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2022-09

Niemelä , M , Uusitalo , V , Pöyhönen , P , Schildt , J , Lehtonen , J & Kupari , M 2022 , ' Incidence and Predictors of Atrial Fibrillation in Cardiac Sarcoidosis A Multimodality Imaging Study ' , JACC : Cardiovascular Imaging , vol. 15 , no. 9 , pp. 1622-1631 . https://doi.org/10.1016/j.jcmg.2022.02.025

http://hdl.handle.net/10138/353773
https://doi.org/10.1016/j.jcmg.2022.02.025

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JACC: CARDIOVASCULAR IMAGING VOL. 15, NO. 9, 2022
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ORIGINAL RESEARCH

Incidence and Predictors of Atrial Fibrillation in Cardiac Sarcoidosis

A Multimodality Imaging Study

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ABSTRACT

BACKGROUND In cardiac sarcoidosis (CS), the risk and predictors of new-onset atrial fibrillation (AF) are poorly known.

OBJECTIVES The authors evaluated the incidence and characteristics of AF in newly diagnosed CS.

METHODS The authors studied 118 patients (78 women, mean age 50 years) with AF-naive CS having undergone cardiac ^{18}F-fluorodexoyglucose positron emission tomography (^{18}F-FDG PET) at the time of diagnosis. Details of patient characteristics and medical or device therapy were collected from hospital charts. The PET scans were re-analyzed for presence of atrial and ventricular inflammation, and coincident cardiac magnetic resonance (CMR) studies and single-photon emission computed tomography (SPECT) perfusions were analyzed for cardiac structure and function, including the presence and extent of myocardial scarring. Detection of AF was based on interrogation of intracardiac devices and on ambulatory or 12-lead electrocardiograms.

RESULTS Altogether 34 patients (29%) suffered paroxysms of AF during follow-up (median, 3 years) with persistent AF developing in 7 patients and permanent AF in 4. The estimated 5-year incidence of AF was 55% (95% CI: 34%-72%) in the 39 patients with atrial ^{18}F-FDG uptake at the time of diagnosis vs 18% (95% CI: 10%-28%) in the 79 patients without atrial uptake ($P < 0.001$). In cause-specific Cox regression analysis, atrial uptake was an independent predictor of AF ($P < 0.001$) with HR of 6.01 (95% CI: 2.64-13.66). Other independent predictors were an increased left atrial maximum volume ($P < 0.01$) and history of sleep apnea ($P < 0.01$). Ventricular involvement by PET, SPECT, or CMR was non-predictive. Symptoms of AF prompted electrical cardioversion in 12 patients (35%). Three of the 34 patients (9%) experiencing AF suffered a stroke versus none of those remaining free of AF.

CONCLUSIONS In newly diagnosed CS, future AF is relatively common and associated with atrial inflammation and enlargement on multimodality cardiac imaging. (J Am Coll Cardiol Img 2022;15:1622–1631) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Cardiac sarcoidosis (CS) is an autoinflammatory cardiomyopathy characterized by epithelioid cell granulomas injuring and scarring the heart muscle.[1] It is a dominantly arrhythmogenic disease with high-grade atrioventricular block, sustained ventricular tachyarrhythmias, and heart failure constituting its most common clinical manifestations.[1,2] Although atrial arrhythmias are also possible,[3] they have been overshadowed by more ominous disease presentations like the

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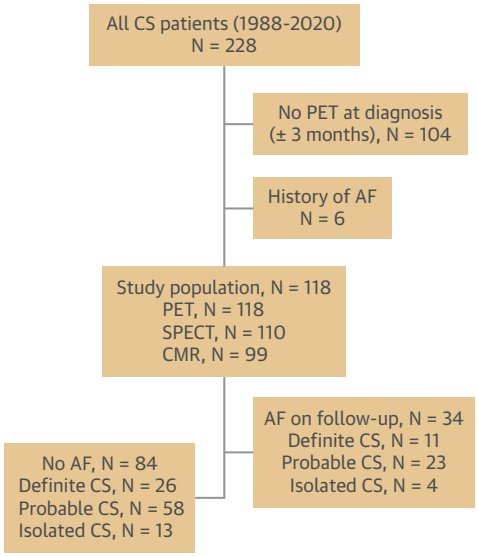
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 13, 2021; revised manuscript received February 7, 2022, accepted February 10, 2022.

ISSN 1936-878X https://doi.org/10.1016/j.jcmg.2022.02.025

FIGURE 1 Flowchart Describing Formation of the Study Population



Rationale for forming the cardiac sarcoidosis population for the study. AF = atrial fibrillation; CMR = cardiac magnetic resonance; CS = cardiac sarcoidosis; N = number of patients; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

preceding triad. Hitherto, only a few small investigations have focused on atrial tachyarrhythmias in CS;[4-8] hence, the epidemiology, risk factors, and characteristics of new-onset atrial fibrillation (AF) in CS remain poorly known. We designed the present work to assess the incidence of AF in CS and to gain insight into its mechanisms by identifying clinical and cardiac imaging factors predictive of AF. To that purpose, we analyzed the time-to-AF data in a cohort of newly diagnosed CS in relation to clinical data; atrial inflammation by cardiac ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET); and cardiac volumes, function, and scarring by cardiac magnetic resonance (CMR) and single-photon emission computed tomography (SPECT) perfusion. Our hypothesis was that the incidence of AF in newly diagnosed CS is related to direct atrial inflammation and that multimodality cardiac imaging including ^{18}F-FDG PET can help predict the risk of future AF.

