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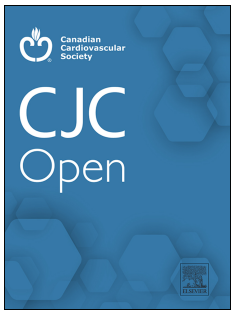

Incidence of Atrial Fibrillation as the Initial Manifestation of Cardiac Sarcoidosis: Insights from a Catheter Ablation Registry

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Incidence of Atrial Fibrillation as the Initial Manifestation of Cardiac Sarcoidosis: Insights from a Catheter Ablation Registry

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Keywords: cardiac sarcoidosis, atrial fibrillation, adenopathy

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Abstract

Background: Cardiac sarcoidosis (CS) is a rare form of arrhythmogenic cardiomyopathy; a delayed diagnosis can lead to significant consequences. Patients with clinically manifest CS often have minimal extra-cardiac involvement and thus frequently initially present to cardiology. Indeed, certain specific arrhythmic scenarios should trigger investigations for undiagnosed CS. Atrial fibrillation (AF) has been described as one of the presenting features of CS; however, the incidence of this presentation is not known.

Methods: At our institution, cardiac computerized tomography is routinely performed prior to catheter ablation for AF. Non-cardiac incidental findings are described by radiologists and followed-up by interval investigations. We systematically reviewed non-cardiac reports from 1574 consecutive patients in our prospective AF ablation registry. Specifically, we used text scraping techniques to search on the following keywords: “adenopathy” and “sarcoidosis”. Detailed chart review of identified cases was then performed to evaluate results of interval investigations and assess long-term outcomes.

Results: Twenty/1574 patients (1.3%) had non-cardiac reports containing “adenopathy” and/or “sarcoidosis”. After interval imaging and a follow-up averaging 60±35 months, only two patients/1574 (0.13%) were diagnosed with CS. Four/20 (20%) had a previous history of extra-cardiac sarcoidosis and another 1/20 (5%) was subsequently diagnosed with extra-cardiac sarcoidosis. However, none of these five patients had evidence of cardiac involvement.

Conclusion: CS is a rare finding among patients undergoing a first-time AF ablation. Our findings would suggest that AF is an uncommon initial presentation of CS. Thus, investigations for CS in patients with AF are not routinely warranted, unless there are additional suggestive clinical features.

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Introduction

Sarcoidosis is a chronic inflammatory condition of unclear origin, characterized by organ infiltration with non-necrotizing granulomas. The lungs and lymph nodes are predilection sites, being involved in about 90% of cases[1-5]. In a small proportion of patients, the inflammatory process may affect the heart leading to the development of clinically manifest cardiac sarcoidosis (CS). This rare form of cardiomyopathy usually manifests in middle-aged individuals; typical presentations include atrioventricular conduction disturbances, ventricular arrhythmias (VAs), and impaired ventricular function[2, 6, 7]. An early diagnosis is paramount to reduce the risk for adverse events.

There is increasing recognition that patients with clinically manifest CS often have minimal extra-cardiac involvement and thus frequently present to cardiology[6]. Guidelines suggest that certain specific clinical scenarios should trigger investigations for undiagnosed sarcoidosis[1, 4, 8, 9]. For example, unexplained high-degree atrioventricular block (AVB) in individuals <60 years, or idiopathic VA, may be caused by underlying CS in up to 47% and 29% of cases, respectively[6, 7]. Atrial tachyarrhythmias, including atrial fibrillation (AF) have been reported to affect 29-33% of CS patients, and can occur at any time during the course of the disease. They have also been described as the initial manifestation of CS[10-16]. Previous research has focused predominantly on the most threatening presentations, little is known about the incidence of AF as the initial manifestation of CS and whether further work-up should be warranted to rule out this condition.

In this study, we sought to investigate the incidence of undiagnosed CS in a population of patients investigated with advanced cardiac imaging (computerized tomography (CT) or cardiac magnetic resonance (CMR)) in preparation for catheter ablation for symptomatic AF. A secondary aim was to describe the ablation findings in the patients with sarcoidosis.

Material and methods

Patients

We evaluated a population of consecutive patients, from our prospective AF catheter ablation registry, accepted for their first ablation. Patients scheduled for AF ablation routinely

undergo a pre-operative cardiac CT scan one to six months prior to the procedure, to assess pulmonary vein anatomy and exclude thrombus in the left atrial appendage. Occasionally, at physician discretion and/or patient preference, pre-ablation imaging is performed using CMR. Non-cardiac structures included in the scanned field (usually from the carina to the lung bases) are evaluated separately by thorax thorax radiologists. Incidental, non-cardiac findings are disclosed to clinicians in dedicated supplemental reports and followed-up by interval investigations, if needed.

