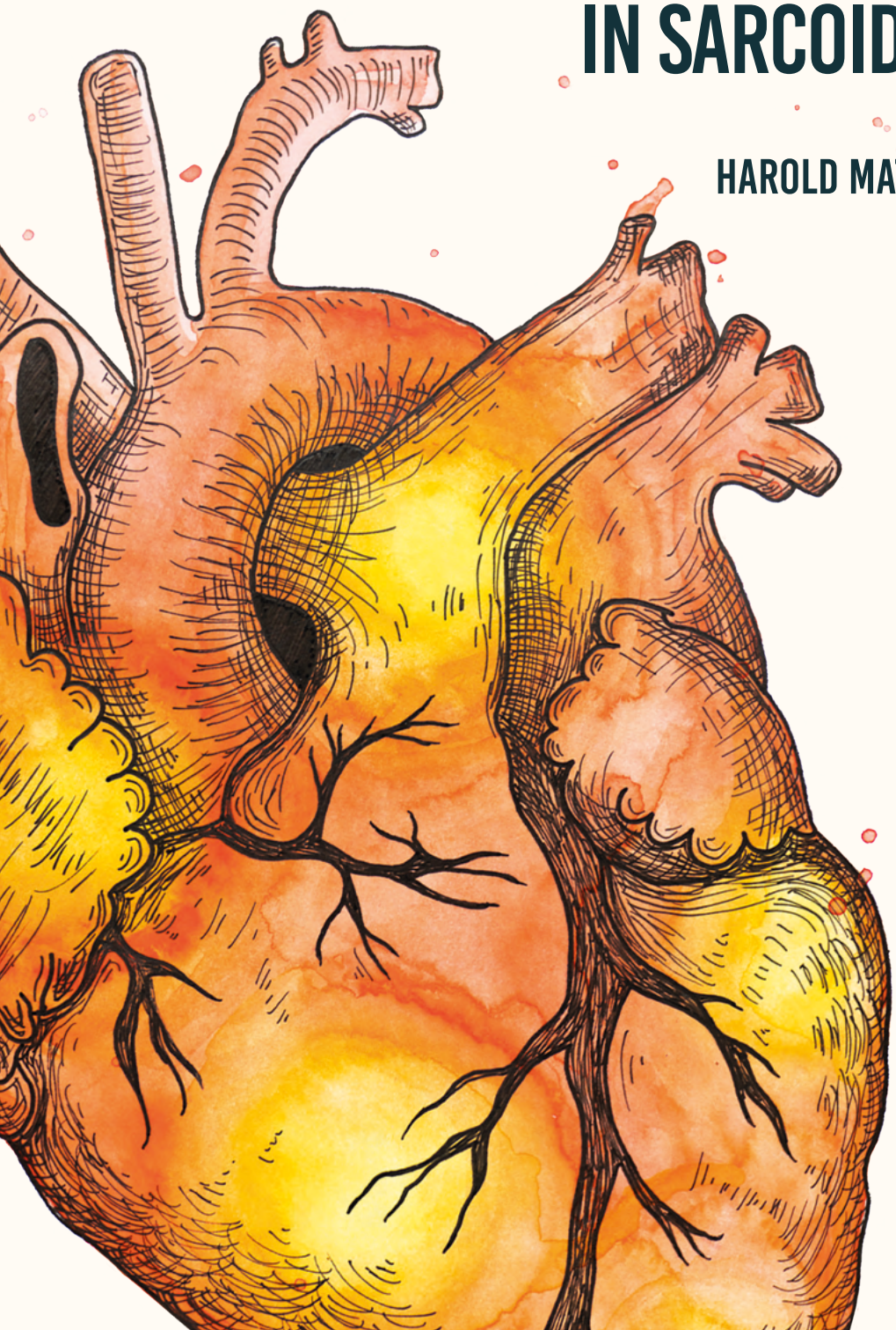
PULMONARY HYPERTENSION AND CARDIAC INVOLVEMENT IN SARCOIDOSIS

HAROLD MATHIJSSEN



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(met een samenvatting in het Nederlands)

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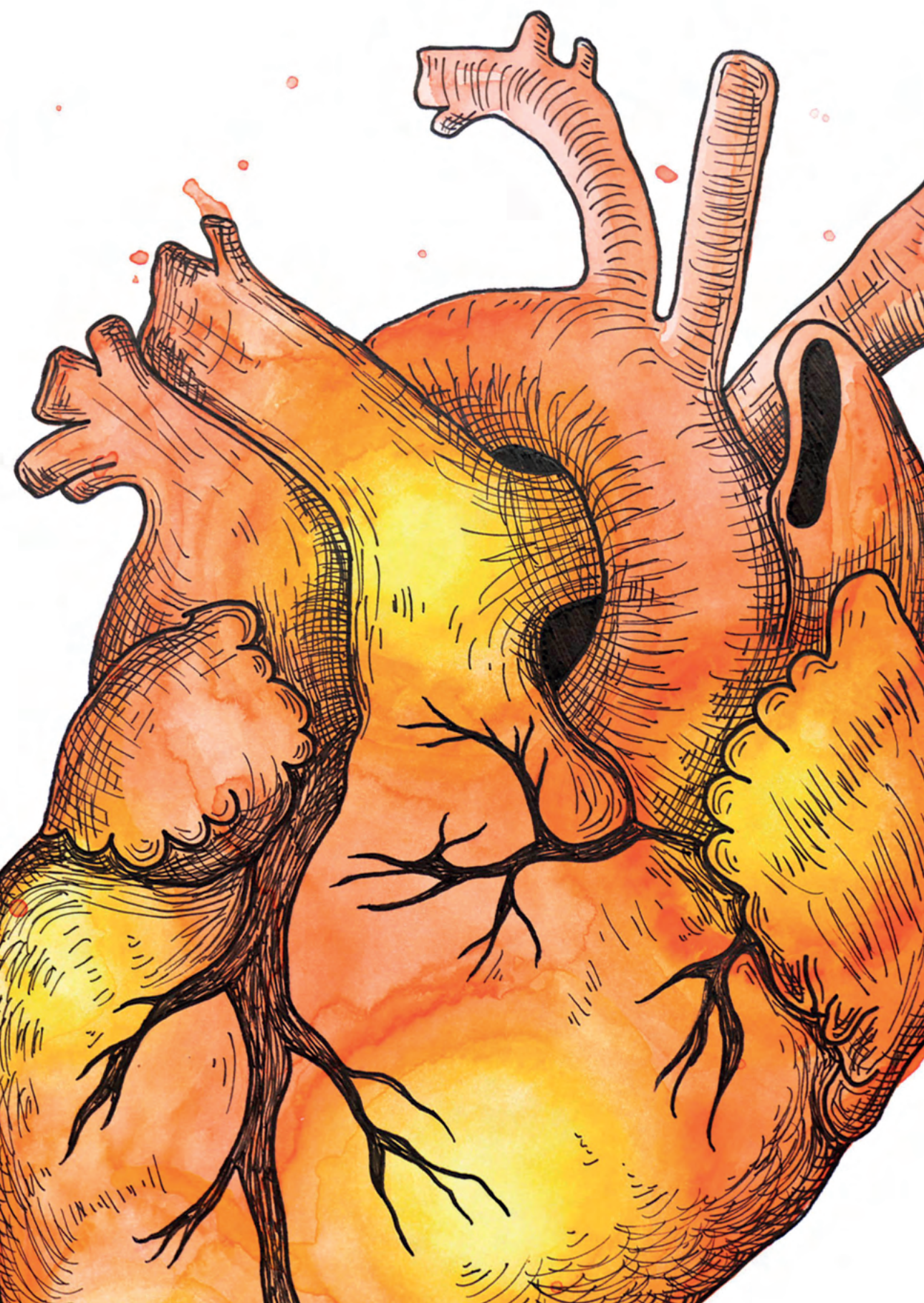

1

GENERAL INTRODUCTION

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SARCOIDOSIS-ASSOCIATED PULMONARY HYPERTENSION

Sarcoidosis is a multisystem inflammatory disease of unknown origin, characterized by the presence of non-caseating granulomas.[1] It is believed that exposure to an unidentified antigen in patients with a genetic predisposition to the disease, results in an exaggerated immune response leading to granuloma formation.[2,3] The most common localizations of sarcoidosis are in the lungs and lymphatic system, although almost any organ can be impacted.

The prevalence of sarcoidosis reflects geographic, ethnic, sex and age-related variation with higher rates present in African Americans and Northern Europeans. The age of the majority of patients with sarcoidosis at first presentation is between 25 and 60 years.[4] In most patients, the disease is self-limiting and resolves spontaneously within two to five years. However, a proportion of patients show no remission but instead a progression of the disease, which can result in the development of (pulmonary) fibrosis.[5] This population often requires immunosuppressive treatment to control the inflammatory response and to prevent irreversible organ damage. Nevertheless, most immunosuppressive therapies have multiple side-effects which negatively affect one's quality of life.

Respiratory failure is the most common cause of death in patients with chronic sarcoidosis, followed by sudden cardiac death (SCD) and heart failure due to cardiac involvement. Sarcoidosis-associated pulmonary hypertension (SAPH) is a well-known complication in pulmonary sarcoidosis, especially in patients with respiratory failure. Pulmonary hypertension (PH) is still defined as a mean pulmonary artery pressure of ≥25mmHg in supine position at rest as measured by right heart catheterization (RHC).[6,7] In the upcoming new guidelines on PH, the definition of PH will be a mean pulmonary artery pressure of at least 20mmHg.[8] Even though the first case of SAPH was described in 1949[9], many challenges remain to further characterize the disease, including aetiology, prognosis and treatment.

The exact prevalence of PH in sarcoidosis remains uncertain and is dependent on the severity and stage of sarcoidosis. It presents more often in patients with more advanced disease and the prevalence increases as the disease advances over years.[10–12] Multiple studies have investigated the prevalence of SAPH with rates ranging from 3% to 21% in patients without suggestive signs or symptoms.[12–15]

The World Health Organization (WHO) classifies PH into five different groups and within each group, there are similar pathological, haemodynamic and therapeutic approaches.[6] According to this classification system, SAPH is classified as group 5, defined as a

multifactorial or unknown mechanism of PH. There are several potential mechanisms of SAPH. Most often, it is attributed to parenchymal lung disease, generally as a manifestation of advanced fibrosis, due to destruction of the pulmonary vascular bed. However, a considerable number of sarcoidosis patients develop PH in the absence of significant parenchymal lung disease[10,13,16–20] or with near-normal lung function tests.[17,21] This suggests that other or multifactorial mechanisms might cause PH in sarcoidosis. Several mechanisms have been hypothesized, including pulmonary vascular disease, left heart disease, pulmonary embolisms, compression by enlarged lymph nodes or fibrosis and sarcoidosis-related comorbidities. Figure 1 shows an overview of suggested mechanisms in SAPH. Further knowledge of the mechanisms of SAPH provides important prognostic information and can guide therapeutic decision-making.

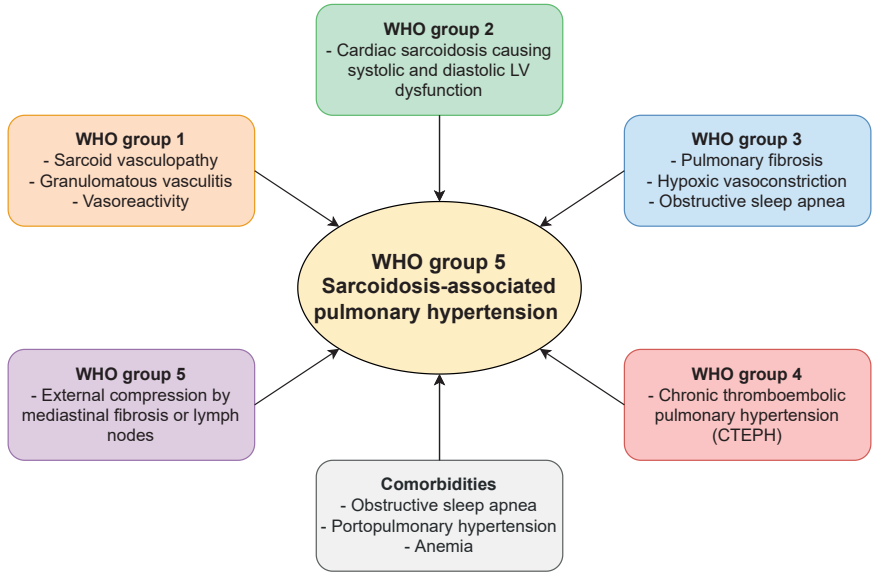

Figure 1. Overview of suggested mechanisms for SAPH. LV = left ventricular; WHO = World Health Organization.

SAPH is associated with significant morbidity and mortality. Patients have an increased supplemental oxygen requirement and reduced exercise capacity. SAPH also has high social impact for the individual patient with a decrease in quality of life.[22,23] Furthermore, multiple studies showed that PH is an independent risk factor for mortality in sarcoidosis patients, although this has primarily been studied in patients with more advanced disease.[24–27] Hence, early recognition of PH in sarcoidosis is crucial. This is challenging, however, as symptoms and signs suggesting PH overlap with symptoms of pulmonary sarcoidosis. SAPH can be suspected based on clinical manifestations includ-

ing disproportional dyspnoea, exertional chest pain and/or syncope, reduced 6-minute walk distance, desaturation with exercise, reduced diffusing capacity for carbon monoxide (DLCO), increased pulmonary artery diameter relative to ascending aorta diameter and fibrotic lung disease. As mentioned, PH is diagnosed by the gold standard RHC, but this is a time-consuming, costly, and invasive procedure. Therefore it is recommended to perform an initial screening with transthoracic echocardiography in patients who are suspected to have PH.[6,28] If the probability for PH on echocardiography is deemed high, a RHC should be performed to validate or reject the SAPH diagnosis. Unfortunately, echocardiography can be limited due to poor visualization of the right ventricle (RV), especially in the presence of pulmonary disease. As right ventricular dysfunction is associated with PH in sarcoidosis and adverse outcomes, there is increasing interest in new methods to determine RV volumes and function.[29,30] Further research is warranted to determine whether these new diagnostic modalities add value in PH screening in sarcoidosis patients.

When SAPH is diagnosed, the treatment highly depends on the underlying cause. Most studies regarding treatment are small and the optimal management strategy is not well defined. Hence, treatment might benefit the individual patient, but there is no strong evidence for effectiveness in the whole SAPH population. Suggested therapies are immunosuppressive therapy, PH-targetedtherapies, and pulmonary artery stenting. In addition, full assessment, and treatment of relevant comorbidities (including left ventricular systolic or diastolic heart failure, pulmonary emboli, and obstructive sleep apnoea) is very important. Immunosuppressive treatment might be indicated if the mechanism of PH is suspected to be due to the inflammatory process of sarcoidosis itself, like granulomatous vasculitis and extrinsic compression of the pulmonary artery due to hilar and mediastinal lymphadenopathy (as shown in figure 2).[17,25,31] PH-targeted therapies, such as prostacyclins, endothelin receptor antagonists and phosphodiesterase-5 inhibitors, are currently used off-label. As only small, predominantly retrospective, studies have been published, these therapies should only be used in selected cases after multidisciplinary evaluation.[18,20,32–34] In other parenchymal lung disease (chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis) the use of oral PH-targeted therapies has resulted in worse outcomes compared with placebo.[35,36] Thus, careful patient selection is essential. In patients with severe SAPH or end-stage pulmonary disease for whom all other treatment options have failed, lung transplantation can be an option - which also carries a high risk of both morbidity and mortality.[37]

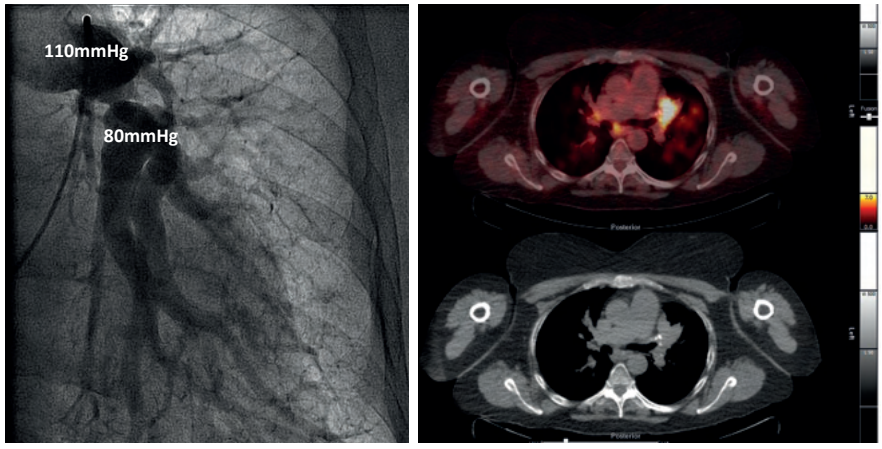

Figure 2. Clinical case of a patient with severe PH (mean pulmonary artery pressure 65mmHg). Further evaluation by fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) showed fibrosing mediastinitis causing arterial compression in the left lower lobe with a significant pressure gradient.

CARDIAC SARCOIDOSIS

Besides respiratory failure, cardiac involvement is another leading cause of death in sarcoidosis patients. Cardiac involvement in sarcoidosis was first reported in 1929 and it is estimated that around 5% of sarcoidosis patients have clinically manifest cardiac involvement.[38–40] However, pathology and advanced cardiac imaging studies suggest higher prevalence rates of 15-25%.[41–43] The disease tends to demonstrate patchy myocardial involvement with successive histologic stages of edema, inflammation and fibrosis resulting in the formation of myocardial scar. The most common sites of involvement are the left ventricular free wall and the septum. Granulomas occur in both the left and right ventricle, although right ventricular involvement is most often seen in patients with more profound disease. Cardiac sarcoidosis (CS) may precede systemic sarcoidosis or can develop subsequently. Its clinical presentation is dependent on the location and extent of myocardial damage as well as the degree of myocardial inflammatory activity. Thus, presentation can be highly variable, and ranges from incidental discovery to conduction abnormalities, ventricular arrhythmias (VA), and congestive heart failure.[44–46]

The diagnosis of CS remains a challenge given the absence of a single reliable biochemical or imaging test for diagnosis. The most widely used diagnostic criteria are those from the 2014 Heart Rhythm Society Expert Consensus Statement (Table 1).[40] Presently, the gold standard to diagnose CS is the presence of granulomas in an endomyocardial biopsy (histological diagnosis). However, this is an invasive technique with a disappoint-

ingly low sensitivity of 20-30% due to the patchy nature of the disease.[47,48] Therefore, CS is most often diagnosed using histological evidence from extracardiac sarcoidosis and clinical evidence of cardiac involvement (clinical diagnosis).[40,49] It is recommended to establish a final CS diagnosis in a multidisciplinary setting with experienced cardiologists, pulmonologists and nuclear physicians or radiologists.

Table 1. Expert Consensus recommendations on the Criteria for the diagnosis of cardiac sarcoidosis (Heart Rhythm Society 2014)[40]

Two pathways for the diagnosis of cardiac sarcoidosis
1. Histological diagnosis from myocardial tissue CS is diagnosed in the presence of non-caseating granulomas on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable)
2. Clinical diagnosis from invasive and non-invasive studies. It is probable that there is CS if: A. There is a histological diagnosis of extracardiac sarcoidosis AND • One or more of following is present • Steroid ± immunosuppressant responsive cardiomyopathy or heart block • Unexplained reduced left ventricular ejection fraction <40% • Unexplained sustained (spontaneous or induced) ventricular arrhythmias • Mobitz type II 2nd degree heart block or 3rd degree heart block • Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS) • Late gadolinium enhancement on CMR (in a pattern consistent with CS) • Positive gallium uptake (in a pattern consistent with CS) AND C. Other causes for the cardiac manifestation(s) have been reasonably excluded

The patients we see in our clinic with a suspicion of CS can be divided into two groups (Figure 3):

1. Patients with known extracardiac sarcoidosis and suspected cardiac involvement based on an abnormal screening. These patients are predominantly asymptomatic or have minor symptoms.
2. Patients who present with (severe) cardiac symptoms as a first manifestation of sarcoidosis, such as atrioventricular (AV) conduction disorders and VA. Unfortunately, it is difficult to differentiate from other cardiomyopathies and CS is often missed. Awareness of the heterogeneous presentation of CS is essential to recognize this entity, especially in patients <60 years of age.

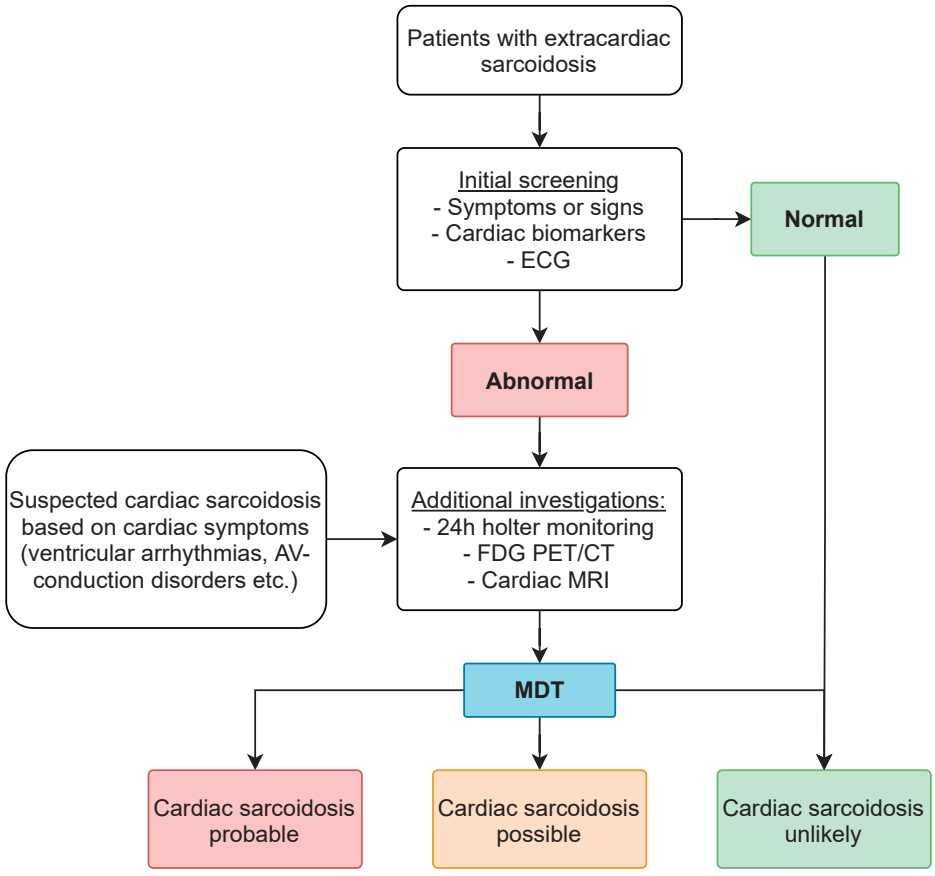

Figure 3. Flowchart showing the diagnostic pathway in patients with suspected CS in the St. Antonius Hospital, the Netherlands. AV = atrioventricular; ECG = electrocardiogram; FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; MDT = multidisciplinary team meeting; MRI = magnetic resonance imaging.

