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ORIGINAL ARTICLE

Electrocardiographic Analysis of Ventricular Repolarization in Patients With Psoriasis: A Cross-Sectional Study

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Abstract

Background: Psoriasis is a chronic inflammatory disease. Cardiovascular diseases, including arrhythmias, tend to occur more frequently in these patients.

Objective: This study aimed to investigate new electrocardiographic markers for assessing ventricular repolarization in outpatients with psoriasis in a tertiary center in Brazil.

Methods: This work is a cross-sectional study, which selected outpatients with psoriasis undergoing follow-up in a tertiary dermatology service in southern Brazil. The controls were selected from a private outpatient clinic. All the electrocardiogram (ECG) analyses were performed by one certified electrophysiologist. Comparative statistical tests and Spearman's correlation analysis were used. Measures with statistically significant differences in the univariate analysis were taken to the multivariate analysis (Generalized Linear Model – Poisson Regression with age adjustment). A P<0.05 value was considered statistically significant for all analyses.

Results: A total of 130 individuals were evaluated, mean age of 53.1±15.1 years. The univariate analysis showed no difference in Corrected QT interval (QTc) between the groups, considering 411.2±21.2 ms in the psoriasis group (PG) versus 412.8±25.2 ms in the control group (CG) (p = 0.694). The median values of Corrected QT dispersion (QTdisc) were lower in the PG as compared to the CG, 15.7 ms (IQR 11.5–24.2 ms) versus 39.8 ms (Interquartile Range, IQR, 32.8–46.6 ms), respectively (p<0.001). For peak-to-end interval of the T wave (Tp-e) and Tp-e/QTc values, the mean values were also lower in patients with psoriasis. For Tp-e, the mean values in the PG were 91.7±11.6 ms versus 96.0±9.2 ms in the CG (p = 0.024). For The Tp-e/QTc, the mean values in the PG were 0.22±0.03 versus 0.23±0.03 in the CG (p = 0.024). The multivariate analysis, adjusted for age, QTdis, Qtdisc, Tp-e, and Tp-e/QTc, remained independently lower in patients with psoriasis.

Conclusion: The evaluation of ventricular repolarization parameters in a sample of outpatients with psoriasis in southern Brazil showed that ventricular repolarization values were generally lower when compared to controls. No significant correlation was found between disease activity and ventricular repolarization parameters.

Keywords: psoriasis; electrocardiography; cardiac arrhythmias; ventricular tachycardia.

Introduction

Psoriasis is a chronic genetic-based inflammatory disease characterized by lesions that primarily affect the skin, although it may have systemic effects. The disease affects up to 3% of the population worldwide and tends to appear similarly in both sexes.[1] The onset of symptoms can occur at any age, but the disease is less common in children than adults.[2]

The inflammation in psoriasis may promote effects on the cardiac conduction system. Additionally, studies demonstrate that patients with this disease have a significantly higher prevalence of cardiovascular risk

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Central Illustration: Electrocardiographic Analysis of Ventricular Repolarization in Patients With Psoriasis: A Cross-Sectional Study

