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# P Wave Analysis in Patients with Sarcoidosis

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## ABSTRACT

**Introduction:** Atrial arrhythmias in patients with sarcoidosis (Sar) are not unusual and can occur due to either atrial myocardial fibrosis and/or due to autonomic nervous system imbalance. Electrocardiographic markers (ECG), like maximum and minimum P wave duration and P wave dispersion $\{P_{dis} = P_{max} - P_{min}\}$ reflect atrial depolarization inhomogeneity and can indicate patients prone to develop atrial arrhythmias while standard deviation of RR interval (SDNN) is an index of heart rate variability, reflecting autonomic nervous system (ANS) activity. **Methods**: 90 patients with sarcoidosis (41 males/49 females) enrolled in this multicenter prospective study underwent digital electrocardiography, echocardiography and pulmonary function tests (PFTs). Diastolic and systolic indices of right and left ventricle were measured echocardiographically including Doppler parameters while $P_{max}$, $P_{min}$, $P_{dis}$ and SDNN were measured in a 5-minute duration digital electrocardiogram. All consecutive patients were compared to 65 healthy volunteers (30 males/35 females). **Results**: Although heart rate and the echocardiographic indices were similar among the two groups, the electrocardiographic indices were significantly prolonged in the patient group compared to controls. Maximum P wave duration was correlated with SDNN ($p < 0.05$, $r = -0.272$) and the age of the patients ($p < 0.05$, $r = 0.219$) while $P_{dis}$ was correlated with SDNN ($p < 0.001$, $r = 0.350$) and the heart rate ($p < 0.005$, $r = 0.323$). Multivariate analysis showed that $P_{max}$ and $P_{dis}$ were independently correlated with SDNN. **Conclusion**: P wave dispersion is significantly increased in patients with systemic sarcoidosis compared to healthy persons while maximum P wave duration and P wave dispersion are negatively correlated with the standard deviation of RR, an index of heart rate variability implying imbalance of ANS function. Further studies are needed for the clarification of the significance of this correlation.

**Keywords:** P Wave Analysis; Systemic Sarcoidosis; Autonomic Nervous System

## 1. Introduction

Sarcoidosis (Sar) is a systemic granulomatous disease of unknown etiology characterized by variable clinical manifestations and an unpredictable course [1]. Myocardial involvement is considered as a major contributor to mortality in patients with sarcoidosis [2-4]. Cardiac manifestations range from an incidentally identified, benign condition to fatal cardiomyopathy causing cardiac arrhythmias and sudden cardiac death [5,6]. Conduction abnormalities that range from first degree AV block to com-

plete heart block are the most common clinical manifestations of cardiac involvement, with ventricular and atrial arrhythmias being less frequent. Atrial arrhythmias have an incidence of up to 19% with atrial tachycardia, atrial flutter and atrial fibrillation being more common.

Simple electrocardiographic markers like maximum ($P_{max}$), minimum ($P_{min}$) and dispersion ($P_{dis}$) of P wave are well known electrophysiological characteristics of atria prone to fibrillate and are associated with inhomogeneous and discontinuous propagation of sinus impulses [7,8]. P wave indices have been studied in several diseases such as hypertension, aortic stenosis, dilated cardiomyopathy and ischemia with common conclusion that

prolongation of $P_{max}$ and P wave dispersion signifies increased risk for the development of atrial fibrillation [8-12]. Standard deviation of RR interval (SDNN) is an index of heart rate variability and is considered as a possible marker of autonomic nervous system imbalance [13].

The incidence of symptomatic cardiac involvement in sarcoidosis is 5%, but autopsy material has shown at least 20% - 27% of the patients [14,15]. Atrial arrhythmias are considered as one of the clinical criteria for the diagnosis of cardiac sarcoidosis according to the Japanese ministry criteria [16]. As a result, the identification of patients prone to develop this kind of arrhythmia might play a significant role in the treatment and alter the course of the disease, since subclinical cardiac involvement may play an important role in the disease's progression and prognosis.

This study was conducted in order to identify these patients with the use of P wave analysis.