A comprehensive prospective database containing all AF ablations performed at our institution, was interrogated to generate a list of consecutive patients between 1st January 2003 (opening of our AF ablation program) and 31st May 2021 (in order to allow for appropriate follow-up).

Chest Imaging and Cohort Creation

A system analyst retrieved supplemental reports from all cardiac CT scans within the period of interest and plotted them in a dedicated database (Excel for Windows, Microsoft Corporation, 2018). Using the text scraping function, we identified reports containing the keywords “adenopathy” and/or “sarcoid”. Each matching report was individually reviewed to assess the presence of significant lymphadenopathy (defined as lymph nodes with a diameter exceeding 1 cm) or findings compatible with sarcoidosis. Reports that fulfilled these criteria were noted with their corresponding case-sensitive identification numbers (MRN codes). The list that was generated was subsequently cross-matched with the one obtained from the AF ablation database, using case-sensitive MRN codes. In this way we could identify those patients scheduled for AF ablation with incidental findings suggestive of sarcoidosis, our final study population. Those patients without a pre-operative cardiac CT but with a CMR were reviewed on an individual basis and included in the analysis.

Lastly, we reviewed in detail medical charts for each patient, looking particularly for further work-up to address incidental pre-operative findings. All available sources of records were consulted, including referral letters, imaging reports and consult notes from other institutions. When appropriate, we reviewed procedural reports and electroanatomic maps

sampled during the ablation procedures. CS diagnosis was defined according to the 2014 Heart Rhythm Society and/or the 2016 Japanese Circulation Society diagnostic criteria[1, 4].

Data management and ethics

Data were managed according to the requirements dictated by our local data protection authority. The study was approved by our institutional board and performed in accordance with the principles stated in the Declaration of Helsinki.

Statistical analysis

Continuous variables are presented using mean and standard deviation, while categorical variables are presented with count and percentage. Statistical analysis was performed using IBM SPSS ver. 28.

Results

Study population

A total of 1,583 patients underwent first-time AF ablation in the investigated time interval. Of these, 1,568 underwent a pre-operative cardiac CT, 6 patients received alternatively CMR and 9 did not undergo any form of cardiac imaging. Our study cohort consisted therefore of 1,574 AF ablation patients, whose baseline data is shown in Table 1.

Supplemental reports including incidental, non-cardiac findings from a total of 22,920 cardiac CT scans were reviewed. Keyword search returned 175 individual patients. The keywords “sarcoid” and “adenopathy” retrieved 109 and 98 hits, respectively, whereas both keywords were included in 32 reports. Cross-matching the list generated by keyword search and our AF ablation cohort resulted in a final population of 20 patients with one or both keywords (Figure 1).

Of note, 4/20 (20%) patients had a previous history of extra-cardiac sarcoidosis: the diagnosis was histologically verified in three, while one had a remote (>40 years old) diagnosis without additional details. None of these 4 patients ever received immunosuppressive treatment, nor ever met criteria for a diagnosis of CS. Demographic data of patients with radiological findings compatible with sarcoidosis are presented in Table 2.

Work-up for incidental findings

Interval chest imaging was performed in 19/20 patients after a mean 11±18 months, with one or a combination of the following modalities: chest CT (14 patients) or conventional chest X-ray (13 patients). Interval imaging showed improvement in 7/19 patients, while findings in the remaining 12 patients either progressed (3) or remained unchanged (9). Supplemental advanced cardiac imaging was performed in 7 patients, either with CMR alone (6) or in combination with fluorodeoxyglucose positron emission tomography (FDG-PET, 3 3). One patient underwent exclusively FDG-PET scan due to non-CMR conditional pacemaker. Work-up for the incidental CT findings led to the diagnoses shown in Table 3.

Notably, only 2/20 (10%) patients were diagnosed with CS. After a follow-up consisting of 60±35 months, none of the remaining 18 patients developed other manifestations that might suggest CS, (i.e. no patient developed high grade AVB, VAs or experienced worsening of their ventricular function). Hence the incidence of undiagnosed CS in this cohort was 2/1,574 (0.13%).

