Value of Hs-CRP as a Predictor of Cardiac Electrical Instability in Diabetic Patients

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Abstract: Background: Diabetic patients are at increased risk of cardiac arrhythmias and sudden death. Interplay of several concomitant factors in diabetic patients may facilitate the occurrence of arrhythmia. Inflammation has been shown to play a direct role in the initiation, maintenance and recurrence of atrial fibrillation (AF) in all patients**.** However, few studies have evaluated the association between diabetes mellitus and cardiac rhythm disorders. We tried to detect the association between inflammation and cardiac electrical instability. **Methods:** Ninety diabetic patients with structurally normal hearts were enrolled in the study and followed up for one year. In every three-months visit, we assessed cardiac rhythm, P wave dispersion, hs-CRP level and random blood sugar.**Results:** One third of the original cohort succeeded to complete the follow up schedule. Arrhythmia developed at a time during the follow up period in about one third of patients. There was positive correlation between hs-CRP and P wave dispersion and rhythm disturbances (r 0.4-0.8 and $p < 0.05$). **Conclusion:** We concluded that diabetic patients are in high risk for cardiac arrhythmias. P wave dispersion and hs-CRP are interrelated and they proved to be strong predictors for cardiac electrical instability and hence arrhythmia production.

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1. Introduction

It was proposed that diabetic patients are at increased risk of cardiac arrhythmias and sudden death (1). Although there are several animal and human studies on this topic, the pathophysiology of the increased electrical vulnerability in diabetes is complex and remains undefined **(1).**

Moreover, interplay of several concomitant factors in diabetic patients may facilitate the occurrence of arrhythmia. Atherosclerosis and microvascular disease, which are increased in diabetic patients, may facilitate myocardial ischemia that predisposes to cardiac instability. In addition, autonomic neuropathy and/or cardiac repolarization abnormalities such as altered T-waves of the diabetic heart also increases electrical instability **(1)**. Inflammation has been shown to play a direct role in the initiation, maintenance and recurrence of atrial fibrillation (AF) in all patients **(2).**

C-reactive protein is an acute phase protein that was discovered in 1930 by William S. Tillet and Thomas Francis at the Rockefeller Institute for Medical Research **(3).** High sensitivity C-reactive protein (hs-CRP) is one of the most established markers of inflammation. It has been associated with the development of AF **(4).** Lowering of CRP has been linked to a proportionally reduced AF incidence and recurrence **(5).**

However, few studies have evaluated the association between diabetes mellitus and cardiac rhythm disorders. The Framingham study had found that diabetes mellitus was a significant independent risk factor for AF. Though only a small number of patients (562 patients out of 4731 the original cohort), who developed AF, were studied **(6)**. In another study, it was found that high glucose level was associated with atrial fibrillation **(7)**.

A recent case-control mega-study involving 293,124 patients with diabetes mellitus and 552,624 control patients has found that diabetes mellitus is a strong independent risk for AF. Due to the large number of patients in that study, this association appears to be valid and reliable **(8)**. In contrast to these studies, **Wilhelmsen et al.** carried out a large follow up study on male patients over 25 years and couldn't find any association between diabetes and AF **(9)**.

The causal link between diabetes mellitus and AF is more likely to be via various pathways including; hypertension, coronary artery disease, heart failure, abnormal thrombotic state and abnormal autonomic tone, factors associated with diabetes mellitus **(10)**. However, the possibility remains that

diabetes may directly (electrophysiologically or chemically at least) affect the atrial tissue, leading to AF. Thus, despite the epidemiological evidence of the association between diabetes and AF, the precise pathophysiological and clinical relationship between AF and diabetes mellitus are not completely understood **(10)**.

Of note, diabetes mellitus may even mask the cardiac symptoms of the first recorded episode of AF possibly due to diabetic neuropathy. Up till now, it is well known that both diabetes and AF are individually bad for patients and the presence of both requires aggressive management strategies **(10)**.

Aim of the work:

(1) To study the association between CRP (as an inflammatory marker) and P wave dispersion (as a marker of cardiac electrical instability) in diabetic patients.

(2) To study the relationship between the level of CRP and the development of rhythm disorders such as AF. This helps to evaluate the role of inflammatory process that is originally present in diabetic patient as a predictor of development of gross cardiac electrical instability.

2. Patients and Methods:

The present study is a longitudinal study carried out between 1st April 2010 and 31st December 2012. Ninety diabetic patients attending the outpatient diabetes clinic at Assiut university Hospital for regular follow up have been recruited. The study protocol has been approved by the Assiut University Medical School Ethical Committee. A written consent has been taken from every participant.