## 2. Patients and Methods

### 2.1. Study Population

An observational case-control study was conducted with patients from three university hospitals with biopsy proven sarcoidosis between October 2002 and June 2004. Presence of non caseating granulomas in the transbrochial biopsy, lymph node or skin biopsies confirmed the diagnosis of sarcoidosis. The possibility of infection, environmental factors or hypersensitivity reaction to medication causing granulomatous inflammation had been eliminated. Treatment with systemic glucocorticoids was not an exclusion criterion. Exclusion criteria were the presence of chronic obstructive lung disease, presence of arrhythmias, known coronary artery disease or structural heart disease, systemic hypertension, diabetes mellitus, pericarditis, pregnancy, alcoholism and the presence of a previously implanted pacemaker. All consecutive patients were compared to a control group of healthy asymptomatic volunteers with no comorbidities and any past or present evidence of heart and/or lung disease. None of the patients or control subjects was receiving any cardiac medication.

All consecutive patients underwent clinical assessment, including determination of serum levels of angiotensin-converting enzyme, 12-lead ECGs, radiologic chest stage by radiography and transthoracic echocardiograms. Chest radiographs were assessed to determine disease stage using standard radiographic staging for sarcoidosis according to the Scadding criteria: I, bilateral hilar lymphadenopathy (BHL) with normal lung parenchyma; II, BHL and parenchymal infiltration; III bilateral infiltrates without BHL and Stage IV pulmonary fibrosis/fibrocystic parenchymal involvement [16]. Serum angiotensin

converting enzyme [SACE] as well as brain natriuretic peptide (BNP, Triage, ROCHE), an estimator of diastolic function in the left ventricle, were measured. High SACE activity was defined as concentration higher than 55 U/L and was considered to reflect disease activity [18,19], while BNP higher than 100 pg/dl implied diastolic heart failure (**Table 1**). Control subjects underwent complete echocardiographic and electrocardiographic study. The study protocol was approved by the institutional ethics committee and informed consent was obtained from all the study subjects.

### 2.2. Pulmonary Evaluation

Pulmonary function tests (PFTs) including Forced Expiratory Volume at 1 sec (FEV1), Forced Vital Capacity (FVC), the ratio of FEV1/FVC and the Total Lung Capacity (TLC) were performed with a body box plethysmograph while Diffusing Capacity for Carbon Monoxide (DLCO) was measured by the single breath method. Values were expressed as a percentage of those predicted.

### 2.3. Standard Echocardiography

An echocardiographic study was performed for all participants in the same echo lab with the patients in partial left decubitus position by an expert sonographer using a commercially available ultrasonic device (Hewlett-Packard, Sonos 5500, Andover, Massachusetts). All M-mode, two dimensional and Doppler images were recorded with a S3 transducer. Two-dimensional guided M-mode quantitative left ventricular analysis was performed in the parasternal short-axis view, according to the recommendations of the American Society of Echocardiography. [20] Left atrial (LA), diastolic (LVEDD) and systolic (LVESD) ventricular dimensions were measured. Left ventricular Ejection Fraction (EF) was determined by the biplane Simpson's method, [21] whereas LV mass by the Penn Conversion Formula. [22] Pulsed Doppler recordings were obtained during transmitral and transtricuspidal flow and the following parameters were measured: maximal velocity of early diastolic filling ($E_m$) or ($E_t$), late diastolic filling ($A_m$) or ($A_t$) and the ratio of early to late diastolic filling velocities ($E/A_m$ or $E/A_t$) in mitral or tricuspid valve, respectively. Furthermore, Deceleration Time (DT) and Isovolumic Relaxation Time (IVRT) of mitral and tricuspid valves were measured.