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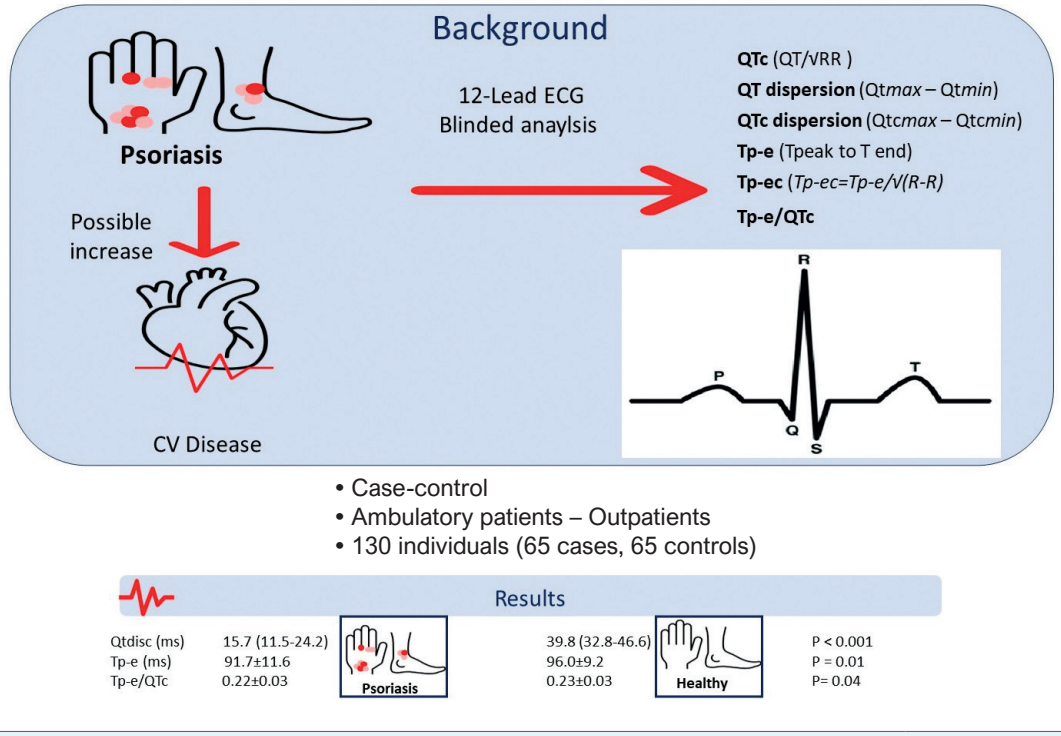

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ECG: electrocardigram; QTc: corrected QT interval; QT: QT interval; CV: cardiovascular

factors, including hypertension, diabetes mellitus, and hyperlipidemia.[3] Cardiovascular disease is the most common cause of morbidity and mortality in patients with psoriasis.[4] Studies have also reported that psoriasis is related to abnormal autonomic function, ventricular repolarization impairment, and arrhythmias (both atrial and ventricular).[5-8]

Previous research demonstrated that transmural dispersion of repolarization plays a significant role in arrhythmogenesis. The QT dispersion (QTdis), the corrected QT dispersion (Qtdisc), the peak-to-end interval of the T wave (Tp -e), the Tp-e/QT ratio, and the corrected Tp-e/QT ratio (Tp-e/QTc) have been accepted as new electrocardiographic markers for the assessment of ventricular repolarization and arrhythmogenesis. The increase in these markers reflects a predisposition to ventricular arrhythmias and a risk of sudden cardiac death.[9] These intervals can be prolonged in psoriasis due to increased inflammation, which suggests the tendency of the myocardium to rhythm disturbances, as previously demonstrated in smaller sample studies.[10-12]

The present study aimed to investigate new electrocardiographic markers to assess ventricular repolarization in outpatients with psoriasis from a tertiary care center in Brazil.

Methods

This was an observational cross-sectional study. The study population consisted of 65 adult patients (≥18 years old) with long-term psoriasis (at least two years of diagnosis), severe disease, characterized by a Psoriasis Area and Severity Index (PASI) score of at least 10 points at the moment of outpatient admission, and requiring systemic treatment. Patients underwent follow-up at the dermatology outpatient clinic at the Hospital Universitário de Santa Maria, between May and December 2018. This is a university hospital in the city of Santa Maria, RS, Brazil, which is a reference for psoriasis care for a population of approximately 500,000 inhabitants. The control group (CG) consisted of a sample of 65 adult (≥ 18 years old), without psoriasis or any other inflammatory systemic diseases,

