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Time and frequency domain assessment of heart rate variability in patients with pulmonary sarcoidosis

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Abstract. *Background and aim:* The association between sarcoidosis and autonomic dysfunction is demonstrated but poorly known. Heart rate variability (HRV) studies can provide a simple, non-invasive analysis of sympathetic and vagal tone in sarcoidosis. To date, the burden of steroid treatment on HRV has not been investigated. We aim to compare the HRV in sarcoidosis with general population and to explorate the burden of steroid treatment in HRV. *Methods:* Prospective analysis of 30 patients enrolled in Sarcoidosis Clinic of Policlinico Gemelli Hospital compared to 72 healthy control subjects. Continuous EKG recording over 24 hours was performed, and HRV was assessed using time and frequency domain analysis. Results were evaluated using a propensity score matching 1:1. *Results:* Patients affected by sarcoidosis presented a mean age of 59.7±10.1 y (SD) and female gender predominance (n=20, 71.4%) %). In contrast, the mean age of the control group was 54.6±16.0 y with a balanced male/female ratio (37 females, 51.4%). The HRV analysis outlined a significant difference when both time/frequency domain were compared to the general, healthy population (ΔSDNN: 89.4±6.7 p=0.0001; ΔrMSSD: 5.7±2.6 p=0.03; ΔLF: 497.0±142.3 p=0.0007; ΔHF: 325.0±159.5 p=0.0442) suggesting a significant impact of sarcoidosis in autonomic activation and baseline activity. Noteworthy, the lung function tests and scadding stage did not show any relationship with the HRV (p=NS). At the same time, steroid treatment of ≥10 mg/day of prednisone for the previous 3 months was associated with a significant reduction of HRV in time (SDNN: Δ17.2±6.9, p=0.020) and frequency domain (LF: Δ355.2±125.7, p=0.009 and HF: Δ116.2±65.2, p=0.087). Lastly, the propensity score matching confirmed the previous results concerning time/frequency domain analysis. *Conclusions:* Heart Rate Variability is an effective tool for autonomic evaluation in patients affected by sarcoidosis. The time (r-MSSD, SDNN, pNN50%) and frequency domain (HF/LF mean) analysis in sarcoidosis suggested that autonomic dysfunction is not related to the lung function or scadding stage. However, steroid treatment highlighted a noteworthy impact. More proper studies should address the role of steroid treatment and inflammation in sarcoidosis and autonomic dysfunction.

Key words: pulmonary sarcoidosis, heart rate variability, autonomic nervous system, glucocorticoids, time-domain analysis

Introduction

The sarcoidosis is a complex, multisystemic and idiopathic disorder characterized by granulomatous disease affecting lungs or other systems in the body. Since the very first case of sarcoidosis in 1877 (1), such disease remains a challenge for physicians, and the relationship between systemic inflammation and

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autonomic dysfunction has not been clarified. Autonomic system plays a pivotal role, especially in patients affected by sarcoidosis and the dysfunction of such a key player could lead to consequences such as arrhythmias, conduction abnormalities, airway constriction, altered intestinal transit and sudden death. Moreover, nowadays, the main treatment for sarcoidosis is represented by steroids. Steroids can alter the regulation of the sympathetic nervous system by altering the hypothalamic and stem regions involved, leading to clinical consequences. Heart Rate variability (HRV) is one of the earliest subclinical manifestations of autonomic dysfunction, and its role has been established for various diseases such as diabetes (2), myocardial infarction, and severe hypertension. We aim to compare the HRV time and frequency domains of patients affected by sarcoidosis with healthy controls to detect a potential role of pulmonary sarcoidosis and investigate the impact of steroids.

Methods

Study groups

This study is a prospective case-control trial.

We enrolled 30 biopsy-proved pulmonary sarcoidosis patients from the Sarcoidosis Clinic of our institution, a tertiary care center for rare interstitial lung diseases (ILDs). Patients older than 18 years to 85 years were eligible. The following conditions led to exclusion from the study: non-sarcoidosis lung disease, known heart disease, systemic hypertension, diabetes, anemia or pregnancy. The control group consisted of healthy subjects aged 18-85 years without coronary artery disease or any other cardiovascular risks available in PhysioBank: a large and open-access database of digitally archived physiologic signals available for the use of medical community as part of the Research Resource for Complex Physiologic Signals (3). The final control group comprises 72 subjects, obtained by combining the MIT-BIH Normal Sinus Rhythm Database (4) (n=18) with the Normal Sinus RR Interval Database (5) (n=54).