METHODS

PATIENTS. The study population consisted of 118 consecutive patients with CS without earlier history of AF and with ^{18}F-FDG PET scan done inside 3 months of CS diagnosis (Figure 1). The patients were diagnosed and treated in the Heart and Lung Center of Helsinki University Hospital between 2006 and 2020. The cohort is also included in the ongoing nationwide registry of Myocardial Inflammatory Diseases in Finland (MIDFIN),[2] and survivors are on continuous follow-up. The diagnosis of CS was based on either positive endomyocardial biopsy or on extracardiac histology of sarcoidosis with clinical manifestations and noninvasive cardiac imaging indicating myocardial involvement according to the Heart Rhythm Society criteria.[9] Patient characteristics at the time of CS diagnosis, including demographics, presenting CS manifestations, and history of extracardiac sarcoidosis or other concomitant diseases were collected from hospital charts and from the MIDFIN database. Coincident data on circulating cardiac troponins, N-terminal pro-brain natriuretic peptide, glomerular filtration rate, and treatment with drugs and devices following CS diagnosis were noted.

DETECTION OF AF AND OTHER EVENTS. AF episodes were collected from medical records, their identification being based on interrogation of intracardiac devices, use of ambulatory electrocardiogram (ECG) recordings, or on standard 12-lead ECGs. To be defined as AF, the arrhythmic episode had to last >30 seconds in rhythm recordings or to cover the entire standard 12-lead ECG.[10] Episodes of atrial flutter were included in the AF data. AF was classified as paroxysmal, persistent, or permanent[10] and further characterized by the duration of its longest episode as lasting either <6 minutes, 6 minutes to 24 hours, or >24 hours.[5] Cerebrovascular events were identified and classified by their clinical manifestations and imaging results.[11] Cardiac transplantations and deaths were noted and dated, as were episodes of life-threatening ventricular arrhythmias (sustained ventricular tachycardia or defibrillated ventricular fibrillation). The study was performed according to the declaration of Helsinki and approved by the local ethical board.

PET STUDIES AND ANALYSES. Patients were advised to fast for at least 12 hours before PET/computed tomography (CT) imaging. After 2013, a high-fat low-carbohydrate diet with 24-hour fasting before PET was applied (n = 62). Thirty-eight patients received heparin intravenously before the study. Blood glucose level was measured and had to be <7.0 mmol/L for continuation to the study. After an intravenous injection of ^{18}F-FDG, patients rested for 60 minutes in a

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CMR = cardiac magnetic resonance

CS = cardiac sarcoidosis

CT = computed tomography

ECG = electrocardiogram

^{18}F-FDG = ^{18}F-fluorodeoxyglucose

LV = left ventricular

PET = positron emission tomography

SPECT = single-photon emission computed tomography

semi-darkened and quiet room. Standard clinical PET/CT cameras were used for imaging (Gemini PET-CT scanner, Philips Inc, USA; Biograph Duo, Siemens Medical Solutions; or Discovery MI, GE Healthcare).

PET images were retrospectively analyzed for abnormal left ventricular (LV) and atrial ^{18}F-FDG activity using Syngo.Via (Siemens Healthcare GmbH) and Hermes (Hermes Medical Solutions) software. The number of PET positive LV segments was summed according to the American Heart Association 17-segment model.[12] The presence and location of atrial ^{18}F-FDG uptake were analyzed visually. The maximal standardized uptake value was determined for both atriums and left atrial blood pool to allow calculation of the target-to-background ratio. For identification of abnormal atrial ^{18}F-FDG uptake and atrial inflammation, a target-to-background ratio ≥1.5 was required based on previous PET studies focused on the LV.[13,14] ^{18}F-FDG activity caused by lipomatous hypertrophy of interatrial septum or lymph nodes adjacent to the atrial walls was excluded by reviewing CT and CMR images. The possibility of attenuation artifacts caused by pacemaker leads was excluded by reviewing non-attenuation-corrected PET data.

To assess interobserver reproducibility of identifying abnormal atrial ^{18}F-FDG uptake, a sample of 30 scans were rated independently by 2 nuclear medicine physicians. The observers agreed in 26 of 30 cases. The disagreement was attributable to the low intensity of ^{18}F-FDG uptake in 2 cases, pacemaker artifact, and interpretation of isolated right atrial appendage. The kappa coefficient (Cohen's κ) was 0.73, indicating good agreement.

SPECT STUDIES AND ANALYSES. Resting SPECT scans of myocardial perfusion were done within 2 weeks after PET imaging using technetium-99m labeled tetrofosmin (Myoview) according to prevailing guidelines.[15] The scans were obtained with standard dual-headed gamma cameras with low-energy, high-resolution collimators (eCam and Symbia by Siemens Healthineers; Brightview by Philips, USA; or GE Discovery NM/CT 670, GE Healthcare). Images were analyzed in retrospect, and the summed rest score (SRS) of LV perfusion defects was calculated by the 17-segment model.[12,15] LV mis-match segments with both ^{18}F-FDG uptake and perfusion defect were visually analyzed and summed likewise.