Inclusion criteria:

1. Being essentially in sinus rhythm in ECG at baseline visit
2. Having structurally normal heart (by Echocardiographic assessment)
3. Having normal baseline CRP level

Exclusion criteria:

1. Any patient who had other than normal sinus rhythm or ECG changes (ischaemic in origin in the baseline ECG)
2. Patients with structural heart disease in echocardiographic assessment
3. Patients with CRP level more than 8.0 mg/dL by Latex test
4. Patients with chronic obstructive airway disease, renal failure, morbid obesity and any non cardiac significant systemic disease
5. Patients with active infection or inflammatory disease, recent trauma or surgery with the last one month
6. Patients under regular steroid or non steroidal anti-inflammatory drugs

All patients were subjected to:

1. **History taking:** including; age, sex and smoking habits.
2. **Baseline 12-leads resting ECG:** to detect the heart rate and P wave dispersion. The 12-lead ECG was recorded in a paper of 50 mm/sec with 1 mV/10 mm standardization from all patients, at the supine position. The P wave duration was measured manually sometimes with the aid of a magnifying lens. P wave dispersion is a measurement of the heterogeneity of atrial depolarization. It is derived by subtracting the minimum P wave duration from the maximum in any of the 12 ECG leads in msec**. (11)**.
3. **Baseline Echocardiographic examination:** using PHILIPS IE-33 device and focusing mainly on the left atrial antero-posterior diameter and the diastolic function.
4. **Laboratory investigations:**
   a. Assessment of random blood sugar in mg/dL
   b. Assessment of high sensitivity C-reactive protein (hs-CRP): Specimens were collected either during the fasting state or three hours post-brandial. The sample was centrifuged within 2 hours. Quantitative assessment of hs-CRP was performed by immunoenzymometric assay in µg/ml using Accu Bind ELISA Microwells®.
5. **Follow up visits**: Every three months, the patients were followed up to have:

a. 12-Leads ECG for non-complaining patients and Holter monitoring for those who complained of palpitations. We aim at detection of the heart rate, rhythm and P wave dispersion.

b. Random blood sugar assessment.

c. Assessment of hs-CRP.

Statistical analysis

Data are expressed as mean ± SD (for continuous data) or frequency and percentage (for categorical data) when appropriate. Continuous variables were compared by Student t test for unpaired data, as appropriate. Categorical variables were compared by use of the chi-square statistic test. Correlation between continuous variables was carried out using Spearman correlation coefficient (r). A p-value less than 0.05 was considered statistically significant. Data were analyzed using the SPSS statistical software (version 16) for windows **(12)**.

3. Results:

The present study was conducted on 90 diabetic patients, 50 (55.6%) males, 54 patients (60%) were smokers with a mean age of 47.3 ± 9.8 years.

(A) Baseline data:

* ECG: At baseline visit, all patients were in sinus rhythm with mean heart rate of 80.3±12.3 beats/min. The mean P wave dispersion was 50.8±10.2 msec.

* Echocardiographic assessment: Fifty six patients (62.2%) had impaired diastolic function. The mean left atrial antero-posterior diameter was 3.7±0.5 cm.

* Laboratory investigations: Mean hs-CRP was 1.5±0.6 µg/ml and the mean random blood sugar was 146.1±44.5 mg/dL.

(B) Follow up data:

About one third (27.8%) of the study sample developed rhythm disorders at a time during the one year follow up. This rhythm disorder varies from simple premature atrial ectopic beats to AF.

Table (1): Follow up data during the 3-months interval follow up visits for the one year study period

	Baseline (N=90)	3-month (N=59)	6-month (N=42)	9-month (N=34)	One year (N=30)
Percentage	100%	66%	48%	37%	33%
Age (mean±SD) in **years**	47.3±9.8	46.3±9.9	45.7±10.1	43.6±9.9	42.2±9.4
Sex (male %)	55.6	54.2	54.8	61.8	60
Smokers (%)	60	39	40.5	44.1	40
HR (mean±SD) in beats/min	80.3±12.3	82.9±13.2	84.9±12.6	85.3±12.8	83.5±12.8
P wave dispersion (mean±SD) in msec.	50.8±10.2	55.3±10.5	56.6±11.2	53.6±8.6	56.9±9.6
Hs-CRP (mean±SD) in µg/ml	1.5±0.6	1.9±0.9	2.0±0.8	2.0±1.0	2.3±0.9
RBS (mean±SD) in mg/dl	146.1±44.5	152.6±49.6	143.8±31.7	143.5±34.1	136.9±30
Sinus rhythm (%)	100%	88%	69%	71%	70%

(C) Factors associated with arrhythmic events:

In all follow up visits, there was consistent statistically significant relationship between rhythm disturbance and the level of hs-CRP.