24-hours holter monitoring

All the patients were scheduled to perform a 24-hour ECG recording using a 7-lead 3-channels recorder (Medilog FD5 Plus®, Schiller Americas Inc®, Doral, FL, US). Holter recordings were processed by a dedicated cardiologist expert in arrhytmology using a diagnostic analysis program (Medilog DARWIN2®, Schiller Americas Inc®, Doral, FL, US). To be an eligible record, we must have at least 12 hours of analyzable data and half of the nighttime (from 00:00 to 05:00 am) and daytime (8:00 am to 10:00 pm) processable. Due to severe record artifacts in 24-hours Holter monitoring, two patients from the Sarcoidosis group were excluded from the final analysis. Heart rate variability (HRV) was analyzed using time and frequency domains. The time domain is the amount of HRV observed during the 24 hours defined by the standard deviation of RR intervals (SDNN), the root mean square of the successive differences (rMSSD), and the percentage of NN intervals that differ from each other by more than 50 ms (pNN50). The frequency domain values defined the total signal energy within component bands: Total power, Ultra Low Frequency (ULF), Very Low Frequency (VLF), Low Frequency (LF) and High Frequency (HF). We also included the LF/HF Ratio in the analysis as a potential marker of sympatho-vagal balance.

Statistical analysis

We analyzed the Heart Rate Variability in cases and controls. The sample was described using descriptive statistics techniques. Quantitative variables were summarized using means ± standard errors; categorical variables were presented using (absolute and percentage) frequency tables. Time and frequency domains were analyzed using a T-test after being tested for normality (unadjusted analysis). Furthermore, statistical results were adjusted for potential HRV confounding variables (age, gender) using the Propensity Score Matching to design a 1:1 match after the balance assessment of baseline covariates. Predictors of HRV in patients with Sarcoidosis were investigated using linear regression analysis. An α-level of 0.05 (double-tail) was chosen for statistical significance. SAS version 9.4 or higher statistical software was used (SAS Institute Inc®, Cary, North Carolina, USA). Figures were designed using STATA v13.0 or higher (STATACorp®, College Station, Texas, USA).

Results

Baseline characteristics

We enrolled 102 patients: 30 affected by Pulmonary Sarcoidosis were compared to 72 healthy control subjects. However, due to 24-hours monitoring

artifacts, two case group patients were excluded from the analysis. Cases presented a mean age of 59.7±10.1 y (SD). Female gender was predominant (n=20, 71.4%), while the mean age of the control group was 54.6±16.0 y, and gender was balanced (37 females, 51.4%). A distributional figure with kernel density estimation of age and gender ratio is summarized in the Figure 1 and depicts an unbalance between the two groups with respect to demography.

Heart rate variability

Results are shown in Figure 2. SDNN was a mean of 136.5±33.4 ms in control groups comparing to 47.0±19.9 ms in Sarcoidosis group, showing a difference of 89.4±6.7 ms (p<0.0001). Also, rMSSD did show lower values of 5.7±2.6 (ms) in case group. Concerning the frequency domain, all the measures were significantly smaller in Sarcoidosis subjects when compared to healthy control group, including the LF (Δ497.0±142.3, p=0.0007) and the HF (Δ325.0±159.5, p=0.0442). The LF/HF Ratio did not significantly differ within the groups (Δ0.6±0.3, p=NS).

Moreover, we conducted a multivariate analysis to assess whether the impact on autonomic function is solely attributable to sarcoidosis or if it is also influenced by the administration of steroids by conducting a multivariate analysis of variance (MANOVA) with groups and steroids as predictors (Table 1). Our analysis revealed that the group predictor remains highly significant ($p < 0.0001$) even after accounting for steroid use, highlighting that sarcoidosis exerts a direct and independent effect on autonomic function. Additionally, steroid use itself demonstrated a strong and significant impact on autonomic measures ($p < 0.0001$), underscoring its substantial contribution to the observed dysfunction. These findings indicate that while steroid use explains a significant portion of the variance in autonomic function, sarcoidosis retains a direct effect that is not fully mediated by steroid treatment.

