized trial. BMC Geriatr., ;18:223.
35. Michelena HI, Powell BD, Brady PA, Friedman PA, Ezekowitz MD. (2010). Gender in atrial fibrillation: Ten years later. Gend Med; 7: 206-17.
36. Monfredi O, Dobrzynski H, Mondal T, et al. (2010). The anatomy and physiology of the sinoatrial node—a contemporary review. Pacing Clin Electrophysiol.;33:1392–1406.
37. Munshi, N. V. (2012). Gene regulatory networks in cardiac conduction system development. .1537-1525 ,(11)**110** ,Circulation research
38. Ozcan F, Turak O, Durak A, et al. (2013). Red cell distribution width and inflammation in patients with non-dipper hypertension. Blood Press.22:80-85.
39. Patel HH, Patel HR, Higgins JM. (2015). Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. Am J Hematol., ;90:422-428.
40. Patel KV, Mohanty JG, Kanapuru B, Hesdorffer C, Ershler WB, Rifkind JM. (2013). Association of the red cell distribution width with red blood cell deformability. In: Welch J, Palm F, Bruley DF, Harrison DK, editors. Oxygen transport to tissue XXXIVW. New York, NY: Springer, ; 211–216.
41. Pfannmuller B, Boldt A, Reutemann A, et al. (2013).Gender-specific remodeling in atrial fibrillation? ThoracCardiovascSurg; 61:66-73.
42. Pierce CN, Larson DF. (2005). Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion., ;20:83-90.
43. Pyngottu A, Werner H, Lehmann P, et al. (2019). Health related quality of life and psychological adjustment of children and adolescents with pacemakers and implanTable cardioverter defibrillators: a systematic review. Pediatr Cardiol.,;40(1):1–16.
44. Sarıkaya S, Şahin Ş, Akyol L, Börekçi E, Yılmaz YK, Altunkaş. (2014). Is there any relationship between RDW levels and atrial fibrillation in hypertensive patient? Afr Health Sci, ; 14:267–272.
45. Semelka M, Gera J, Usman S. (2013). Sick sinus syndrome: a review. Am Fam Physician,;87:691–6.
46. Tadros, R., Ton, A. T., Fiset, C., &Nattel, S. (2014). Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. ,Canadian Journal of Cardiology .796-783 ,(7)**30**
47. Tanindi A, Topal FE, Topal F, Celik B. (2012). Red cell distribution width in patients with prehypertension and hypertension. Blood Press, ; 21:81.
48. Unudurthi, S. D., Wolf, R. M., & Hund, T. J. (2014). Role of sinoatrial node architecture in maintaining a balanced source-sink relationship and synchronous cardiac pacemaking. ***,5** ,Frontiers in physiology* .446
49. Uyarel H, Isik T, Ayhan E, Ergelen M. (2012). Red cell distribution width: a novel risk factor for cardiovascular disease. Int J Cardiol.; 154:351- 352.
50. Weiss G, Goodnough LT. (2005). Anemia of chronic disease. N Engl J Med,;352:1011–23.
51. Wolf, C. M., &Berul, C. I. (2006). Inherited conduction system abnormalities—one group of diseases, many genes. Journal of ,cardiovascular electrophysiology; 14(7), 446-455.
52. Wolf, C. M., Wang, L., Alcalai, R., Pizard, A., Burgon, P. G., Ahmad, F., ... & See, V. (2008). Lamin A/C haploinsufficiency causes dilated cardiomyopathy and apoptosis-triggered cardiac conduction system disease. ular and cellular cardiologyJournal of molec:; ,(2) **44** .323-303