who had periodically undergone follow-up (at least annually) in a primary outpatient clinic for periodic cardiovascular health control. The CG was selected from a primary cardiovascular outpatient clinic in the private health system. The selection strategy was based on simple random sampling of a list of 2,000 patients who had been evaluated at the cardiovascular outpatient clinic since 2013. The diagnosis of psoriasis was made by two dermatologists certified by the Brazilian Society of Dermatology (LPV and RMLC), based on a clinical or histopathological examination of all patients. To determine the level of systemic inflammation at the moment of the evaluation, levels of the C-reactive protein (CRP) testing were determined, using the immunoturbidimetric method. The exclusion criteria for both cases and controls included individuals with coronary artery disease, heart failure, moderate or severe valvular disease, any documented arrhythmogenic disease (including atrial fibrillation and ventricular arrhythmias), the presence of conduction disturbances (including those who had pacemakers), and bundle branch block. Those individuals with inflammatory diseases (other than psoriasis), active infections, neoplasm (diagnosis or suspected), and electrocardiograms (ECGs) with artifacts or no clearly analyzable QT segment were also excluded from the present study. All individuals had at least one provocative test that was negative for ischemic heart disease and one echocardiographic test showing normal left ventricular function without signs of segmental dysfunction.

The present study was approved by the local Research Ethics Committee.

PASI

In patients with psoriasis, the severity of the disease was evaluated using the PASI. All evaluations were performed by an experienced dermatologist, certified by the Brazilian Society of Dermatology (LPV), who was blinded for the ECG results at the time of the evaluation.

PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72 points. In general, a PASI score of 5 to 10 is considered a moderate disease, and a score of more than 10 is considered severe.[13] However, other authors and health agencies have considered a PASI score ≤12 a sign of mild to moderate disease, and a score >12 a sign of severe disease.[14]

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l), which account for 10%, 20%, 30%, and 40% of the total body surface area, respectively.[15] Each of these areas is assessed separately for erythema, induration, and scaling, which are rated on a scale of 0 (none) to 4 (very severe). Extent of psoriatic involvement is graded as follows: 0=no involvement; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%.

The following formula was used to calculate the PASI score: $\mathbf{PASI = 0.1\ (E_h + I_h + S_h)\ A_h + 0.2\ (E_u + I_u + S_u)\ A_u + 0.3\ (E_t + I_t + S_t)\ A_t + 0.4\ (E_l + I_l + S_l)\ A_l}$, where E = erythema, I = induration, S = scaling, A = area score.[15,16]

Electrocardiographic Analysis

A 12-lead surface ECG with 10 mm/mV amplitude and 25 mm/s speed was obtained for all participants at rest in the supine position (DMS 300, CardioScan, DMS®, São Paulo, Brazil). All ECGs were transferred to a PC in a digital format and then analyzed through an electronic caliper (EP Calipers, 2.6.0, EP Studios Inc.). All the analyses were performed by one electrophysiologist, certified by the Brazilian Society of Arrhythmias (SOBRAC), with expertise in QT measurement (DC), who was blinded to the clinical data of the patients or controls at the time of the evaluation. The average value of two measurements was calculated for each parameter.

The QT interval was measured using a standardized method, which encompasses the time between the first deflection of the QRS complex and the end of the T wave. The end of the T wave was defined as the intersection of a tangent to the steepest slope of the last limb of the T wave and the baseline, in as many leads as possible. The QTc was defined as $QT/\sqrt{RR}$ from the RR interval between the measured and the preceding complex (Bazett).[17,18] Subjects with U waves on their ECGs were excluded from the study.

QT dispersion was measured from the subtraction of the highest QT interval and lowest QT interval obtained from the 12-lead ECG. The Tp-e interval was measured using the tail method, which defined Tp-e as the time from the peak to the end of the T wave.[19] The Tp-e interval was also corrected for heart rate using the formula $Tp\text{-}ec=Tp\text{-}e/\sqrt{(R\text{-}R)}$. If the height or depth of the T wave was <1.5 mm, its ECG was excluded from the analysis. The

Tp-e/QT ratio was calculated from these measurements.

To minimize the risk of errors in the evaluation process, we assessed all ECGs for intraobserver variations. All ECGs were interpreted two times by the same observer (DC).

