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Exploring the intersection of sarcoidosis and cardiac arrhythmias

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ABSTRACT

Sarcoidosis is a multi-organ granulomatous disease of uncertain origin, characterized by the formation of non-necrotizing granulomas in various organs, including the heart. Cardiac involvement in sarcoidosis is rare, with approximately 5% of sarcoidosis patients developing clinically apparent cardiac disease, which is associated with significant morbidity and mortality. Genetically predisposed individuals develop granuloma in myocardium musculature, leading to aberrant conduction of cardiac impulses and the development of various arrhythmias. Common arrhythmias range from atrial fibrillation to ventricular tachycardia and can lead to sudden cardiac death because of ventricular fibrillation. The diagnostic challenge results from high specificity but rather limited sensitivity of endomyocardial biopsy, which is the gold standard diagnostic test, making advanced imaging techniques, such as cardiac magnetic resonance imaging and fluorine-18 fluorodeoxyglucose positron emission tomography, crucial for early detection. Management involves a complex approach with immunosuppression, antiarrhythmic medications, and catheter ablation, often supplemented by implantable cardioverter-defibrillators to prevent sudden cardiac death. In cardiac sarcoidosis, ventricular arrhythmias are common and cause high mortality. Timely intervention and management are crucial for a better prognosis. The disease's growing prevalence requires further research on refining early detection techniques and developing efficient treatment strategies for these high-risk patients. This review focuses on the etiopathogenesis of arrhythmias in cardiac sarcoidosis, diagnosis, and effective management strategies.

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Review

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INTRODUCTION

Sarcoidosis is a multisystem inflammatory disorder of unknown etiology, typically characterized by non-caseating granulomas in the affected organ. The global incidence of sarcoidosis ranges from 1 to 15 per 100,000, with the highest rates occurring in Northern European as well as North American populations, with black Americans being more affected by it than white, Hispanic, or Asian Americans. It usually develops in people under 40, peaking between 20 and 29, with a second peak occurring in specific groups, such as Japanese and European women beyond the age of 50.[1] Some studies suggest that it affects women more than men, with a recent estimate of 57% of sarcoidosis patients being women.[2] Sarcoidosis pathogenesis is still evolving and is linked to specific environmental, genetic, infectious, and idiopathic factors. In genetically susceptible individuals, specific environmental factors can prompt an inflammatory response driven by T cells. This process leads to the development of non-caseating granulomas that have the potential to either resolve on their own or advance to fibrosis, causing damage and destruction to the affected tissue.[3] Patients usually present with pulmonary symptoms like chronic cough, dyspnea, and chest pain but can present with other symptoms depending on the system involved.[4]

Cardiac involvement in sarcoidosis is a pretty rare entity, with around 5% of patients having clinically apparent cardiac disease. The majority have clinically silent illnesses and are associated with increased morbidity and mortality, contributing to approximately 10-25% of all sarcoidosis-related deaths in the United States.[5,6] Cardiac sarcoidosis (CS) can affect any portion of the heart; the left ventricle is the most commonly affected area, with focal non-caseating granulomas disrupting normal myocardial function, giving rise to a spectrum of cardiac manifestations. The most common of these include syncope, sudden death, heart block, atrial or ventricular tachyarrhythmia, and heart failure.[3,7] Conduction abnormalities, ventricular tachycardia (VT), and cardiac failure comprise the classical CS triad.[8] The prevalence of atrioventricular (AV) block in CS ranges from 26% to 62%, and bundle branch block is documented to have a 12% to 61% prevalence. VT is the most common tachyarrhythmia, with a prevalence of 2% to 42%, followed by supraventricular tachycardia, with a prevalence of 0% to 15%[9] and the most common mechanism is macro-reentrant arrhythmias in the vicinity of the granulomatous scar.[10] As cardiac involvement worsens, it can lead to systolic or diastolic dysfunction, eventually resulting in heart failure.[11] Diagnosing CS can be challenging due to the disease's scattered distribution and the limited effectiveness and invasiveness of endomyocardial biopsy in detecting it. Hence, advanced imaging techniques, like cardiac magnetic resonance imaging (MRI) and fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG-PET), are now used for early detection and accurate diagnosis.[12,13] Management of CS-related arrhythmias can be complex and involves the use of immunosuppression, antiarrhythmic medications, and ablation, in addition to implantable cardioverter defibrillator (ICD) placement to prevent sudden cardiac death in selected patients.[8] Also, the resolution of arrhythmias after starting immunosuppressive therapy can be used to monitor treatment response. However, some studies claim otherwise.[14] Since there are no well-established standardized screening guidelines for CS, setting more robust criteria for the detection of cardiac arrhythmia in asymptomatic individuals will result in a reduction in the number of sudden cardiac fatalities linked to these conditions. This narrative review aims to comprehensively understand CS arrhythmia, its pathogenesis's complexity, and management strategies that can potentially reduce associated mortality rates.