CMR STUDIES AND ANALYSES. CMR studies closest to PET imaging were selected. The studies were conducted using standard 1.5-T/3.0-T CMR-scanners (Avanto, AvantoFit, Aera, Sonata, Verio, Skyra; Siemens) with phased-array receiver coils. Breath-hold cine studies were performed using retrospectively electrocardiographically gated segmented true fast imaging with balanced steady-state free precession. Late gadolinium enhancement imaging was performed 10 minutes after an intravenous injection of 0.15 mmol/kg of gadoterate meglumine (Dotarem) using an inversion-recovery spoiled gradient echo technique.

CMR images were checked for adequate quality before analysis. Ventricular volumes and LV mass were traced from short-axis cine images. Left atrial volumes were calculated using the modified biplane area-length method: volume = $(0.848 \times \text{area}_{4ch} \times \text{area}_{2ch})/([\text{length}_{4ch} + \text{length}_{2ch}]/2)$.[16] Right atrial area was traced on 4-chamber image. Cardiac chamber volumes were normalized to body surface area. The extent of LV late enhancement as percentage of LV mass was quantified by the full width at half maximum technique.[17] Medis Suite Qmass 8.1 software was used for CMR analyses (Medis Medical Imaging Systems B.V.).

STATISTICAL ANALYSES. Continuous variables are summarized as mean ± SD and as median (IQR) for normally distributed and skewed data, respectively. Categorical variables are given as numbers and percentages. Group comparisons were done with Student's *t*-test and Mann-Whitney *U* test as appropriate. Categorical variables were compared using chi-squared test of independence. Cause-specific cumulative incidence analysis was used to calculate the incidence estimates and 95% CIs for AF; the Gray-test was used for comparisons between groups. Follow-up time was calculated from the date of the PET study. Cause-specific univariable and multivariable Cox regression analyses were applied to identify predictors of AF. Variables with a univariate *P* value <0.10 were selected for multivariable modeling with no more than 4 potential predictors per model due to the restricted number of events.[18] Deaths and cardiac transplantations were included as competing first events in all analyses of time-to-AF data.[19] The assumption of proportional hazard was checked using log-log survival plots and time-dependent Cox model with time as a linear covariable. Two-tailed *P* values of <0.05 were considered statistically significant. The analyses were performed using the MedCalc software 17.1, SPSS statistics 27 (SPSS Inc), and R (RStudio, version 1.4.1717, The R Foundation).

RESULTS

PATIENT CHARACTERISTICS. Table 1 summarizes the clinical and laboratory characteristics of the study population at the time of CS diagnosis by subgroups with and without future AF. The diagnosis of CS was based on myocardial biopsy and histology in 37 cases

(31%) and on coexistence of extracardiac sarcoid granulomas with cardiac involvement clinically and by cardiac imaging in 81 cases (69%). Seventeen patients (14%) were free of signs of extracardiac sarcoidosis at diagnostic examinations and thus likely had isolated CS.

RESULTS OF CARDIAC IMAGING. Table 2 summarizes the results of studies with ^{18}F-FDG PET, CMR, and SPECT done inside 3 months of CS diagnosis. At the time of imaging, 22 patients undergoing PET (19%) and 11 patients undergoing CMR (11%) were on immunosuppressive drug therapy. The median interval between PET and CMR imaging was 17 days (8-44 days). Characteristic LV ^{18}F-FDG uptake pattern for CS was seen in 84 patients (71%). Altogether 39 of the 118-patient study population (33%) had abnormal atrial ^{18}F-FDG uptake on PET by the target-to-background ratio criterion (see Methods). Of the 22 patients imaged during immunosuppression (median duration, 20 days), 8 patients (32%) had abnormal atrial uptake. Thirty-four patients (87%) had ^{18}F-FDG uptake in the in interatrial septum, 23 (59%) in left atrial body, 5 (13%) in the left atrial appendage, 16 (41%) in the right atrial body, and 11 (32%) in the right atrial appendage. Examples of atrial activity on PET are shown in Figure 2. Isolated atrial ^{18}F-FDG uptake without ventricular uptake was not detected. Left or right atrial size on CMR did not correlate with atrial ^{18}F-FDG uptake on PET (data not shown). Of note, none of the patients' original clinical PET reports included comments on either presence or absence of atrial uptake.

CS-TARGETED TREATMENT IN BRIEF. In all, 114 patients (97%) received immunosuppression with corticosteroids after diagnosis of CS. Other immunosuppressants, used to support or replace steroids, included azathioprine in 43 patients, mycophenolic acid in 6, cyclosporine in 6, methotrexate in 4, and infliximab in 3 patients. Altogether 109 patients (92%) were on beta-adrenergic blockers, 67 (57%) on either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 41 (35%) on spironolactone at some point of the disease course. Twenty-eight patients (24%) were prescribed antiarrhythmic agents, mostly amiodarone or sotalol. An intracardiac device was implanted in 103 patients (87%), of whom 72 received a cardioverter-defibrillator and 19 received a cardiac resynchronizing device. Apart from 3 patients, all received the device before the first episode of AF.