Statistical analysis

The analyses were performed with the Statistical Package for Social Sciences (SPSS), version 21.0. The distribution of quantitative data was verified using the Kolmogorov-Smirnov test. The continuous variables were described as mean and standard deviation, or median and interquartile range, according to the distribution of data. Categorical variables were presented as absolute and relative values.

The comparison of the means between the case and CGs was performed using the unpaired-Student's t-test and the Mann-Whitney test, as appropriate (univariate analysis). The association between categorical data was verified using Pearson's chi-square test and the correlation between numerical variables was verified using Spearman's correlation test. Electrocardiographic measures with statistically significant differences in the univariate analysis were taken to the multivariate analysis (Generalized Linear Model – Poisson Regression with age adjustment). A P<0.05 value was considered statistically significant for all analyses.

Results

The main results are presented in the Central Illustration. A total of 130 individuals were evaluated, with a mean age of 53.1±15.1 years (range 18 to 90 years), most males (50.8%). There were 65 cases of psoriasis and 65 controls. The mean age of individuals with psoriasis was lower than that of those without psoriasis (P= 0.003). Despite the absence of cardiovascular disease in all patients, the cardiovascular risk (determined by Atherosclerotic Cardiovascular Disease Atherosclerotic Cardiovascular Disease [ASCVD] risk assessment of the American College of Cardiology).[20] showed an elevated risk of cardiovascular diseases in both samples of patients with psoriasis and the CG. There was also a high proportion of diagnosis of hypertension in the CG when compared to the psoriasis group (PG). Additionally, the proportion of active smokers among those with psoriasis was significantly higher than the individuals in the CG. The detailed characteristics of the groups are described in Table 1.

Table 1 – Characteristics of the study groups (psoriasis and controls).

Population = 130	CASES	CONTROLS	P
Number (N)	65	65	
Male[a]	32 (49.2%)	34 (52.3%)	0.726
Age (years)	49.2±14.2	57.07±15.1	0.003
CRP (mg/dl)[b]	0.97±2.06	0.75±1.42*	0.752
ASCVD Risk[b] (10-years risk)	10.7±11.55	12.01±12.17	0.606
Lifetime ASCVD[b]	43.63±15.49	44.41±13.45	0.817
Smoker[a]	19(29,2%)	3(4,6%)	0.05
Diabetes Mellitus[a]	12(18.5%)	6(9,2%)	0.203
Hypertension[a]	20(30.8%)	39(60%)	0.01
Cholesterol[b] (mg/dL)	196.62±35.9	195.82±38.6	0.905
HDL[b] (mg/dL)	49.86±14.2	53.08±11.4	0.163
LDL[b] (mg/dL)	121.15±33.2	112.88±31.2	0.157
Systolic blood pressure[b] (mmHg)	129.18±18.2	135.25±18.4	0.062
Diastolic blood pressure[b] (mmHg)	81.43±12.2	83.77±10.9	0.253

*a: Absolute value; b: Mean and standard deviation; * Control group: in 10 patients PCR was used in the other hsPCR. hsPCR: high-sensitive C-reactive Protein; ASCVD: 10-year Atherosclerotic Cardiovascular Disease Risk from the American College of Cardiology; Lifetime ASCVD: lifetime Atherosclerotic Cardiovascular Disease Risk from the American College of Cardiology; mg/dL: milligrams per deciliter; mmHg: millimiters of mercury; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein.*

Parameters of Ventricular Repolarization

Intraobserver variations were characterized by kappa values of 0.971 for QTdisc and 0.815 for Tp-e/QTc. The univariate analysis showed no difference in QTc between the groups. The median values of QTdis and corrected QTdis (Qtdisc) were lower in patients with psoriasis. For QTdis, the median values observed in the PG were 14.6 ms versus 36.8 ms in the CG (p< 0.001). For QTdisc, the median was 15.7 ms in the PG versus 39.8 ms in the CG (p<0.001) (Figure 1).