PATHOPHYSIOLOGY

CS, a rare entity with arduous and inexplicable etiology, is a disease affecting the heart. Genetic, infectious, and environmental factors are speculated in the pathogenesis of CS.[15] It has been observed that sarcoidosis has familial relations, indicating a robust genetic component. Studies on gene linkage have suggested that the genes that play a role in the clinical presentation of sarcoidosis are likely different from those that contribute to the susceptibility of the disease. Associations have been identified with HLA DQB*0601 and the TNFA2 allele of the tumor necrosis factor (TNF) gene, particularly in the Japanese population.[10] Various HLA studies have explicated the HLA genes, particularly HLA-A1 and -B8 and HLA DR3, about cardiac and systemic sarcoidosis.16 In addition to the genetic component encircling the CS, distinct potential antigens, including infectious entities such as Mycobacterium tuberculosis, Mycoplasma species, Corynebacterium species, and spirochetes and environmental agents like aluminum,

pollen, clay, talc have been implicated as potential antigens in the pathogenesis of sarcoidosis.[3]

CS is characterized by the formation of the characteristic discrete, compact, non-caseating epithelioid cell granuloma,[9] which can affect any region of the heart, with the left ventricular free wall being the most frequently affected area, followed by the left basal interventricular septum and the right ventricle by an exaggerated cellular immune response in genetically predisposed individuals.[17] A group of highly specialized cells forms these discrete non-caseating epithelioid cell granulomas called mononuclear phagocytes, consisting of epithelioid cells, giant cells, Schaumann bodies or asteroid bodies, patchy fibrosis, and lymphocytes through delayed cell-mediated hypersensitivity immune response. After antigen processing by antigen-presenting cells (APCs), the CD4+ helper T cells release interleukin (IL)-2 and interferon (IFN)-γ, triggering a Th1 immune response. These macrophages have an increased expression of major histocompatibility complex (MHC)-class-II and other co-stimulatory accessory molecules, probably induced by interaction with the potential sarcoidosis antigen or antigens.[18] These macrophages recognize, process, and present the potential antigen to Th1 lymphocytes. The activated sarcoid macrophages produce IL-12, a crucial cytokine that shifts towards a Th1 profile and stimulates T-cells' IFN-c production. The activated T-cells then release IL-2 and chemotactic factors for blood monocytes, further recruiting monocytes/macrophages to the site of disease activity. IFN-c can further activate macrophages, and IL-2 activates and expands various T-lymphocyte clones. IFN-c is essential for transforming macrophages into giant cells (macrophage fusion factor), critical granuloma building blocks. The pro-inflammatory macrophage cytokines IL-1, IL-6, and TNF-alpha are essential to induce and maintain granuloma formation, and all are increased in sarcoidosis. In contrast, the anti-inflammatory cytokine IL-10 is not increased in sarcoidosis. As the lesion progresses, there is a transition toward a T-helper type 2 reaction, which involves the secretion of IL-10, transforming growth factor (TGF)-β, which initiates the fibro-proliferative phase of the granuloma and is thought to have anti-inflammatory effects and leads to tissue scarring.[11,19]