It is recommended to screen every sarcoidosis patient for cardiac involvement. The initial screening is in most cases performed by the pulmonologist and contains a clinical history of cardiac symptoms (including chest pain, palpitations, dizziness and syncope), cardiac biomarkers and an ECG. Various ECG abnormalities, like AV- or bundle branch block can be the first sign of CS. In some centres, echocardiography is also used as a screening tool, but its usage is impaired by low sensitivity.[43] In case of abnormal screening results, patients should undergo further testing including 24h ambulatory holter arrhythmia monitoring, cardiac magnetic resonance imaging (CMR) and/or fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT).

CMR is the most used diagnostic modality worldwide for the diagnosis of CS. A broad range of myocardial abnormalities can be identified, like: edema, fibrosis, thickening or

thinning of the myocardium and wall motion abnormalities. One of the most important tools of CMR is the usage of late gadolinium enhancement (LGE). This technique is based on the washout of gadolinium, which is slow in the areas of edema and scar, leading to its visualization on the delayed images on CMR. The presence of LGE in certain patterns can be diagnostic for CS. However, the presence of LGE is nonspecific and CS-like LGE patterns can also be seen in other diseases. Furthermore, it is not always easy to differentiate between LGE caused by inflammation or scar tissue. FDG PET/CT can be a valuable addition to CMR, as it is the best clinical tool to assess sarcoidosis inflammatory activity. FDG PET/CT relies on persistent uptake of radioactive labelled glucose (FDG) by the granulomatous inflammatory myocardial cells. Therefore, a metabolic setting is required in which cardiac myocytes have switched from glucose to fatty acid metabolism as an energy substrate. This means that all sarcoidosis patients need to be extensively prepared with a low carbohydrate diet followed by prolonged fasting, of at least 12 hours, to effectively supress the physiological myocardial glucose uptake. The presence, localisation and extend of myocardial FDG-uptake can provide valuable information for CS diagnosis and prognosis, but only if adequate suppression is established.

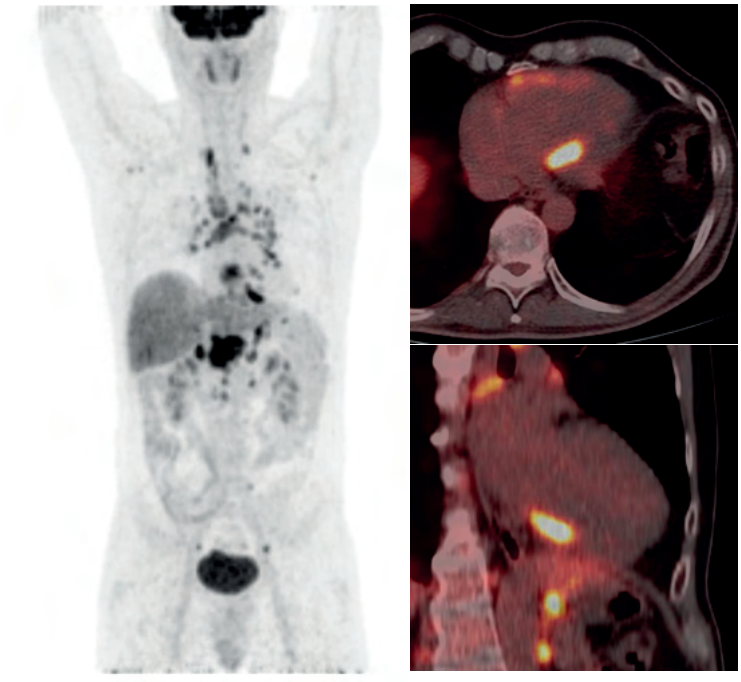

Figure 4. Example of a full body FDG PET/CT with FDG-uptake in the mediastinal, hilar and extrathoracic lymph nodes, lungs (perihilar), liver (diffuse uptake) and heart. The heart shows FDG-uptake in the septum, inferior wall and right ventricle, which is very suspicious for CS localizations.

The treatment of CS is largely empirical and there is a lack of large, randomized clinical trials evaluating different treatment strategies. Due to the chronic course of the disease, it is necessary to treat patients with immunosuppressive therapies for several years. A multidisciplinary team approach for the treatment of CS is recommended in order to address the complex clinical issues that patients and clinicians often face. Commonly, immunosuppressive therapy is started in symptomatic patients with active myocardial inflammation based on FDG PET/CT. Nevertheless, there are large differences between sarcoidosis expert centres regarding the choice of immunosuppressive therapies and their dosage. Corticosteroids are generally the first line of therapy, followed by second line therapies such as methotrexate and azathioprine.[50–53] Lately, there has been increasing attention regarding the role of TNF-alpha inhibitors infliximab and adalimumab in refractory CS patients.[54,55] The treatment goal in CS is to completely suppress the myocardial inflammation process and granuloma formation, thereby preventing further scar formation, left ventricular remodelling and clinical deterioration. Therefore, treatment is usually aggressive with high dosages of immunosuppressive therapies or a combination of therapies. Side effects and intolerance for treatment are often documented and patients need to be monitored closely. Patients are followed up on regularly with FDG PET/CT, echocardiography and arrhythmia monitoring to assess treatment response and to guide treatment strategy.[56,57] However, the best strategy for (immunosuppressive) treatment remains one of the largest gaps in our current knowledge on CS.

As mentioned previously, CS is associated with a high risk of VA and SCD compared to other non-ischemic cardiomyopathies.[58,59] Therefore, a large group of sarcoidosis patients with cardiac involvement receive an implantable cardioverter defibrillator (ICD). An ICD can prevent SCD with a shock or anti-tachycardia pacing and it can provide electrical stimulation (pacing) in patients with conduction abnormalities. Unfortunately, an ICD can also lead to adverse events such as inappropriate shocks, lead complications, and infections.[58,60] Furthermore, current guidelines handle different recommendations for ICD implantation for primary prevention in CS patients.[40,61] The dominant substrate for VA and SCD in CS is thought to be myocardial scar secondary to inflammatory damage from granulomas.[62,63] LGE on CMR can represent myocardial scarring and current literature shows a strong association between LGE and the occurence of VA in CS.[43,64–67] Some data even suggests that the presence of LGE might be a better predictor for VA than the left ventricular ejection fraction and that the absence of any LGE is associated with a very low risk for VA or SCD.[68] However, it is important to note that the existing literature on CMR for risk stratification in CS may be subject to several limitations, including single centre retrospective studies, potential referral bias and a lack of a uniform methodology in quantifying LGE burden. Current data shows that many patients with CS display LGE at diagnosis and that not all patients benefit from an ICD implantation. Therefore, there is a need for risk-stratification techniques to determine which CS patients warrant placement of ICDs.

THESIS AIMS AND OUTLINE

This thesis aims to achieve the following:

1. To gain more insight into the pathophysiological mechanisms and diagnosis of both SAPH and CS.
2. To describe the effect of PH-targeted therapies in SAPH and the effect of immunosuppressive therapies in CS.
3. To identify predictors of mortality and adverse events in both disease entities.

The first part **(A)** of this thesis evaluates the diagnosis and treatment of SAPH. In **Chapter 2** different clinical phenotypes of SAPH are proposed. **Chapter 3** evaluates the usage of a new echocardiographic method to determine RV volumes in pulmonary sarcoidosis patients screened for PH. In **Chapter 4** the safety and effectiveness of the endothelin receptor antagonist macitentan is described in a case series of five SAPH patients. Part A ends with **Chapter 5**, in which the survival rate and impact of SAPH on prognosis in a large pulmonary sarcoidosis population is presented. The second part of this thesis **(B)** focusses on CS and its diagnosis, prognosis and treatment. In **Chapter 6** the usage of repeated CMR and FDG PET/CT for the diagnosis of patients with initial uncertain CS diagnosis is explored. In **Chapter 7** the immunosuppressive therapies prednisone and methotrexate are compared as treatment for CS on FDG PET/CT remission. **Chapter 8** evaluates the usage of the TNF-alpha inhibitor infliximab in refractory CS patients. In **Chapter 9** the results of long-term arrhythmia monitoring in a low risk CS population are presented, along with an **editorial** by Birnie et al. This parts ends with **Chapter 10**, which describes predictors of appropriate implantable cardiac defibrillator (ICD) therapy in CS. **Chapter 11** consists of the summary and general discussion where new insights described in this thesis are put into perspective.

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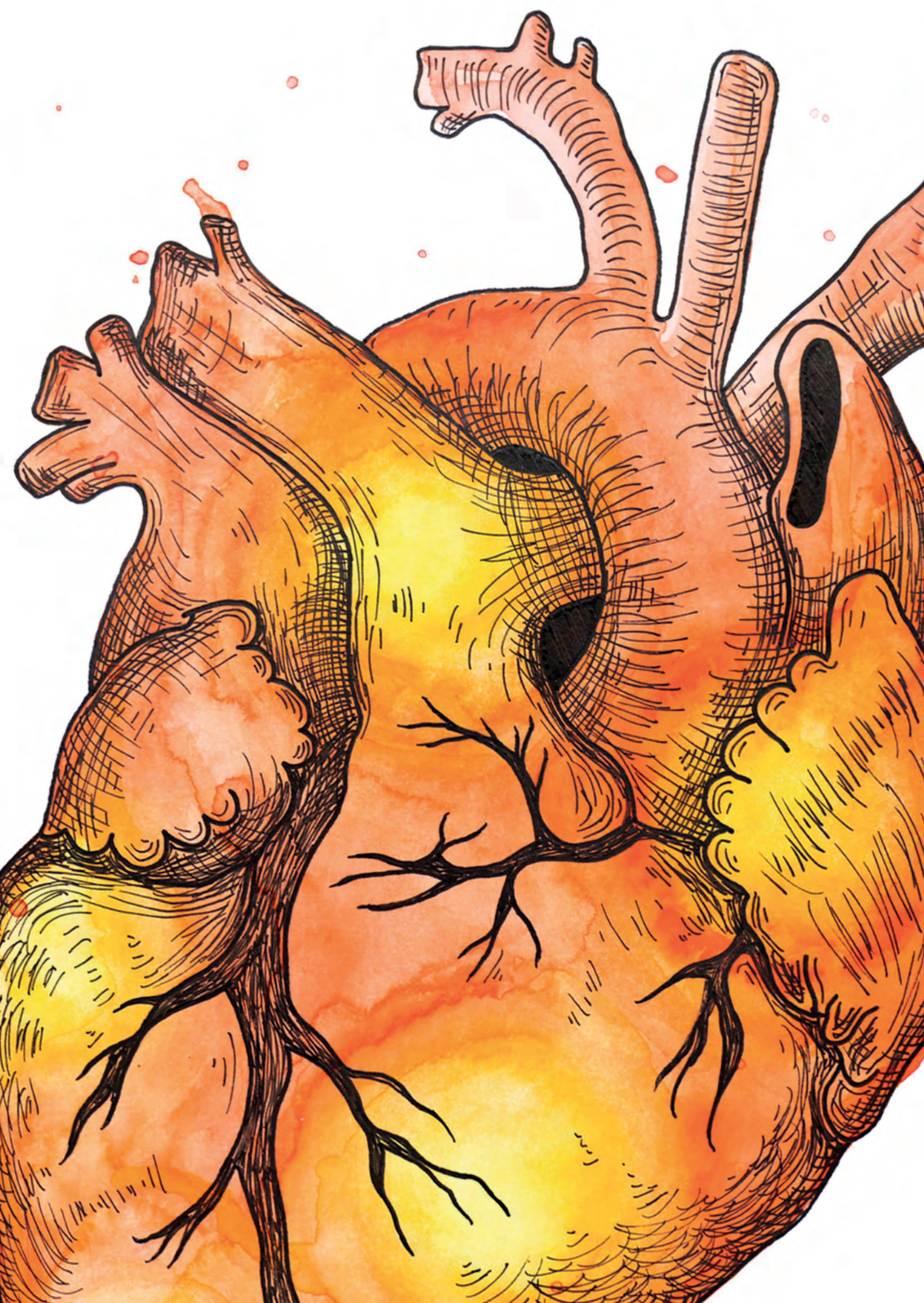
PART A

SARCOIDOSIS-ASSOCIATED PULMONARY HYPERTENSION



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Clinical phenotypes of sarcoidosis-associated pulmonary hypertension

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ABSTRACT

Background: Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis and its aetiology is unclear. Different pathophysiological mechanisms in sarcoidosis-associated pulmonary hypertension (SAPH) are known. Clinical phenotyping can aid clinicians in choosing the optimal treatment strategy. This study aimed to describe clinical phenotypes of SAPH and their characteristics.

Methods: A retrospective cohort study was performed on all SAPH patients at a tertiary referral centre. All patients were extensively analysed and discussed case by case in a multidisciplinary expert team to determine the most likely pathophysiological mechanism of PH. Patients were then classified into conceptual clinical phenotypes.

Results: Forty (40) patients with SAPH were identified between 2010 and 2019. Three patients were classified as the postcapillary phenotype. Of the remaining 37 patients with precapillary PH, six were classified as 'compression of pulmonary vasculature', 29 as 'parenchymal', one as 'suspected vasculopathy' and one as 'chronic pulmonary emboli' phenotypes. Of the patients with compression of pulmonary vasculature, four showed compression by fibrotic disease and two by active sarcoidosis-based disease. Within the parenchymal phenotype, 20 patients (69%) showed pulmonary vascular resistance >3.0WU and had significantly lower diffusing capacity of the lung for carbon monoxide compared with the nine patients (31%) with pulmonary vascular resistance ≤3.0WU.

Conclusion: SAPH has multiple pathophysiological mechanisms and clinical phenotypes in this retrospective study. Future studies are necessary to examine how these phenotypes can affect appropriate treatment and prognosis.

INTRODUCTION

Sarcoidosis is a rare systemic inflammatory disease of unknown aetiology. It is characterised by formation of non-caseating granulomas in the affected tissues. Pulmonary hypertension (PH) is a serious complication of sarcoidosis, with a suggested prevalence of 3-20%, and is associated with increased morbidity and mortality.[1–4] Based on the European PH guidelines, PH is classified into five different groups and within each group there is similar pathology, haemodynamics and therapeutic approaches.[5] Sarcoidosis-associated PH (SAPH) is classified into group V; this is based on the diverse underlying pathophysiological mechanism of SAPH. SAPH is most commonly due to destruction of pulmonary vasculature by fibrosis and subsequent hypoxaemia. However, SAPH can also occur in the absence of significant pulmonary fibrosis. Furthermore, there is a poor correlation between pulmonary function test results, blood gas tensions and pulmonary haemodynamics, which indicates that fibrosis and hypoxaemia alone cannot account for all.[3,6–8] Other mechanisms have been described, such as specific vasculopathy, left heart disease and extrinsic compression of the pulmonary vasculature.[3,9–11] Patients with sarcoidosis also have a higher prevalence of pulmonary emboli and sleep apnoea.[12–15] These different mechanisms might have implications for the disease, including therapy and prognosis.[9] Differentiating between clinical phenotypes of SAPH may guide clinicians, but this has only been described in review articles.[16,17] This study aimed to describe clinical phenotypes of SAPH based on the analysis of a single-centre cohort study. We report the analysis of demographics, pulmonary haemodynamics, aetiology, and functional parameters between clinical phenotypes of SAPH.

METHODS

Patient selection

All patients with sarcoidosis who were diagnosed with PH between 2010–2019 at the St. Antonius Hospital (The Netherlands), which is a tertiary referral centre for both sarcoidosis and PH, were identified and retrospectively studied by chart review. Sarcoidosis diagnosis was based on current guidelines.[18] The diagnosis of PH was based on the results of right heart catheterisation (RHC).[5] Local institutional review board approval was obtained.

Clinical and functional assessment

Echocardiography, laboratory testing, pulmonary function tests, chest X-rays and high-resolution chest computed tomography (HRCT) were performed for all patients within 6 months of RHC. If available, data regarding arterial blood gas analysis, ventilation

perfusion scintigraphy (V/Q scan), contrast-enhanced chest CT, pulmonary angiography, polysomnography (PSG), cardiac magnetic resonance imaging (CMR), and fluorodeoxyglucose positron emission tomography (FDG PET/CT) were obtained. Predicted values of the pulmonary function test were calculated according to the European Respiratory Society guidelines.[19] An experienced independent radiologist reviewed all chest X-rays and HRCTs. Scadding classification on chest X-ray was used to classify patients into Scadding stages 0-IV.[20] HRCT was evaluated for lung parenchymal abnormalities including ground-glass opacities, honeycombing, consolidations, emphysema, traction bronchiectasis, and fibrosis. The total disease extent was classified as not significant (<5% in the total lung area), intermediate (5-20%) or severe (>20%).[21] A V/Q scan was performed if chronic pulmonary emboli were suspected. A pulmonary angiography was performed when V/Q was abnormal. PSG was performed when obstructive sleep apnoea (OSA) was suspected. Diagnosis of OSA was based on an apnoea/hypopnoea index (AHI) >5 events/hour. Severity of OSA was classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI >30).[22] FDG PET/CT was used to determine sarcoidosis activity and location of disease. An experienced independent nuclear physician reviewed all FDG PET/CT-scans.

PH diagnosis

A diagnosis of PH was based on discussion by the multidisciplinary team (MDT) consisting of a cardiologist, pulmonologist, rheumatologist, radiologist, and nurse practitioner. PH was defined as a resting mean pulmonary artery pressure (mPAP) of ≥25 mmHg at RHC. Precapillary PH was defined as a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg, and PH was diagnosed as postcapillary if the PAWP was >15mmHg. In accordance with international guidelines, if the PAWP was elevated, a diastolic pressure gradient ≥7 mmHg and/or a pulmonary vascular resistance (PVR) >3.0 Wood Units (WU) were used to establish a diagnosis of combined postcapillary and precapillary PH.[5]

After discussion in the MDT, treatment was suggested according to the hypothesised pathophysiological mechanism. For study purposes, all patients were retrospectively classified in an unblinded manner into phenotype subgroups according to clinical characteristics and the most likely pathophysiological mechanism mentioned in the MDT report. The following clinical phenotypes classification were designed for this study:

- Postcapillary phenotype: patients with postcapillary PH, using a PAWP >15 mmHg as threshold.
- Compression phenotype: patients with precapillary PH and compression of pulmonary vasculature (central or segmental pulmonary arteries) by active sarcoidosis-based inflammation, calcified lymph nodes, fibrosis or fibrosing mediastinitis. The

presence of compression was assessed by contrast-enhanced chest CT or HRCT, and pulmonary angiography if necessary.

- Parenchymal phenotype: patients with precapillary PH with moderate-severe pulmonary parenchymal disease due to sarcoidosis. Patients had to fulfil one of the following criteria for moderate-severe pulmonary disease: Scadding type III or IV disease, severe obstructive (FEV1 ≤60%) or restrictive disease (FVC ≤70%). Patients of this phenotype were further stratified using PVR 3.0 WU as threshold.
- Suspected vasculopathy phenotype: patients with precapillary PH, PVR >3.0WU and a vasculopathy as the hypothesised mechanism of SAPH. Patients had no or mild pulmonary disease, defined as no obstructive (FEV1 >60%) or restrictive (FVC >70%) lung disease and minimal parenchymal changes on HRCT. Other causes of PH had to be excluded, such as severe OSA, chronic thromboembolic pulmonary hypertension (CTEPH), and compression of pulmonary vasculature.
- Chronic pulmonary emboli phenotype: presence of chronic pulmonary emboli detected by V/Q scan and confirmed by pulmonary angiography despite anticoagulation therapy for at least 3 months. This phenotype included sarcoidosis patients diagnosed with CTEPH.

Statistical analysis

Data were stored in the web-based datamanager REDCap. All statistical analyses were performed using SPSS Statistics for Windows, version 26 (Armonk, NY: IBM Corp). Descriptive statistics were used for both continuous and categorical variables. The chi-squared test or Fisher's Exact Test was used to compare categorical variables. The Student's t-test or Mann-Whitney U test was used to compare mean or median values of continuous variables. A two-tailed p-value <0.05 was considered significant.

RESULTS

Table 1 shows the baseline characteristics of the study population. Forty patients with both sarcoidosis and PH were identified. The cohort mainly consisted of male patients (60.0%), with a mean age of 59.0 ±12.2 years. Sarcoidosis was biopsy-proven in 85.0% of patients; the diagnosis in the other patients was based on consensus by an expert team. Functional capacity was impaired in 31 patients (77.5%), with a New York Heart Association functional class of III or IV. A PSG was performed in 19 patients, of whom 13 were diagnosed with OSA (median AHI 10.5/h). A V/Q scan to exclude chronic pulmonary emboli was performed in 22 patients.

Table 1. Characteristics of all patients

Variable	Value (n = 40)
Male	60.0%
Age (years)	59.0 ± 12.2
Caucasian ethnicity	72.5%
Body mass index (kg/m^2)	27.3 ± 5.1
Biopsy-proven sarcoidosis	85.0%
Time between sarcoidosis diagnosis and PH diagnosis (years)	12.1 [7.0 – 21.0]
Scadding stage IV	80.0%
FDG PET/CT activity (n = 35)	88.6%
Current immunosuppressive treatment - Corticosteroids - Non-steroid agents	75.0% - 52.5% - 45.0%
NYHA functional class - II - III - IV	 - 22.5% - 70.0% - 7.5%
Comorbidities	
Obstructive sleep apnoea	32.5%
Active or past smoker	45.0%
COPD	7.5%
Hypoxaemia requiring oxygen usage	42.5%
History of pulmonary embolism	12.5%
Cardiac sarcoidosis	10.0%
Pulmonary function tests	
FEV1 %pred	49.9 ± 17.2
FVC %pred	63.3 ± 22.5
FEV1/FVC	68.6 ± 18.0
$DLCO_{SB}$ %pred (n = 33)	46.5 ± 20.7
Chest HRCT	
Total disease extend - <5% - 5-20% - >20%	 5.0% 12.5% 82.5%
Pulmonary haemodynamics	
Mean PAP (mmHg)	37.0 ± 10.7
PAWP (mmHg)	10.1 ± 4.0
Cardiac output (L/min)	5.8 ± 1.9
Pulmonary vascular resistance (Wood Units)	5.5 ± 3.3

COPD = chronic obstructive pulmonary disease; $DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension

As shown in figure 1, all patients except for one could be classified into different clinical phenotypes. This patient (Scadding II) had only mild parenchymal lung disease with a preserved FVC and FEV1. However, this patient showed a mildly elevated mPAP of 26mmHg and low PVR of 2.6WU. Other causes such as compression of pulmonary vasculature, OSA and chronic pulmonary emboli were ruled out. Therefore, this patient was classified as the parenchymal phenotype. Pulmonary haemodynamics of all phenotypes are shown in table 2. Supplementary table S1 shows baseline characteristics of all phenotypes.