INCIDENCE AND CHARACTERISTICS OF AF DURING FOLLOW-UP. Episodes of AF (n = 32) or atrial flutter (n = 2) occurred in 34 (29%) patients during median

TABLE 1 Characteristics of Patients With CS by Subgroups With and Without Occurrence of AF During Follow-Up

	No AF (n = 84)	AF (n = 34)	*P* Value
Demographics			
Female	58 (69)	20 (59)	0.29
Age, y	49 ± 11	50 ± 11	0.70
Body mass index, kg/m^2	27.4 ± 5.1	28.3 ± 7.9	0.71
Body surface area, m^2	1.9 ± 0.2	2.0 ± 0.3	0.14
Associated diseases			
Hypertension	14 (17)	11 (32)	0.06
Diabetes	7 (8)	6 (16)	0.14
Coronary artery disease	3 (4)	2 (6)	0.57
Sleep apnea	7 (8)	7 (21)	0.06
Hyperthyroidism	3 (4)	0 (0)	0.27
Extracardiac sarcoidosis	68 (81)	28 (82)	0.64
Main presenting manifestation			
Atrioventricular block	49 (58)	22 (65)	0.52
Ventricular tachyarrhythmia	13 (15)	8 (24)	0.30
Heart failure	8 (10)	1 (3)	0.22
Other	14 (17)	3 (9)	0.27
Selected laboratory values			
Elevated plasma troponin[a]	22 (26)	14 (41)	0.10
Plasma NT-proBNP, ng/L	159 (75-472)	198 (85-558)	0.18
Glomerular filtration rate, mL/min	89 ± 15	89 ± 17	0.95

Values are n (%), mean ± SD, or median (IQR). [a]Plasma cardiac troponin concentration exceeding the upper reference limit of the local laboratory at the time of the study.

AF = atrial fibrillation; CS = cardiac sarcoidosis; NT-proBNP = N-terminal pro B-type natriuretic peptide.

TABLE 2 Results of Multimodality Cardiac Imaging in Patients With CS by Subgroups With and Without AF During Follow-Up

	No AF (n = 84)	AF (n = 34)	*P* Value
CMR			
LVEDV, mL/m^2	97 ± 22	103 ± 20	0.26
LVEF, %	50 ± 11	46 ± 12	0.16
LV mass, g/m^2	62 ± 12	69 ± 13	0.02
LGE extent, % of LV mass	14 ± 9	18 ± 10	0.13
RVEDV, mL/m^2	85 ± 17	91 ± 26	0.15
RVEF, %	56 ± 9	52 ± 11	0.18
LAV_{max}, mL/m^2	41 ± 11	45 ± 13	0.14
Right atrial area, cm^2/m^2	12 ± 3	12 ± 4	0.85
PET and SPECT			
Atrial ^{18}F-FDG uptake	21 (25)	18 (53)	<0.01
Atrial target-to-background ratio	2.4 (1.7-3.2)	2.5 (1.6-3.6)	0.82
LV segments with ^{18}F-FDG uptake (n)	5 ± 4	5 ± 3	0.66
LV SUV_{max}	8.6 ± 3.5	9.0 ± 3.8	0.70
SRS on SPECT	3 (1-9)	5 (2-9)	0.51
Mismatch LV segments (n)	2 ± 2	2 ± 2	0.82

Values are mean ± SD, n (%), or median (IQR).

CMR = cardiac magnetic resonance; ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; LAV_{max} = maximum left atrial volume; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; PET = positron emission tomography; RVEDV = right ventricular end diastolic volume; RVEF = right ventricular ejection fraction; SPECT = single-photon emission computed tomography; SUV_{max} = maximal standardized uptake value; SRS = summed rest score; other abbreviations as in Table 1.