The tissue scarring can give rise to a range of conduction abnormalities, with a prevalence ranging from 12% to 62%, affecting any part of the conduction system, leading to left or right bundle branch block (complete or incomplete), AV block of any degree, and even sinus node arrest. Complete heart block is the most commonly presented conduction abnormality (23-30%), which can often manifest without any significant evidence of cardiomyopathy. In addition to the complete heart block, ventricular and supraventricular arrhythmias can occur in CS patients.[20] The direct granulomatous involvement of the myocardium and the spread of inflammation to the conduction systems, such as the AV node or His–Purkinje system, is thought to be a primary mechanism for developing conduction abnormalities in CS with AV block is a significant complication of CS, primarily caused by scar tissue or granulomas affecting the basal septum or nodal artery, which disrupts the heart's conduction system.[21] Atrial fibrillation (AF) is recognized as the most prevalent supraventricular arrhythmia, with atrial tachycardia, atrial flutter, and AV nodal reentry tachycardia following in incidence. The mechanisms underlying supraventricular arrhythmias can vary, including triggered activity, abnormal automaticity, reentry circuits, or scar formation.[22] Triggered activity occurs when a single cardiac cell or a small group of cells depolarizes spontaneously due to abnormal ion channel behavior. This depolarization can generate an early or delayed after depolarization, which may initiate supraventricular arrhythmias.[23] Furthermore, increased atrial pressures occurring in the presence of advancing ventricular impairment and pulmonary hypertension play a significant role.[24] Conversely, ventricular arrhythmias are most likely caused by macro reentrant circuits around regions of granulomatous scar.[25] Reentrant arrhythmias occur when a depolarizing impulse confronts an obstructed region, such as a granuloma or scar, through which it can only pass on one side. Successfully navigating around the central blockage, the impulse circulates and returns, creating a circular motion. This continuous circuit, known as reentry, occurs rapidly, emitting depolarizing impulses to the surrounding myocardium and activating it at a high rate.[26] While this mechanism is standard, active inflammation may also contribute to monomorphic VT by either triggering reentry through ventricular ectopy or impairing conduction in diseased tissue within the granulomatous scar.

In addition to the arrhythmias caused by abnormalities involving the conduction system, widespread inflammation with granulomas infiltrating the walls of the heart muscle can lead to heart failure

with systolic dysfunction. Mitral regurgitation can also occur due to left ventricular (LV) or mitral annular dilatation, scarred LV wall restricting valve closure, or granulomas invading the valve leaflets, which can cause myocardial systolic dysfunction. Infiltration of the myocardium with edematous or fibrotic left ventricle walls also limits the myocardial diastolic function, resulting in myocardial diastolic dysfunction. Additionally, infiltration of the right ventricle may resemble arrhythmogenic right ventricular cardiomyopathy.[27] Figure 1 illustrates the pathophysiology mechanism behind CS and associated arrhythmias.

DISCUSSION

CS, a granulomatous disease, can present as palpitations, chest pain, and syncope. Palpitations can present as atrial fibrillation or supraventricular tachycardia, while syncope may be caused by complete AV block or VT, leading to sudden cardiac death.[22] A diagnosis of CS can be established by two widely accepted guidelines: the Heart Rhythm Society (HRS) and the Japanese Ministry of Health & Welfare (JMWH) criteria (Table 1).[14,21,28] These guidelines have recently been updated through a collaborative effort involving the Japanese Society of Sarcoidosis and the World Association of Sarcoidosis