* 3-months follow up visit: There was statistically significant relationship between arrhythmia development and level of hs-CRP ($P < 0.001$). There was no relationship between rhythm disorders and age ($P > 0.05$), sex ($P > 0.05$), smoking ($P > 0.05$), left atrial diameter ($P > 0.05$), diastolic dysfunction ($P > 0.05$), P wave dispersion ($P > 0.05$) and random blood sugar at that visit ($P > 0.05$).

* 6-months follow up visit: There was statistically significant relationship between arrhythmogenic events and level of hs-CRP and ($P < 0.01$) (fig. 1). There was no relationship between rhythm disorders and age ($P > 0.05$), sex ($P > 0.05$), smoking ($P > 0.05$), diastolic dysfunction ($P > 0.05$), P wave dispersion ($P > 0.05$) and random blood sugar at that visit ($P > 0.05$). Moreover, there was a trend that increased left atrial diameter may be related to arrhythmic events, however, this relationship didn't reach a statistically significant level (P value 0.06).

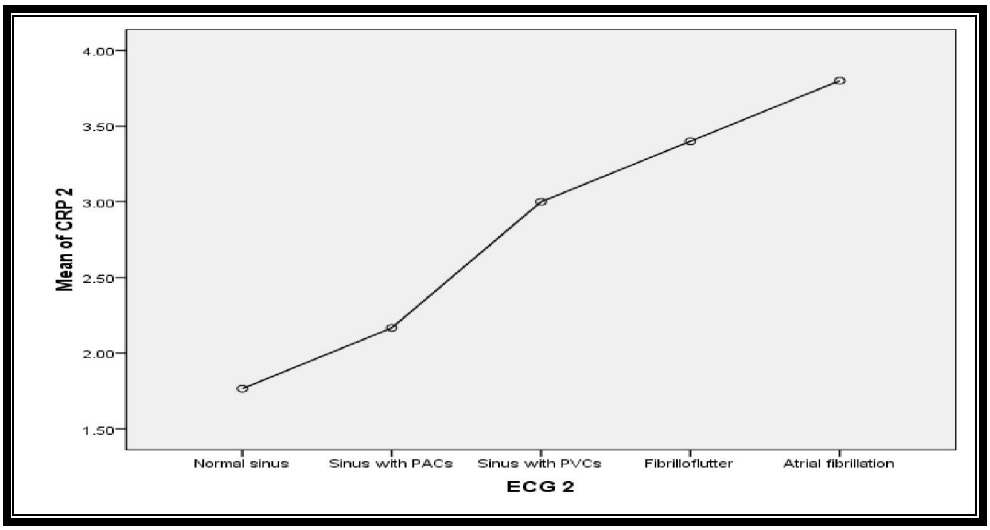

Figure (1): Relationship between CRP and rhythm disorders

* 9-months follow up visit: There was statistically significant relationship between arrhythmogenic events and level of hs-CRP and (P < 0.01), left atrial diameter (P < 0.01) and diastolic dysfunction (P < 0.05). There was no relationship between rhythm disorders and age (P > 0.05), sex (P > 0.05 by Kendalls Tau-c test), smoking (P > 0.05), P wave dispersion (P > 0.05) and random blood sugar at that visit (P > 0.05).
* One-year follow up visit: There was statistically significant relationship between arrhythmogenic events and level of hs-CRP and (P < 0.05), and diastolic dysfunction (P < 0.05). There was no relationship between rhythm disorders and age (P > 0.05), sex (P > 0.05), smoking (P > 0.05), left atrial diameter (P > 0.05), P wave dispersion (P > 0.05) and random blood sugar at that visit (P > 0.05).

(D) Correlation between CRP level and P wave dispersion:

During all follow up visits there was statistically significant positive correlation (ranged from moderate to strong) between hs-CRP level and P wave dispersion (r 0.4-0.8, P < 0.05) (fig. 2).