JACC: CARDIOVASCULAR IMAGING, VOL. 15, NO. 9, 2022
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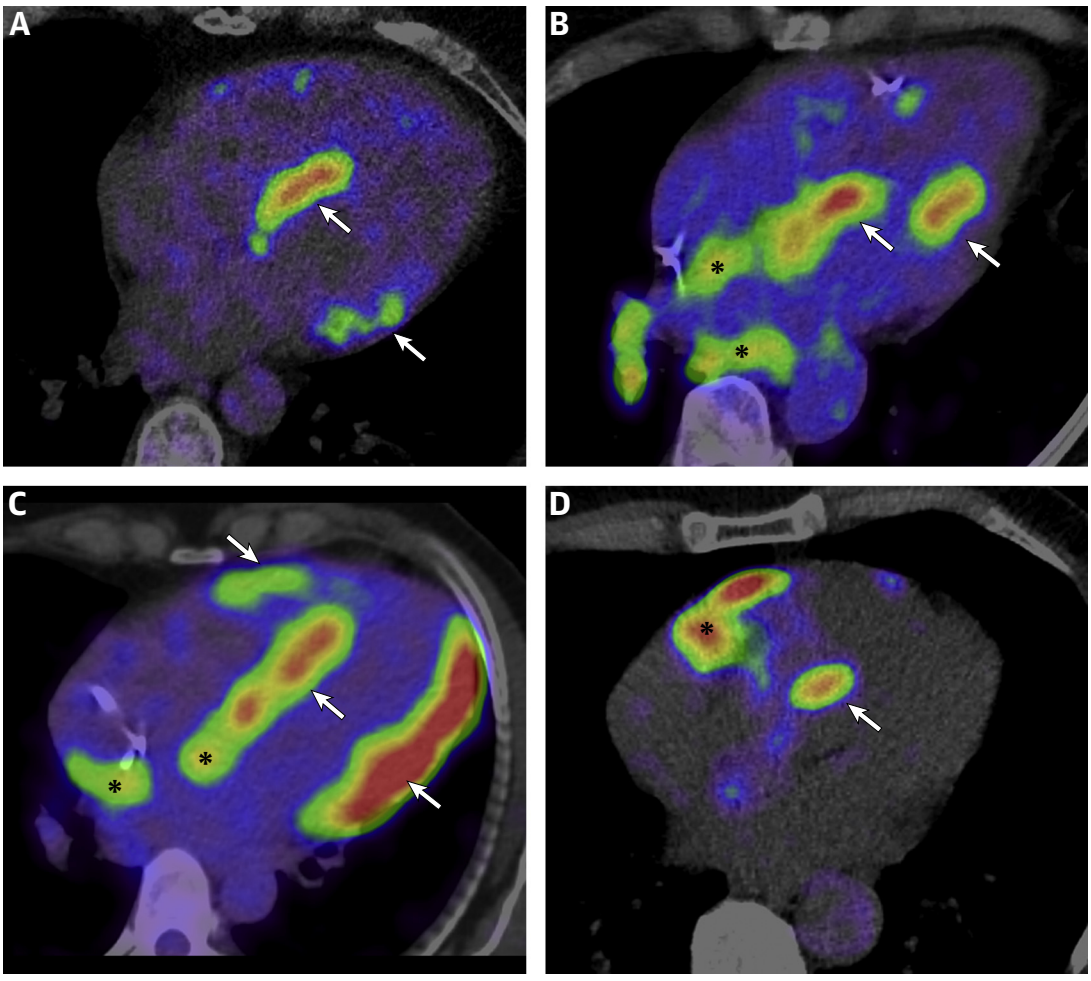
FIGURE 2 Examples of Atrial and Ventricular ^{18}F-FDG Uptake on PET/CT Imaging in Patients With CS



(A) ^{18}F-FDG uptake on basal ventricular septum and lateral left ventricular wall without any atrial uptake in a patient free of AF during follow-up. **(B)** Left atrial ^{18}F-FDG activity with uptake also in the basal ventricular septum and anterolateral papillary muscle. **(C)** Left and right atrial ^{18}F-FDG uptake with extensive activity in the septal and lateral walls of the left ventricle and some activity in the right ventricular free wall. **(D)** ^{18}F-FDG uptake in the right atrial appendage with a "hot spot" also in the basal ventricular septum. **(B to D)** are from patients suffering episodes of AF during follow-up. **White arrows** depict ventricular and **black asterisks** atrial ^{18}F-FDG uptake.
CT = computed tomography; ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; other abbreviations as in Figure 1.

follow-up of 3 years (1-6 years). The cumulative incidence (95% CI) of AF in the entire cohort, calculated with deaths (n = 7) and heart transplantations (n = 2) as competing first events, was 14% (8%-21%) at 1 year and 30% (21%-39%) at 5 years of follow-up. For comparison, nonfatal sustained ventricular tachyarrhythmias occurred in 26 patients, with a cumulative 5-year incidence of 17% (10%-27%). Episodes of AF were detected by pacemaker surveillance in 29 cases (85%) and by Holter monitoring or 12-lead ECG in 5 cases (15%). Nine patients (26%) had a solitary paroxysm of AF, and 25 (74%) had 2 or more episodes. AF was classified persistent in 7 patients (21%) and permanent in 4 (12%). The longest episode lasted <6 minutes in 11 patients (32%), 6 minutes to 24 hours in 16 patients (47%), and >24 hours in 7 patients (21%). Electrical cardioversion was used for rhythm control in 12 patients, and 2 individuals were submitted to catheter ablation. Anticoagulant therapy was initiated in 19 (56%) individuals. Three patients (9% of the entire cohort), all belonging to the AF subgroup, were hospitalized for treatment of

ischemic stroke during follow-up. Transient ischemic attacks were diagnosed in 2 patients, neither of whom had AF during follow-up.