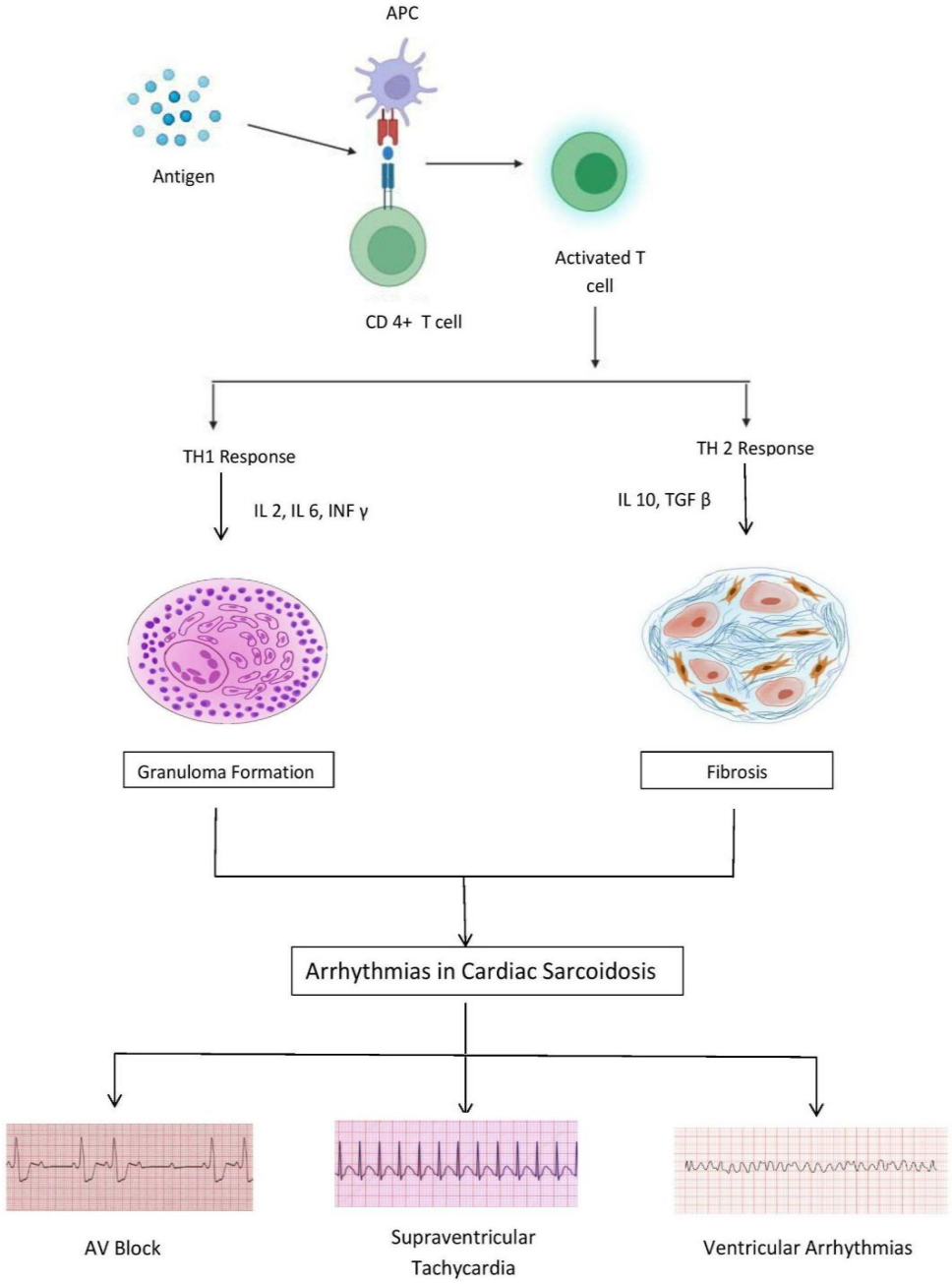

Figure 1. Diagram depicting the mechanism of granuloma formation and arrhythmias in cardiac sarcoidosis.

and Other Granulomatous Disorders Sarcoidosis Organ (WASOG) to address the limitations of the HRS criteria for identifying isolated CS through cardiac tissue biopsy. In 2017, the JMWH guidelines were revised to allow CS diagnosis without relying solely on endomyocardial biopsy.[29] To enhance the diagnostic process, high-grade AV block is now considered a significant criterion, along with fatal ventricular arrhythmias (sustained VT, ventricular fibrillation). Since ventricular arrhythmias are the primary cause of sudden cardiac death in CS patients, early diagnosis and screening are crucial. The diagnosis of CS depends on the presence of extracardiac disease. When extracardiac disease is established, cardiac MRI (CMRI) is the preferred initial test. 18F-FDG PET combined with myocardial perfusion imaging is a validated diagnostic strategy for patients who cannot undergo CMRI. CMRI/PET hybrid imaging is also a reasonable option in institutions that offer this technique. Diagnosing isolated CS is challenging and needs a consensus. Possible CS evaluations should include chest computed tomography (CT) to check for extracardiac sarcoidosis and advanced cardiac imaging (CMRI or 18F-FDG PET). Suspected extracardiac lesions found on chest imaging can be targeted for biopsy. Unfortunately, cardiac imaging findings in

Table 1. Table describing three commonly used guidelines for CS (HRS, JMHW and WASOG) criteria