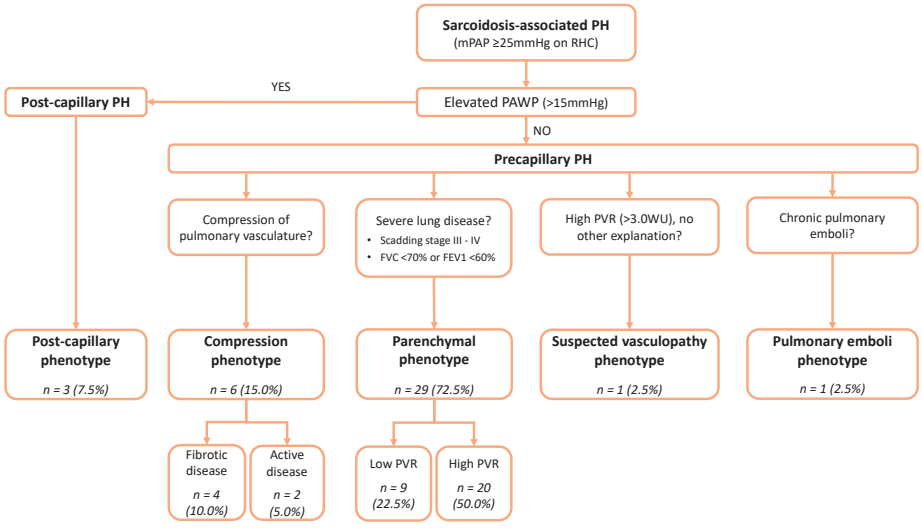

Figure 1. Flowchart of SAPH phenotype classification.

Table 2. Pulmonary haemodynamics of all phenotypes

	Postcapillary phenotype (n=3)	Compression phenotype (n=6)	Parenchymal phenotype (n=29)	Suspected vasculopathy phenotype (n=1)	Pulmonary emboli phenotype (n=1)
Right atrial pressure (mmHg)	9.0 [8.0 – 10.0]	6.0 [4.0 – 10.8]	6.0 [3.5 – 7.5]	8.0	4.0
Systolic PAP (mmHg)	65.0 [52.0 – 85.0]	72.5 [42.5 – 106.3]	50.0 [44.0 – 66.0]	40.0	55.0
Diastolic PAP (mmHg)	25.0 [18.0 – 28.0]	29.5 [20.0 – 40.0]	25.0 [19.5 – 30.0]	28.0	33.0
Mean PAP (mmHg)	38.3 [36.0 – 40.3]	42.5 [29.5 – 62.1]	34.7 [26.8 – 42.0]	32.0	40.3
PAWP (mmHg)	18.0 [16.0 – 22.0]	8.0 [4.8 – 10.0]	10.0 [7.5 – 12.0]	10.0	6.0
Cardiac output (L/min)	8.5 [6.0 – 8.5]	5.7 [3.8 – 7.5]	5.1 [4.5 – 6.4]	7.0	7.2
PVR (Wood Units)	2.4 [1.9 – 3.7]	7.3 [2.6 – 10.9]	4.6 [2.7 – 8.1]	3.1	4.8

PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance

Postcapillary phenotype

Of the three patients (7.5%) classified as postcapillary phenotype, one was diagnosed with isolated postcapillary PH and two with combined postcapillary and precapillary PH. The patient with isolated postcapillary PH presented with a mPAP of 38 mmHg, a PAWP of 22 mmHg and a diastolic pressure gradient of 3 mmHg, with a normal systolic but impaired diastolic left ventricular (LV) function. There was no significant valve disease and there were no signs of cardiac sarcoidosis on CMR and FDG PET/CT. The two patients with combined precapillary and postcapillary PH (mPAP 36 mmHg and 40 mmHg, PAWP 15 mmHg and 18mmHg, PVR 2.4 WU and 3.7 WU) were both in Scadding stage IV and showed diastolic dysfunction with preserved systolic function on echocardiography. CMR was not performed; however, there were no suggestive symptoms of cardiac sarcoidosis and FDG PET/CT was negative in one patient.

Compression phenotype

Six patients (15.0%) showed compression of pulmonary vasculature. The baseline characteristics are shown in supplementary table S2. In four patients, compression of pulmonary vasculature was due to fibrosis or calcified lymph nodes, as seen on HRCT. One of these patients was diagnosed with fibrosing mediastinitis. All four patients had severe parenchymal lung disease (Scadding stage IV). The remaining two patients showed compression by an active inflammatory process confirmed by FDG PET/CT (figure 2). Both patients (Scadding stages I and IV) responded well to immunosuppressive treatment. After 6 months, they showed improvement in functional capacity and normalisation of PAP on echocardiography.

Parenchymal phenotype

Twenty-nine patients (72.5%) were classified as the parenchymal phenotype, including the patient mentioned earlier with moderate parenchymal disease. Scadding stage IV was seen in 24 patients, stage III in one patient and stage II was seen in three patients. These three patients showed parenchymal disease on HRCT, with reduced FEV1 and FVC values. All patients within the parenchymal phenotype were further categorised into two groups according to pulmonary haemodynamics, using PVR >3.0 WU as threshold. In total, 20 patients showed a PVR >3.0 WU. Characteristics of both groups are shown in supplementary table S3. Comparing baseline characteristics, patients with PVR >3.0 WU showed a significantly lower DLCO %pred (35.7 vs 67.0, p=0.016) and more groundglass opacities on HRCT (55% vs 0%, p=0.005). There was a trend towards worse New York Heart Association functional class (p=0.056) and lower FVC (p=0.095).

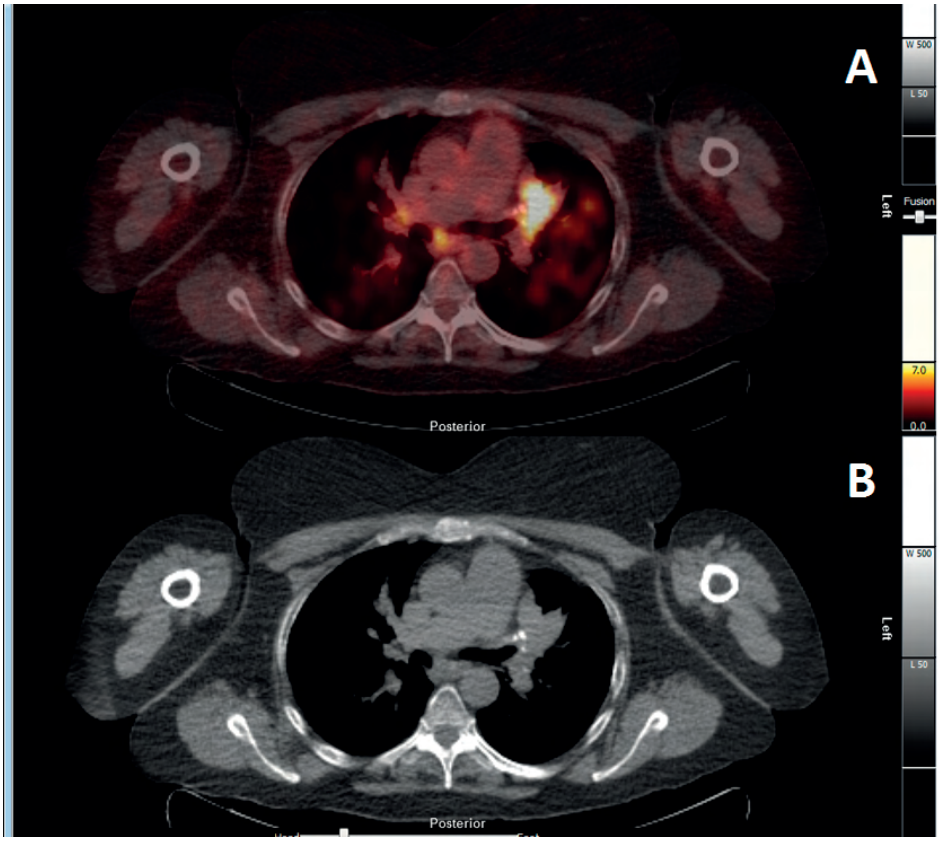

Figure 2. Example of compression by active disease on FDG PET/CT (A) and chest CT (B).

Suspected vasculopathy phenotype

One patient was classified as suspected vasculopathy phenotype. This patient showed Scadding stage I disease with <20% disease extent on HRCT. He had been diagnosed with OSA several years ago and had been successfully treated, showing an AHI 1.6/h on his latest PSG. RHC showed precapillary PH with mPAP 32mmHg and PVR 3.1WU. Chronic pulmonary emboli and compression of pulmonary vasculature were ruled out and FDG PET/CT showed no uptake. He was classified as suspected vasculopathy phenotype and treated with PH-targeted therapies.

Chronic pulmonary emboli phenotype

One patient (2.5%) was diagnosed with CTEPH. RHC showed mPAP 40 mmHg and PVR 4.8 WU. The V/Q scan was suggestive of chronic pulmonary emboli, which was confirmed by pulmonary angiography with no signs of extrinsic compression. This patient had been diagnosed with sarcoidosis 22 years previously and showed Scadding stage IV disease

with severe parenchymal disease on HRCT. PH-targeted therapies were started after diagnosis. After 6 months of treatment, the 6-minute walking distance and estimated right ventricular systolic pressure on echocardiography showed improvement; however, there was no improvement in functional class.

DISCUSSION

This is the first study to classify a cohort of SAPH patients into clinical phenotypes according to the underlying pathophysiological mechanisms and pulmonary haemodynamics. In this cohort, postcapillary PH was found in 7.5% and precapillary in 92.5% of patients. The majority of patients with precapillary PH had severe pulmonary disease. Nevertheless, the presence of fibrosis is not essential for the development of SAPH, as 20.0% showed no fibrosis. This single-centre population showed many similarities in terms of severity of pulmonary disease and haemodynamics with the ReSAPH registry.[23] Populations differed, as the majority of the ReSAPH population consisted of African-Americans and females. Besides haemodynamics and pulmonary disease severity, the ReSAPH registry describes no other pathophysiological mechanisms. Different reviews have addressed this subject, although only two published reviews have proposed different phenotypes.[16,17] The current clinical phenotype classification system is based on the underlying pathophysiological mechanisms, as described in previous studies.[24,25] Most phenotypes were based on clear-cut diagnostic criteria; however, the suspected vasculopathy phenotype was more difficult to define. Nathan et al. described several criteria to discriminate between Group 1 (pulmonary arterial hypertension) and group 3 (severe lung disease) as a cause of PH in patients with chronic lung disease and PH. These criteria use pulmonary haemodynamics, extent of parenchymal disease and pulmonary function variables to stratify patients. This led to the criteria of PVR >3.0 WU in the absence of other explanations, including severe lung disease, to classify one patient as the suspected vasculopathy phenotype. Furthermore, the distinction between PH due to chronic lung disease and pulmonary arterial hypertension is difficult, as the spectrum of severity of both the pulmonary vascular and parenchymal lung disease is most likely a continuum. This is shown in patients classified as the parenchymal phenotype, where large differences in pulmonary haemodynamics were seen. Patients with high PVR had a significantly lower DLCO as %pred and a trend towards lower functional class and lower FVC %pred. Interestingly, most patients in both groups presented with Scadding stage IV sarcoidosis and similar radiological features, which indicates that the difference in pulmonary haemodynamics is most likely driven by worsening vasculopathy. Whether this has consequences for prognosis or therapy needs to be investigated. The ReSAPH

registry showed that the severity of pulmonary haemodynamics is not associated with worse outcomes.[26] However, lower DLCO is associated with worse outcome.[10,26]

In this population, 7.5% of patients were classified as postcapillary phenotype, compared with 16-29% reported in literature.[9,23] Baughman et al. reported impaired LV systolic function in 35% of patients in the postcapillary PH group, whereas LV diastolic dysfunction was observed in all postcapillary PH patients in the current study. This could be clinically important, since LV diastolic dysfunction in patients with sarcoidosis can be a first sign of cardiac sarcoidosis.[27] Compression of the pulmonary vasculature was found in 15% of patients. Remarkably, patients with compression by fibrotic disease or calcified lymph nodes showed higher mPAP and PVR compared to patients with compression by active disease, although statistical significance was not reached due to the low number of patients. Patients with compression by active disease showed a very good clinical and haemodynamic response to immunosuppressive therapy. This has previously been reported [3,10] and suggests that PH secondary to extrinsic compression due to an inflammatory process may be (partially) reversible. One patient showed chronic pulmonary emboli. An important limitation is that a V/Q scan was only performed for 22 patients. The risk of pulmonary emboli is higher in the sarcoidosis population compared with controls.[14,15,28] However, the association between CTEPH and sarcoidosis leading to PH has only been described in one case series.[29] According to current PH guidelines a V/Q scan should be performed in patients with precapillary PH to exclude chronic pulmonary emboli, since this might have major clinical consequences.[5]

Limitations

There were several limitations to this study. The classification into phenotypes was based on clinical features and not on histopathological findings. Therefore, other pathophysiological mechanisms such as pulmonary veno-occlusive disease were not taken into account for phenotype classification. Second, the used classification system could imply that patients with multiple pathophysiological mechanisms cannot be classified. Each individual SAPH patient has to be fully assessed and multiple phenotypes are possible, as SAPH is based on a multifactorial mechanism. In addition, patients can switch between phenotypes during the course of their disease. Another limitation was the retrospective character of the study. All data were obtained by chart review and not all patients had a complete diagnostic workup. Also, patients were classified in an unblinded manner, which could impact our results. Blinding could have been useful to prevent possible bias. Furthermore, the time interval between different assessments and RHC could be up to 6 months. During this interval, other events such as new sarcoidosis-based inflammation could have impacted RHC results. Finally, the clinical setting was a tertiary-care hospital where selection bias towards patients with

more advanced disease is inevitable, which could influence the prevalence of the found phenotypes and comorbidities. Nevertheless, SAPH is a rare entity and its diagnosis and treatment should be performed in a PH expertise centre.

CONCLUSION

SAPH has multiple pathophysiological mechanisms and clinical phenotyping can be helpful to differentiate between these mechanisms. The majority of patients present with precapillary PH and the parenchymal phenotype is most common. Clinical phenotyping can be a first step towards personalised therapeutic decision-making in SAPH patients. However, the prognostic implications of the proposed phenotypes need to be examined in future studies.

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Supplementary table S1. Baseline characteristics of different phenotypes

	Postcapillary phenotype (n=3)	Compression phenotype (n=6)	Parenchymal phenotype (n=29)	Suspected vasculopathy phenotype (n=1)	Pulmonary emboli phenotype (n=1)
Male sex	66.7%	50.0%	58.6%	100%	100%
Age (years)	63.6 [70.0 – 84.0]	64.5 [58.1 – 71.4]	59.1 [46.7 – 65.6]	71.7	67.1
Duration of disease (years)	20.2 [6.9 – 23.1]	15.9 [6.9 – 28.8]	10.6 [6.5 – 18.0]	8.0	22.8
Scadding stage IV	66.7%	83.3%	82.8%	0%	100%
Immunosuppressive treatment	0%	33.3%	89.7%	100%	100%
- NYHA functional class I-II	0%	50%	20.7%	0%	0%
- NYHA functional class III-IV	100%	50%	79,3%	100%	100%
Comorbidities					
Obstructive sleep apnoea	100%	33.3%	24.1%	100%	0%
Hypoxaemia requiring oxygen usage	33.3%	33.3%	48.3%	0%	100%
Pulmonary function					
FVC %pred	70.3 [68.7 – 71.0]	53.3 [50.1 – 103.3]	66.6 [44.1 – 77.5]	54.0	63.0
$DLCO_{SB}$ %pred	53.0 [22.8 – 74.5]	36.1 [30.5 – 69.3]	40.2 [29.3 – 63.4]	62.0	25.0
Total disease extend on HRCT					
- <20%	33.3%	16.7%	13.8%	100%	0%
- >20%	66.7%	83.3%	86.2%	0%	100%

$DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association

Supplementary table S2. Characteristics of patients with compression of pulmonary vasculature

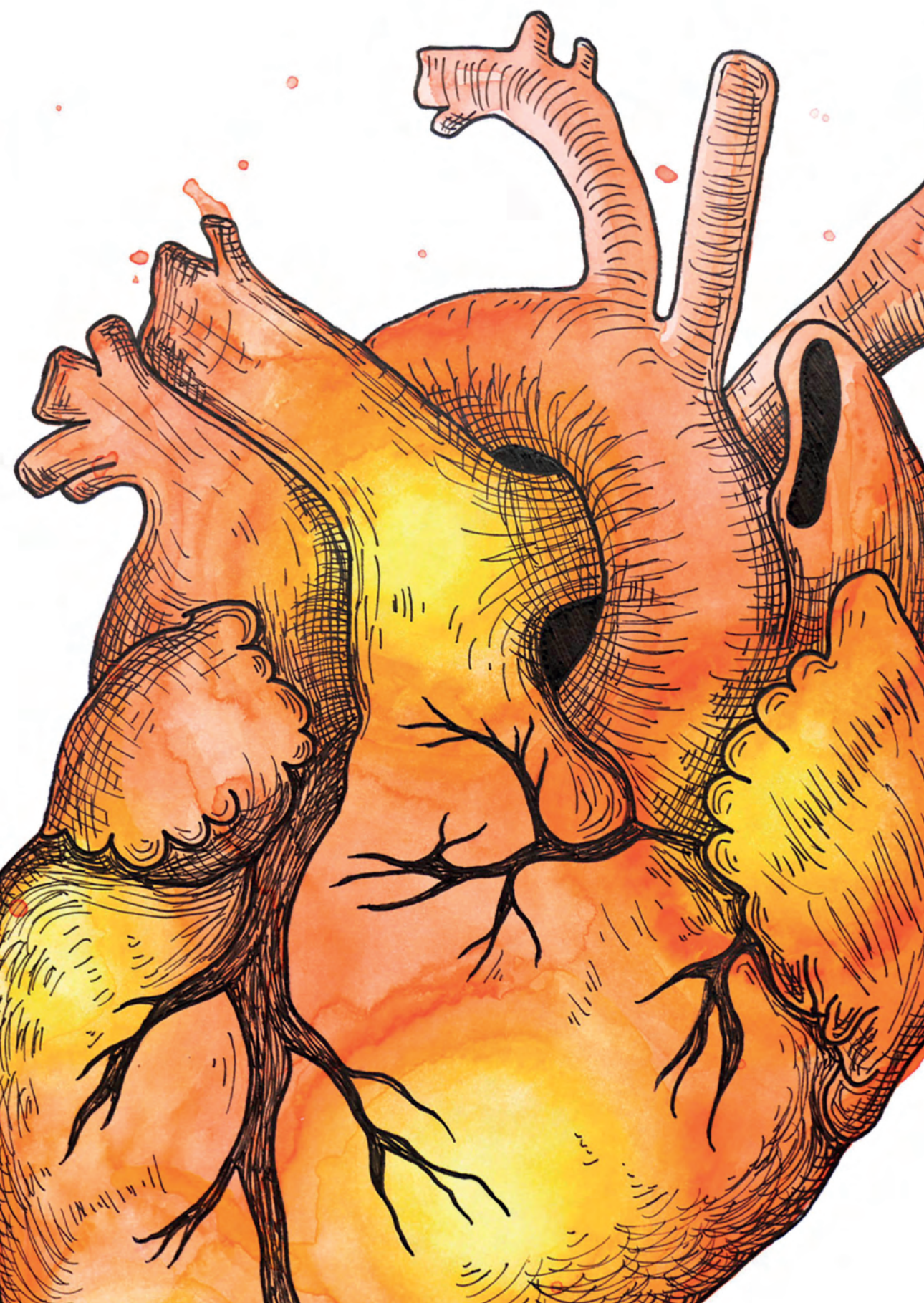
	Compression by fibrotic disease (n=4)	Compression by active inflammation (n=2)
Male	1	2
Age (years)	64.5 [59.6 – 70.0]	54.7 – 78.5
Duration of disease (years)	19.4 [10.3 – 41.2]	2.8 – 15.4
Scadding stage IV	4	1
Immunosuppressive treatment	2	0
- NYHA functional class I-II - NYHA functional class III-IV	1 3	2 0
Pulmonary function		
FVC %pred	50.7 [49.5 – 89.3]	55.6 – 107.0
$DLCO_{SB}$ %pred	36.1 [19.4 – 66.0]	36.0 – 67.0
Total disease extend on HRCT - <20% - >20%	 0 4	 1 1
Pulmonary haemodynamics		
Mean PAP (mmHg)	56.7 [37.9 – 62.9]	25.0 – 31.0
PAWP (mmHg)	5.5 [4.3 – 9.0]	10.0 – 10.0
Cardiac output (L/min)	4.8 [3.7 – 6.8]	5.8 – 8.3
PVR (Wood Units)	8.9 [7.3 – 12.3]	2.5 – 2.6

$DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance

Supplementary table S3. Characteristics of parenchymal phenotype

	PVR ≤ 3.0WU (n=9)	PVR >3.0WU (n=20)	p-value
Male	55.6%	60%	NS
Age (years)	58.8 [43.8 – 61.3]	59.1 [46.2 – 66.0]	NS
- Caucasian ethnicity - Non-Caucasian ethnicity	55.6% 44.4%	70% 30%	NS
Duration of disease (years)	9.1 [3.1 – 13.3]	12.4 [7.0 – 21.0]	NS
Scadding stage IV	77.8%	85%	NS
FDG PET/CT activity	100% (n=6)	80% (n=19)	NS
Immunosuppressive treatment	77.8%	95%	NS
- NYHA functional class I-II - NYHA functional class III-IV	44.4% 55.6%	10% 90%	0.056
Hypoxaemia requiring O2 usage	22.2%	60%	NS
Pulmonary function tests			
FEV1 %pred	49.0 [39.6 – 71.5]	46.1 [31.9 - 52.0]	NS
FVC %pred	79.0 [46.1 – 94.0]	63.6 [43.9 – 71.9]	0.095
$DLCO_{SB}$ %pred	67.0 [55.0 – 76.0]	35.7 [28.1 – 47.3]	0.016
Chest HRCT			
Groundglass	0%	55%	0.005
Honeycombing	22.2%	30%	NS
Consolidations	55.6%	40%	NS
Traction bronchiectasis	77.8%	80%	NS
Emphysema	11.1%	25%	NS
Total disease extend - <20% - >-20%	 22.2% 77.8%	 15% 85%	NS
Pulmonary haemodynamics			
Mean PAP (mmHg)	26.3 [25.7 – 28.3]	38.7 [32.4 – 43.7]	
PAWP (mmHg)	12.0 [10.0 – 13.5]	9.5 [6.0 – 11.8]	
Cardiac output (L/min)	7.4 [5.5 – 8.3]	4.9 [3.7 – 5.5]	
PVR (Wood Units)	2.3 [1.7 – 2.7]	6.6 [4.5 – 9.5]	

$DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance



3

Value of echocardiography using knowledge-based reconstruction in determining right ventricular volumes in pulmonary sarcoidosis: comparison with cardiac magnetic resonance imaging

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ABSTRACT

Background: Right ventricular (RV) dysfunction in sarcoidosis is associated with adverse outcomes. Assessment of RV function by conventional transthoracic echocardiography (TTE) is challenging due to the complex RV geometry. Knowledge-based reconstruction (KBR) combines TTE measurements with three-dimensional coordinates to determine RV volumes. The aim of this study was to investigate the accuracy of TTE-KBR compared to the gold standard cardiac magnetic resonance imaging (CMR) in determining RV dimensions in pulmonary sarcoidosis.