Propensity score 1:1 matching

With regards to the unbalance of age and gender within the experimental and control group,

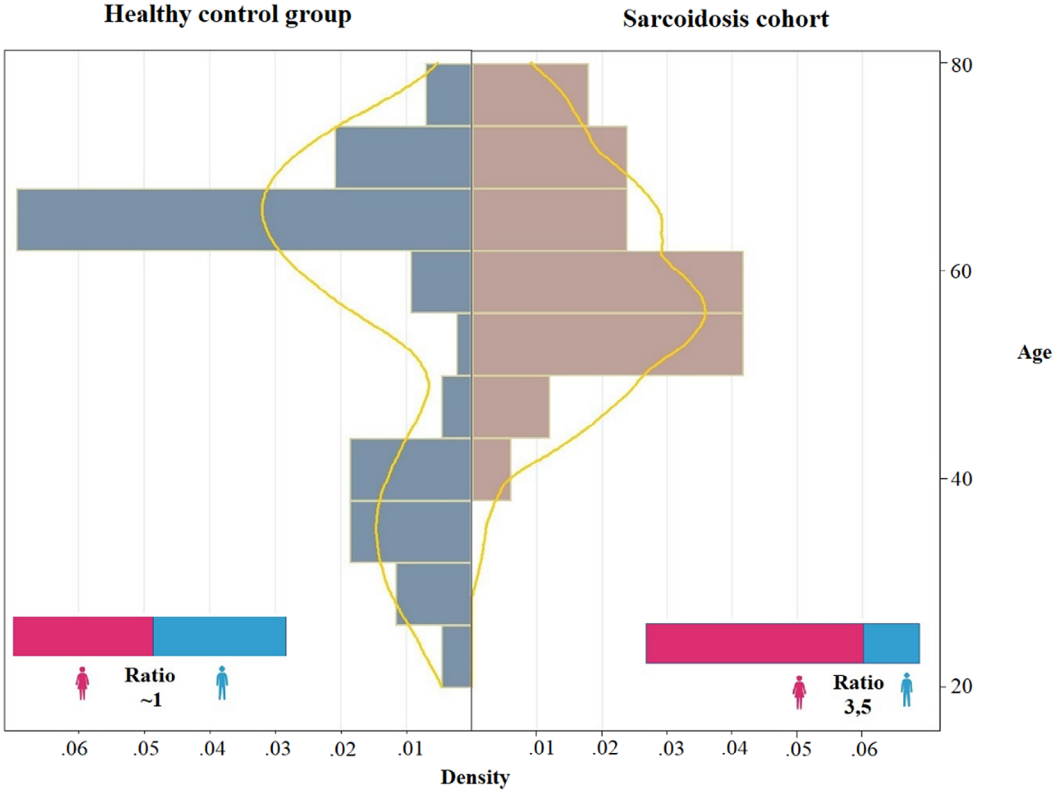

Figure 1. Distributional plot with kernel density estimation of age and gender ratio of healthy subjects and Sarcoidosis group.