HRS Guidelines - Expert consensus recommendations on criteria for the diagnosis of CS[21]	Japanese Society of Sarcoidosis and Other Granulomatous Disorders, 2017-JMWH[14]	The WASOG criteria for the diagnosis of CS[40]
There are 2 pathways to a diagnosis of CS: 1. Histological diagnosis: involves the presence of non-caseating granuloma on histological examination of myocardial tissue with no other cause identified 2. Clinical diagnosis: based on invasive and non-invasive studies: Criteria for a probable diagnosis of CS: 1. There is a histological diagnosis of extra-cardiac sarcoidosis and 2. One or more of the following is present • Steroid ± immunosuppressant responsive cardiomyopathy or heart block • Unexpected reduced LVEF <40% • Unexplained sustained (spontaneous or induced) VT • Mobitz type II 2nd degree heart block or 3rd degree heart block • Patchy uptake on dedicated cardiac PET (pattern consistent with CS). • Late gadolinium enhancement on CMRI (pattern consistent with CS) • Positive gadolinium uptake (pattern consistent with CS) and 3. Other causes for the cardiac manifestation(s) have been excluded. *In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.	Histological diagnosis group-CS is diagnosed when EMB or surgical specimens demonstrate non-caseating epithelioid granulomas. Clinical diagnosis group- • Epithelioid granulomas are found in organs other than the heart and • ≥2 of the 5 major criteria below are satisfied • 1 of the major criteria and ≥2 of the 3 minor criteria below are satisfied or • Patient demonstrates clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis, and ≥2 of the 5 major lab criteria below are satisfied: a. Bilateral hilar lymphadenopathy b. Elevated serum ACE activity or elevated lysozyme level c. High serum soluble interleukin-2 receptor levels d. Significant accumulation of 67Ga citrate or 18F-FDG-PET e. High % lymphocytes with CD4/CD8 ration >3.5 in BAL fluid f. ≥2 of the 5 major criteria below are satisfied g. 1 of major criteria and ≥2 of minor criteria are satisfied Major criteria: • High-grade AV block or fatal ventricular arrhythmia • Basal thinning of the ventricular septum or abnormal ventricular wall anatomy • Abnormally high uptake with 67Ga citrate or 18F-FDG-PET • Decreased LVEF (<50%) • Delayed enhancement on gadolinium-enhanced MRI Minor criteria: • ECG: showing ventricular arrhythmias, Bundle branch block, axis deviation, or abnormal Q waves • Perfusion defects by myocardial perfusion scintigraphy • EMB: monocyte infiltration and moderate or severe myocardial interstitial fibrosis.	Highly probable • Biopsy with granulomatous inflammation of no alternate cause At least probable • Treatment-responsive cardiomyopathy or AV block • Reduced LVEF without other clinical risk factors • Spontaneous or induced sustained VT with no other risk factors • Mobitz type II or third-degree AV block • Patchy uptake on dedicated cardiac PET • Delayed enhancement on CMRI • Positive gallium uptake • Defect on perfusion scintigraphy or SPECT scan • T2 prolongation on CMRI Possible • Reduced LVEF in the presence of other clinical risk factors (e.g., hypertension and diabetes mellitus) • Atrial dysrhythmias No consensus • Frequent ectopy (>5% QRS) • Bundle branch block • Impaired right ventricular function with a normal PVR • Fragmented QRS or pathologic Q waves in two or more anatomically contiguous leads • At least one abnormal signal-averaged ECG domain • Interstitial fibrosis or monocyte inflammation

CS: cardiac sarcoidosis, HRS: Heart Rhythm Society, JMWH: Japanese Ministry of Health & Welfare, WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ, LVEF: left ventricular ejection fraction, VT: ventricular tachycardia, PET: positron emission tomography, CMRI: cardiac magnetic resonance imaging, EMB: endomyocardial biopsy, ACE: angiotensin-converting enzyme, 18F-FDG-PET: 18-FDG-PET-fluorine-18 fluorodeoxyglucose positron emission tomography, BAL: bronchoalveolar lavage, MRI: magnetic resonance imaging, ECG: electrocardiogram, AV: atrioventricular, SPECT: single-photon emission computerized tomography, PVR: pulmonary vascular resistance.

patients without established extracardiac sarcoidosis can be non-specific. In such cases, electroanatomic mapping or imaging-guided endomyocardial biopsy should be considered.[30] A meta-analysis of eight studies involving 164 patients found that PET CT had a pooled sensitivity of 89% and a pooled specificity of 78% in diagnosing CS.[31] Electrocardiography (ECG) and ambulatory monitoring are crucial for diagnosing CS and reassessment. However, due to its limited sensitivity, the ECG alone can't screen patients with extra CS. A comprehensive screening strategy involving ECG, ambulatory monitoring, and transthoracic echocardiography (TTE) was employed by Mehta et al.[32] to identify CS in patients with extrapulmonary sarcoidosis.[33] Researchers have identified basal interventricular septal thinning on echocardiography as a defining feature of CS patients. Not only this, but according to one study, interventricular septal thinning is linked to poor long-term clinical outcomes.[34]