History of the patients diagnosed with CS

- A 55-year-old gentleman underwent a previous catheter ablation for symptomatic typical atrial flutter. He also had a history of non-ischemic cardiomyopathy with the lowest recorded left ventricular ejection fraction (LVEF) of 29%. He was later considered for catheter ablation of persistent AF. At that time, ECG showed sinus bradycardia 51 beats/min, left axis deviation, left bundle branch block (QRS duration of 158 ms) and 1st degree AV block (PR duration of 222 ms). Preoperative cardiac CT revealed mild bilateral hilar and subcarinal lymphadenopathy, suggesting sarcoidosis as a possible cause. Supplementary CMR revealed severe biventricular hypokinesia, LVEF 26% and right ventricular ejection fraction 20%. Subendocardial and mesocardial LGE involving the basal, mid anteroseptal and septal walls of the left ventricle was highly suggestive of sarcoid infiltration (Fig. 2). A baseline FDG-PET study did not show any active FDG uptake. However, a repeat study two years later showed intense focal uptake in the anterolateral wall suggesting active inflammation (Fig. 3a). Rest perfusion scan showed mild reduction in

tracer uptake across multiple segments of the left ventricle (Fig 3b). After AF ablation he was administered guideline-directed heart failure medical therapy and was implanted with a CRT-D. His symptoms and LVEF improved significantly, and systemic immunosuppression was felt not to be indicated. However, eight years after baseline he developed a significant worsening of his LVEF: a repeat FDG-PET scan showed focal uptake in basal to mid anteroseptal segments, suggestive of active inflammation. Immunosuppression with a combination of prednisone and methotrexate was started. Despite ablation and antiarrhythmic drugs, his AF was poorly controlled, and he recently underwent AV-node ablation. His last recorded LVEF is 45%. His defibrillator has never delivered any therapy.

- A 54-year-old gentleman with previous history of obesity and obstructive sleep apnea, developed recurrent, symptomatic AF requiring multiple cardioversions. Baseline echocardiography revealed mildly reduced LVEF of 40%. Baseline ECG showed sinus rhythm with left axis deviation and borderline 1st degree AV block (PR duration of 200 ms). Cardiac CT prior to catheter ablation, showed multiple enlarged mediastinal lymph nodes: these findings remained unchanged at an interval study, 9 months later. Despite being in sinus rhythm, LVEF did not improve. After three years, he experienced recurrence of AF, and a repeat ablation procedure was performed. Supplementary CMR revealed mild left ventricular dysfunction, and patchy, non-ischemic LGE involving the septum, inferior and inferolateral segments. A recent FDG-PET scan showed focal tracer uptake, suggestive of active, albeit mild myocardial inflammation. Although his symptoms have improved, he is currently considered for a trial of immunosuppression.

Findings from the ablation procedures

We reviewed procedural reports as well as electroanatomic maps for those patients with a previous sarcoidosis diagnosis (4) and for those that received a sarcoidosis diagnosis following additional interval imaging (4). Four/8 of these patients were ablated before the era of multipolar voltage mapping. Amongst the four with detailed left atrial voltage mapping (CARTO™ Confidense™, Biosense Webster, USA), only one patient (ultimately receiving a CS diagnosis) had significant areas of low voltage in the posterior wall of the left atrium (Fig. 4).

Discussion

In this study we could show that undiagnosed CS is an exceedingly rare (only 2 in 1,574 patients) finding among patients undergoing first-time catheter ablation for AF. These results suggest that AF is an uncommon initial manifestation of CS.

Incidence of AAs as initial presentation of CS

A previous study from our group found that only 1/33 (3%) clinically manifest CS patients presented with AA[12]. Other evidence describing AF as initial manifestation of CS is limited to case reports[14-16]. Hussain and colleagues described the case of a young male with several catheter ablation procedures for symptomatic AF and normal ventricular function[14]. Three years after his initial ablation, chest pain work-up with cardiac CT revealed incidental findings suggestive of sarcoidosis. Transbronchial biopsy confirmed the diagnosis and additional FDG-PET scan could show hypermetabolic lesions in both atria, suggestive of active inflammation[14]. Golwala described a 45-year-old, previously healthy male, with multiple visits to the emergency department due to paroxysmal atrial tachycardia/AF. Further work-up, including a chest CT showing marked lymphadenopathy, led to diagnosis of CS[15]. Finally, Lau et al presented a 55-year-old Caucasian male that was referred to catheter ablation for symptomatic persistent AF. Enlarged lymph nodes were detected on the pre-operative cardiac CT scan, and advanced cardiac imaging with CMR and FDG-PET confirmed CS[16].