PREDICTORS OF AF. None of the clinical characteristics, associated diseases, or presenting manifestations listed in Table 1 were statistically significantly predictive of AF by univariate Cox regression analysis (all $P > 0.05$). Sleep apnea, however, had a statistically borderline predictive power with an HR of 2.09 (95% CI: 0.91-4.81; $P = 0.08$). Table 3 summarizes the results of the comparable univariate analyses involving laboratory measurements and cardiac imaging variables. The HRs indicate that abnormal atrial ^{18}F-FDG uptake, elevated circulating cardiac troponin, and LV mass by CMR were statistically significant univariate predictors of AF. In multivariable analyses, presented in Table 4, atrial ^{18}F-FDG uptake was a consistent independent predictor of AF together with left atrial maximum volume and presence of sleep apnea. The Central Illustration shows the cumulative incidence of AF by the presence of atrial ^{18}F-FDG uptake, and Figure 3 shows the incidence after additional stratification of the cohort by the size of the left atrium. In all, an episode of AF was observed during follow-up in 18 of the 39 patients with atrial ^{18}F-FDG uptake and 16 of the 79 without uptake. The estimated 5-year incidences of AF were 55% (34%-72%) and 18% (10%-28%) in the respective subgroups ($P < 0.001$). The median time from positive atrial PET scan to the first episode of AF was 8 months (2-24 months).

TABLE 3 Results of Cause-Specific Univariate Cox Regression Analyses on Selected Laboratory and Imaging Variables for Prediction of Incident AF in Patients With CS

	n	HR	95% CI	*P* Value
Laboratory variables				
Elevated cardiac troponin	115	2.40	1.19-4.84	0.01
NT-proBNP, per 100 ng/L	115	1.01	0.99-1.03	0.37
Glomerular filtration rate, mL/min	118	1.00	0.98-1.02	0.88
Imaging variables				
LVEDV, mL/m^2	99	1.01	0.99-1.02	0.41
LVEF, %	99	0.98	0.95-1.02	0.34
LV mass, g/m^2	99	1.03	1.01-1.06	0.02
LV LGE extent, %	97	1.03	0.99-1.07	0.17
RVEDV, mL/m^2	94	1.01	1.00-1.03	0.09
RVEF, %	94	0.98	0.94-1.01	0.21
LAV_{max}, mL/m^2	97	1.03	1.00-1.06	0.07
Right atrial area, cm^2/m^2	98	1.04	0.94-1.16	0.40
Atrial ^{18}F-FDG uptake	118	3.12	1.59-6.14	0.001
Atrial target-to-background ratio[a]	39	1.03	0.74-1.45	0.85
LV segments with ^{18}F-FDG uptake (n)	94	1.05	0.93-1.18	0.44
LV SUV_{max}	77	1.03	0.92-1.16	0.60
SRS on SPECT	106	1.01	0.96-1.07	0.75
Mismatch LV segments (n)	91	1.05	0.88-1.25	0.61

[a]Measured in patients with visible atrial ^{18}F-FDG uptake.
n = number of patients with analyzable data; other abbreviations as in Tables 1 and 2.

DISCUSSION

Our work showed that patients with clinically manifest CS have a 30% cumulative risk of future AF at 5 years from diagnosis. Atrial ^{18}F-FDG uptake on PET scans, a sign of atrial inflammation found in one-third of patients, was a strong independent risk factor for AF with left atrial enlargement on CMR and clinical history of sleep apnea having lesser predictive effects. Although most AF episodes were short and silent, more than one-third were symptomatic enough to require electrical cardioversion or, more rarely, catheter ablation. Ischemic strokes occurred only in patients with AF during follow-up.

EARLIER STUDIES IN BRIEF. Although atrial arrhythmias have remained in the background of CS research, a few original studies exist predating our investigation.[4-8] These works reported overall prevalence figures[4-8] or incidence densities[4] for a mixture of atrial tachyarrhythmias instead of analyzing individual time-to-arrhythmia data for cumulative incidence. One work[5] was prospective and focused on patients with newly diagnosed CS, whereas others were retrospective enrolling cases from cardiac imaging registries[6-8] or from referrals for an electrophysiological study.[4] In 2 studies,[4,8] practically all atrial arrhythmias were symptomatic and many[8] or all[4] required an invasive electrophysiological study, whereas in others either most were subclinical[5] or symptom status was not reported.[6,7] The prevalence of any atrial tachyarrhythmia, AF or non-AF, ranged from 16% (9 of 50 patients) over mean follow-up of 4.4 years in the study by Habibi et al[6] to 40% (25 of 62 patients) over an unspecified follow-up time in the study of Yodogawa et al.[7] For AF, the prevalence ranged from 16% to 37%.[6,7] The only prospective study involved 33 treatment-naive patients with CS of whom 8 (24%) developed a fast (>190 beats/min) atrial arrhythmia over a mean follow-up of 4 years. The prevalence of atrial inflammation on cardiac PET scans was analyzed in 3 studies.[5-7] Weng et al[5] and Yodogawa et al[7] found abnormal atrial ^{18}F-FDG uptake in 48% and 52% of their respective patients, whereas the prevalence was only 8% in the study by Habibi et al.[6] For

TABLE 4 Clinical, Laboratory, and Imaging Predictors of Incident AF in CS by Multivariable Models Based on Cause-Specific Cox Regression Analyses