Methods: Pulmonary sarcoidosis patients prospectively received same-day TTE and TTE-KBR. If performed, CMR within 90 days after TTE-KBR was used as reference standard. Outcome parameters included RV end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke volume (RVSV) and ejection fraction (RVEF).

Results: 281 patients underwent same day TTE and TTE-KBR. In total, 122 patients received a CMR within 90 days of TTE and were included. TTE-KBR measured RVEDV and RVESV showed strong correlation with CMR measurements (R=0.73, R=0.76), while RVSV and RVEF correlated weakly (R=0.46, R=0.46). Bland-Altman analyses (mean bias ±95% limits of agreement), showed good agreement for RVEDV ($\Delta RVEDV_{KBR\text{-}CMR}$, 5.67 ± 55.4mL), while RVESV, RVSV and RVEF showed poor agreement ($\Delta RVESV_{KBR\text{-}CMR}$, 21.6 ± 34.1mL; $\Delta RVSV_{KBR\text{-}CMR}$, -16.1 ± 42.9mL; $\Delta RVEF_{KBR\text{-}CMR}$, -12.9 ± 16.4%). The image quality and time between CMR and TTE-KBR showed no impact on intermodality differences and there was no sign of a possible learning curve.

Conclusion: TTE-KBR is convenient and shows good agreement with CMR for RVEDV. However, there is poor agreement for RVESV, RVSV and RVEF. The use of TTE-KBR does not seem to provide additional value in the determination of RV dimensions in pulmonary sarcoidosis patients.

INTRODUCTION

Sarcoidosis is a rare systemic inflammatory disease of unknown etiology. It is characterized by formation of non-caseating granulomas in affected tissues. Sarcoidosis may manifest in different organs, most often the lungs and lymphatic system. Right ventricular (RV) dysfunction in sarcoidosis is associated with an increased prevalence of pulmonary hypertension (PH) and adverse outcomes.[1–3] Assessment of RV function by conventional transthoracic echocardiography (TTE) is challenging due to the complex crescent shape of the RV, which cannot be properly visualized in single two-dimensional views.[4] Cardiac magnetic resonance imaging (CMR) is the gold standard for evaluating RV volumes and function.[5,6] However, the use of CMR is limited by high costs, long procedural times and several limitations. To bridge the gap between both imaging modalities, TTE with knowledge-based reconstruction (KBR) is increasingly used for imaging the right heart. This method uses conventional TTE images to construct a RV three-dimensional image, which is compared to a database of RV shapes based on CMR. TTE-KBR correlated well with CMR in determination of RV volumes and function in both PH and congenital heart disease populations.[7–10] Also, it demonstrated good inter- and intra-observer reproducibility. However, little is known about the utility of TTE-KBR in populations with interstitial lung diseases such as sarcoidosis, with predominantly normal RV dimensions. The goal of this study is to investigate the value of TTE-KBR compared to CMR in the determination of RV volumes and function in a large pulmonary sarcoidosis population.

METHODS

We performed a single-centre, prospective, cross-sectional study. The study was in compliance with the principles outlined in the Declaration of Helsinki, and was approved by the MEC-U Institutional Review Board (NL49594.100.14). Between August 2015 and November 2018, all consecutive pulmonary sarcoidosis patients who were newly referred to the pulmonary outpatient clinic of the St. Antonius Hospital, a tertiary care centre for sarcoidosis, were invited to participate in this study. Furthermore, sarcoidosis patients visiting our pulmonary outpatient clinic with symptoms or signs for PH, based on the interpretation of the treating physician, who were referred for PH screening, were invited. Written informed consent was obtained from all participating patients.

Inclusion criteria were: an age of 18 years or above, a diagnosis of sarcoidosis according to current guidelines[11] and a CMR within 90 days of TTE-KBR. Patients with a pacemaker were excluded from TTE-KBR, since safety of this technique in patients with pacemakers

had not yet been determined at the time of the study. The decision to perform a CMR was at the discretion of the treating physician, as CMR was not part of the study workup. In most cases, suspected cardiac sarcoidosis was the reason to perform a CMR. At baseline, medical history, self-reported ethnicity, New York Heart Association functional class, pulmonary function test and laboratory testing were obtained. Both TTE and TTE-KBR were performed prospectively. Predicted values of the pulmonary function test were calculated according to the European Respiratory Society guidelines.[12] PH was defined as mean pulmonary artery pressure ≥25 mmHg measured by right heart catheterization.[13]

Echocardiography and KBR

All TTE and TTE-KBR acquisition and analysis were performed and analyzed by the same experienced physician (M.P.H.). The echocardiogram was considered inconclusive if image quality was too poor, or in case of a pulmonary valve stenosis. TTE images were acquired using standard ultrasound equipment (iE33 system and S5 transducer; Philips Medical Systems). Right heart metrics were measured according to Rudski et al.[14] TTE-KBR images were made according to the VentriPoint user guide, by adding a magnetic localizer attached to the S5 transducer and a magnetic field generator hanging above the patient (VentriPoint Diagnostics Ltd. Seattle, USA). Before each study, the optimal ultrasound depth for the visualization of all relevant structures were determined and pre-set in the specialized console. Throughout the imaging protocol, the patients remained entirely stationary in the left lateral decubitus position. A series of standard and nonstandard TTE views were obtained: parasternal long and short axis, RV inflow and outflow tract, standard apical four-chamber and focused RV apical. Each acquisition consisted of two or three heartbeats during breath holds, preferably end-expiratory. Image analysis was performed using the VentriPoint software. End-diastolic and end-systolic time point was selected as the time at which RV volume was the largest and smallest respectively. The same end-diastole to end-systole interval was applied to all other acquisitions. A minimum of nine points corresponding to several predefined anatomic landmarks were required for a reconstruction model of the right heart and placed in both end-diastole and end-systole. RV endocardial points were placed at the base of trabeculations. A proprietary algorithm, KBR (VentriPoint Diagnostics Ltd), processes the images into a three-dimensional model of the right ventricle at end-diastole (figure 1). This model is compared with a database of RV shapes based on CMR. TTE images with superimposed outlines of the three-dimensional model were reviewed by adding and deleting points as needed and reprocessed. In cases of obvious border misalignment (suggesting shifts in the patients position), all points were deleted and the images were excluded from the model. For end-systolic measurements the same procedure was executed, resulting in both an end-diastolic and end-systolic model. Finally, a nested view of both models was

reviewed to confirm appropriate alignment of tricuspid and pulmonic annular planes. RV end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke volume (RVSV) and ejection fraction (RVEF) were calculated using these models.

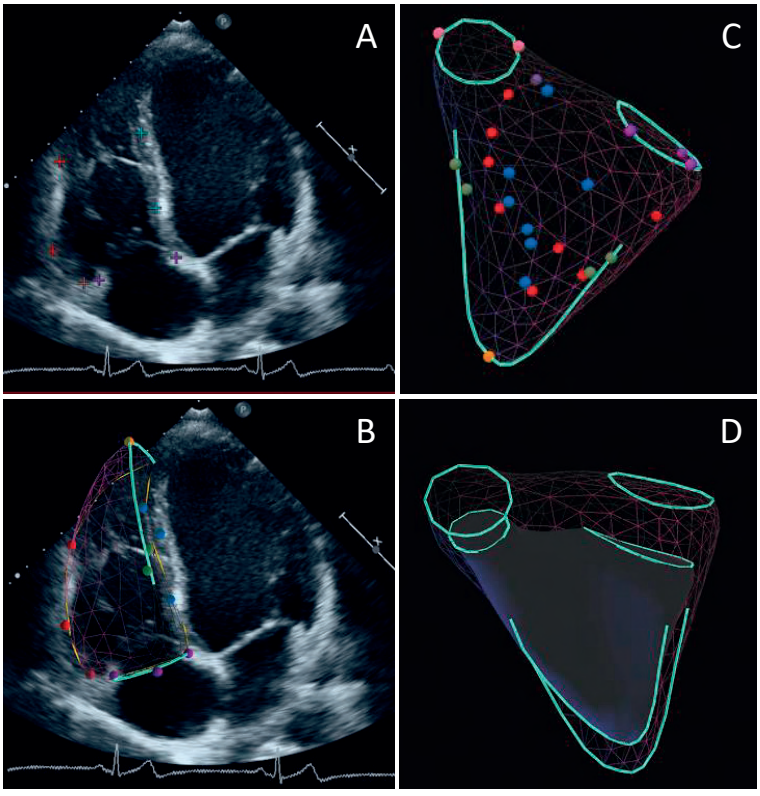

Figure 1. Transthoracic echocardiographic images of the standard apical four-chamber view with points placed to define anatomic landmarks (A) and borders of the three-dimensional model (B). Three-dimensional model of the right ventricle at end-diastole. The two circles represent the position of the tricuspid and pulmonary valves (C). Nested view of the end-diastolic and end-systolic RV model (D). Different colors represent different anatomic landmarks: red = RV endocardium, blue = RV septum, brown = basal bulge, violet = tricuspid annulus, pink = pulmonic annulus, green = RV septal edge, orange = RV apex.

CMR acquisition and analysis

CMR was performed using a 1.5T Philips MRI scanner with an eight-element phased-array cardiac coil. A vector electrocardiographic system was used for cardiac gating. A stack of short-axis cine slices of both the RV and left ventricle (8-mm thickness, no gap) from the base to the apex of the entire heart were acquired. Cine images were obtained during end-expiratory breath holds. Analysis was performed offline on a workstation using Philips Intellispace Portal® software (version 10.1). Based on the short axis cine slices, ventricular volumes and EFs were calculated using Simpson's method of disks. Endo-

cardial RV borders were traced manually at end-diastole and end-systole, which were identified by the largest and smallest RV cavity areas, respectively. SV was the difference between EDV and ESV. EF was calculated as (SV/EDV) × 100%. RV dysfunction was defined as an EF <40% in males and <45% in females.[15] All measurements were performed by a single experienced observer (F.A.) who was blinded to TTE and TTE-KBR results.

Statistical analysis

Data were stored in the web-based datamanager REDCap. All statistical analyses were performed using SPSS Statistics, version 26.0 for Windows (Armonk, NY:IBM Corp). Descriptive statistics were used for both continuous and categorical variables. All continuous data were expressed as mean ± standard deviation or median [interquartile range]. The chi-squared test and Fisher's Exact Test were used to compare categorical variables. The student's paired t-test was used to compare TTE-KBR and CMR-derived RV dimensions. The student's unpaired t-test or Mann-Whitney U test was used to compare means or medians of unpaired variables. A two-tailed p-value of <0.05 was considered significant. The relationship between variables was evaluated using Pearson or Spearman correlation analysis. A correlation coefficient >0.7 was considered strong, between 0.5-0.7 moderate and <0.5 weak. In addition, Bland-Altman analysis was performed to assess intermodality agreement, in terms of mean bias (average difference between measurements) and 95% limits of agreement.

RESULTS

Figure 2 shows the flowchart for patient selection. Image quality of TTE-KBR was sufficient for 265 of 281 patients, resulting in a feasibility of 94.3%. In total, 122 patients had a CMR within 90 days of TTE-KBR and were included for analysis. Baseline characteristics are shown in table 1. Sarcoidosis diagnosis was biopsy proven in 78.7%. In 21.3% a clinical diagnosis was made based on clinical, laboratory and radiological findings. Cardiac involvement was diagnosed in 9.8% of patients. Compared to patients who did not undergo CMR within this timeframe, included patients had a significantly higher prevalence of obstructive sleep apnea (22.1% vs 11.2%, p=0.016), higher tricuspid annulus velocity as measured by tissue Doppler imaging (12.7 cm/s vs 12.2 cm/s, p=0.042) and a higher New York Heart Association functional class (24.5% vs 11.9% in class III, p=0.007) (supplementary table S1). TTE-KBR measurements did not differ between both groups.

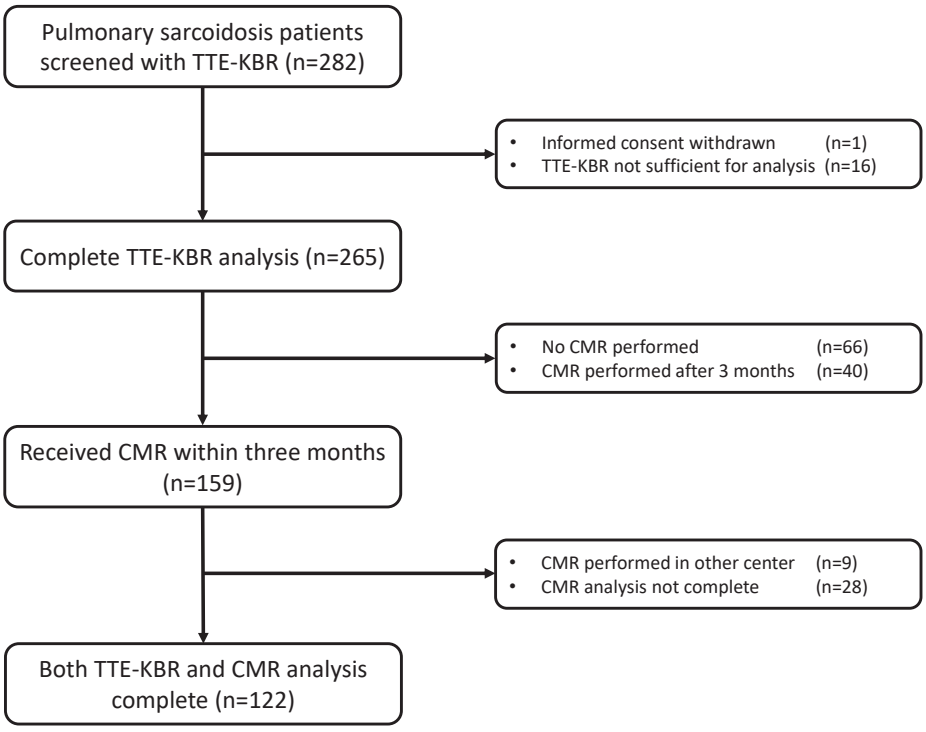

Figure 2. Flowchart showing patient selection.

Accuracy of TTE-KBR

Mean time between TTE-KBR and CMR was 37.8 ± 22.2 days. Image quality of TTE-KBR was bad, moderate and good in 9.8%, 45.1% and 45.1% of patients respectively. Table 2 shows the comparison of RV volumes and EF between TTE-KBR and CMR. All RV parameters showed significant differences. As figure 3 shows, correlation was strong for both RVEDV (*R*=0.73) and RVESV (*R*=0.76) and weak for both RVSV (*R*=0.46) and RVEF (*R*=0.46). Comparison of the TTE-KBR and CMR results with Bland-Altman statistics are shown in figure 4. There was good agreement for RVEDV with a marginal overestimation ($\Delta RVEDV_{KBR\text{-}CMR}$, 5.67 ±55.4 mL), and poor agreement for RVESV with a large overestimation ($\Delta RVESV_{KBR\text{-}CMR}$, 21.6 ± 34.1 mL). For both RVSV and RVEF there was a large underestimation ($\Delta RVSV_{KBR\text{-}CMR}$, -16.1 ± 42.9 mL; $\Delta RVEF_{KBR\text{-}CMR}$, -12.9 ± 16.4%). RV dysfunction was present in 4.9% of patients based on CMR. No impact on the intermodality differences was seen when taking only patients with at least moderate image quality or time between TTE-KBR and CMR <30 days into account and there were no signs of a possible learning curve. Comparison between patients with and without PH or with and without CS showed no significant differences in RV dimensions of both TTE-KBR and CMR (supplementary

tables S2 and S3). Although there was a trend towards a higher RVESV (median 71.0 vs 58.0mL, p=0.08) and lower RVEF (median 57.0% vs 60.0%, p=0.09) on CMR in patients with PH. Echocardiographic RV parameters, pulmonary function values, laboratory testing (including NT-proBNP), pulmonary artery diameter on chest CT, Scadding stage and functional class all showed a weak or no correlation with both TTE-KBR and CMR derived RV dimensions. Supplementary tables S4 and S5 show all correlation values.

Table 1. Baseline characteristics

Variable	Value (n=122)
Age (years)	50.9 ± 12.0
Male	54.1%
Body mass index (m^2/kg)	27.8 ± 4.6
Body surface area (m^2)	2.01 ± 0.21
Caucasian ethnicity	87.7%
Biopsy-confirmed sarcoidosis	78.7%
Duration of disease (years)	2.3 [0.6 – 8.3]
Immunosuppressive therapy - Steroid monotherapy - Non-steroid monotherapy - Combination therapy	41.8% - 18.9% - 18.0% - 4.9%
Scadding stage (0 / I / II / III / IV)	25.0 / 22.4 / 21.6 / 2.6 / 28.4% (n=116)
NYHA functional class (I, II, III, IV)	23.0 / 52.5 / 24.5 / 0%
LVEF measured by CMR (%)	58.2 ± 7.1
Pulmonary function, laboratory testing	
FVC % of predicted	96.4 ± 18.2
FEV1 % of predicted	87.3 ± 19.6
$DLCO_{SB}$ % of predicted	73.7 ± 17.1
NT-proBNP (pg/mL)	54.0 [28.0 – 97.5]
Comorbidities	
Hypertension	22.1%
Prior coronary artery disease	4.1%
Obstructive sleep apnea	22.1%
Pulmonary hypertension	4.1%
Cardiac sarcoidosis	9.8%
Echocardiography	
TAPSE (mm)	22.4 ± 4.2 (n=120)
Tricuspidal annulus velocity by TDI (cm/s)	12.7 ± 2.2 (n=115)
Right ventricular systolic pressure (mmHg)	28.4 ± 8.4 (n=60)

$DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging

Table 2. Right ventricular dimensions measured by TTE-KBR and CMR

	TTE-KBR (n=122)	CMR (n=122)	p-value Paired t-test	Pearson rho
EDV (mL)	155.9 ± 39.5	150.2 ± 37.5	0.028	0.732
ESV (mL)	84.1 ± 25.8	62.4 ± 24.0	<0.001	0.758
Stroke volume (mL)	71.7 ± 20.6	87.8 ± 21.5	<0.001	0.461
Ejection fraction (%)	46.3 ± 7.7	59.2 ± 8.4	<0.001	0.463

CMR = cardiac magnetic resonance imaging; EDV = end-diastolic volume; ESV = end-systolic volume; TTE-KBR = transthoracic echocardiography with knowledge-based reconstruction

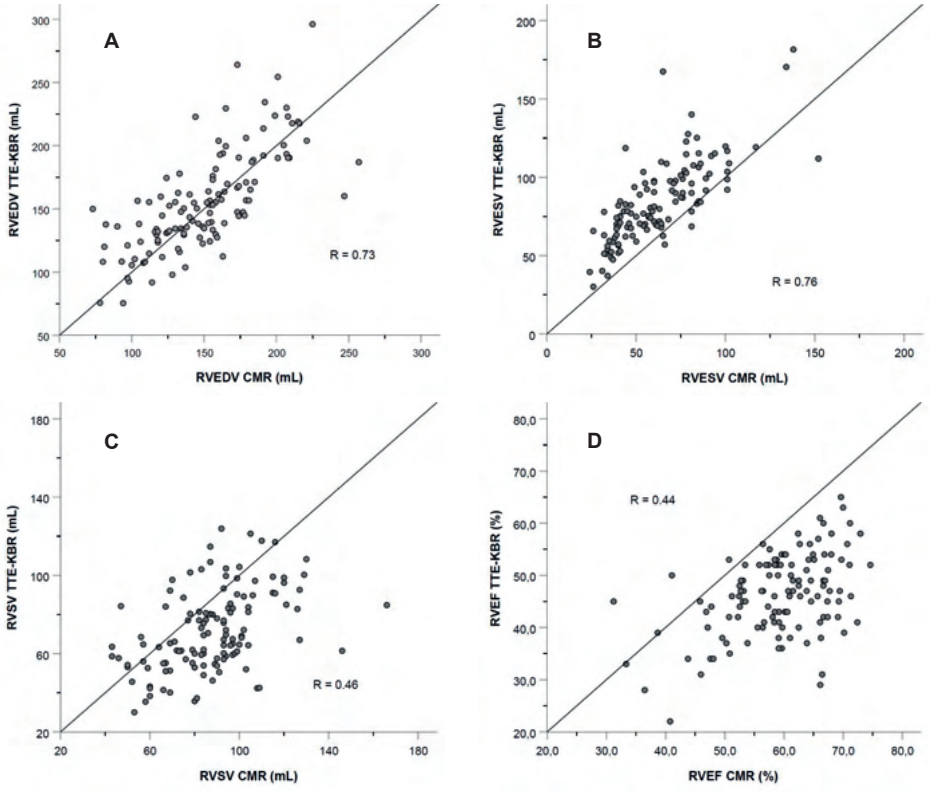

Figure 3. Correlation plots of RVEDV (A), RVESV (B), RVSV (C) and RVEF (D) measured by TTE-KBR versus CMR.

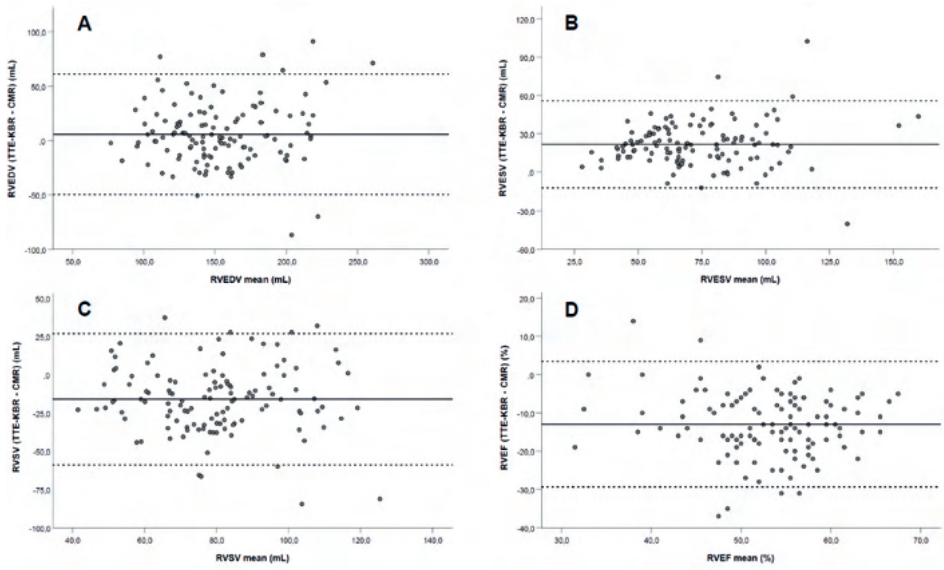

Figure 4. Bland-Altman analysis of bias (black solid line) and 95% limits of agreement (dashed line) for TTE-KBR versus CMR quantification of RVEDV (A), RVESV (B), RVSV (C) and RVEF (D).

DISCUSSION

To our knowledge, this is the first study using echocardiography with KBR in patients with pulmonary sarcoidosis to determine RV volumes and function. The main finding of the study is that only TTE-KBR derived RVEDV shows good agreement with CMR. TTE-KBR is highly feasible, but significantly overestimates RVESV and underestimates RVSV and RVEF compared to the gold standard CMR.