### 2.4. 12-Lead Surface ECG

In all participants, a 12 lead digital ECG was recorded in the supine resting position using a computer-based ECG system (CardioControl NV, the Netherlands). The 12 leads of ECG were recorded simultaneously at a sampling rate of 1200 Hz for 5 minutes. During each re-

**Table 1. Baseline demographic and clinical patients' and controls' characteristics, ultrasound and electrocardiographic parameters among groups of patients with and without therapy and controls.**

| Patients | Total patients | Without therapy (n = 53) | With therapy (n = 37) | Controls |
|---|---|---|---|---|
| Males/Females | 41/49 | 25/28 | 16/21 | 30/35 |
| Age (years) | 48 ± 13 | 50.21 ± 12.99 | 49.88 ± 13 | 44 ± 9 |
| BMI (Kg/m$^2$) | 28 ± 5 | 27.93 ± 4.5 | 27.69 ± 5.55 | 26 ± 6 |
| Smokers | 24 | 13 | 11 | 18 |
| SACE (U/L) | 44 ± 25 | 46.76 ± 25 | 46.52 ± 28 | |
| Brain Natriuretic   Peptide (pg/dl) | 17 ± 15 | 19.95 ± 22.69 | 23.26 ± 28.37 | 15.8 ± 14.3 |
| Systolic Arterial Pressure (mmHg) | 122 ± 16 | 126.34 ± 16.85 | 119.04 ± 15.38 | 119 ± 17 |
| Ultrasound Parameters | | | | |
| Left Atrium (mm) | 38 ± 5 | 37.7 ± 4.12 | 38.38 ± 4.86 | 36 ± 7 |
| LV End Diastolic Diameter (mm) | 50 ± 4 | 49.62 ± 3.97 | 50.31 ± 3.24 | 45 ± 5 |
| Mitral E wave | 0.7 ± 0.1 | 0.7 ± 0.12 | 0.66 ± 0.13 | 0.9 ± 0.2 |
| Mitral A wave | 0.67 ± 0.1 | 0.69 ± 0.143 | 0.69 ± 0.125 | 0.5 ± 0.2 |
| Mitral Deceleration Time (ms) | 180 ± 26 | 177.09 ± 25.51 | 177.96 ± 21.29 | 185 ± 35 |
| Mitral E/A wave | 1.08 ± 0.32 | 1.09 ± 0.31 | 1.03 ± 0.33 | 1.2 ± 0.4 |
| Tricuspidal E wave | 0.5 ± 0.1 | 0.5 ± 0.08 | 0.49 ± 0.07 | 0.6 ± 0.2 |
| Tricuspidal A wave | 0.49 ± 0.135 | 0.51 ± 0.147 | 0.5 ± 0.1 | 0.4 ± 0.125 |
| Tricuspidal E/A | 1.08 ± 0.34 | 1.08 ± 0.35 | 1.04 ± 0.28 | 1.2 ± 0.35 |
| Tricuspidal Deceleration Time (ms) | 200 ± 38 | 177.09 ± 25.51 | 177.96 ± 21.29 | 195 ± 40 |
| Ejec. Fraction (%) | 57 ± 5 | 61.49 ± 8.59 | 62.14 ± 7.88 | 61 ± 6 |
| Left Ventricular Mass (mg) | 206 ± 56 | 202.85 ± 57 | 215.6 ± 50.21 | 195 ± 13 |
| Electrocardiographic   Parameters | | | | |
| HR(bpm) | 76 ± 12 | 77.76 ± 12.36 | 75.96 ± 11.43 | 74 ±11 |
| Pmax (ms) | 120 ± 14[*] | 122.15 ± 11.47[*] | 116.54 ± 15.72[*] | 97 ± 11 |
| Pmin (ms) | 76 ± 12[*] | 76.67 ± 11.81[*] | 76.06 ± 13.16[*] | 59 ± 17 |
| Pdis (ms) | 44 ± 13[*] | 45.48 ± 12.41[*] | 40.48 ± 12.56[*] | 38 ± 10 |
| Standard Deviation Of RR | 60 ± 50[*] | 54.93 ± 45.27[*] | 63.57 ± 54.49[*] | 90 ± 25 |

[*]Statistical significant ($p < 0.05$).

cording, the subjects remained silent and breathed freely. From each lead, the average complex was calculated by the modular ECG analysis system (MEANS). Individual average complexes were stored digitally. The mean heart rate (HR) was calculated. The standard deviation of normal R-R interval (SDNN) in the 5 minute ECG recording was used as a short-term heart rate variability index.