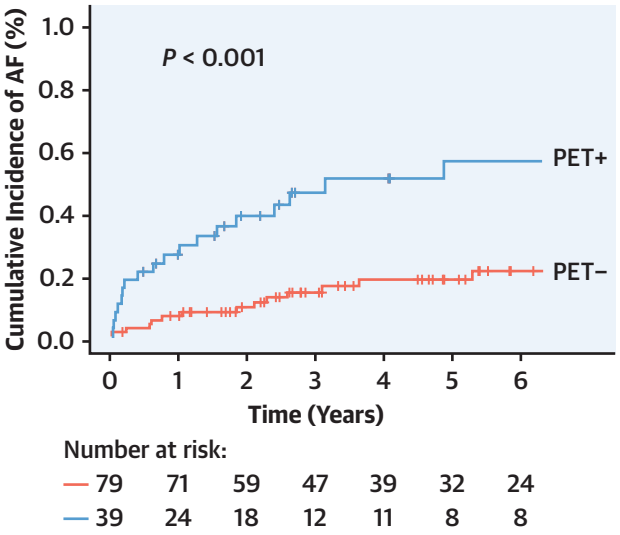
	Model 1 (n = 97, e = 29)		Model 2 (n = 96, e = 29)		Model 3 (n = 92, e = 28)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sleep apnea	3.78 (1.48-9.65)	<0.01	3.98 (1.55-10.20)	<0.01	–	N/A
Hypertension	1.71 (0.74-3.96)	0.21	–	N/A	–	N/A
Elevated cardiac troponin	–	N/A	1.42 (0.60-3.41)	0.43	–	N/A
LV mass, g/m^2	–	N/A	–	N/A	1.03 (1.00-1.06)	0.08
RVEDV, mL/m^2	–	N/A	–	N/A	1.00 (0.99-1.02)	0.98
LAV_{max}, mL/m^2	1.05 (1.02-1.09)	<0.01	1.05 (1.01-1.09)	0.01	1.04 (1.00-1.08)	0.03
Atrial ^{18}F-FDG uptake	6.01 (2.64-13.66)	<0.001	6.09 (2.66-13.95)	<0.01	4.10 (1.76-9.56)	0.001

e = number of events; n = number of patients; N/A = not applicable; other abbreviations as in Tables 1 and 2.

comparison, autopsy studies have shown granulomatous atrial involvement in on average 20% of patients dying from or with CS.[20,21] In the study of Yodogawa et al,[7] the prevalence of atrial arrhythmias was higher in patients with than without ^{18}F-FDG uptake (72% vs 38%; $P = 0.017$), whereas the smaller works[5,6] failed to show such an association. In 3 studies,[4,6,7] the prevalence of atrial arrhythmias was related to increased size or impaired function of the left atrium.

PATHOGENESIS OF AF IN CS. Our observation of atrial ^{18}F-FDG uptake and elevated circulating cardiac troponins predicting future AF suggests that active atrial wall inflammation with injury and edema, and with subsequent scarring, provides both triggers and re-entrant circuits for local arrhythmias. Left or right atrial remodeling from direct atrial involvement or secondary to either upstream effects of ventricular scarring or severe pulmonary sarcoidosis and/or pulmonary hypertension may

CENTRAL ILLUSTRATION Cumulative Incidence of Atrial Fibrillation in Relation to Presence of Atrial Inflammation in Patients With Newly Diagnosed Cardiac Sarcoidosis



Niemelä M, et al. J Am Coll Cardiol Img. 2022;15(9):1622-1631.

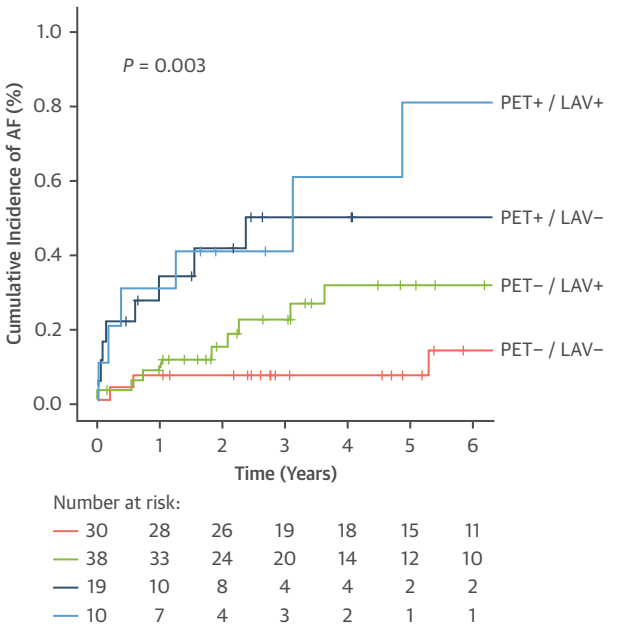
A cohort of 118 patients with clinically manifest cardiac sarcoidosis undergoing PET was followed in retrospect for occurrence of new-onset AF starting from the PET study. Based on atrial uptake of ^{18}F-fluorodeoxyglucose, the cohort was divided into subgroups with (PET+) and without (PET−) atrial inflammation. The curves deviate early, and at 5 years of follow-up the AF incidence estimate is 55% in the former group vs 18% in the latter. AF = atrial fibrillation; PET = positron emission tomography.