TTE-KBR has not been described in populations with interstitial lung diseases, such as sarcoidosis. Nevertheless it has been validated in PH and congenital heart disease populations showing favorable results in determination of RV volumes and function compared to CMR.[7–10] However, most studies were small and investigated less than fifty patients. Dragulescu et al. were one of the first to describe the usage of TTE-KBR in patients after tetralogy of Fallot repair. They studied thirty patients and found good intermodality agreement with a small underestimation of RVEDV and RVESV, with low intra- and interobserver variability.[9] Neukamm et al. observed similar results in patients with tetralogy of Fallot, although they found poor agreement for RVEF (r=0.38).[10] Bhave et al. studied 27 patients with PH and found a slight overestimation of RVEDV, RVESV and RVSV, while RVEF was slightly underestimated.[7] They concluded that TTE-KBR was accurate and reproducible in patients with PH, which was also stated by Knight et al. who investigated twenty-eight PH patients.[8] The differences between our findings and the previously mentioned studies

are not explained by the time between TTE-KBR and CMR, image quality or a possible learning curve. First, the poor intermodality agreement for both RVSV and RVEF can be explained by the significant overestimation of the RVESV, as RVSV and RVEF are both calculated using RVESV. A possible explanation for the differences in intermodality agreement with previous reported studies is our unselected pulmonary sarcoidosis population in which many patients had normal RV function and dimensions. In other studies, patients had known congenital heart disease or PH. The KBR algorithm takes the impact of the underlying disease on the RV morphology into account, so knowledge of underlying cardiac pathology is beneficial.[16] As we screened pulmonary sarcoidosis patients for PH without further data on RV function, all RV shapes were compared by the KBR algorithm to 'regular' right ventricles in the CMR reference data library. This could explain the intermodality differences, as 4.1% of patients was diagnosed with PH and these patients were not compared to a library of RV shapes of PAH patients. Furthermore, it is unknown whether this reference library contains patients with (cardiac) sarcoidosis, which could also explain the differences with our findings. Finally, the difference between acquisition positioning of TTE-KBR and CMR might impact our findings. TTE-KBR was performed in left lateral decubitus position, while CMR was performed in supine position.

Limitations

An important limitation of our study is that CMR acquisition was not part of standard study protocol. As screening for cardiac sarcoidosis was the main reason for CMR in many patients, there is a risk for referral bias with patients with more profound cardiac symptoms, abnormal cardiac biomarker results, electrocardiogram abnormalities or echocardiographic abnormalities. However, there were no significant differences between TTE-KBR derived values between patients with and without CMR within 90 days. In addition, TTE-KBR and CMR were not performed on the same day, with a mean time difference of 35 days. Nevertheless, analysis of patients with CMR <30 days only, showed no change in the differences between both modalities. Also, our population had mainly normal RV size and function, therefore the results cannot be generalized to patients with RV involvement in (cardiac) sarcoidosis. Furthermore, it is unknown whether the used reference library contains patients with (cardiac) sarcoidosis. All echocardiographic images were acquired using a transducer without 3D features. Therefore, KBR could not be compared to RV models created by 3D echocardiography. Lastly, a single observer performed all TTE-KBR studies and intra-, inter- and test-retest variability could therefore not be determined, which may limit generalizability. Previous studies have shown no significant intra- and inter-observer test-retest variability for both RV volumes and function.[7,8]

CONCLUSION

TTE-KBR is convenient, feasible and shows good agreement with CMR for RVEDV. However, there is poor intermodality agreement for RVESV, RVSV and RV function with a significant overestimation of RVESV and underestimation of RVSV and RVEF. The use of TTE-KBR does not seem to provide additional value in the determination of RV dimensions in pulmonary sarcoidosis patients.

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APPENDIX

Supplementary table S1. Baseline characteristics of patients with complete TTE-KBR analysis who received CMR within 90 days (included in the study) and did not receive CMR within 90 days

Variable	Included in study (n=122)	Not included in study (n=143)	p-value
Age (years)	50.9 ± 12.0	49.9 ± 11.7	0.506
Female sex	45.9%	35.7%	0.090
Body mass index (m^2/kg)	27.8 ± 4.6	27.6 ± 5.5	0.756
Body surface area (m^2)	2.01 ± 0.21	2.01 ± 0.25	0.847
Caucasian ethnicity	87.7%	89.5%	0.644
Biopsy confirmed sarcoidosis	78.7%	79.0%	0.947
Duration of disease (years)	2.3 [0.6 – 8.3]	4.0 [0.8 – 10.1]	0.303
Immunosuppressive therapy - Steroids - Non-steroids	41.8% - 23.8% - 22.1%	43.4% - 28.7% - 25.2%	0.799 0.367 0.562
Scadding stage (0 / I / II / III / IV)	25.0 / 22.4 / 21.6 / 2.6 / 28.4% (n=116)	19.3 / 17.8 / 22.2 / 9.6 / 31.1% (n=135)	0.142
NYHA functional class (I, II, III, IV)	23.0 / 52.5 / 24.5 / 0.0%	29.4 / 58.7 / 11.9 / 0.0%	0.019
Pulmonary function, laboratory testing			
FVC % of predicted	96.4 ± 18.2	93.3 ± 19.5	0.192
FEV1 % of predicted	87.3 ± 19.6	85.7 ± 21.1	0.520
$DLCO_{SB}$ % of predicted	73.7 ± 17.1	72.4 ± 16.4	0.554
NT-proBNP (pg/mL)	54.0 [28.0 – 97.5]	48.0 [22.0 – 103.8]	0.760
Comorbidities			
Hypertension	22.1%	28.0%	0.322
Prior coronary artery disease	4.1%	1.4%	0.253
Obstructive sleep apnea	22.1%	11.2%	0.016
Pulmonary hypertension	4.1%	2.1%	0.477
Cardiac sarcoidosis	9.8%	9.8%	0.990
Echocardiography			
TAPSE (mm)	22.4 ± 4.2 (n=120)	23.0 ± 4.3 (n=142)	0.239
Tricuspidal annulus velocity by TDI (cm/s)	12.7 ± 2.2 (n=115)	12.2 ± 1.9 (n=142)	0.042
Right ventricular systolic pressure (mmHg)	28.4 ± 8.4 (n=60)	26.7 ± 10.9 (n=60)	0.337

$DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging

Supplementary table S2. RV volumes and EF by TTE-KBR and CMR in PH vs no PH

	No PH (n=117)	PH + (n=5)	p-value
TTE-KBR EDV (mL)	150.0 [130.2 – 175.3]	199.6 [142.9 – 219.3]	0.100
TTE-KBR ESV (mL)	78.4 [68.0 – 97.8]	102.8 [76.6 – 139.7]	0.129
TTE-KBR SV (mL)	67.4 [56.6 – 84.6]	68.2 [62.4 - 97.9]	0.427
TTE-KBR EF (%)	47.0 [41.5 – 52.0]	45.0 [34.5 – 51.0]	0.473
CMR EDV (mL)	150.0 [122.5 – 173.5]	179.0 [138.5 – 206.5]	0.123
CMR ESV (mL)	58.0 [41.0 – 78.0]	71.0 [65.5 – 115.0]	0.075
CMR SV (mL)	88.0 [74.5 – 99.0]	94.0 [57.5 – 114.0]	0.887
CMR EF (%)	60.0 [53.5 – 66.0]	57.0 [36.0 – 61.5]	0.094

CMR = cardiac magnetic resonance imaging; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; PH = pulmonary hypertension; RV = right ventricular; SV = stroke volume; TTE-KBR = transthoracic echocardiography with knowledge-based reconstruction

Supplementary table S3. RV volumes and EF by TTE-KBR and CMR in patients with cardiac sarcoidosis vs without cardiac sarcoidosis

	No CS (n=110)	CS + (n=12)	p-value
TTE-KBR EDV (mL)	149.5 [121.0 – 178.3]	155.0 [133.8 – 165.5]	0.747
TTE-KBR ESV (mL)	60.0 [41.0 – 78.0]	59.0 [50.5 – 77.5]	0.205
TTE-KBR SV (mL)	87.0 [73.8 – 100.0]	93.5 [71.0 – 98.5]	0.331
TTE-KBR EF (%)	60.0 [53.8 – 66.0]	61.0 [52.3 – 65.0]	0.089
CMR EDV (mL)	150.2 [130.3 – 187.1]	154.9 [131.7 – 174.5]	0.966
CMR ESV (mL)	78.3 [67.4 – 98.8]	89.7 [76.2 – 106.0]	0.976
CMR SV (mL)	69.2 [57.4 – 84.9]	60.3 [55.4 – 80.2]	0.724
CMR EF (%)	47.0 [42.0 – 52.0]	43.0 [35.3 – 48.5]	0.931

CMR = cardiac magnetic resonance imaging; CS = cardiac sarcoidosis; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; PH = pulmonary hypertension; RV = right ventricular; SV = stroke volume; TTE-KBR = transthoracic echocardiography with knowledge-based reconstruction

Supplementary table S4. Correlations of RV volumes by TTE-KBR

Pearson *rho*	RV EDV	RV ESV	RV SV	RV EF
Age	-0.161	-0.095	-0.191	-0.045
Body mass index	0.362	0.291	0.332	0.015
Body surface area	0.690	0.647	0.519	-0.179
TAPSE (mm)	0.231	0.047	0.374	0.320
Tricuspidal annulus velocity (TDI)	0.223	0.072	0.330	0.226
RV systolic pressure	0.128	0.157	0.061	-0.083
FVC % of pred	0.048	-0.079	0.192	0.294
FEV1 % of pred	0.058	-0.071	0.201	0.283
$DLCO_{SB}$ % of pred	0.322	0.203	0.365	0.145
NT-proBNP	-0.062	-0.034	-0.075	-0.047

Supplementary table S4. Correlations of RV volumes by TTE-KBR (*continued*)

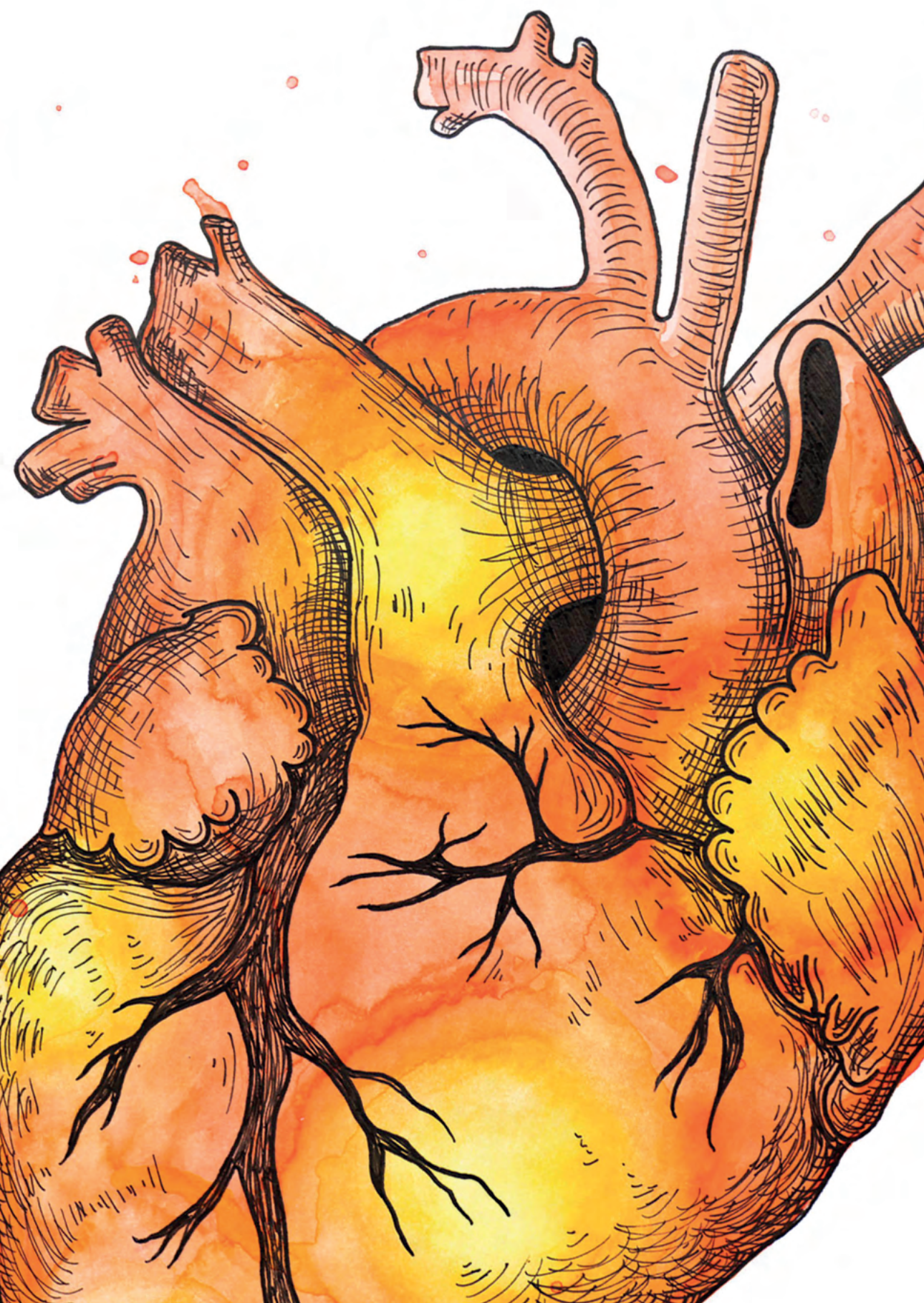
	RV EDV	RV ESV	RV SV	RV EF
Pearson *rho*				
Log NT-proBNP	-0.156	-0.157	-0.099	0.052
Mean PA diameter	0.222	0.283	0.080	-0.196
Mean PA diameter indexed for BSA	-0.278	-0.209	-0.258	-0.022
Spearman *rho*				
Scadding stage	-0.083	0.006	-0.162	-0.131
NYHA functional class	-0.130	-0.083	-0.194	-0.119

BSA = body surface area; $DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; PA = pulmonary artery; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging

Supplementary table S5. Correlations of RV volumes by CMR

	RV EDV	RV ESV	RV SV	RV EF
Pearson *rho*				
Age	-0.392	-0.279	-0.372	0.067
Body mass index	0.121	0.084	0.117	0.017
Body surface area	0.632	0.524	0.516	-0.224
TAPSE (mm)	0.107	-0.030	0.213	0.180
Tricuspidal annulus velocity (TDI)	0.104	0.001	0.177	0.087
RV systolic pressure	-0.050	0.089	-0.196	-0.226
FVC % of pred	0.104	-0.041	0.227	0.218
FEV1 % of pred	0.139	-0.048	0.295	0.260
$DLCO_{SB}$ % of pred	0.368	0.205	0.409	0.049
NT-proBNP	-0.044	-0.070	0.002	0.087
Log NT-proBNP	-0.227	-0.225	-0.145	0.152
Mean PA diameter	0.264	0.318	0.110	-0.262
Mean PA diameter indexed for BSA	-0.232	-0.091	-0.306	-0.097
Spearman *rho*				
Scadding stage	-0.167	-0.067	-0.297	-0.093
NYHA functional class	-0.241	-0.160	-0.247	-0.030

BSA = body surface area; $DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; PA = pulmonary artery; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging



4

Safety of macitentan in sarcoidosis-associated pulmonary hypertension: a case-series

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ABSTRACT

Background: Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis and is associated with higher morbidity and mortality. Currently, there are no approved PH-targeted therapies for sarcoidosis-associated pulmonary hypertension (SAPH). Macitentan is frequently used as treatment for pulmonary arterial hypertension, but no results are known in the SAPH population. The aim of this study was to investigate the safety and effect of macitentan as treatment for SAPH.

Methods: We retrospectively reviewed our patient database for all SAPH patients receiving macitentan as treatment, with a minimum follow-up of twelve months for monitoring safety. Safety outcomes included reported side effects, hospitalisations and mortality. Furthermore, six-minutes walking distance, New York Heart Association functional class and NT-proBNP levels were collected.

Results: Six cases (three men) with a median age of 64 years (range 52-74 years) were identified. During macitentan treatment, one patient experienced side effects and aborted therapy after five days of treatment and died 16 months later. Three patients were hospitalised during treatment for congestive heart failure. Four patients showed improvement of their functional class and three patients in exercise capacity after 12 months of therapy.

Conclusion: Macitentan was well tolerated in five out of six cases with severe pulmonary sarcoidosis and PH. Functional capacity improved in four cases. Prospective controlled trials are warranted before therapeutic recommendations can be made.

INTRODUCTION

Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis. Prevalence numbers range from 3% in early stage pulmonary sarcoidosis, up to 70% in patients awaiting lung transplantation.[1,2] Sarcoidosis-associated pulmonary hypertension (SAPH) is associated with increased morbidity and mortality.[3,4] The underlying pathophysiological mechanism of SAPH remains unclear. Hypothesised mechanisms include destruction of the pulmonary vascular bed by pulmonary fibrosis, granulomatous vasculopathy, extrinsic compression from thoracic lymphadenopathy, mediastinal fibrosis and cardiac involvement. [4–6] Currently, there are no approved PH-targeted treatments for SAPH. Although endothelin receptor antagonists are well used in pulmonary arterial hypertension, studies have shown mixed results in SAPH.[7,8] To our best knowledge, the safety and effect of the endothelin receptor antagonist macitentan in SAPH patients has not been evaluated. We report the results of a single centre case-series.

METHODS

The St. Antonius hospital is a tertiary referral centre for sarcoidosis and PH. We retrospectively reviewed our patient database between 2014-2018 to include all patients aged ≥18 years, diagnosed with both sarcoidosis and PH, who received macitentan as treatment (mono- or dual therapy), and had at least 12 months of follow-up for monitoring safety outcomes. The diagnosis of sarcoidosis was based on current clinical diagnostic guidelines.[9] PH was confirmed by right heart catheterization (RHC) and defined as a resting mean pulmonary artery pressure (mPAP) ≥25mmHg. The decision to start treatment was made by a multidisciplinary team. Safety outcomes included side effects leading to (temporarily) aborting therapy, hospitalisation for heart failure or dyspnoea, and death.

Baseline was defined as the start of PH-targeted treatment. At baseline, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, forced vital capacity (FVC), New York Heart Association (NYHA) functional class were determined and a six-minute walking distance (6-MWD) was obtained. Macitentan was administered at a dose of 10mg/day. If applicable, sildenafil was dosed 20mg three times daily. All outcome parameters were obtained by chart review. Written informed consent was obtained in all cases. The study was approved by the local institutional review board.

RESULTS

Figure 1 shows the flowchart of case selection. In total, 27 patients with SAPH were identified between 2014-2018. Of these patients, 8 were treated with macitentan. Of these, 6 patients had a follow-up of at least twelve months, while the other two patients were recently started on macitentan. The baseline characteristics and outcome parameters of all cases are shown in table 1. Six patients (three men) with a median age of 64 years (range 52-74 years) were identified. All cases were Caucasian patients with biopsy confirmed sarcoidosis. RHC showed a median mPAP of 49 (27 – 66) mmHg and the pulmonary vascular resistance (PVR) was >3 Wood Units (WU) in all cases.

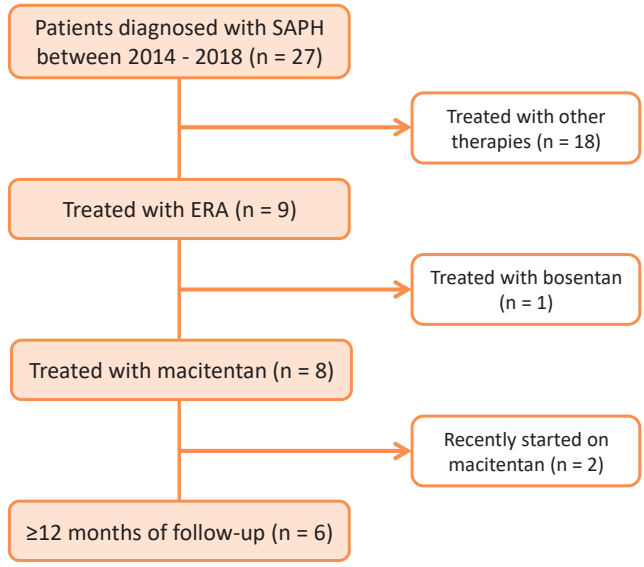

Figure 1. Flowchart of case selection.

Case 1 was a 60-year old female with suspected fibrosing pulmonary sarcoidosis and severe PH. Macitentan was started after PH diagnosis. After two months, sarcoidosis was proven on biopsy and immunosuppressive therapy with methotrexate 15mg/week was initiated due to active disease on FDG-PET (fluorodeoxyglucose-positron emission tomography) with compression of the pulmonary artery. At three months, echocardiography showed improved right ventricular function and sildenafil was added. At 7 months, immunosuppressive therapy was switched to azathioprine 100mg/day due to side effects of methotrexate. At one year, there was an improvement of mPAP (47mmHg), PVR (5.0 WU), 6-MWD, and NYHA functional class. NT-proBNP levels and the FVC remained stable. During 3.5 years of follow-up, macitentan was well tolerated with no reported side effects.

Table 1. Case characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Demographics						
Age (years)	60	74	64	52	69	65
Male / female	Female	Male	Male	Female	Female	Male
Time since sarcoidosis diagnosis (years)	8,3	4,3	20	0,2	22,5	12,2
Pulmonary function						
FEV1 % predicted	75.9	90.0	49.0	54.9	36.9	25.6
FVC % predicted	104.1	88.0	69.0	62.5	50.4	75.0
DLCO SB % predicted	76.4	25.0	-	40.3	13.9	57.1
Fibrosis on HRCT	Yes	Yes	No	No	Yes	Yes
Heamodynamics						
sPAP / dPAP (mmHg)	110/40	60/32	43/19	96/49	85/35	76/30
mPAP (mmHg)	63	37	27	66	55	43
PAWP (mmHg)	6	11	10	18	5	12
PVR (Wood Units)	10.3	10.4	3.2	11.3	13.9	7.2
Cardiac output (L/min)	5.6	2.5	5.3	4.3	3.6	4.6
Sarcoidosis treatment						
Supplemental oxygen use	No	Yes	Yes	Yes	Yes	No
Immunosuppressive treatment	No	Yes	Yes	Yes	No	Yes
Escalation of immunosuppressive treatment during follow-up	Yes	No	No	No	Yes	No
PH treatment						
Initial PH-targeted therapy	Macitentan	Macitentan	Dual	Macitentan	Dual	Sildenafil
Time before start dual treatment (months)	3	1	-	10	-	15
Follow-up duration (months)	42	12	12	42	36	18
Outcome parameters						
NYHA functional class at baseline	III	III	III	III	IV	III
NYHA functional class at 12 months	II	III	II	II	III	III
NYHA functional class at 24 months	II	III	II	II	III	IV
6-MWD at baseline (meters)	327	365	445	364	145	341
6-MWD at 12 months (meters)	439	-	457	367	340	244
6-MWD at 24 months (meters)	456	-	-	422	243	-
NT-proBNP at baseline (pg/mL)	136	959	52	3382	5875	346
NT-proBNP at 12 months (pg/mL)	110	1516	45	3512	343	688
NT-proBNP at 24 months (pg/mL)	38	-	-	1543	210	-

6-MWD = six minute walking distance; DLCO SB = diffusing capacity of the lung for carbon monoxide single breath; dPAP = diastolic pulmonary artery pressure; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high resolution chest tomography; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; sPAP = systolic pulmonary artery pressure

Case 2 was a 74-year old male with fibrosing pulmonary sarcoidosis. RHC showed severe PH and macitentan was started. After four weeks, he was admitted for pneumonia and congestive heart failure. After recovery, sildenafil was added. At 12 months, no side effects were reported. NT-proBNP levels had increased, while NYHA functional class and FVC remained stable. A 6-MWD was not performed during follow-up due to persisting disabilities after a cerebrovascular event.