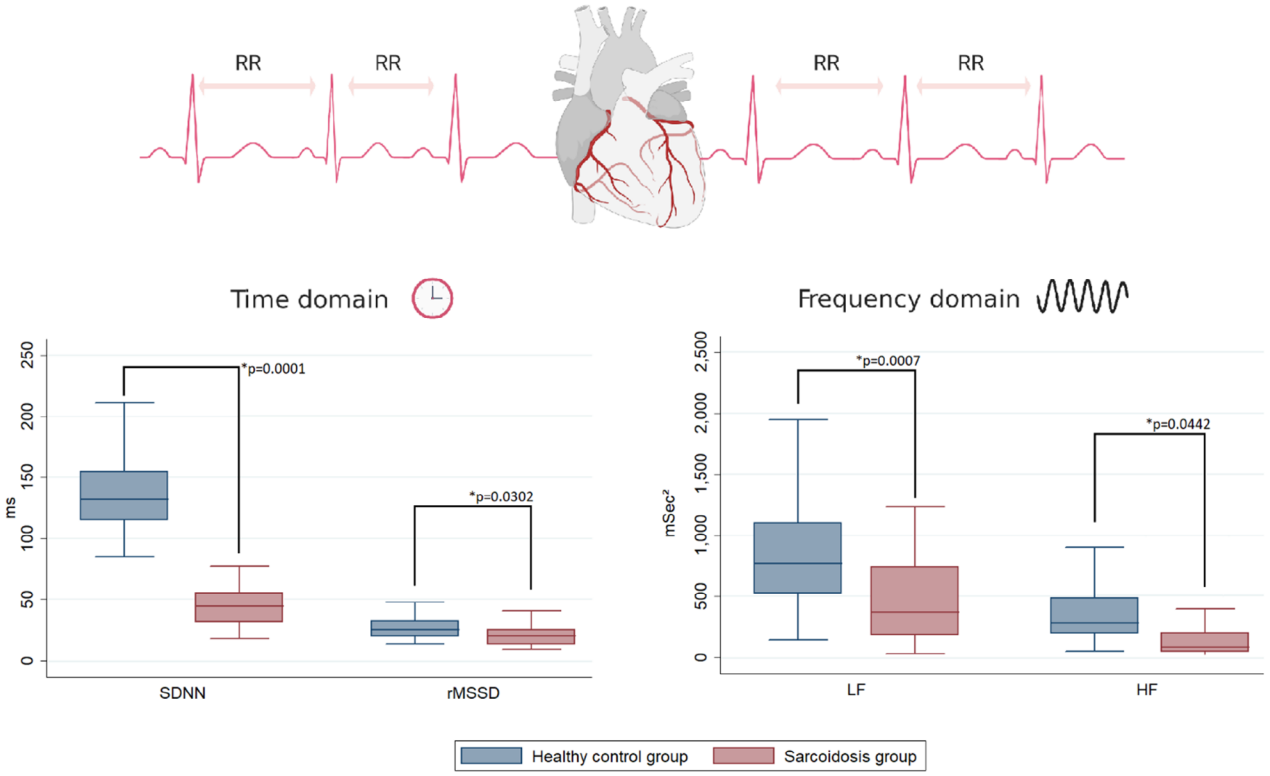

Figure 2. Heart Rate Variability time and frequency analysis in Sarcoidosis.
Abbreviations: SDNN: Standard Deviation of NN Intervals, rMSSD: root Mean Square of the Successive Differences, LF: Low Frequency, HF: High Frequency.

Table 1. Effect on autonomic function of group and steroid treatment

Predictor	Wilks' Lambda	Pillai's Trace	Hotelling-Lawley Trace	Roy's Largest Root	F Value	p-Value
Group (Sarcoidosis vs Healthy)	0.0480	0.9520	19.812	19.812	465.582	***P<0.0001***
Steroids	0.3914	0.6086	1.555	1.555	36.534	***P<0.0001***

we conducted a propensity-score 1:1 matching outlined in Table 2**,** that substantially confirmed the results of the adjusted analysis apart from the rMSSD that missed the statistical significance in the time domain analysis (ΔrMSSD: 5.0±3.6, p=NS). The frequency domain did demonstrate a stronger relationship when compared to the unadjusted analysis: the total power (Δ18432.3±1277.1, p=0.0001), ULF (Δ17188.7±1090.2, p=0.0001), VLF (Δ552.8±226.3, p=0.015), LF (Δ446.4±105.3, p=0.0001) and HF (Δ251.5±101.7, p=0.013) were significantly reduced. Still, the LF/HF Ratio didn't reach both clinical and statistical significance (Δ0.4±0.4, p=NS).

Predictors of HRV in sarcoidosis

We investigated the predictors of HRV in patients affected with Sarcoidosis and the results are summarized in the Table 3.

Even though the demography (except for the male gender in the frequency domain) and lung function tests did not show any relationship with the HRV, we observed that ongoing steroid therapy with at least ≥10 mg/day of prednisone for the previous 3 months is associated to a significant reduction of HRV in time (SDNN: Δ17.2±6.9, p=0.020) and frequency domain (LF: Δ355.2±125.7, p=0.009 and HF: Δ116.2±65.2, p=0.087) (Figure 3). Interestingly,

Table 2. Heart Rate Variability (HRV) time and frequency domains in the experimental group (Sarcoidosis) and control group (Healthy). HRV was analyzed after a 1:1 matching for age and gender using the Propensity Score Matching