also contribute to the pathogenesis AF in CS. Supporting this, and congruent with earlier studies.[4,6,7] left atrial enlargement and increased LV mass by CMR were AF risk factors in our work. Finally, as inflammation in general may contribute to the pathogenesis of AF,[22] sarcoid granulomas in remote organs or in epicardial fat could promote AF via effects of circulating or locally released cyto- and adipokines.[22,23] In accord with this, a recently published registry study from Denmark showed that patients with any diagnosis of sarcoidosis have an increased long-term risk of AF compared with background population matched for age, sex, and comorbidities.[24]

CLINICAL CONSIDERATIONS. The clinical significance of AF in CS relates to the symptoms it causes or exacerbates, to the need of therapies including interventions for rhythm control, and to complications like embolic strokes or inappropriate shocks in patients with intracardiac defibrillators. The risk of stroke deserves recognition because sarcoidosis can be considered a prothrombotic state[25] and as there are also other mechanisms potentially enhancing stroke risk in CS.[26] There is no good evidence to suggest efficacy of immunosuppressive or antiarrhythmic drugs in the control of CS-related AF,[9] nor is there evidence to prefer rhythm over rate control in deviation from today's guidance.[10] Small case series on AF ablation have shown favorable results from pulmonary venous isolation, though.[27] Although AF presents less imminent threat to life than ventricular tachyarrhythmias, experts reading PET studies should take care to report abnormal atrial activity to raise clinicians' vigilance for future AF.

STRENGTHS AND LIMITATIONS. Compared with previous studies, our work involves a larger cohort of proven CS and is the only one with analysis of time-to-AF data. We excluded patients with past AF to focus on incident AF following the diagnosis of CS. This is important, as AF per se may lead to atrial ^{18}F-FDG uptake because of remodeling of the atrial myocardium.[28] The long coverage (14 years) of our work and its retrospective design explain why there were patients with missing data on some potentially important risk factors for AF and why adequate CMR studies coinciding with diagnosis were not always available for reanalysis. We only evaluated the baseline predictors of AF without being able to consider the role of changes in some AF risk factors during the follow-up, such as weight gain or new hypertension caused by corticosteroid treatment. A methodological limitation relates to the evolution of scanners and dietary preparation for PET studies between 2006 and 2020. Some of the early studies were done after only a 12-hour fast (see Methods) and with PET cameras having lower image resolution, which were more challenging to read. Perfusion imaging was not done simultaneously with the ^{18}F-FDG PET in our study. Finally, as all patients did not have intracardiac devices for interrogation of rhythm disturbances, our data may underestimate the true incidence of episodic AF.

FIGURE 3 Patients With and Without Atrial ^{18}F-FDG Uptake on PET Were Further Stratified by the Maximum LAV



PET+ and PET− indicate presence and absence of atrial inflammation, respectively, LAV+ and LAV− standing correspondingly for volumes above and below the median LAV of 42 mL/m^2 on cardiac magnetic resonance imaging. In pairwise comparison, the incidence curves were statistically significantly different between PET+/LAV+ vs PET−/LAV− ($P < 0.001$), PET+/LAV+ vs PET−/LAV+ ($P = 0.02$), and PET+/LAV− vs PET−/LAV− ($P < 0.01$). LAV = left atrial volume; other abbreviations as in Figures 1 and 2.

CONCLUSIONS

Patients with newly diagnosed CS have a 30% risk of suffering 1 or more episodes of AF over the first 5 years of follow-up. Atrial inflammation by ^{18}F-FDG uptake on PET constitutes a strong risk factor for AF with increased left atrial size and clinical history of sleep apnea being additional independent contributors. Although most AF episodes are silent and short, recurrences are common, some episodes turn persistent or even permanent, and at least one-third of patients require hospitalization for cardioversion.

We think that both experts reading cardiac imaging studies and clinicians responsible for patient care need to pay attention to signs of atrial inflammation by ^{18}F-FDG-PET.

ACKNOWLEDGMENTS The authors thank all colleagues and staff in the Helsinki University Hospital for their support in this study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by a Finnish government grant for medical research, the Aarne Koskelo Foundation, and the Finnish Foundation for Cardiovascular Research. Dr Uusitalo has received scientific collaboration with and a lecture fee from GE Healthcare; and has received a lecture fee and has advisory board activity with Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF is neither an uncommon nor an innocent arrhythmia in CS. Atrial inflammation on ^{18}F-FDG-PET and atrial enlargement on CMR help predict its risk at the time of CS diagnosis. Physicians evaluating and reporting PET studies should pay attention to ^{18}F-FDG activity beyond the LV.

TRANSLATIONAL OUTLOOK: Characterization of atrial scar burden by refined CMR techniques or applying repeat PET imaging to define atrial response to treatment could further improve AF risk assessment in CS. Hybrid PET/magnetic resonance imaging might facilitate reliable identification of atrial wall inflammation and provide means to match ^{18}F-FDG signal to atrial late gadolinium enhancement at one imaging session.

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KEY WORDS atrial fibrillation, cardiac magnetic resonance, cardiac sarcoidosis, positron emission tomography