In this study we sought to investigate this issue from the other direction: instead of studying a CS population, we reviewed a large cohort of patients with sufficiently symptomatic AF to warrant ablation. Pulmonary findings and/or thoracic lymphadenopathy are found in the majority (>90%) of patients with sarcoidosis, making chest CT a reasonable screening modality (sensitivity of 94%, specificity of 86%) for sarcoidosis[2, 3, 5]. Indeed chest CT is recommended as initial screening to look for possible underlying sarcoidosis in a number of clinical scenarios including patients <60 years with unexplained AV block, patients with idiopathic VT and patients with new-onset uveitis of unknown origin[1, 3, 8, 9]. The diagnostic yield in these subgroups is substantial, potentially unveiling undiagnosed CS in 11-35% of patients[2, 9].

After reviewing radiological findings in 1,574 patients, we found only two patients with undiagnosed CS. Very importantly, both these patients had concomitant evidence of conduction system disease and impaired ventricular function. Hence, given the enormous burden of AF and the results of the present study, we argue that, in absence of other cardiac manifestations, AF alone does not justify further work-up aimed at excluding CS.

Incidence of AF in patients with sarcoidosis and CS

Patients with sarcoidosis are at increased risk for AF[17-19]. A recent investigation among over 20 million Californian residents showed that patients with sarcoidosis had a 10-fold higher risk of developing incidental AF when compared to a healthy population [18]. Presence of pulmonary hypertension secondary to lung involvement, chronic activated inflammatory response, treatment with high-dose corticosteroids may all contribute to the development of AF in this population[10, 20]. Additionally, AF may be caused by cardiac involvement of sarcoidosis, either through increased filling pressures in presence of impaired ventricular function or by direct sarcoid infiltration in the atrial myocardium[11, 12, 21, 22]. In the former scenario, one may except AF to present later in the course of the disease, while in the latter it may manifest early, potentially even as the initial manifestation of CS.

Vilés-Gonzales and colleagues investigated the presence of supraventricular arrhythmias including AF, in a CS population. The authors found a prevalence of 18%: left atrial enlargement was found to be the only independent predictor, suggesting that AF may be a consequence of heart failure in these patients[23]. Other reports, including a prospective study that used arrhythmia monitoring from implanted cardiac devices, showed that atrial arrhythmias occur in roughly a third of CS patients[12, 21, 22, 24]. These studies confirmed the role of left atrial enlargement as a predictor for the development of atrial arrhythmias but indicated the presence of atrial FDG uptake, a marker of atrial inflammation, as an additional prognostic parameter[12, 21, 22, 24]. These findings indicate that atrial inflammation may be an important contributor to the development of AF. Furthermore, the work of Niemelä and colleagues showed that, in patients with atrial FDG uptake, AF occurs earlier and more often than in those without signs of atrial inflammation[22].

Findings at ablation

In the ventricles, low electrogram voltage is commonly found in those areas with either active granulomatous inflammation or fibrosis[2]. Low voltage has also been associated with fibrosis in the atria. In this study, we found low voltage atrial electrograms in one patient with CS. It is possible that myocardial inflammation had affected the left atrium, at some point in his clinical course. Nevertheless, the association between AF, low electrogram voltage and atrial inflammation remains unclear and deserves future research.

Limitations

The intrinsic limitations of this single center investigation should be acknowledged.
Sarcoidosis was not the primary focus of the CT scans analyzed in this study, thus raising the possibility of pathological findings being overlooked. This circumstance, however, is unlikely, as non-cardiac structures were systematically evaluated by external thorax radiologists.
Mean age of patients (60±10 years) was relatively higher than in a typical CS population (51±9 years[7]); however, half of our cohort was <60 years.
Six patients were further investigated only by interval chest X-ray, known to have lower sensitivity than chest CT in diagnosing sarcoidosis. Nevertheless, the long duration of our follow-up, averaging 60 months, without development of any typical manifestations, suggests that no CS patients were missed.

Conclusion

Undiagnosed CS is an exceedingly rare (only 2 in 1,574 patients) finding among patients undergoing first-time catheter ablation for AF. Thus, screening investigations are not routinely warranted unless there are additional suggestive clinical features.