			Unadjusted		Propensity Score Matching	
HRV	**Healthy group**	**Sarcoidosis**	**Δ Diff.**	**pvalue**	**Coeff.**	**pvalue**
SDNN	136.5±33.4	47.0±19.9	89.4±6.7	**0.0001**	86.5±5.5	**0.0001**
rMSSD	28.3±12.0	22.5±10.7	5.7±2.6	**0.0302**	5.0±3.6	NS
pNN50	7.5±7.6	5.3±5.8	2.3±1.6	NS	0.8±2.3	NS
Total	21497.2±11587	2128.1±1413	19369±2202	**0.0001**	18432.3±1277	**0.0001**
ULF	18131.1±10139	356.5±251.5	17774.6±1922	**0.0001**	17188.7±1090	**0.0001**
VLF	1915.2±1053.0	1132.6±809	782.6±220.9	**0.0006**	552.8±226.3	**0.015**
LF	962.6±714.7	465.6±372.1	497.0±142.3	**0.0007**	446.4±105.3	**0.0001**
HF	498.3±833.9	173.3±179.0	325.0±159.5	**0.0442**	251.5±101.7	**0.013**
LF/HF	2.8±1.3	3.4±1.6	0.6±0.3	NS	0.4±0.4	NS

Abbreviations: *HRV time domain is expressed as mean±SE (mSec) while frequency domain as mean±SE (mSec²). **HRV = Heart Rate Variability, ULF = Ultra Low Frequency, VLF = Very Low Frequency, LF = Low Frequency, HF = High Frequency, NS = Not Significant.

Table 3. Regression analysis summary for independent predictors of HRV in Sarcoidosis

	SDNN		**LF**		**HF**	
Variable	**B±SE**	**P>|t|**	**B±SE**	**P>|t|**	**B±SE**	**P>|t|**
Age	-0.9±0.4	NS	-20.1±4.1	NS	-8.4±4.9	NS
Male gender	6.6±8.4	NS	285.4±133.8	**0.035**	71.5±75.2	NS
BMI	-0.03±0.7	NS	-5.07±12.5	NS	-5.17±5.9	NS
FVC (%)	0.17±0.25	NS	3.90±4.8	NS	-1.63±2.41	NS
TLC (%)	-0.1±0.3	NS	-0.3±6.6	NS	-3.2±3.01	NS
DLCO (%)	0.16±0.27	NS	-1.60±5.03	NS	-0.3±2.5	NS
Advanced stages*	5.9±7.6	NS	9.6±143.3	NS	84.1±66.9	NS
Steroids**	17.2±6.9	**0.020**	355.2±125.7	**0.009**	116.2±65.2	*0.087*
	Time domain		*Frequency domain*			

**Advanced stages*: Stage II-III-IV according to Scadding chest X-ray classification
***Steroids*: Ongoing therapy with at least ≥10 mg/day of prednisone for at least 3 months

advanced radiological stages assessed with chest X-ray (Scadding stage) were not associated with HRV variation. Our findings underscore the significant impact of sarcoidosis on autonomic function, as assessed through (HRV metrics. The observed reductions in both time and frequency domain parameters align with the notion of heightened autonomic dysfunction in chronic inflammatory diseases, as previously reported in literature. For instance, studies on sarcoidosis have highlighted similar reductions in HRV, emphasizing the interplay between systemic inflammation and autonomic regulation. These findings are consistent with the broader evidence linking systemic inflammatory burden to disrupted autonomic function, as also observed in other inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus. The significant reductions in HRV observed in our study, particularly among those receiving steroid therapy at doses ≥10 mg/day of prednisone, mirror prior observations of steroid-associated modulation of autonomic function. Corticosteroids are known to affect sympathetic and parasympathetic balance (6-7), likely mediated through hypothalamic-pituitary-adrenal axis interactions (8). This finding is pivotal, as it underscores the dual contributions of sarcoidosis and its treatment regimen to autonomic dysfunction. However, our results diverge from some earlier studies that