Case 3 was a 64-year old male with pulmonary sarcoidosis. After PH diagnosis, macitentan and sildenafil were started with good effect on NYHA functional class at 12 months while other outcome parameters remained stable or showed mild improvement. Macitentan was well tolerated.

Case 4 was a 52-year old female, with recently diagnosed pulmonary sarcoidosis and severe PH. Macitentan treatment was started with initial good effect on functional capacity. At 10 months, she was hospitalized due to congestive heart failure. After recovery, RHC was repeated which showed a mPAP of 58 mmHg and a PVR of 12.5 WU. Sildenafil was added and after 24 months all outcome parameters improved, while FVC remained stable. After 3.5 years of follow-up, macitentan was well tolerated and the patient remained clinically stable.

Case 5 was a 69-year old female patient with fibrosing pulmonary sarcoidosis and severely reduced exercise capacity. Dual treatment with macitentan and sildenafil was started. The FDG-PET showed enhanced inflammatory activity, and high-dosage prednisone was started at 6 weeks. At 12 months, there was an improvement in 6-MWD (340 vs 145m), NT-proBNP and NYHA functional class. FVC also improved during treatment (74.0% vs 50.4%). Echocardiography showed improvement in right ventricular function after 12 months. No side effects were reported during follow-up.

Case 6 was a 65-year old male patient with fibrosing pulmonary sarcoidosis. After PH diagnosis, initial treatment with sildenafil was started. After 12 months of treatment, RHC showed a mPAP of 47mmHg with no subjective improvement. FDG-PET revealed no signs of inflammatory activity and macitentan was initiated. Macitentan was not well tolerated and aborted after five days due to severe muscle aches and fatigue. Several days later, this patient was hospitalised for increasing dyspnoea and sildenafil was aborted due to no clinical improvement. The patient was discharged home with oxygen therapy and diuretics and died sixteen months later due to right ventricular failure.

DISCUSSION

To the best of our knowledge, this is the first case series describing the safety and effect of macitentan, either as monotherapy or as dual treatment with sildenafil, as treatment for SAPH in predominantly patients with fibrosing pulmonary sarcoidosis. We found that macitentan was well tolerated in five patients, but one patient aborted macitentan therapy due to side effects and died sixteen months later.

Judson et al. investigated the role of the endothelin receptor antagonist ambrisentan as treatment for SAPH. They found that 11 out of 21 patients aborted ambrisentan therapy, mostly due to increasing dyspnoea.[7] In our case series, no patients aborted therapy due to dyspnoea. However three patients were hospitalised for dyspnoea due to congestive heart failure, but recovered with diuretic treatment. A known side effect of a pulmonary vasodilator in parenchymal lung disease is the possible worsening of ventilation/perfusion mismatch, which could lead to increasing dyspnoea.[10,11] Unfortunately, we were not able to evaluate the effect of macitentan on gas exchange before and during treatment due to missing data for arterial blood gas analyses. The found rate of adverse events are in line with the MUSIC trial. This study showed that 12 months of macitentan therapy was well tolerated in patients with idiopathic pulmonary fibrosis, with 12.6% of patients aborting therapy due to adverse events.[12]

Furthermore, in four patients functional class improved and in three patients exercise capacity improved after 12 months of therapy. A possible confounder for this improvement is the escalating immunosuppressive treatment for increased sarcoidosis activity. It is known that immunosuppressive treatment can improve FVC in pulmonary sarcoidosis patients.[13] This could explain the functional improvement in case 5 as this was the only case with an improved FVC during follow-up. In all other cases the FVC remained stable.

In conclusion, this is the first case-series describing the safety and effect of macitentan therapy in SAPH. Macitentan was well tolerated in five out of six cases with severe pulmonary sarcoidosis and PH. Functional capacity improved in four out of six cases. However, results of this case series need to be interpreted with caution. Prospective controlled trials are warranted before therapeutic recommendations can be made.

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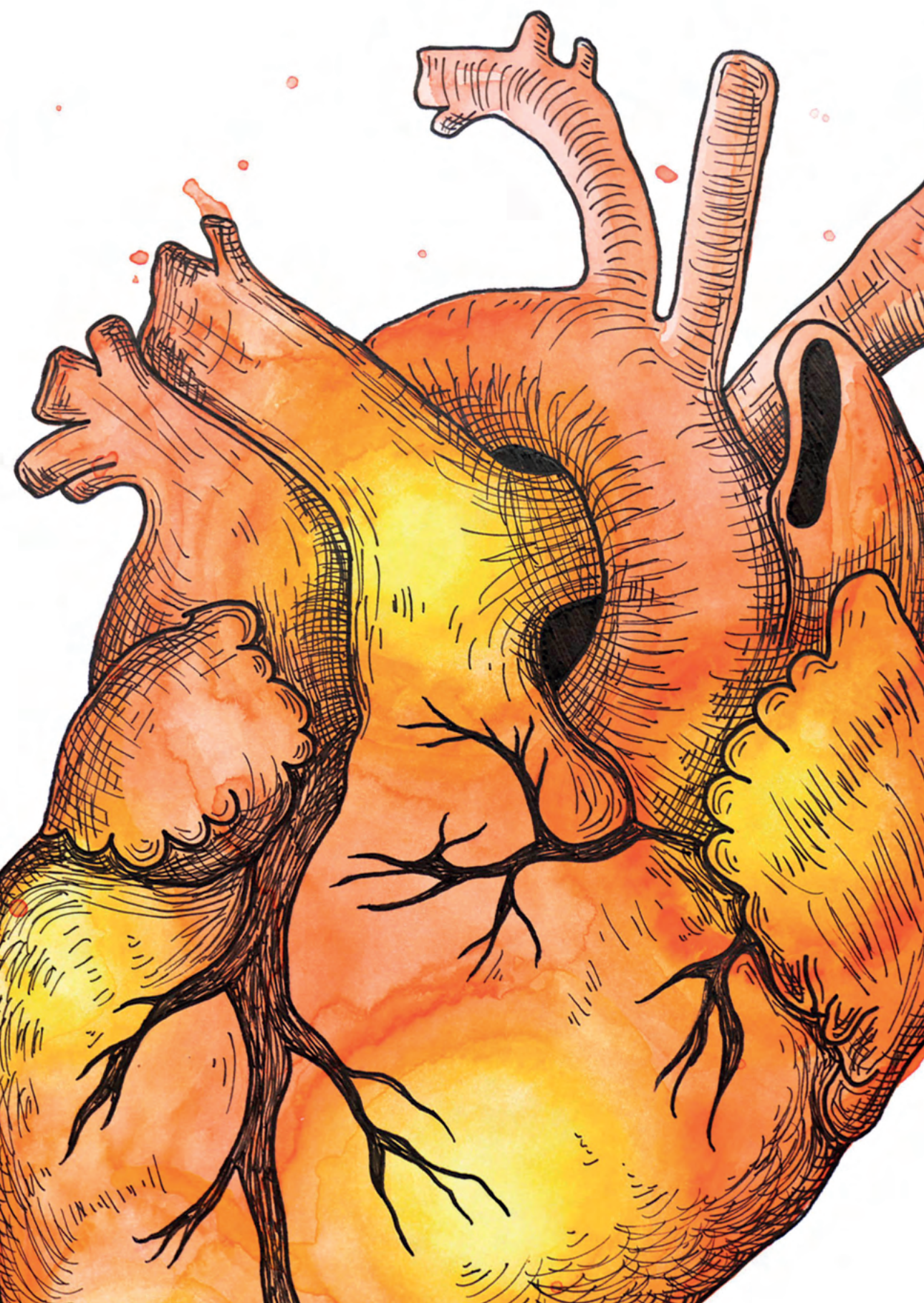

5

Four-year survival rate in pulmonary sarcoidosis with extensive pulmonary hypertension screening

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ABSTRACT

Background: Sarcoidosis is a systemic disease of unknown aetiology with significant morbidity and mortality. The PULSAR study prospectively performed cardiac analysis including systematic pulmonary hypertension screening in sarcoidosis patients newly referred to a tertiary sarcoidosis center. In this manuscript we studied the four-year mortality of this population.

Methods and main findings: Between August 2015 and October 2017, 399 patients (58% male, mean age 49.4 years, 90.5% Caucasian) were included and followed for a mean period of 4.3 ± 0.7 years. In total, 10 patients had died at the time of analysis. 1-, 2-, 3- and 4-year survival rate was 100% (n=399), 99.0% (n=399), 98.2% (n=399) and 96.4% (n=276). Most patients died of respiratory failure, other causes were heterogeneous including cardiac, neurological and non-sarcoidosis origin. A low CPI score or modified Walsh score was associated with higher mortality, similar for high PH probability on echocardiography and elevated right ventricular systolic pressure.

Conclusion: This study highlights that elevated RVSP and presence of PH on echocardiography and progression of fibrotic disease with subsequent decline in pulmonary function test are important factors for mortality in sarcoidosis patients.

INTRODUCTION

Sarcoidosis is a systemic disease of unknown aetiology which may result in chronic disease with significant morbidity and mortality, depending on disease stage and severity.[1–7] Previous studies have never performed systematic cardiac analysis including pulmonary hypertension (PH) screening. In 2019, the PULmonary hypertension in pulmonary SARcoidosis (PULSAR)-study showed a PH prevalence of 3%.[8] We present four-year follow-up data on mortality of this well-defined group of pulmonary sarcoidosis patients.

METHODS

The PULSAR study is a cross sectional prospective cohort study performing systematic cardiac evaluation in a large well-defined cohort of mainly Caucasian pulmonary sarcoidosis patients newly referred to a national center of excellence for both sarcoidosis and PH. An extensive description of study design can be found in the previously published article.[8] All patients underwent transthoracic echocardiography (TTE), and were referred for right heart catheterization (RHC) in case of intermediate or high PH probability as defined by the ESC/ERS guideline.[9] PH was defined as a mean pulmonary artery pressure (PAP) ≥25mmHg by RHC, and absence of PH as a mean PAP <25mmHg or a low PH probability on TTE. Patients with reduced left ventricular ejection fraction, elevated cardiac biomarkers, ECG abnormalities or symptoms suggestive for cardiac sarcoidosis (CS) were evaluated by cardiac magnetic resonance imaging and 24-hour ECG monitoring and FDG PET/CT, and classified as CS unlikely/possible/probable by a multidisciplinary team according to the Heart Rhythm Society consensus statement.[10] Furthermore, data was collected on demographics, imaging and pulmonary function test. Composite Physiologic Index (CPI), Walsh and modified Walsh algorithm scores were calculated.[5,11] Data on mortality of all patients were obtained from the Dutch national death registration (consultation date 26-02-2021). The cause of death was determined by chart review and if necessary by consulting the general practitioner. Survival was analyzed using Kaplan Meier analysis, with the Log-Rank test for comparison between curves. Predictors for mortality were analyzed using Univariate Cox regression. Event numbers were too low for multivariate analysis.

RESULTS

Between August 2015 and October 2017, 399 patients (57.9% male, mean age 49.4 ± 11.6 years, 90.5% Caucasian) were included in the PULSAR study[8], and followed for a mean period of 4.3 ± 0.7 years. During follow-up, ten (2.5%) patients died and none were transplanted. Main findings between the groups 'alive' and 'death' are displayed in table 1. The overall 1-, 2-, 3- and 4-year survival rate was 100% (n=399), 99.0% (n=399), 98.2% (n=399) and 96.4% (n=276). The main cause of death was respiratory failure (n=5), of whom one due to COVID-19. One patient with concomitant CS died due to end stage heart failure. One patient was found dead at home with unknown cause. Another patient died in palliative setting due to neurological paralysis, possibly related to neurosarcoidosis. Furthermore, two patients died from non-sarcoidosis related comorbidities. As shown in table 1, patients who had died were significantly older and were more likely to be on immunosuppressive or oxygen therapy. Troponin T was more often elevated in deceased patients. The FVC% predicted and DLCOcSB% predicted were lower in the deceased group. The alive patients had a significantly lower CPI score and modified Walsh algorithm score. For the Walsh algorithm there was a trend towards significance. Low, intermediate and high PH probability was present in 368, 22 and 6 patients respectively. 28 patients underwent RHC. Among the deceased patients, one had confirmed PH due to chronic thrombo-embolic pulmonary embolisms and severe fibrotic pulmonary sarcoidosis. Seven patients had a low PH probability on echocardiography. In the other two patients PH was excluded by RHC. Right ventricular systolic pressure (RVSP) was significantly higher in deceased patients. A high PH probability on TTE was associated with increased mortality (HR 8.7; 95% CI 1.1-69.1, p=0.042). All deceased patients had a normal left ventricular function at baseline. CS was diagnosed as 'probable' in 9.3% of the alive and 10.0% of the deceased patients.

Table 1. Baseline characteristics

Parameter		Alive (n=389)	Deceased (n=10)	p-value	Hazard ratio
Age (years)		49.0 [40.4 – 56.9]	64.0 [46.1 – 72.8]	0.005	HR 1.08 [95% CI 1.02 – 1.14]
Male sex		58.4%	40.0%	0.238	-
Caucasian ethnicity		90.2%	100%	0.302	-
Duration of disease (years)		2.31 [0.66 – 7.60]	4.97 [0.53 – 24.04]	0.084	-
Immunosuppressive therapy at baseline		37.0%	80.0%	0.006	HR 6.5 [95% CI 1.4 – 30.8] p=0.018
Oxygen therapy		0.8%	10.0%	0.002	HR 12.6 [95% CI 1.6 – 99.4] p=0.016
NYHA functional class	I	30.1%	20.0%	0.306	-
	II	56.6%	50.0%		
	III	13.4%	30.0%		
High sensitive troponin T >0.014 (ug/L) (n=386)		7.2%	33.3%	0.004	HR 6.1 [95% CI 1.5 – 24.4] p=0.011
NT-proBNP (pg/mL)		48.0 [24.0 – 91.5]	79.0 [32.0 – 373.5]	0.277	-
Scadding stage (n=374)	0	27.2%	30.0%	0.790	-
	I	21.2%	10.0%		
	II	26.1%	30.0%		
	III	5.8%	0.0%		
	IV	19.8%	30.0%		
FVC % predicted (n=381)		100.0 [88.0 – 110.0]	83.5 [60.3 – 104.0]	0.021	HR 0.96 [95% CI 0.93-0.99]
FEV1 % predicted (n=383)		92.0 [78.0 – 104.0]	76.5 [61.3 – 99.3]	0.149	-
DLCOcSB % predicted (n=345)		77.0 [66.1 – 86.0]	56.5 [39.0 – 80.8]	0.006	HR 0.95 [95% CI 0.92 – 0.99]

Table 1. Baseline characteristics (*continued*)

Parameter		Alive (n=389)	Deceased (n=10)	p-value	Hazard ratio
CT MPAD (mm) (n=316)		27.0 [25.0 – 30.0]	28.0 [25.0 – 30.0]	0.306	-
CT MPAD/BSA ratio (n=316)		13.5 [12.4 – 15.0]	15.3 [11.9 – 15.8]	0.097	-
CT MPAD/AAD (n=316)		0.88 [0.79 – 0.96] (n=306)	0.84 [0.71 – 0.98]	0.376	
CT total disease extend (n=311)	<5% 5-20% >20%	42.4% 18.1% 39.5%	40.0% 30.0% 30.0%	0.613	-
RVSP (mmHg) (n=193)		25.3 [21.2 – 30.2]	33.3 [27.9 – 45.0]	0.004	HR 1.07 [95% CI 1.02 – 1.11]
Echocardiographic PH classification	Low Intermediate High	93.5% 5.2% 1.3%	80.0% 10.0% 10.0%	0.046	HR 8.7 (high vs low) [95% CI 1.1 – 69.4] p=0.042
LV ejection fraction impaired <50% (n=397)		5.8%	0.0%	0.893	-
Diastolic function normal (n=385)		92.2%	100.0%	0.680	-
TAPSE (mm) (n=392)		22.0 [20.0 – 25.0]	20.0 [17.9 – 24.3]	0.179	-
CPI (n=345)		19.9 [11.9 – 27.6]	34.6 [13.6 – 59.8]	0.002	-
CPI >40 (n=345)		8.9%	50.0%	<0.001	HR 9.6 [95% CI 2.4 – 38.5] p=0.001
Walsh algorithm poor prognosis (n=284)		22.1%	50.0%	0.063	HR 3.4 [95% CI 0.86 – 13.7] p=0.081
Modified Walsh algorithm poor prognosis (n=284)		18.8%	50.0%		HR 4.2 [95% CI 1.05 – 16.8] p=0.042

AAD = ascending aorta diameter; BSA = body surface area; CPI = Composite Physiologic Index; CT = computed tomography; DLCOSB = diffusing capacity for carbon monoxide single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; HR = hazard ratio; LV = left ventricle; MPAD = mean pulmonary artery diameter; NT-proBNP = N-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; PH = pulmonary hypertension; RVSP = right ventricular systolic pressure; TAPSE = tricuspid annular plane systolic excursion

DISCUSSION

This study shows that the four-year mortality rate in pulmonary sarcoidosis patients, newly referred to a tertiary sarcoidosis center, is low with a four-year survival rate of 96.4%. Especially compared to studies with a more severely diseased population[5,7,11–13], showing an increased mortality in patients with more severe lung disease with 5 year survival rates of 91.5%[6], and with PH (3-5 year survival rates around 55%).[4,7] In our study, we found that the Modified Walsh algorithm, elevated RVSP and presence of PH on echocardiography, treatment with immunosuppressive agents, need for oxygen therapy, and decreased FVC% and/or DLCOcSB% predicted were significant predictors for mortality. These findings are in line with previous population based and clinical studies, which have identified several potential predictors for increased mortality, such as age[3], presence of PH[3–6] severity of pulmonary fibrosis on chest CT[3,5] or Scadding stage IV disease[3,4] and risk scores like CPI, Walsh or modified Walsh algorithm.[5,11] In our cohort CPI score was significantly higher in the deceased patients. The Walsh algorithm showed a trend towards significance between alive and deceased patients. However, the Modified Walsh algorithm incorporating the pulmonary artery diameter corrected for body surface area, was a significant predictor for mortality with a HR of 4.2. The Walsh algorithm was validated by Walsh et al. and showed to be a strong predictor for mortality with a HR of 4.91.[11] In the study by Jeny et al., poor prognosis by the Walsh algorithm and especially the Modified Walsh algorithm was a powerful predictor with a HR of 5.54 and 11.0 respectively.[5] In contrast to the present study, only patients with Scadding stage IV sarcoidosis were included and there was a higher prevalence of non-white patients, higher CPI scores and worse pulmonary function tests. Presence of PH on echocardiography, defined as an RVSP >35mmHg, was a significant predictor with a HR of 3.42. Kirkil et al. studied a more similar population, with Scadding Stage IV in 17.3% of the patients and comparable pulmonary function tests and CPI scores, but a higher prevalence of black patients (30.1%).[3] In this study the Walsh algorithm poor prognosis was associated with increased mortality with a HR of 3.21. PH, defined as a mean PAP ≥25mmHg during RHC, was a significant predictor for mortality with a HR of 8.96. Our study was the first to perform prospective cardiac evaluation including extensive PH screening in all patients, showing a high PH probability on echocardiography as predictor for mortality during follow-up with a HR of 8.7 (high vs low PH probability). This is in line with other studies, however it should be noted that other studies often use non-guideline definitions for PH and no systematic screening for PH was performed. Furthermore, this study showed that the cause of death is highly variable and can be either due to pulmonary, cardiovascular or neurologic complications of sarcoidosis.

This study has several limitations. Due to a study population with less severe disease compared to other studies, event numbers are relatively low and therefore robust statistical analysis including multivariate analysis could not be performed. Furthermore, not all patients underwent RHC and/or cardiac magnetic resonance imaging and therefore the prevalence of PH or CS might be underestimated.

CONCLUSION

In this well-defined cohort of pulmonary sarcoidosis patients newly referred to a tertiary center, overall 4-year survival was 96.4%. This study highlights that elevated RVSP and presence of PH on echocardiography and progression of fibrotic disease with subsequent decline in pulmonary function test are important factors for mortality in sarcoidosis patients.

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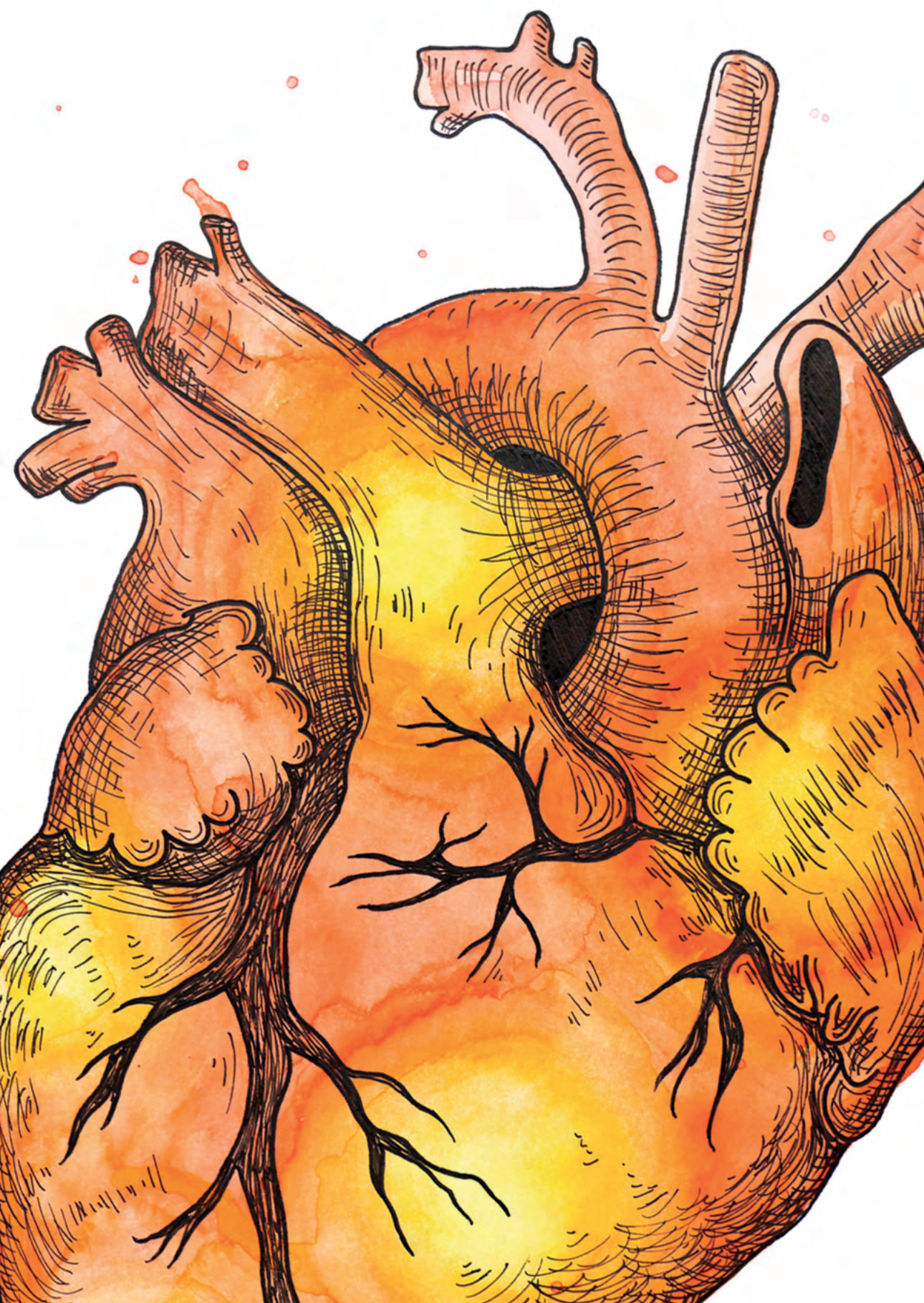
PART B

CARDIAC SARCOIDOSIS



6

The usefulness of repeated CMR and FDG PET/CT in the diagnosis of patients with initial possible cardiac sarcoidosis

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ABSTRACT

Background: Cardiac sarcoidosis (CS) diagnosis is usually based on advanced imaging techniques and multidisciplinary evaluation. Diagnosis is classified as definite, probable, possible or unlikely. If diagnostic confidence remains uncertain, cardiac imaging can be repeated. The objective is to evaluate the usefulness of repeated cardiac magnetic resonance imaging (CMR) and fluorodeoxyglucose positron emission tomography (FDG PET/CT) for CS diagnosis in patients with an initial "possible" CS diagnosis.