### 2.5. P Wave Measurements

The averaged stored ECG's of patients and controls were displayed on a high resolution computer screen. Each averaged complex in each lead was separately magnified at a magnification of 160 mm/s and 60 mm/mV. The onset and offset of the P wave were defined as the junction between the P wave pattern and the isoelectric line and were marked with a cursor. If the baseline noise was >10 µV and/or the peak to isoelectric line P wave ampli-

tude <15 µV, the lead was excluded from the analysis. Two independent investigators measured the P waves without access to other information. The measurements of the two observers were averaged. Subjects with P waves measurable <9 ECG leads were excluded from the analysis.

### 2.6. Definition of ECG Analysis Indices

The following indices were derived from each measurement of each ECG:

1) The maximum P wave duration in any of the measurable leads ($P_{max}$).

2) The minimum P wave duration in any of the measurable leads ($P_{min}$).

3) P wave dispersion ($P_{dis}$), defined as the difference between $P_{max}$ and $P_{min}$.

4) Standard Deviation of RR (SDNN), was calculated

and used as an indirect index of autonomic system.

## 2.7. Accuracy of the Measurements

Intra-observer and inter-observer mean percentage errors (absolute difference between two observations divided by the mean and expressed as a percentage for P-wave duration measurements were determined in 30 randomly selected study participants and were less than 10% in all leads.

## 2.8. Statistical Analysis

Statistical analysis was carried out with a commercially available statistical software package. Continuous data are reported as mean ± SD. Continuous variables were normally distributed as indicated by the Kolmogorov-Smirnov 1-sample test except standard deviation of RR, which was log-transformed. Differences between the two groups were evaluated by using the Student's unpaired t-test for continuous and $\chi^2$ test for categorical variables. Bivariate correlations were calculated with Pearson's product moment method. Analysis of variance (one way ANOVA) was performed for ECG parameters among different stages of sarcoidosis and Scheffe's adjustment was performed in order to correct the significant differences among multiple comparisons. Stepwise multivariate linear regression analysis was performed to estimate independent determinants of P wave indices. P value of <0.05 was assumed to represent statistical significance.

## 3. Results

### 3.1. Patient Characteristics

Among 106 consecutive patients referred for possible enrollment into the study, fifty met the criteria and 16 were excluded due to arterial hypertension (8 patients), chronic obstructive pulmonary disease (6 patients) and cardiac arrhythmias (2 patients). The remaining 90 patients (41 males/49 females) were compared to 65 healthy volunteers (30 males/35 females). Patients' and controls' characteristics are presented in **Table 1**. The mean age of patients was 48 ± 13 years and that of the control group was 44 ± 9 years. The mean duration of the disease was 4.3 ± 5.6 years. Both the compared groups were age, sex, BMI and smoking matched (**Table 1**). Fifty nine patients (65.5%) were classified as stage I, fifteen patients (17%) stage II, five (5.5%) at stage III while eleven (12%) patients were at stage IV. Thirty six patients (40%) were currently under cortisone treatment while additionally twenty six (28.9%) had received cortisone treatment in the past (mean capture time of cortisone: 12 ± 7 months). The average level of SACE was within normal range while only twenty four patients

(27%) had increased levels of SACE. Twenty four patients (27%) were currently smokers. No significant differences were observed between sarcoidosis and control group concerning heart rate, blood pressure (Systolic and Diastolic) as well as echocardiographic indices (**Table 1**).

### 3.2. Pulmonary Evaluation

Pulmonary function tests showed impairment of lung function in 43 (48%) patients. More specific, the averaged values (% of the predicted values) were FEV1: 94 ± 19%, FVC: 97 ± 19%, FEV1/FVC: 92 ± 11, TLC = 87 ± 15% and DLCO = 85 ± 18%. Restrictive pattern (DLCO < 80%, TLC < 80%) was present in 25 (29%), isolated DLCO reduction in 12 (13%), obstructive pattern (FEV/FVC < 70%) and mixed form (DLCO < 80%, TLC < 80%, FEV/FVC < 70%) in 6 (6.6%) patients.