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Table 1 – Baseline characteristics of patients in the AF ablation database with chest imaging

	n=1,574
Female sex	459 (29%)
Age at the index procedure (years)	60±10
- <50	256 (16%)
- <60	782 (50%)
- <70	1,459 (93%)
Persistent AF	467 (30%)
Coronary artery disease	204 (13%)
Diabetes mellitus	158 (10%)
Hypertension	626 (40%)
Significant lung disease	84 (5%)
Obstructive sleep apnea	329 (21%)
Previous cardiac surgery	74 (5%)
Cardiomyopathy	178 (11%)
• Tachycardia-mediated cardiomyopathy	132
• Idiopathic dilated cardiomyopathy	18
• Hypertrophic cardiomyopathy	11
• Ischemic cardiomyopathy	17
Implanted cardiac device	42 (3%)
• Pacemaker	31
• Defibrillator	11

AF: atrial fibrillation

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Table 2 – Demographic characteristics of patients with incidental findings possibly suggestive of sarcoidosis

	Previous history of extracardiac sarcoidosis	**No previous history of extracardiac sarcoidosis**
	n=4	n=16
Female sex (%)	1 (25%)	3 (19%)
Age at baseline (years)	65±1	64±10
Body mass index (kg/m^2)	27±5	30±6
Persistent AF (%)	1 (25%)	6 (38%)
Hypertension (%)	1 (25%)	8 (50%)
Obstructive sleep apnea (%)	2 (50%)	5 (31%)
Coronary artery disease (%)	1 (25%)	4 (25%)
History of cardiomyopathy	0	3 (19%)
History of sustained ventricular arrhythmias	0	0
History of sustained high-degree AV block	0	0
History of any AV conduction disturbances	1 (25%)	5 (31%)
- First-degree AV block	1 (25%)	5 (31%)
- Hemiblock (R axis <-30° or >+90°)	1 (25%)	4 (25%)
- Bundle branch block (QRS>120 ms)	0	1 (6%)

AF: atrial fibrillation, AV: atrioventricular

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Table 3 – List of interval investigations performed to follow-up incidental findings, and final diagnoses emerging from follow-up

Patient	Interval CT scan	Interval CXR	Change incidental findings	CMR scan	FDG-PET scan	Follow-up (months)	Final diagnosis
1	**Yes**	**Yes**	**Resolution**	**Yes**	**Yes**	**111**	**CS**
2	No	Yes	Unchanged	Yes	Yes	17	Extra-cardiac sarcoidosis
3*	Yes	No	Resolution	Yes	No	60	Reactive adenopathy
4	Yes	No	Resolution	Yes	No	96	Reactive adenopathy
5*	Yes	Yes	Unchanged	Yes	No	110	Extra-cardiac sarcoidosis
6	Yes	Yes	Unchanged	No	No	99	Interstitial lung disease
7*	No	No	-	No	No	100	Reactive adenopathy
8†	No	Yes	Unchanged	No	No	73	Reactive adenopathy
9	No	Yes	Unchanged	No	No	102	Hematological malignancy
10‡	Yes	Yes	Unchanged	No	No	89	Interstitial lung disease
11‡	Yes	Yes	Progression	No	No	50	Primary lung cancer
12	Yes	No	Resolution	No	No	66	Reactive adenopathy
13‡	Yes	Yes	Unchanged	No	No	17	Hematological malignancy
14	**Yes**	**No**	**Unchanged**	**Yes**	**Yes**	**51**	**CS**
15	Yes	No	Resolution	No	No	39	Reactive adenopathy
16	Yes	No	Progression	No	No	25	Interstitial lung disease
17	No	Yes	Resolution	No	No	20	Reactive adenopathy
18*	No	Yes	Unchanged	No	Yes	25	Extra-cardiac sarcoidosis
19	Yes	Yes	Resolution	No	No	17	Reactive adenopathy
20	Yes	Yes	Progression	No	No	25	Hematological malignancy

CMR: cardiac magnetic resonance, CS: cardiac sarcoidosis, CT: computed tomography, CXR: chest X-ray, FDG-PET: fluorodeoxyglucose positron emission tomography

* Patient with previous diagnosis of extra-cardiac sarcoidosis

† Lost to follow-up

‡ Deceased

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Figure legend

Figure 1 – Flowchart showing patients' inclusion process. AF: atrial fibrillation, CCT: chest computed tomography, CMR: chest magnetic resonance.

Figure 2 – Cardiac magnetic resonance imaging showing short axis view with mid myocardial late gadolinium enhancement with the mid anteroseptal segment (white arrows).

Figure 3 – F-18 fluorodeoxyglucose positron emission tomography with coronal (A) and axial (B) computerized tomography of the thorax (^{18}FDG-PET/CT) showing multiple areas of FDG uptake in the anteroseptal, anterior, and anterolateral segments (white arrows). (C) Rubidium-82 perfusion (upper row) and FDG (lower row) short axis, horizontal axis, and vertical long axis showing perfusions defects (white arrows) and myocardial FDG uptake (yellow arrows).