Methods: A retrospective cohort study was performed in 35 patients diagnosed with possible CS by our multidisciplinary team (MDT), who received repeated CMR and FDG PET/CT within 12 months after diagnosis. Imaging modalities were scored on abnormalities suggestive for CS and classified as CMR+/PET+, CMR+/PET-, CMR-/PET+ and CMR-/PET-. Primary endpoint was final MDT diagnosis of CS.

Results: After re-evaluation, nine patients (25.7%) were reclassified as probable CS and 16 patients (45.7%) as unlikely CS. Two patients started immunosuppressive treatment after re-evaluation. At baseline, eleven patients (31.4%) showed late gadolinium enhancement (LGE) on CMR (CMR+) and 26 (74.3%) patients showed myocardial FDG-uptake (PET+). At re-evaluation, nine patients (25.7%) showed LGE (CMR+), while 16 patients (45.7%) showed myocardial FDG-uptake (PET+). When considering both imaging modalities together, 82.6% of patients with CMR-/PET+ at baseline were reclassified as possible or unlikely CS, while 36.4% of patients with CMR+ at baseline were reclassified as probable CS. Three patients with initial CMR-/PET+ showed LGE at re-evaluation.

Conclusion: Repeated CMR and FDG PET/CT may be useful in establishing or rejecting CS diagnosis, when initial diagnosis is uncertain. However, clinical relevance has to be further determined.

INTRODUCTION

Sarcoidosis is a multisystem disease of unknown aetiology, characterized by non-caseating granulomas in multiple organs sometimes including the heart. About 5% of patients with systemic sarcoidosis have clinical evidence of cardiac sarcoidosis (CS), whereas autopsy and imaging studies suggest a higher prevalence around 20-30%.[1–3] Cardiac involvement is often non-specific and may range from asymptomatic to symptomatic conduction abnormalities, heart failure and sudden cardiac death.[1,4–6] Considering the potential risk, early detection of cardiac involvement and appropriate treatment is of importance. However, the diagnosis of CS remains challenging due to the low sensitivity of endomyocardial biopsy, which is required for a "definite" diagnosis.[4] Therefore, diagnosis is usually based on advanced imaging techniques and multidisciplinary evaluation. In the St. Antonius Hospital, the diagnosis of CS is made by a multidisciplinary team (MDT) consisting of experienced cardiologists specialized in cardiac magnetic resonance imaging (CMR), pulmonologists and nuclear medicine physicians. The MDT classifies the diagnosis of CS as "probable" or "unlikely". However, if no consensus can be reached, the diagnosis is classified as "possible" CS. In these patients, CMR and fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) are repeated, in order to reject or establish a CS diagnosis by the MDT. The aim of this study was to evaluate the usefulness of repeated CMR and FDG PET/CT for the diagnosis of CS in patients whom were initially diagnosed as "possible" CS.

METHODS

Study design

A retrospective single-centre cohort study was performed at the St. Antonius Hospital, a tertiary referral centre for sarcoidosis. Local institutional review board approval was obtained with a waiver of informed consent. All patients discussed in the CS MDT between January 2014 and March 2020 were evaluated. The diagnosis of CS in our MDT was based on the diagnostic criteria from the 2014 Heart Rhythm Society (HRS) consensus statement and 2016 Japanese Circulation Society (JCS) guideline.[4,7] Before initial diagnosis, all patients received both CMR and FDG PET/CT. After multidisciplinary evaluation, the likelihood of CS was classified as "definite", "probable", "possible" or "unlikely". When no consensus in the MDT could be reached, but imaging or clinical findings could be specific for CS (based on the 2014 HRS and 2016 JCS criteria), the diagnosis was deemed "possible". These patients were re-assessed after 6-12 months with CMR and FDG PET/CT and included in the study. The variability between 6 and 12 months was based on logistical reasons and patient preference. After repeated imaging, patients were re-evaluated by

the MDT and classified as either “probable”, “possible” or “unlikely”. Exclusion criteria included an interval between initial and repeated imaging >12 months, insufficient imaging quality and suspected isolated CS. The primary outcome was the final CS diagnosis by the MDT after re-evaluation with CMR and FDG PET/CT. Secondary outcome parameters included change in immunosuppressive treatment, new cardiac symptoms, new/increased conduction abnormalities, ventricular arrhythmias, a decrease in left ventricular ejection fraction (LVEF) >10% and all-cause mortality. Data were collected retrospectively by chart review. All data were stored in the web-based data manager REDCap.

CMR and FDG PET/CT acquisition and analysis

All CMR images were acquired using a 1.5T Philips MRI scanner with an eight-element phased-array cardiac coil. A vector electrocardiographic system was used for cardiac gating. A stack of short-axis cine slices of both the right- and left ventricle (8-mm thickness, no gap) from the base to the apex of the entire heart were acquired. If performed, T2-weighted short-tau inversion recovery images (indication myocardial edema) with 8-mm slice thickness were acquired at short-axis orientation. Late gadolinium enhancement (LGE) images were obtained 12-20 minutes after intravenous administration of 0.4ml/kg gadolinium. All CMR images were analysed by two experienced observers (F.A. and H. E.) blinded for clinical outcomes. The CMR images were scored on LVEF, increased T2-weighted signal, LGE and localization of LGE. Patients with abnormalities on CMR suggestive for CS were labelled as CMR+, while patients with no abnormalities suggestive for CS were labelled as CMR–.

FDG PET/CT examination was performed with a TF-64 combined PET/CT device (Philips Gemini, Eindhoven, The Netherlands). Patients were instructed to have a carbohydrate-restricted diet for 24 hours followed by a fast of at least 6 hours before injection of FDG. Dosage was based on body weight. 50 IE/kg unfractionated heparin was pre-administered intravenously to suppress physiologic uptake in the myocardium, with a maximum of 5000 IE. PET images were scored by a single experienced nuclear medicine physician (R.G.K.) for myocardial FDG-uptake, localization and pattern. FDG-uptake patterns were classified as: none, diffuse, focal and focal on diffuse. Maximum standardized uptake value (SUVmax) and normalized SUVmax (SUVmax divided by the SUVmean of the blood pool) were measured for all focal and focal on diffuse FDG-uptake. The threshold for active inflammation was a SUVmax >2.5 or a higher activity than the myocardial blood pool. SUVmax was measured at the active lesion. If no activity was present, SUVmax was measured at the basal interventricular septum. SUVmean was measured at the descending thoracic aorta at the level of the carina. Patients with myocardial uptake on FDG PET/CT, including a ‘diffuse’ pattern were labelled as PET+. After CMR and FDG PET/CT analysis, four sub-groups were defined: CMR+/PET+, CMR+/PET-, CMR-/PET+ and CMR-/PET-.

Statistical analysis

All statistical analyses were performed using SPSS Statistics (version 26.0 for Windows; Armonk, NY: IBM Corp). Continuous data were expressed as mean ± standard deviation or median [interquartile range]. Categorical data were reported as frequencies and percentages. Normality of data distribution was assessed using the Shapiro-Wilk test or Kolmogorov-Smirnoff test. The chi-squared test or Fisher's Exact Test was used to compare categorical variables. The McNemar test was used to compare categorical variables of two related samples. The independent *t*-test or Mann-Whitney U Test was used to compare mean or median values of continuous variables. The paired samples *t*-test or Wilcoxon signed rank test was used to compare means or medians of two related samples. A two-tailed p-value of <0.05 was considered significant.

RESULTS

A total of thirty-five patients were included in this study. Table 1 summarizes the baseline characteristics. In total, 74.3% was male with a mean age of 52.5±12.7 years. Extracardiac sarcoidosis was histologically or cytologically confirmed in 94.3%, while in 5.7% the diagnosis was based on clinical, laboratory and radiological findings.[8] Fourteen patients (40%) were already on immunosuppressive therapy for extracardiac sarcoidosis before the first MDT.

Primary outcome

Mean time between both MDTs was 7.3 ± 2.1 months. In none of the patients repeated imaging was performed earlier due to clinical worsening. As shown in Figure 1, twenty-five patients (71.4%) were reclassified after repeated imaging. Nine patients (25.7%) were reclassified as probable CS and sixteen patients (45.7%) as unlikely CS. Ten patients (28.6%) remained classified as possible CS. When using the 2014 HRS criteria or 2016 JCS criteria, 8 patients (22.9%) and 5 patients (14.3%) were diagnosed with probable CS, respectively.

Table 1. Baseline characteristics

Variable	Value (n=35)
Age at diagnosis (years)	52.5 ± 12.7
Male sex	26 (74.3%)
Caucasian ethnicity	32 (91.4%)
Body mass index (m^2/kg)	27.5 ± 3.7
Symptoms prior to first evaluation	
- Chest pain	7 (20.0%)
- Palpitations	17 (48.6%)
- Syncope	3 (8.6%)
- Dizziness	6 (17.1%)
NYHA functional class (I/II/III/IV)	12 / 18 / 5 / 0
Comorbidities	
- Hypertension	9 (25.7%)
- Diabetes mellitus	1 (2.9%)
- Coronary artery disease	1 (2.9%)
Extracardiac sarcoidosis histologically or cytologically confirmed	33 (94.3%)
Extracardiac organ involvement	
- Bilateral hilar lymphadenopathy	29 (82.9%)
- Pulmonary	33 (94.3%)
- Skin	1 (2.9%)
- Neurologic	5 (14.3%)
- Liver	3 (8.6%)
- Ocular	5 (14.3%)
Laboratory results	
- CRP (mg/L)	3.0 [2.0 – 4.5]
- NT-proBNP (pg/mL) (n=28)	44.0 [26.5 – 120.5]
- ACE (U/L)	46.0 [33.0 – 68.0]
- sIL-2R (pg/mL)	4057 [2887 – 5745]
Electrocardiogram results (n=32)	
- Sinus rhythm	31 (96.9%)
- PQ-interval >200ms	4 (12.5%)
- QRS duration (ms)	98.0 [91.0 – 112.0]
- Left bundle branch block	0 (0.0%)
- Right bundle branch block	4 (12.5%)
Left ventricular ejection fraction (%)	60.0 [55.0 – 62.0]
Immunosuppressive therapy at baseline	14 (40%)
Anti-arrhythmic drugs	6 (17.1%)
ACE-inhibitors or ARBs	11 (31.4%)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRP = C-reactive protein; NT-proBNP = N-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; sIL-2R: soluble interleukin-2 receptor

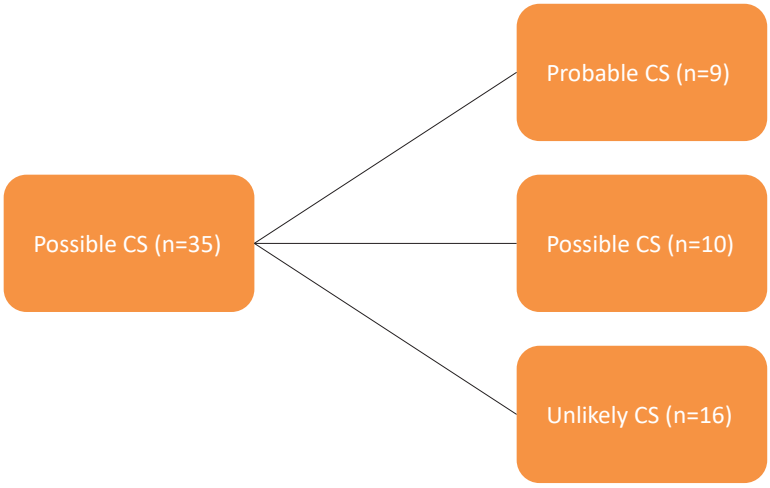

Figure 1. Reclassification of CS diagnosis after repeated imaging.

Imaging results

At baseline, eleven patients (31.4%) showed LGE on CMR. No patients showed increased T2-weighted signal at baseline, which was determined in 29 patients (82.9%). Myocardial FDG-uptake was detected in twenty-six patients (74.3%), of whom ten (28.6%) showed a diffuse FDG-uptake pattern, six (17.1%) showed a focal on diffuse FDG-uptake pattern and ten patients (28.6%) showed a focal FDG-uptake pattern (table 2). Focal myocardial FDG-uptake was seen in the anterior (n=2), antero-septal (n=3), infero-septal (n=2), inferior (n=1), infero-lateral (n=4), antero-lateral (n=2) and apico-lateral wall (n=1). When taking both imaging modalities into account, the majority of patients (65.7%) were classified as CMR-/PET+ at baseline, while one patient (2.9%) showed no abnormalities on cardiac imaging (CMR-/PET-) (Figure 2A). This patient with histologically confirmed extracardiac sarcoidosis showed a second-degree atrioventricular block (AVB); however, this patient was also using beta-blockers which could have caused the AVB and was therefore classified as possible CS.

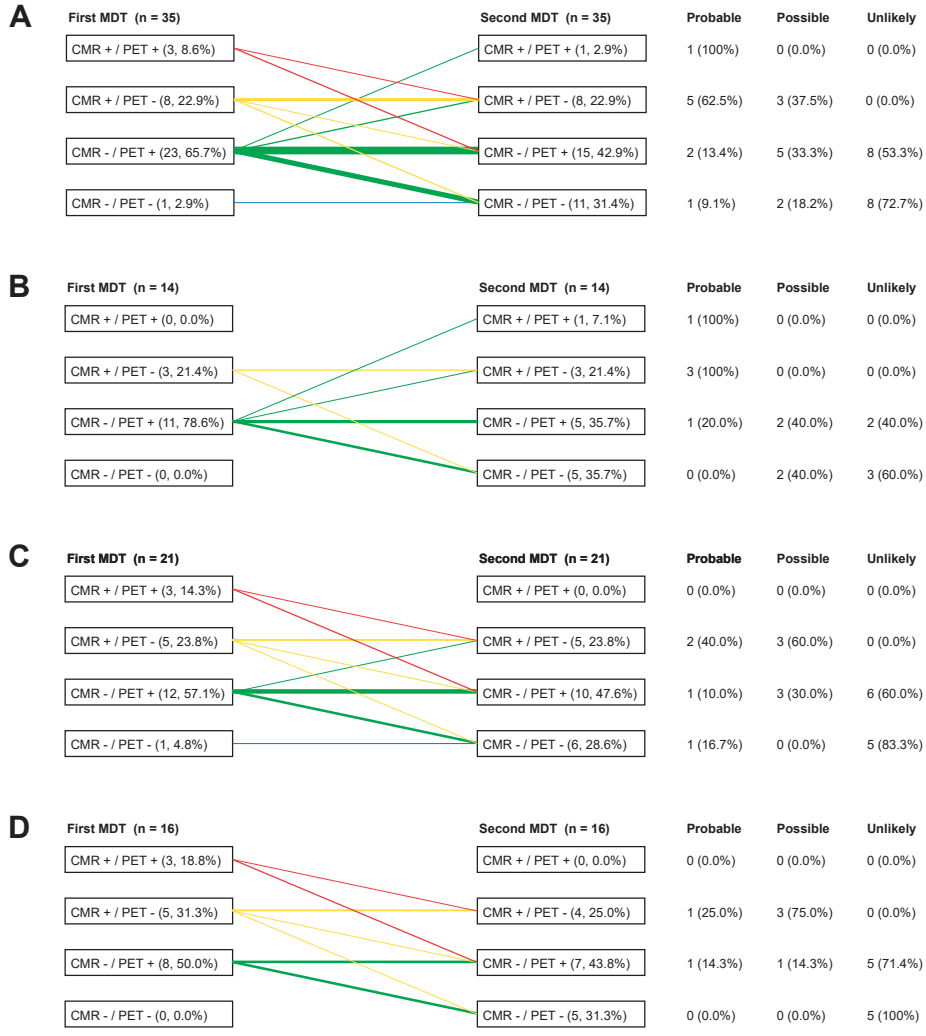

Figure 2. Imaging abnormalities at first and second MDT and corresponding final CS diagnosis in all patients (A), only patients with baseline immunosuppressive treatment (B), only patients without baseline immunosuppressive treatment (C) and only patients without baseline or newly started immunosuppressive treatment (D).

Table 2. FDG PET/CT results at baseline and re-evaluation

	Baseline (n= 35)	Re-evaluation (n=35)	p-value
Myocardial FDG uptake pattern			
• Focal	10 (28.6%)	7 (20.0%)	0.51
• Focal on diffuse	6 (17.1%)	4 (11.4%)	0.63
• Diffuse	10 (28.6%)	5 (14.3%)	0.13
• None	9 (25.7%)	19 (54.3%)	<0.01
Cardiac SUVmax	4.2 [2.2 – 5.8]	1.8 [1.1 – 4.1]	<0.01

FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; SUVmax = maximum standardised uptake value

Examples of different CMR and FDG PET/CT patterns are shown in figure 3. After repeated imaging, LGE was present in nine patients (25.7%), while one patient showed increased T2-weighted signal, indicating myocardial oedema. This patient also showed an increased area of LGE compared to baseline, but without any myocardial FDG-uptake (figure 3A). Of the eleven patients classified as CMR+ at baseline, five were classified as CMR- after repeated imaging. In one patient this was due to inferior hinge point fibrosis, interpreted as innocent at repeated imaging and not suspect for CS (figure 3D). The remaining four patients initially all showed abnormalities, but at the 2nd CMR these abnormalities were absent and the findings at first CMR were interpreted as artefacts and not as LGE.

The presence of myocardial FDG-uptake was seen in sixteen patients (45.7%) at re-evaluation, which was significantly lower compared to baseline (74.3%, p<0.001). Additionally, the presence of a diffuse myocardial uptake pattern was seen in five (14.3%) versus ten patients (28.6%) at baseline (p=0.13). A focal on diffuse or a focal pattern at re-evaluation was seen in four (11.4%) and seven patients (20.0%), respectively (table 2). Focal myocardial FDG-uptake was seen in the antero-septal (n=3), infero-septal (n=1), infero-lateral (n=3) and antero-lateral wall (n=1). SUVmax was significantly higher at baseline compared to re-evaluation (median 4.2 vs 1.8, p<0.01), however as table 2 shows, a higher proportion of patients showed no myocardial FDG-uptake at re-evaluation (54.3% vs 25.7%, p<0.01). SUVmax of the focal or focal on diffuse myocardial FDG-uptake at baseline and re-evaluation was comparable (median 4.2 vs 4.0). Of the twenty-three patients who were initially classified as CMR-/PET+, three patients (13%) showed LGE on CMR after repeated imaging (figure 2). All three showed a focal myocardial FDG-uptake pattern at initial FDG PET/CT and were reclassified as probable CS. Only one patient showed matching LGE and focal myocardial FDG-uptake (figure 3B). No patients with diffuse myocardial uptake on FDG PET/CT at initial imaging (CMR-/PET+) developed CMR abnormalities at re-evaluation.

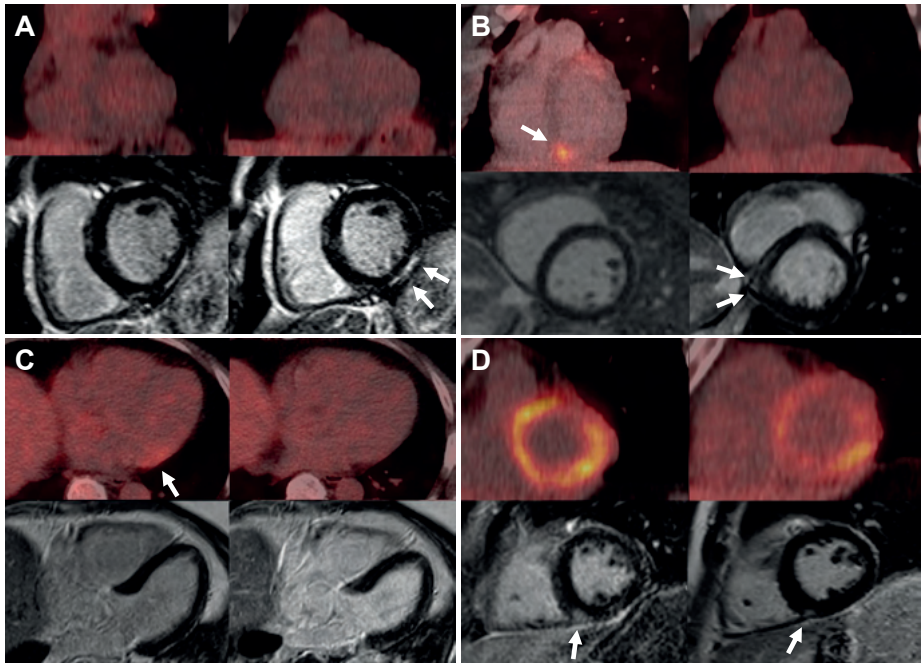

Figure 3. Examples of different FDG PET/CT and CMR patterns. In every image, baseline FDG PET/CT and CMR are shown on the left and repeated imaging on the right.
Image A. 48-year-old male patient who showed LGE uptake infero-lateral at first CMR (white arrows, short axis view) without cardiac FDG-uptake (CMR+/PET-). The LGE increased at 2nd CMR with also increased T2-weighted signal (not shown); however, still no cardiac FDG-uptake was seen (CMR+/PET-), while the patient did not receive any immunosuppressive treatment. He was reclassified as probable CS.
Image B. A 36-year-old female patient who showed focal FDG-uptake infero-septal (white arrows) without LGE on CMR at baseline (CMR-/PET+). Between first and 2nd MDT, she was started on methotrexate 15mg/week due to pulmonary sarcoidosis. Repeated imaging showed complete remission of cardiac FDG-uptake; however, CMR showed new LGE infero-septal (short axis view, white arrows) and she was classified as CMR+/PET-. This patient was diagnosed with probable CS.
Image C. A 56-year-old male with focal FDG-uptake in the antero-lateral wall (white arrow, SUVmax 4.3) at baseline. He showed no LGE uptake on CMR (4 chamber view) and was classified as CMR-/PET+. The FDG-uptake was suspected to be physiologic and repeated imaging showed no cardiac FDG-uptake or LGE on CMR (CMR-/PET-). This patient received no immunosuppressive treatment between both MDT's and CS was deemed 'unlikely'.
Image D. A 47-year-old male patient who showed initial LGE inferoseptal on CMR (white arrow, short axis view). However, after repeated imaging this LGE was interpreted as inferior hinge point fibrosis and not suspect for CS. Both FDG PET/CTs showed diffuse cardiac FDG-uptake (CMR+/PET+, CMR-/PET+). This patient did not receive any immunosuppressive therapies and he was reclassified as 'unlikely' CS.