Although the most prevalent arrhythmia in CS is VT, there has been a growing trend of increased atrial arrhythmia in recent years. A clinical investigation involving 192 patients conducted by Cain et al.35 demonstrated that a finding of late gadolinium enhancement (LGE) on CMRI significantly increases the risk of developing atrial arrhythmias (36%) compared to ventricular arrhythmias. A comprehensive analysis of seven observational studies comprising 694 participants conducted by Hulten et al.[36] revealed that positive LGE on CMRI among patients with CS significantly elevates the risk of mortality and ventricular arrhythmia. FDG-PET, in addition to aiding in diagnosis and prognosis, is particularly useful for visualizing regions of myocardial inflammation and assessing the effectiveness of immunosuppressive therapy.[37] This enables timely diagnosis during reversible phases of CS, facilitating early management and potentially reducing morbidity and mortality.[21] While long-term continuous heart rhythm monitoring using implanted loop recorders can potentially identify dangerous arrhythmia early on. Its ability to predict long-term patient outcomes is still under investigation.[33]

Currently, there are no definitive guidelines for treating arrhythmias in CS.[37] Ventricular arrhythmias are often treated with a multifaceted approach that may include immunosuppressive medication, arrhythmias, implanted devices, and, in some cases, catheter ablation.[38] Although the impact of corticosteroids on ventricular arrhythmias is unknown, immunosuppression in conjunction with anti-arrhythmic drugs can benefit patients with frequent symptomatic VT.[14] Since inflammation is one of the predisposing factors for arrhythmogenicity in the early stages of CS, treating active inflammation and preventing permanent cardiac fibrosis and remodeling is crucial. For this reason, immunosuppressants are used initially, followed by steroid-sparing medicines such as mycophenolate, azathioprine, and methotrexate.[34] TNF alpha inhibitors like adalimumab[39] and infliximab[40] were reported to be efficacious when steroid-sparing medications and steroids failed to be effective.[38] The HRS recommends managing patients with VT/ventricular fibrillation storms using antiarrhythmic medications like amiodarone.[21] Ventricular ablation should be considered for patients with refractory VTs, even though active inflammation is treated with immunosuppressants.[25] A recent study by Tan et al.[41] found that cardiac ablation was more effective than medical therapy alone in improving outcomes for patients with sarcoidosis-associated VT. Specifically, the ablation group had a mortality rate of 1.9% compared to 6.6% in the medical therapy group.[41] ICD is suggested in class I indications for individuals with a history of persistent VT, those who have survived sudden cardiac arrest, and those with a left ventricular ejection fraction up to 35%, while Class IIa indications include syncope, myocardial scar detected by CMRI or PET, and positive electrophysiological study and a requirement for permanent pacing therapy.40 For individuals with CS who are unresponsive to antiarrhythmic drugs and catheter ablation, cardiac sympathetic denervation may be a viable therapeutic adjuvant[42] in case of refractory VT and excessive ICD therapy.[43]

CONCLUSIONS

CS is an inflammatory condition that affects the heart, causing life-threatening arrhythmias and disrupting normal electrical pathways. The severity of CS symptoms can vary widely from a completely symptom-free state to sudden cardiac death. Arrhythmias are often a precursor of adverse outcomes in CS patients. Complication arises from differing consensus on diagnosing CS. CMRI and PET scans are emerging as vital investigative

modalities. Recent research indicates that CMRI has a sensitivity of 93.4% and a specificity of 87.5%, while PET CT has a sensitivity of 89% and a specificity of 78%. In addition to facilitating risk stratification, identifying arrhythmias will assist in making informed decisions regarding monitoring intensity, the need for ICDs, and the selection of appropriate medical treatment. Managing arrhythmia effectively in CS patients may improve their quality of life by reducing symptoms, hospitalizations, and the need for invasive procedures. A comprehensive understanding of the underlying mechanisms and clinical manifestations of arrhythmias associated with CS is crucial for developing effective strategies to mitigate the arrhythmogenic events related to this condition.

Conflict of Interest

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Authors' Contribution

Study Conception: HB, SGK, RJ, SS, SGU; Study Design: HB, SGK, RJ, SS, SGU; Literature Review: HB, SGK, RJ, SS, SGU; Critical Review: SGK, RJ, JV; Manuscript preparing: HB, SGK, RJ, SS, SGU.

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