Figure 4 – Electroanatomic map of a 55 years-old patient, with a previous history of obesity, obstructive sleep apnea and hypertension. Incidental pre-procedural findings led to a diagnosis of thoracic sarcoidosis. Supplemental cardiac magnetic resonance and positron-emission tomography were consistent with cardiac sarcoidosis. Electroanatomic map sampled following pulmonary vein isolation, revealed a large low voltage area in the posterior wall of the left atrium (marked with asterisk). Grey dots represent ablation lesions. LIPV: Left inferior pulmonary vein, RIPV: Right inferior pulmonary vein, RSPV: Right superior pulmonary vein.

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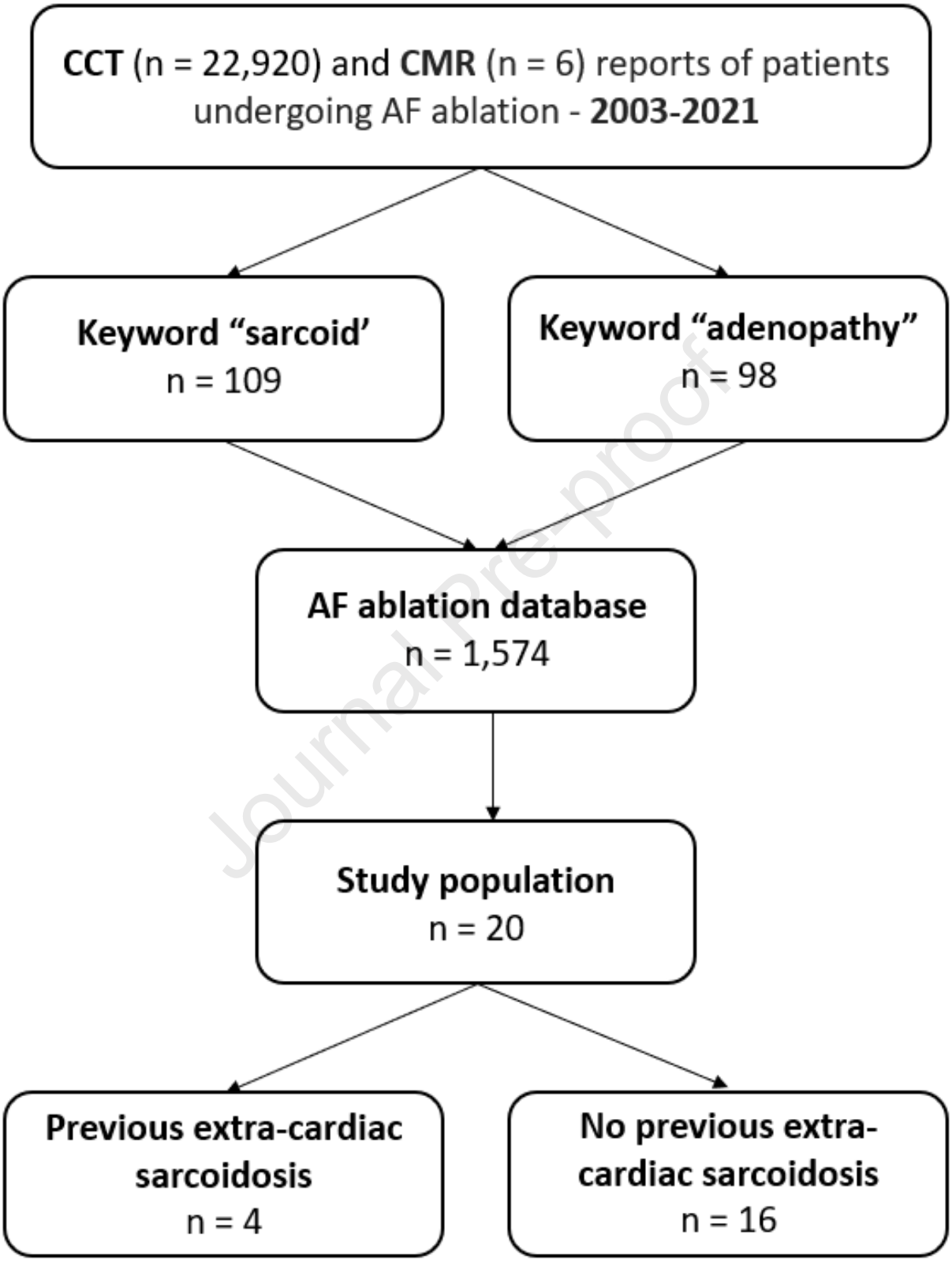