For Tp-e and Tp-e/QTc values, the mean values were also lower in patients with psoriasis. (Figure 2). The Tp-e/QT showed no significant difference between the groups. Table 2 specifies the values obtained from the various ventricular repolarization parameters between

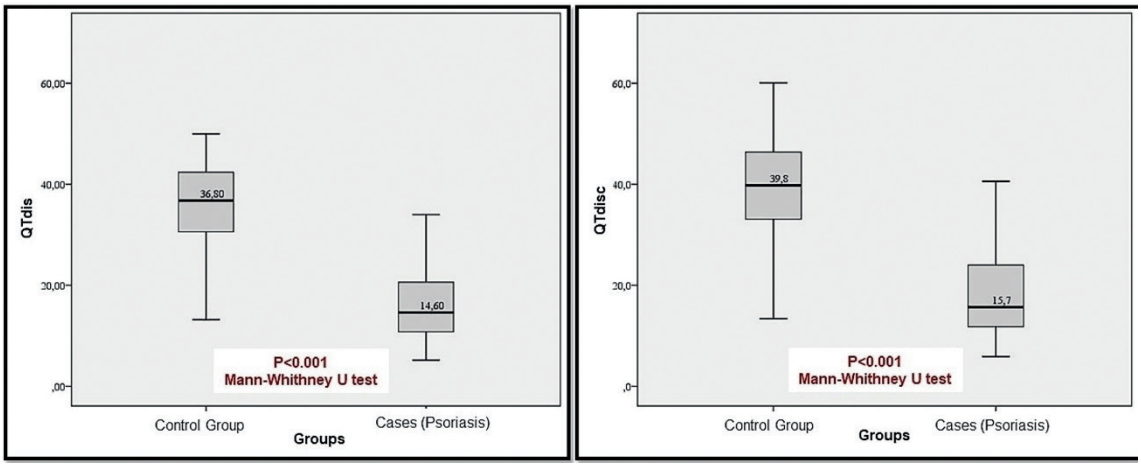

Figure 1 – Comparison of QTdis and QTdisc measurements among the groups of patients with psoriasis and controls (N = 111).
QTdis: QT dispersion; QTdisc: corrected QT dispersion

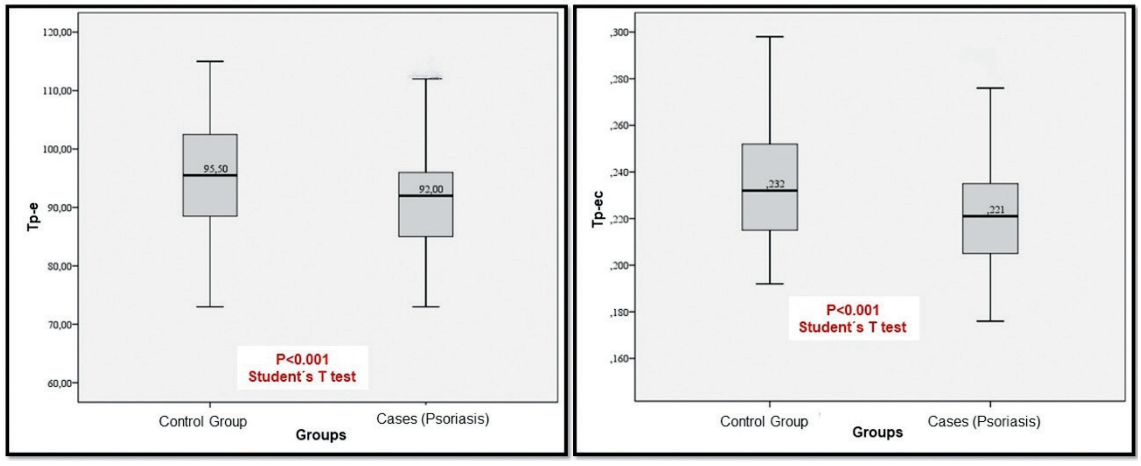

Figure 2 – Comparison of Tp-e and Tp-e/QTc measurements among the groups of patients with psoriasis and controls (N = 126).
Tp-e: peak-to-end interval of the T wave; Tp-ec: corrected Tp-e

cases and controls. In the multivariate analysis adjusted for age, QTdis, Qtdisc, Tp-e, and Tp-e/QTc, remained independently lower in patients with psoriasis (Central Illustration and Table 3).