### 3.3. P Wave Indices

Measurements of maximum, minimum and dispersion of P wave in the two study groups are presented in **Table 1**. More specific, P maximum (120 ± 14 vs 97 ± 11, p < 0.001), P minimum (76 ± 12 vs 59 ± 171, p < 0.001), P wave dispersion (44 ± 18 vs 38 ± 10, p < 0.001) and SDNN (60 ± 50 vs 90 ± 25, p < 0.005) were found to be significantly different in patient group than in controls. Further analysis of the patient group concerning P wave indices didn't show significant differences among the patients' groups of disease staging or the groups based on corticosteroid treatment uptake. Significant prolongation of $P_{max}$ (123 ± 15 msec vs 116 ± 11, p = 0.035) and $P_{min}$ (79 ± 13 msec vs 73 ± 11, p < 0.041) was seen in those patients with levels of SACE higher than 55 U/L compared to those with levels of SACE less than 54 U/L. In bivariate analysis performed in patients group, ECG indices, cardiac ultrasound indices, biochemical variables and pulmonary parameters were included. Maximum P wave was found negatively correlated to SDNN (p < 0.005, r = −0.305) and positively correlated to the age of the patients (p = 0.042, r = 0.212), while minimum P wave was not related with any parameter. P wave dispersion was correlated positively with HR (p = 0.003, r = 0.323) and negatively with SDNN (p < 0.001, r = −0.388). Multivariate stepwise regression analysis showed that maximum P wave was independently related only with the SDNN (p = 0.005, β = −0.305), while P wave dispersion was independently related with HR (p = 0.09, $\beta$ = 0.193) and SDNN (p = 0.006, $\beta$ = −0.318).

## 4. Discussion

The main finding of this study was that patients with sarcoidosis have significant higher values of maximum, minimum and dispersion of P wave on the surface ECG

compared to those of healthy individuals. Also, SDNN was significant decreased in patient's group, implying a functional imbalance between sympathetic and para-sympathetic system in favor of the former [23]. Of great importance is the finding that these indices did not im-prove with corticosteroid treatment and that they were not influenced by the stage of the disease while pro-longed P wave was observed in patients with higher lev-els of SACE. P wave analysis studies have been utilized in various diseases for the assessment of arrhythmia's risk [7-12,21,24]. To our knowledge this is the first study that uses P wave analysis in patients with sarcoidosis.

P wave represents the electrical activation of both atria, which takes place sequentially from right to left atrium. P wave duration is, among others, determined by the fol-lowing factors: 1) Atrial conduction velocity, which is non uniform, 2) the length of the longest pathway be-tween the right atrial site of impulse origin or sinus node and the latest area to be activated, which is typically the lateral left atrium; and 3) although not generally appre-ciated, both P-wave duration and morphology are not static, but dynamic, and change with shifts in the sites of the predominant atrial pacemaker [25]. The association between atrial arrhythmias and P wave analysis during periods of sinus rhythm is well established [7-12,21,24]. The relationship of prolonged P wave indices to atrial arrhythmias has clinical significance since prolonged conduction can provide an etiologic basis for the ap-pearance of atrial arrhythmias. Turgut et al. showed that prolonged atrial conduction was a predisposing factor for the development of atrial flutter [26]. Susceptibility to this type of arrhythmias is present when there exists ab-errant conduction between the atria. Prolongation of $P_{dur}$ may possibly indicate the presence of intra- or inter-atrial conduction disturbance and inhomogeneous spread can occur independently of the increase in atrial dimensions. Indeed, in this study no correlation was observed be-tween P wave analysis indicis and left atrium.

Recently, P wave dispersion, defined as the difference between maximum and minimum P wave duration in 12 lead ECG, has been used to separate patients with a high risk of AF while on sinus rhythm [7,8]. Previous studies revealed the significantly higher values of $P_{max}$ and $P_{dis}$ in patients with paroxysmal atrial fibrillation, either idio-pathic or due to hypertension compared to those of healthy subjects while another study showed that $P_{max}$ was a significant independent predictor of the recurrence of the arrhythmias [7,8,21].