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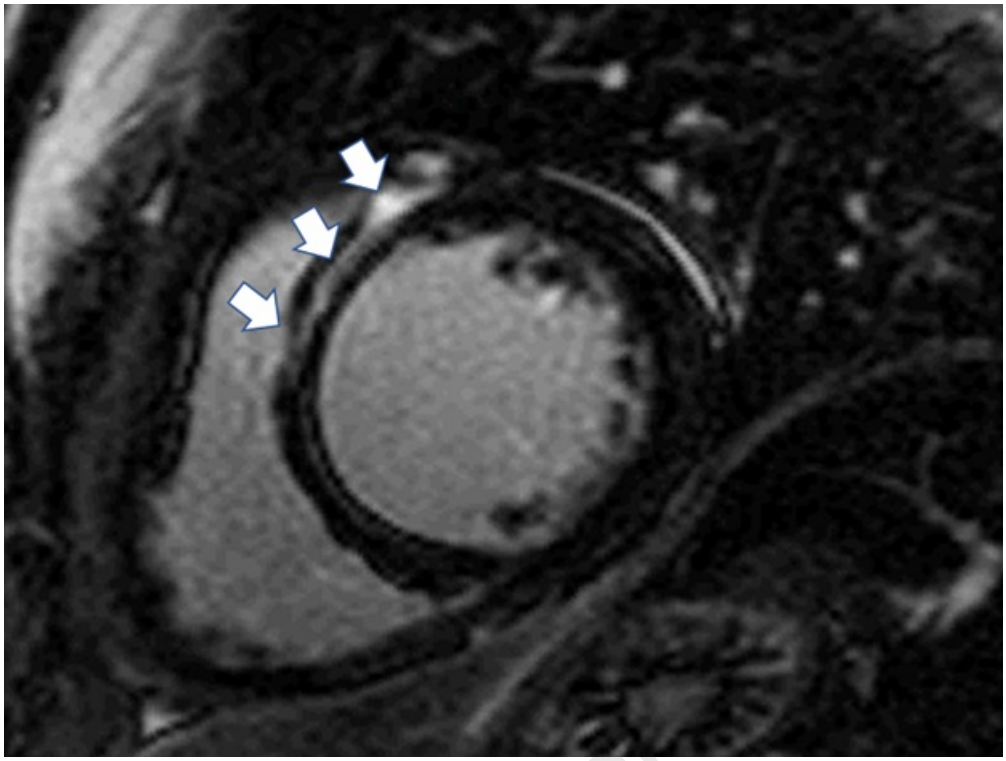

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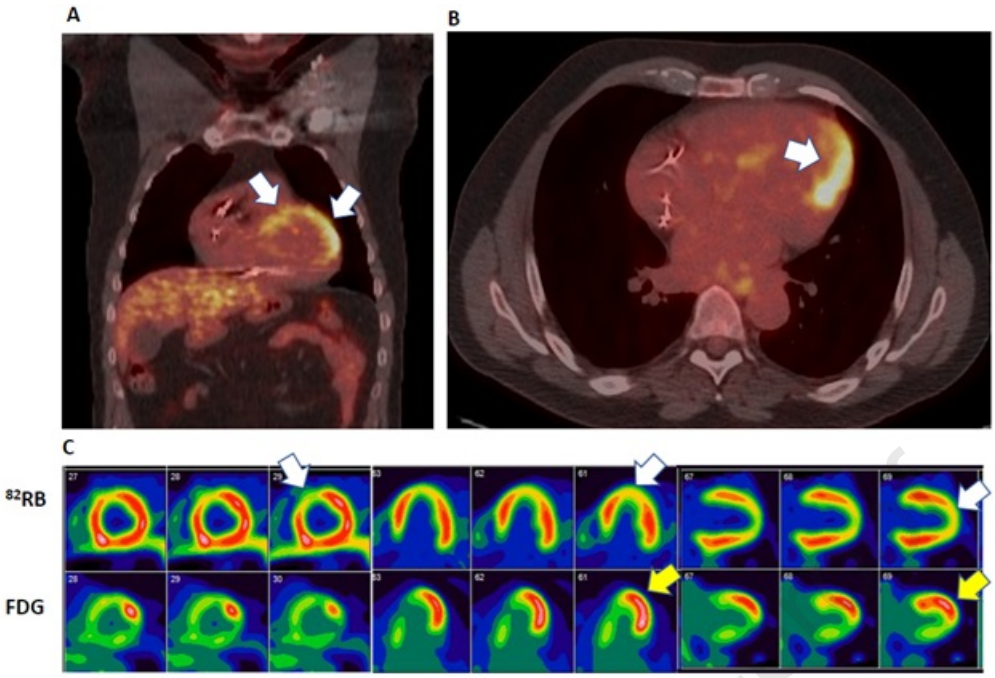