Disease activity and ventricular repolarization parameters

Within the PG, it was observed that 56 (86.1%) presented good disease control at the time of evaluation, as shown by the PASI score ≤12. There was no statistical difference among the analyzed repolarization parameters (QT, QTc, QTdis, Qtdisc, Tp-e, Tp-e/QT, and Tp-e/QTc), according to the PASI score category (Table 4). The correlation of psoriasis severity (assessed by PASI) and the repolarization measures evaluated in this study were considered to be insignificant. There was a statistically significant correlation between CRP and QTdisc, but this proved to be weak (Spearman correlation 0.262, p = 0.035).

Discussion

Psoriasis is a chronic inflammatory disorder that

Table 2 – Comparison between electrocardiographic measurements in patients with and without psoriasis (N = 130)

Measure	Psoriasis		P
	Yes (Cases)	No (Controls)	
QTc (ms)	411.2±21.2	412.8±25.2	0.694[a]
QTdis Median (IR)	14.6 (10.7-21.2)	36.8 (30.2-42.7)	<0.001[b]
QTdisc Median (IR)	15.7 (11.5-24.2)	39.8 (32.8-46.6)	<0.001[b]
Tp-e	91.7±11.6	96.0±9.2	0.024[a]
Tp-e/QT	0.24±0.03	0.25±0.03	0.071[a]
Tp-e/QTc	0.22±0.03	0.23±0.03	0.024[a]

a: Student's T test; b: Mann-Whitney test; SD: Standard deviation; IR: Interquartile range; QTc: corrected QT interval. Note: the missing data were three for QTc, 19 for QTdis and QTdisc, five for Tp-e; four for Tp-e/QT, and Tp-e/QTc. P univariate analysis.

Table 3 – Multivariate analysis of electrocardiographic measurements in patients with and without psoriasis (N = 130)

Measure	β	Prevalence Ratio	95% confidence interval	P
QTc (ms)	0.003	1.003	0.994-1.012	0.523
QTdis Median (IR)	0.013	1.013	1.007-1.019	<0.001
QTdisc Median (IR)	-0.041	0.960	0.944-0.977	<0.001
Tp-e	-0.020	0.981	0.965-0.996	0.015
Tp-e/QT	-7.154	0.001	0.000-0.182	0.010
Tp-e/QTc	-8.984	0.003	0.000-0.050	0.003

P: Generalized linear models – Poisson Regression with age adjustment. Note: the missing data were three for QTc, 19 for QTdis and QTdisc, five for Tp-e; four for Tp-e/QT and Tp-e/QTc. QTc: Tp-e; QT

affects both the skin and the cardiovascular system. This disease tends to show higher mortality rate, mainly because of cardiovascular diseases.[21] Inflammation plays a significant role in the pathogenesis of psoriasis. Several studies have also suggested that there is a link between arrhythmias and chronic inflammation.[22,23] This can be corroborated by the fact that some systemic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, are associated with a higher incidence of atrial and ventricular arrhythmias.[24-26]

The present study showed that some ventricular repolarization features were shorter in psoriatic patients when compared to the controls (Qtdisc, Tp-e and Tp-e/QTc). Moreover, no relevant correlation was found between psoriatic activity (measured by PASI score or CRP) and repolarization parameters. These findings were surprising and somehow contrary to the current biological and clinical evidence so far available.[10,27] For example, Arisoy et al. observed impaired repolarization parameters in patients with psoriasis when compared to controls. This finding was reflected in higher values of QTc, Qtdis, Tp-e, and Tp-e/QT in patients with the disease.[10] Despite a median PASI score of 8.7, most of the repolarization parameters in psoriasis were higher in the study of Arisoy et al. than those in our study.[10] Additionally, Ozluk et al. demonstrated mean QTc values of 415.1±22 ms in patients with psoriasis, which is slightly higher than the mean values of 411.2±21.2 ms observed in the present study.[27] Such factors highlight a different profile of psoriatic patients in our study, which consisted of a population with a long-term diagnosis and severe systemic disease.