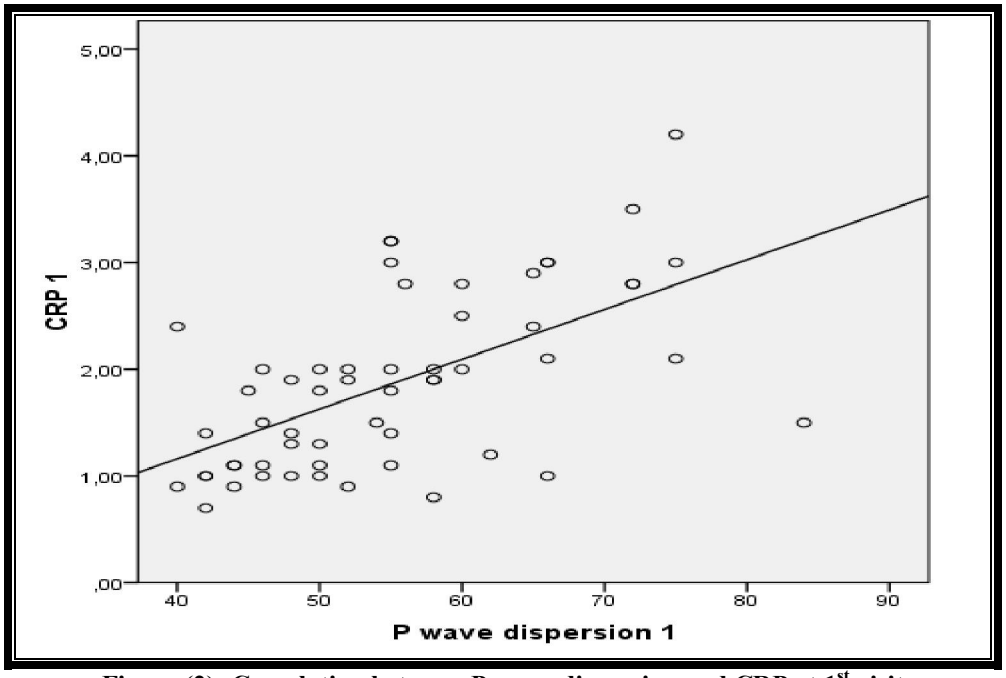

Figure (2): Correlation between P-wave dispersion and CRP at 1st visit

4. Discussion:

It has been reported that there is a higher incidence of cardiac arrhythmias and sudden cardiac death among diabetic patients. The pathophysiology behind this increased electrical vulnerability is multifactorial, complex, and still remains undefined (1). It is conceivable that the interplay of different concomitant factors contributes to the genesis of arrhythmia by altering cardiac electrophysiology. First, atherosclerosis as well as microvascular disease, which are increased in diabetic patients, may facilitate the development of myocardial ischemia that predisposes to cardiac arrhythmias. Second, autonomic neuropathy is associated with abnormal reflexes and innervation of the diabetic heart affecting electrical instability. Finally, cardiac repolarization abnormalities manifesting as prolonged QT/QTc intervals and altered T-waves on the ECG are common in patients with diabetes **(1)**.

The present study is a longitudinal observational study. It has been conducted for more than one year on 90 diabetic patients. We did find that P wave dispersion was a strong predictor for arrhythmia development in diabetic patients. P-wave duration and P-wave dispersion on standard ECG are non invasive markers of intraatrial conduction disturbances, which are believed to be correlated with the genesis of atrial arrhythmia as AF **(13)**. In a review published in 2009, **Magnani et al.** reported that P wave indices (including P wave dispersion) have been applied in a wide range of clinical contexts. They have been associated with clinical risk factors for arrhythmia development mainly AF and other atrial arrhythmias. They have stated that despite the volume of studies, P wave indices reference (normal) values have not been standardized. This may be due to difficult and different measurement techniques **(11).**

In a cross-sectional case-control study, subjects with diabetes were found to have significantly longer P wave indices than controls **(14)**. The exact mechanism of P wave dispersion prolongation in diabetics is not well known. However, there are many speculations to explain this phenomenon. It is thought that both electrical and structural changes of the atrial myocardium associated with diabetes may play role. Firstly diabetic neuropathy may lead to electrophysiological changes in the atrial myocardium. Secondly chronic hyperglycemia causes structural and functional disorders by changing the chemical composition of the proteins present in cell membrane structure. Furthermore, in diabetics there is extracellular protein deposition and interstitial fibrosis of myocardium. All the above can lead to heterogeneity in atrial conduction velocity and atrial refractoriness in diabetic patients **(14).** In an experimental study, it was determined that fibrous tissue deposition was significantly increased at atria of diabetic rats and atrial activation time was longer than controls. This prolongation of atrial activation time was attributed to the atrial fibrosis **(15)**.