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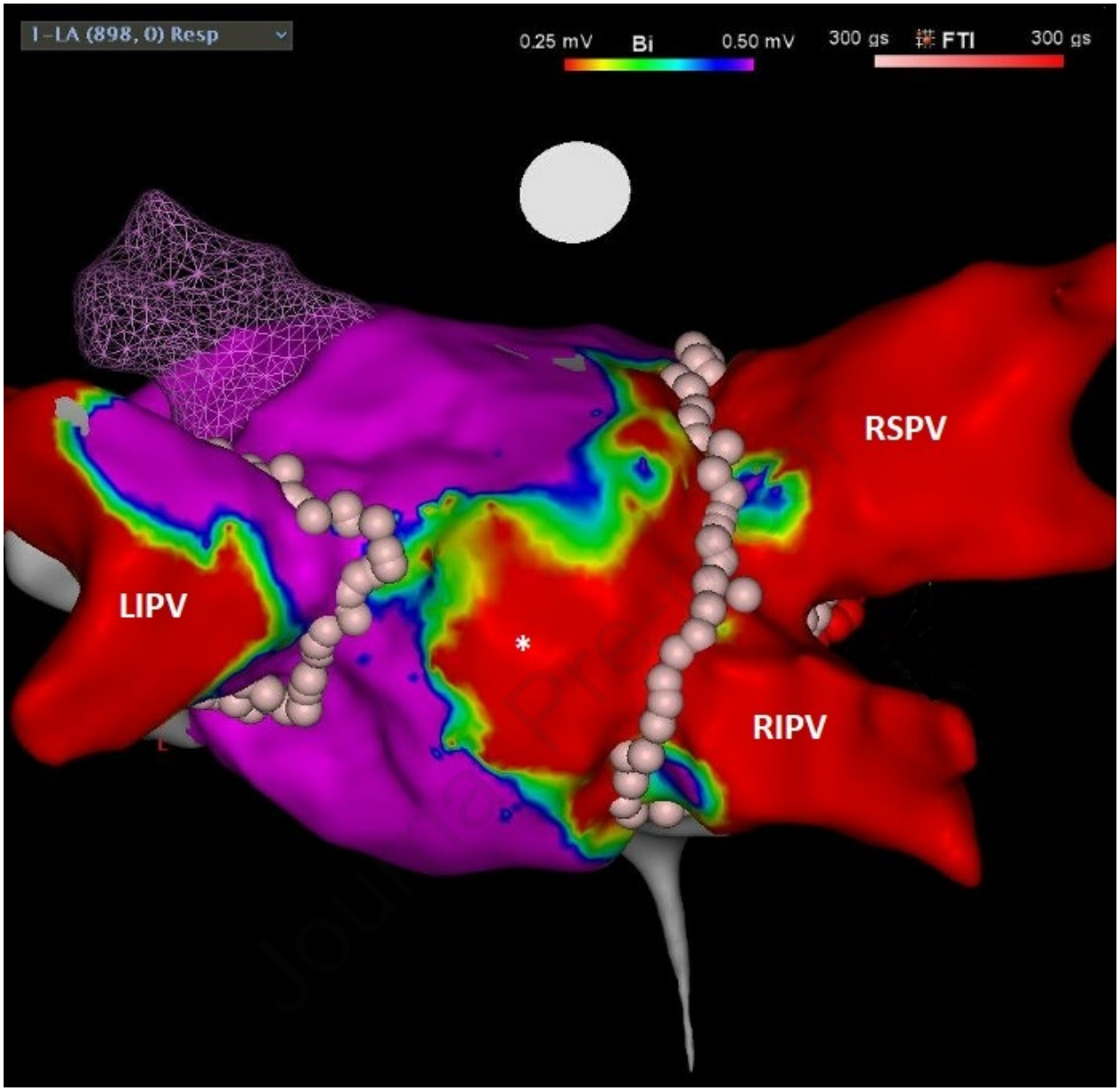
I-LA (898, 0) Resp
0.25 mV
Bi
0.50 mV
300 gs
FTI
300 gs
RSPV
LIPV
*
RIPV