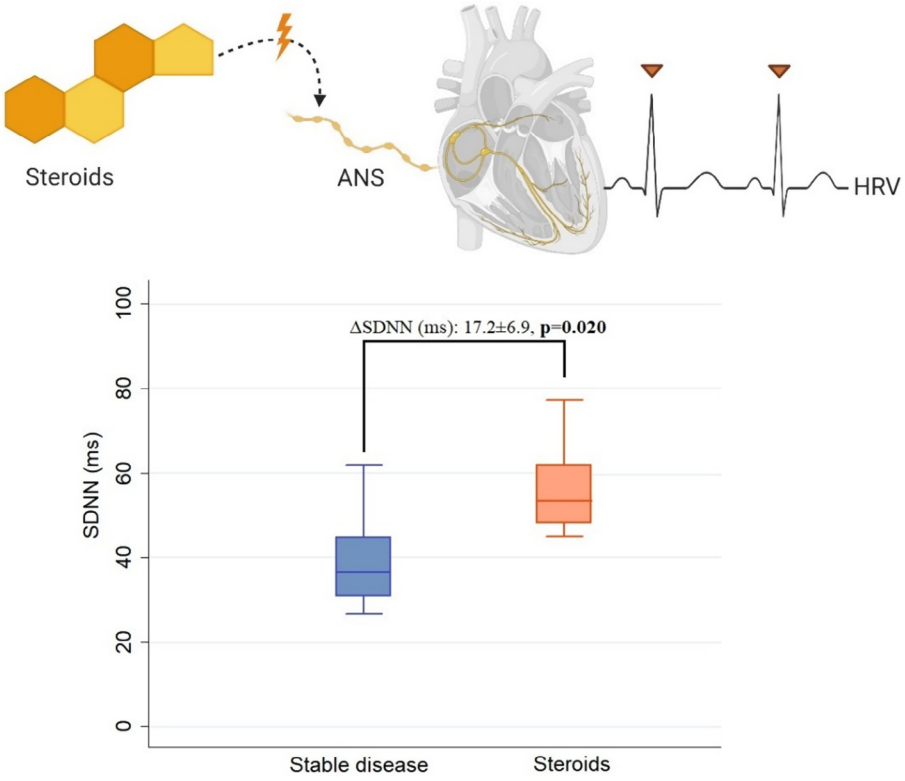

Figure 3. Impact of steroid therapy in patients affected by Sarcoidosis on Heart rate Variability with a special angle on the time domain. *Abbreviations:* ANS: Autonomic Nervous System, HRV: Heart Rate Variability, SDNN: Standard Deviation of NN Intervals on 24-hour Holter monitoring.

suggested a more limited role of steroid therapy in modulating autonomic responses. This discrepancy may be attributable to differences in study designs, dosages, or populations studied, underscoring the need for standardized protocols to better elucidate these relationships.

Limitations

This study acknowledges several limitations that warrant consideration. First, the sample size was relatively small, which may limit the generalizability of the findings. Second, while the association between sarcoidosis, steroid use, and HRV was clearly demonstrated, the study relied on qualitative rather than quantitative data regarding steroid dosages, which could introduce variability in interpreting the impact of treatment. Additionally, the exclusion of cardiac sarcoidosis cases may have limited the scope of autonomic dysfunction assessed, as cardiac involvement is known to exacerbate arrhythmogenic risk and HRV abnormalities. Future studies incorporating quantitative steroid dosing and including patients with cardiac sarcoidosis would provide a more comprehensive understanding of these dynamics.

Conclusion

Sarcoidosis is a multisystem disease with a special regard for the lungs, and autonomic dysfunction may be a possible consequence of its inflammatory burden. Heart Rate Variability is a practical, non-invasive tool for the autonomic evaluation in patients affected by sarcoidosis. The analysis of the HRV suggested that sarcoidosis, a chronic inflammatory disease, impacted on the autonomic dysfunction leading to possible and serious consequences. The time (r-MSSD, SDNN, pNN50%) and frequency domain (HF/LF mean) analysis in pulmonary sarcoidosis displayed not only that autonomic dysfunction is relevant but that is not related to the lung function or scadding stage though steroid treatment underlined

a significant effect when ongoing ≥10 mg/day of prednisone since the previous 3 months. The study, though, experienced some limitation such as the sample size of the analysis, the possible role of immunosuppressant therapy and the need of considering the cardiac localization of sarcoidosis due to the possibility of serious arrhythmias induced by autonomic dysfunction. Future research should address the role of steroid treatment and the impact of the previous limitations regarding the autonomic dysfunction in sarcoidosis.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: MP-V and MV conceptualized and designed the study. AC and MS performed data acquisition and statistical analysis. FM and GP contributed to data interpretation and literature review. MP-V, MV, FM and GP drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

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