Another important finding was the negative correlation of P wave indices with the SDNN, a marker of heart rate variability [13,23,27]. This relationship is in agreement with another work that showed reduced values of high frequency spectral components of heart rate variability, implying altered sympatho-vagal balance due to de-creased parasympathetic tone caused by changes of res-piratory pattern in patients with sarcoidosis [13]. P wave duration and P wave dispersion have been reported to be influenced by the autonomic tone, which induces changes in the velocity of impulse propagation [28]. In addition, another study showed that increased sympathetic activity causes a significant increase in P wave dispersion. [29] As a result of these findings, the authors can suggest that the imbalance between the parasympathetic and sympa-thetic systems may be an underlying cause of higher va-lues of P wave maximum and dispersion in sarcoidosis.

It is important to note that the authors observed pro-longation of P wave indices in patients with increased level of SACE, implying concordance with the severity of the disease and a dynamic nature of P wave, which responds to fluctuations in pulmonary function tests and in the disease activity. In addition renin-angiotensin-aldosterone system has been found to promote atrial fib-rillation by enhancing atrial myocardial fibrosis [30]. Moreover although it is uncertain whether captopril, a well known ACE inhibitor, suppresses the production of ACE enhanced from macrophages in the granulomatous lesion, studies have demonstrated inhibition of serum ACE activity with subsequent decrease in plasma angio-tensin and aldosterone, indicating that captopril may of-fer an effective therapeutic approach to the treatment of active stage of sarcoidosis [31].

On the other hand, Asad et al showed a rapid reversal of P wave characteristics responding to therapy in pa-tients with Chronic Obstructive Lung Disease [32]. Fur-thermore, Carilli et al showed in a retrospective study the predictive value of P-wave amplitude and axis in esti-mating the severity of nonasthmatic airway obstructive disease in the quiescent state and they demonstrated a good correlation of P wave amplitude and axis with FEV1/FVC and the residual volume/total lung capacity in a continuous regression equation [33]. These findings show that P-wave analysis may be used in estimating the progression of the disease severity in multiple diseases.

Identification of patients with sarcoidosis that are prone for cardiac arrhythmias is important since the prognosis of sarcoidosis is mainly determined by pul-monary and cardiac manifestations and is improved by aggressive treatment [34]. Moreover, studies have shown that survival of the patients was limited to 2 years after the development of cardiac symptoms while 67% of the patients of them died suddenly [35]. The principal histo-logical features of heart involvement in sarcoidosis in-clude increased fibrotic activity, lymphocyte infiltration, interstitial edema and presence of granulomas which show a localized distribution within the myocardium [36]. Postmortem studies have revealed the presence of vari-ous amounts of myocardial scar tissue, which is consid-ered to provide the substrate for supraventricular and

ventricular arrhythmias. Deranged microarchitecture and non-uniform anisotropic properties of the atrial myocardium may cause inhomogeneous and discontinuous propagation of sinus impulses. In addition to this effect of atrial fiber geometry on the impulse propagation, other intracellular or intercellular factors might account for the non-uniform anisotropic conduction of the atrial myocardium such as the presence of site-specific conduction delays. Expression of these pathologic findings in the ECG can be found in as many as 50% of patients even without clinical evidence of cardiac involvement, with repolarization changes, arrhythmias and conduction disturbances being the most frequent.

The main limitation of the study is the absence of follow-up. This might have been necessary in order to evaluate these indices as predictors of future arhythmic events in this setting of patients and establish their clinical significance. Also, although structural inhomogeneity in ultra-structural properties is considered to play a major role in the initiation of reentrant circuits due to the increased likelihood of unidirectional block of the premature impulse, the study showed no correlation between the atrial size and P-wave regarding the atrial structure [33]. Data regarding these indices are not available for the period before the study. These data could show this correlation.

## 5. Conclusion

Patients with sarcoidosis, in comparison to the control subjects, displayed increased values of $P_{max}$, $P_{min}$ and $P_{dis}$ possibly reflecting an effect of the disease while an inverse correlation with SDNN was established implying an imbalance of autonomic nervous system activity. Prolongation of $P_{max}$ and P wave dispersion and autonomic nervous system imbalance signified increased risk for the development of atrial fibrillation, a major clinical criterion of cardiac involvement in patients with systemic sarcoidosis. This might be of importance, since identification of patients prone to develop arrhythmias played a role in the treatment and altered the course of the disease.

## 6. Acknowledgements

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