Inflammation has been recognized as a factor with the potential to mediate the induction or maintenance of AF **(4)**. However, it is still uncertain whether any inflammatory changes represent a cause or consequence of AF **(16).**

In a recently published study by **Tsioufis et al.** carried out on 100 patients, they stated that in hypertensive patients, hs-CRP and P wave dispersion are interrelated and associated with paroxysmal AF. This has suggested an active implication of inflammation in the atrial electrophysiological remodeling predisposing to AF. These findings highlighted the potential prognostic role of increased CRP in the prediction of paroxysmal AF in hypertensive patients **(17)**.

Our study emphasizes the relationship between inflammation and electrical instability. The repeated follow up visits have demonstrated the consistent relationship between rhythm disturbances, p wave dispersion and hs-CRP. To a lesser extent, other factors were demonstrated to be related to rhythm disturbance such as left atrial dimensions and diastolic dysfunction.

Study limitation:

The current study encountered some limitations; the small number of patients included in the study may jeopardize the power of the results. However, we have tried to use the appropriate statistical analyses to overcome this problem. Also, using random blood sugar as a marker for glycemic control in diabetic patients is considered to be low validity analysis, while using HbA1C would be much better.

5. Conclusions:

In summary, the current study added evidence to confirm that diabetic patients are in high risk for cardiac arrhythmias and to emphasize the relationship between inflammation and electrical instability. P wave dispersion and hs-CRP are interrelated and they proved to be strong predictors for cardiac electrical instability and hence arrhythmia production.

References

1. Pappone C, Santinelli V. Cardiac electrophysiology in diabetes. Minerva Cardioangiol. 2010;58(2):269-76.
2. Crandall M, Horne B, Day J, Anderson J, Muhlestein J, Crandall B, et al. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol. 2009;32(8):981-6.
3. Tillett W, Francis T. Serological Reactions in pneumonia with a non-protein somatic fraction of Pneumococcus. J Exp Med. 1930;52(4):561-71.
4. Aviles R, Martin D, Apperson-Hansen C, Houghtaling P, Rautaharju P, Kronmal R, et al. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108(24):3006-10.
5. Young-Xu Y, Jabbour S, Goldberg R, Blatt C, Graboys T, Bilchik B, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. Am J Cardiol 2003;92:1379-83.
6. Benjamin E, Levy D, Vaziri S, D'Agostino R, Belanger A, Wolf P. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271:840-4.
7. Psaty B, Manolio T, Kuller L, Kronmal R, Cushman M, Fried L, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997;96(7):2455-61.
8. Movahed M, Hashemzadeh M, Jamal M. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int J Cardiol. 2005;105(3):315-8.
9. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. J Intern Med. 2001;250(5):382-9.
10. Lip G, Varughese G. Diabetes mellitus and atrial fibrillation: perspectives on epidemiological and

pathophysiological links. Int J Cardiol. 2005;105(3):319-21.
11. Magnani J, Williamson M, Ellinor P, Monahan K, Benjamin E. P wave indices: current status and future directions in epidemiology, clinical, and research applications. Circ Arrhythm Electrophysiol. 2009;2(1):72-9.
12. SPSS. Statistical Package for Social Science. Ver.17. Standard version. Copyright © SPSS Inc., 2007-2008. 2007.
13. Chang C, Lee S, Lu M, Lin C, Chao H, Cheng J, et al. The role of P wave in prediction of atrial fibrillation after coronary artery surgery. Int J Cardiol. 1999;68(3):303-8.
14. Yazici M, Ozdemir K, Altunkeser B, Kayrak M, Duzenli M, Vatankulu M, et al. The effect of diabetes mellitus on the P-wave dispersion. Circ J. 2007;71(6):880-3.
15. Kato T, Yamashita T, Sekiguchi A, Sagara K, Takamura M, Takata S, et al. What are arrhythmogenic substrates in diabetic rat atria? J Cardiovasc Electrophysiol. 2006;17(8):290-894.
16. Kallergis E, Manios E, Kanoupakis E, Mavrakis H, Kolyvaki S, Lyrarakis G, et al. The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. Heart. 2008;94(2):200-4.
17. Tsioufis C, Syrseloudis D, Hatziyianni A, Tzamou V, Andrikou I, Tolis P, et al. Relationships of CRP and P wave dispersion with atrial fibrillation in hypertensive subjects. Am J Hypertens. 2010;23(2):202-7.

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