The present study also failed to observe any clinically relevant correlation between PASI scores or CRP levels and ventricular repolarization values. However, a statistically significant correlation was identified between CRP and Qtdisc. However, this correlation was weak and of negligible clinical relevance. Such findings also differ from the study conducted by Arisoy et al., who observed that CRP was an independent predictor of the Tp-e/QT ratio.[10]

Several factors may explain the differences between the present study and the observed publications. There was a significant difference of age between groups, with a significantly higher mean age in the CG. Despite the absence of clinical cardiovascular disease, it is possible that subclinical atherosclerotic disease may have influenced the repolarization parameters. It is also important to mention that, despite a negative screening for coronary artery disease in our population, a substantial risk for cardiovascular diseases must be addressed. This was observed by a high 10-year ASCVD risk calculated in both cases and controls, a factor that could impact the repolarization parameters.[28,29]

Additional limitations should be stressed in the present study. First, due to the cross-sectional design, it is difficult to derive casual relationships. At the same time, because

Table 4 – Comparison between electrocardiographic measurements and inflammatory markers in patients with psoriasis, according to the Area Psoriasis Severity Index - PASI (N = 65)

Measure	Psoriasis Severity Index by Area - PASI		P
	≤12 N=56	>12 N=9	
QTc	411.5±22.2	409.3±15.1	0.781[a]
QTd Median (IR)	15.0 (10.7-22.1)	13.6 (10.7-19.5)	0.615[b]
QTdc Median (IR)	16.0 (11.4-24.6)	15.7 (11.8-22.5)	0.812[b]
Tp-e	92.2±11.7	88.2±11.4	0.342[a]
Tp-e/QT	0.24±0.03	0.24±0.04	0.986[a]
Tp-e/QTc	0.22±0.03	0.22±0.03	0.447[a]
Median CRP (IR)	0.2 (0.2-0.5)	0.2 (0.2-1.6)	0.396[b]

a: Student's T test; b: Mann-Whitney test. SD: Standard deviation; IR: Interquartile range; CRP: C-reactive protein; QTc: corrected QT interval; QTd: QT dispersion; Tp-e: peak-to-end interval of the T wave

individuals were not followed prospectively, it was not possible to determine whether or not repolarization parameters actually predict ventricular arrhythmias in the population with psoriasis. Second, our CG was not age-matched with cases, and there were significant differences in comorbidities and risk factors between case and CGs (such as hypertension and smoking). These factors may have influenced repolarization parameters. Third, the sample size was small, and the repolarization differences may well be related to statistical error.

Conclusions

The evaluation of ventricular repolarization parameters in a sample of outpatients with psoriasis in southern Brazil showed that ventricular repolarization values were lower than the controls. In addition, it was not possible to relate disease activity with ventricular repolarization parameters. Further studies with larger sample sizes and prospective designs are needed to elucidate the above results.

Author Contributions

Conception and design of the research: Schmitz GB, Chemello RML, Vargas LP, Chemello D; acquisition of data: Schmitz GB, Vargas LP; analysis and interpretation of the data: Saffi ML, Chemello D; statistical analysis: Saffi ML; writing of the manuscript: Chemello RML, Chemello D; critical revision of the manuscript for intellectual content: Schmitz GB, Chemello RML, Saffi ML, Chemello D.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Comitê de Ética em Pesquisa com Seres Humanos under the protocol number 89122218.4.0000.5346 - Parecer 2.644.861. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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