When considering both imaging modalities together, the majority of patients (n=19, 82.6%) with CMR-/PET+ at baseline, were reclassified as unlikely CS (n=12, 52.2%) or remained diagnosed as possible CS (n=7, 30.4%). On the contrary, four of the eleven (36.4%) patients with LGE presence at baseline were reclassified as probable CS (all CMR+/PET- at baseline). At follow-up, nine patients showed CMR abnormalities (both CMR+/PET+ and CMR+/PET-) of whom six (66.7%) were diagnosed as probable CS and three (33.3%) as possible CS. In eleven patients (31.4%) no imaging abnormalities were observed at follow-up, of whom eight (72.7%) were reclassified as unlikely CS.

Impact of immunosuppressive therapies

At baseline, 14 patients were already on immunosuppressive therapies, all due to extracardiac sarcoidosis. Indications for immunosuppressive treatment were pulmonary- (n=8) and neurosarcoidosis (n=4) and sarcoidosis-related fatigue (n=2). Used immunosuppressive therapies included prednisone monotherapy (n=5), methotrexate monotherapy (n=3), azathioprine monotherapy (n=1) and prednisone and methotrexate combination therapy (n=5). When comparing the patients with and without baseline therapy, QRS duration on electrocardiogram was the only significant different parameter (supplementary table S1). There were no differences in LVEF or FDG PET/CT results. Of the 14 treated patients, 11 were classified as CMR-/PET+ and three as CMR+/PET- at baseline (figure 2B). At the second MDT, the majority of this group was classified as either CMR-/PET+ or CMR-/PET- (n=10, 71.4%). However, two patients showed new LGE on CMR at the second MDT (CMR+), but without myocardial FDG-uptake (PET-) and both were reclassified as probable CS. The 21 patients without baseline immunosuppressive treatment are shown in figure 2C. Of these, new treatment was started between both MDT's in five patients due to pulmonary- (n=4) or neurosarcoidosis (n=1). Only in one of these five patients, FDG-uptake at baseline differed from follow-up (PET+ at baseline, PET- at baseline), but this patient also showed new LGE on CMR and was diagnosed with probable CS. Finally, figure 2D shows the remaining 16 treatment naïve patients who remained without therapy between both MDT's. The proportion of patients with baseline FDG-uptake (PET+) or follow-up FDG-uptake (PET+) between this group (n=16) and the treated group (n=21) is comparable, 68.8% vs 78.9% (p=0.70) and 43.8% vs 47.4% (p=0.83) respectively.

Secondary outcomes

After re-evaluation, immunosuppressive treatment was initiated in two patients who were reclassified as probable CS. Overall median LVEF was 60.0% [55.0 – 60.0] at baseline and 60.0% [51.0 – 61.0] at re-evaluation (p=0.41). No patients showed a decrease in LVEF >10%. Between both MDTs, one patient developed a third degree AVB despite discontinuation of beta-blockers. This was the patient who initially presented with a second-degree AVB while using beta-blockers. This patient was diagnosed with probable CS, despite the absence of imaging abnormalities at re-evaluation (CMR-/PET-). Another patient showed a second degree AVB during follow-up (CMR+/PET-, at both baseline and follow-up) and was also diagnosed as probable CS. Three patients showed a first degree AVB at baseline, which remained stable during follow-up. No other cardiac symptoms, ventricular arrhythmias or conduction disorders were observed. No patients died during follow-up. Serum markers (including CRP, ACE, NT-proBNP and sIL-2R) did not change significantly between both MDTs.

DISCUSSION

The purpose of this study was to evaluate the usefulness of repeated CMR and FDG PET/CT for the diagnosis of CS in patients initially diagnosed with possible CS. Most importantly, 25 patients (72%) could be reclassified as either probable (n= 9) or unlikely CS (n= 16). Furthermore, 3 out of 24 patients (13%) with an initially negative CMR but with myocardial FDG-uptake, developed CMR abnormalities during follow-up and were diagnosed with probable CS. The clinical relevance of repeated imaging has to be investigated in future studies, since immunosuppressive treatment was initiated in only 6% of patients after re-evaluation. Nevertheless, clinical relevance does not only entail the change in treatment, since regular follow-up and prevention also prove to be valuable in patients with CS. Furthermore, rejecting a possible CS diagnosis can also prove valuable for the patient in terms of psychological uncertainty and follow-up burden.

To our knowledge, this is the first study to evaluate the usefulness of repeated CMR and FDG PET/CT for the diagnosis of CS in patients with possible CS diagnosis. In comparison to prior studies, all patients in our cohort routinely received both imaging modalities. We found that non-specific PET abnormalities rarely resulted in a probable CS diagnosis, as 83% of patients with initial CMR-/PET+ were re-evaluated as unlikely or possible CS. Several small studies have analysed findings of combined CMR and FDG PET/CT for the evaluation of CS but these studies showed mixed results.[9–12] Okune et al. performed a retrospective study and reported in a sub-analysis that two out of two patients (100%) with CMR-/PET+ were diagnosed as unlikely CS.[9] Similar results were reported by Soussan et al. [10], as they found that all three individuals with CMR-/PET+ out of a total of 35 included patients, were considered unlikely CS by the Japanese Ministry of Health and Welfare (JMHW) criteria.[13] On the contrary, a retrospective study by Vita et al. with 107 patients, reported that of eight patients with CMR-/PET+, four patients (50%) had probable or even highly probable CS.[11] Similarly, a study by Wicks et al. reported eleven patients with CMR-/PET+ of whom four patients (36.3%) were diagnosed with probable CS using the JMHW guidelines.[12]

We found that patients with solely PET abnormalities were often reclassified as possible or unlikely CS at re-evaluation. However, three patients (13%) with initial CMR-/PET+ developed CMR abnormalities during follow-up and were reclassified as probable CS. All three patients showed focal myocardial FDG-uptake at baseline. This emphasizes that, although not often, CMR-/PET+ can indicate early, active CS and precede CMR abnormalities. This is probably due to the presence of metabolically active inflammatory cells such as lymphocytes and macrophages in early stage CS. CMR with LGE is less sensitive in detecting this early inflammatory stage compared to FDG PET/CT.[14] Nevertheless,

myocardial oedema as detected by increased T2-weighted signal can also prove valuable in detecting early stage CS.[15] Only one patient in our population showed myocardial oedema, but T2-weighted imaging was not consistently used. Remarkably, this patient did not show FDG-uptake and was not treated with immunosuppressive therapies. A possible explanation might be the 30 day time difference between repeated CMR and FDG PET/CT. An important finding was that none of the patients with diffuse FDG-uptake developed abnormalities on CMR or were diagnosed with probable CS. This suggests that in patients with diffuse myocardial FDG-uptake and normal CMR at initial evaluation it is sufficient to repeat only FDG PET/CT with an adequate dietary preparation. In patients with focal or focal on diffuse FDG-uptake and an uncertain diagnosis, our data underline the importance of both repeated CMR and FDG PET/CT.

In our study, diffuse FDG-uptake was classified as abnormal (PET+), whereas this is generally considered normal due to inadequate suppression of physiologic cardiac uptake.[4,16] This might lead to differences in results compared to other studies. Although, Wicks et al. reviewed 51 patients with suspected CS undergoing hybrid FDG PET/CT and CMR, who were diagnosed using the JMHW guidelines.[12,13] They compared annualized adverse event rates for patients with focal, focal on diffuse, diffuse and no myocardial FDG-uptake. Remarkably, there was an event rate of 24% in patients with a diffuse uptake pattern versus 8% in patients with complete suppression of myocardial FDG-uptake. Furthermore, they describe a patient with definite CS confirmed by endomyocardial biopsy, who had a diffuse uptake pattern on FDG PET/CT. This suggests that in some cases, diffuse myocardial uptake may represent CS and therefore cannot with certainty be classified as normal metabolism.

An important confounder in our study is that 40% of patients at baseline were already treated with immunosuppressive therapies. There were no clinically significant differences between both groups at baseline. Nonetheless, this treatment could have impacted FDG PET/CT results as earlier studies have shown that CS patients have reduction in cardiac FDG-uptake and lower cardiac SUVmax during treatment with immunosuppressive therapies.[17–19] However, in daily clinical practice clinicians will encounter sarcoidosis patients who are already treated with immunosuppressive treatment and in whom cardiac involvement is suspected. Our data show that when CS diagnosis is uncertain, repeated imaging with CMR and FDG PET/CT can also be valuable in this subpopulation. Furthermore, our population also included five patients who were newly started on immunosuppressive therapies for extracardiac sarcoidosis between both MDTs. Theoretically, myocardial inflammation could have been suppressed by these therapies; however, only one of these patients classified as PET+ at baseline was reclassified as PET-. This patient was still diagnosed as probable CS due to new LGE on CMR.

Our study had several limitations. Firstly, the modest sample size, which is a result of disease prevalence and supports the need for larger multicentre cohorts. Second, the retrospective character may lead to missing data or selection bias. Also, additional calculations like LGE as a percentage of left ventricular mass and heterogeneity of FDG-uptake could not be evaluated in this study. Another limitation is that myocardial perfusion imaging was not performed in this study and could therefore not be used in the analysis. Also, our CMR studies did not consistently include T2-weighted sequences that could have detected myocardial oedema in the acute phases of CS. However, previous studies have shown that myocardial oedema was always accompanied with LGE [17,18], while FDG PET/CT is considered a more sensitive imaging modality for acute inflammation.[20] Moreover, like all studies regarding the diagnosis of CS, this study is limited by the absence of a clinically functional reference standard. In our study the MDT discussion functioned as a reference standard and the MDT decision was based on a comprehensive clinical evaluation including laboratory tests, electrocardiogram, 24-hour ambulatory heart rhythm monitoring and both CMR and FDG PET/CT. This approach is supported by other sarcoidosis expert centres.[11,21] Finally, appropriate patient preparation prior to FDG administration is essential for achieving sufficient suppression of physiological myocardial glucose uptake to visualize inflammation. In our cohort, a large proportion of the FDG PET/CT scans showed a diffuse uptake pattern, considered as inadequate dietary preparation. This could have caused a high rate of false-positive FDG PET/CT scans, resulting in a high number of patients diagnosed with possible CS. A systematic review of Tang et al. concluded that the diagnostic accuracy improves after fasting for at least 12h and a high fat low carbohydrate diet given at 3-6h before imaging or heparin infusion.[22] A retrospective study from Sankaran et al. concluded that excellent myocardial FDG suppression can be achieved using a 24h high fat very low carbohydrate diet and prolonged fasting.[23] Based on current literature, we recently changed the patient preparation instructions for FDG PET/CT. Patients are now instructed to have a carbohydrate restricted diet for 24h followed by a prolonged 12h fasting period in order to reduce physiologic myocardial FDG uptake and decrease the need for repeated imaging.

CONCLUSION

In conclusion, repeated CMR and FDG PET/CT may be useful in establishing or rejecting the diagnosis CS, when initial diagnosis is uncertain. Additional studies are required to determine the prognostic implications of repeated cardiac imaging for CS diagnosis as well as clinical relevance.

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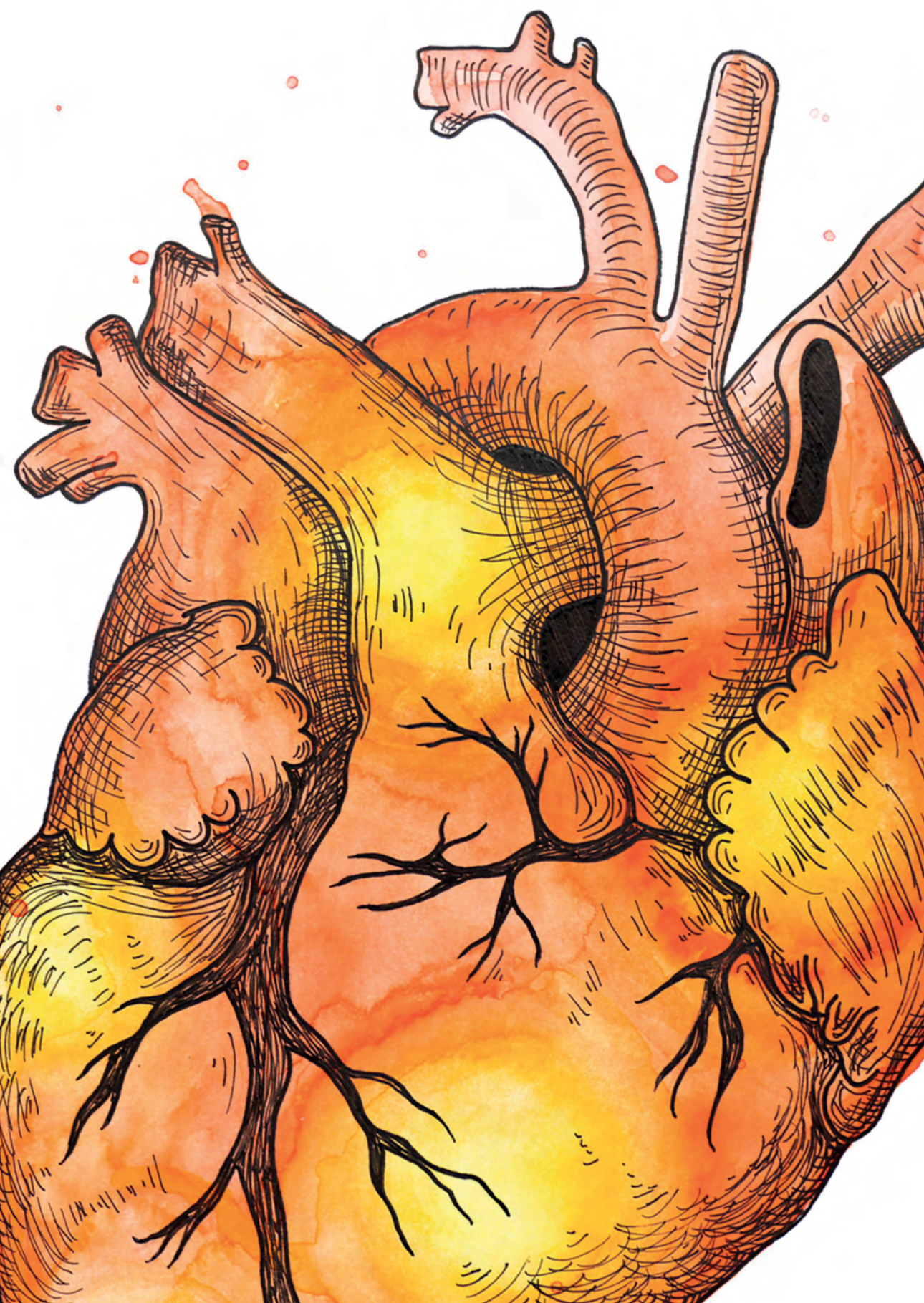
APPENDIX

Supplementary table S1. Comparison of baseline characteristics and FDG PET/CT results between treated and treatment naïve patients at baseline

Variable	Patients without BL immunosuppressive treatment (n=21)	Patients with BL immunosuppressive treatment (n=14)	p-value
Age at diagnosis (years)	54.0 ± 13.0	50.4 ± 12.4	0.43
Male sex	17 (81.0%)	9 (64.3%)	0.43
Caucasian ethnicity	19 (90.5%)	13 (92.9%)	1.00
Body mass index (m^2/kg)	26.3 [24.7 – 29.4]	28.4 [25.5 – 31.6]	0.28
NYHA functional class (I/II/III/IV)	10 / 8 / 3 / 0	2 / 10 / 2/ 0	0.09
Comorbidities			
- Hypertension	7 (33.3%)	2 (14.3%)	0.26
- Diabetes mellitus	0 (0.0%)	1 (7.1%)	0.40
- Coronary artery disease	1 (4.8%)	0 (0.0%)	0.40
Extracardiac sarcoidosis histologically or cytologically confirmed	20 (95.2%)	13 (92.9%)	1.00
Extracardiac organ involvement			
- Bilateral hilar lymphadenopathy	19 (90.5%)	10 (71.4%)	0.19
- Pulmonary	20 ((95.2%)	13 (92.9%)	0.41
- Skin	0 (0.0%)	1 (7.1%)	0.40
- Neurologic	1 (4.8%)	4 (28.6%)	0.13
- Liver	2 (9.5%)	1 (7.1%)	1.00
- Ocular	3 (14.3%)	2 (14.3%)	1.00
Laboratory results			
- CRP (mg/L)	2.5 [2.0 – 4.0]	3.0 [1.5 – 9.5]	0.50
- NT-proBNP (pg/mL) (n=28)	39.5 [22.0 – 146.0]	56.5 [36.0 – 92.5]	0.49
- ACE (U/L)	46.0 [34.0 – 65.0]	44.0 [29.0 – 73.5]	0.65
- sIL-2R (pg/mL)	4301 [2817 – 7365]	3232 [2613 – 4385]	0.17
Electrocardiogram results	(n=18)	(n=14)	
- Sinus rhythm	17 (94.4%)	14 (100%)	1.00
- PQ-interval >200ms	4 (22.2%)	0 (0.0%)	0.11
- QRS duration (ms)	100 [96.0 – 121.0]	94.5 [86.0 – 100.5]	0.03
- Left bundle branch block	0 (0.0%)	0 (0.0%)	-
- Right bundle branch block	2 (11.1%)	2 (14.3%)	1.00
Left ventricular ejection fraction (%)	59.0 [54.0 – 61.0]	60.0 [56.8 – 60.0]	0.75
Anti-arrhythmic drugs	5 (23.8%)	1 (7.1%)	0.37
ACE-inhibitors or ARBs	8 (38.1%)	3 (21.4%)	0.46
Myocardial FDG uptake pattern			
• Focal	6 (28.6%)	4 (28.6%)	1.00
• Focal on diffuse	3 (14.3%)	3 (21.4%)	0.66
• Diffuse	6 (28.6%)	4 (28.6%)	1.00
• None	6 (28.6%)	3 (21.4%)	0.71
Cardiac SUVmax at baseline	4.2 [1.1 – 5.4]	4.2 [3.1 – 6.2]	0.63

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BL = baseline; CRP = C-reactive protein; NT-proBNP = N-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; sIL-2R = soluble interleukin-2 receptor; SUVmax = maximum standardized uptake value



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Prednisone vs methotrexate in treatment naïve cardiac sarcoidosis

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ABSTRACT

Background: Side effects limit the long-term use of glucocorticoids in cardiac sarcoidosis (CS), and methotrexate has gained attention as steroid sparing agent although the supporting evidence is poor. This study compared prednisone monotherapy, methotrexate monotherapy or a combination of both, in the reduction of myocardial fluorodeoxyglucose (^{18}F-FDG) uptake and clinical stabilization of CS patients.

Methods: In this retrospective cohort study, 61 newly diagnosed and treatment naïve CS patients commenced treatment with prednisone (n=21), methotrexate (n=30) or prednisone and methotrexate (n=10) between January 2010 and December 2017. Primary outcome was metabolic response on follow-up ^{18}F-FDG PET/CT and secondary outcomes were treatment patterns, major adverse cardiovascular events (MACE), left ventricular ejection fraction (LVEF), biomarkers and side effects.

Results: At a median treatment duration of 6.2 [5.7 – 7.2] months, 71.4% of patients was ^{18}F-FDG PET/CT responder, and overall myocardial maximum standardized uptake value (SUVmax) decreased from 6.9 [5.0 – 10.1] to 3.4 [2.1 – 4.7] ($p<0.001$), with no significant differences between treatment groups. During 24 months of follow-up, 7 patients (33.3%; prednisone), 6 patients (20.0%; methotrexate) and 1 patient (10.0%; combination group) experienced at least one MACE ($p=0.29$). LVEF was preserved in all treatment groups.

Conclusion: Significant suppression of cardiac ^{18}F-FDG uptake occurred in CS patients after 6 months of prednisone, methotrexate or combination therapy. There were no significant differences in the occurrence of MACE or the preservation of LVEF during follow-up. These results warrant further investigation of methotrexate treatment in CS patients.

INTRODUCTION

Clinically manifest cardiac involvement occurs in approximately 5% of sarcoidosis patients and involves conduction abnormalities, ventricular arrhythmias (VA) and heart failure.[1] Cardiac sarcoidosis (CS) is often subclinical and under-recognized,[2] with autopsy and cardiac magnetic resonance imaging (CMR) studies reporting cardiac involvement in 20% to 30% of cases.[3] A clinical diagnosis of CS can be made based on a combination of extracardiac histology, clinical findings and results from advanced cardiac imaging such as CMR and fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET/CT).[1,4] ^{18}F-FDG PET/CT detects active inflammation in the myocardium,[5] and visual- and quantitative analysis has prognostic value.[6–8] ^{18}F-FDG PET/CT is used in the monitoring of immunosuppressive treatment and several studies have reported an association between cardiac PET/CT improvement and favourable clinical outcomes.[9–13]

Treatment of CS with immunosuppressive therapies is recommended in patients with conduction abnormalities or VA, as well as heart failure.[1,3,4] These recommendations are based on a limited number of observational studies, in absence of randomised controlled trials in CS.[14,15] Furthermore, less is known about the treatment of CS patients with myocardial ^{18}F-FDG uptake, but without rhythm or conduction disorders and with a preserved left ventricular ejection fraction (LVEF).[3] It has been proposed that myocardial ^{18}F-FDG uptake should be considered an indication for treatment.[2] Although this has not yet been validated in clinical studies. The management of CS is therefore highly empiric and heterogeneous, although glucocorticoids and methotrexate are generally considered as the first and second-line therapy of choice.[2,15] Multiple side effects such as hypertension, diabetes, weight gain and osteoporosis limit the long-term use of glucocorticoids,[16] and methotrexate has gained attention as steroid sparing agent with a potentially more favourable safety profile.[3,16] The objective of this study was to compare the effects of prednisone monotherapy, methotrexate monotherapy or a combination of low-dose prednisone and methotrexate on myocardial ^{18}F-FDG uptake and clinical outcomes in treatment naïve CS patients.

METHODS

Study design

A retrospective, single centre cohort study was performed in the St. Antonius Hospital, the Netherlands, a tertiary referral centre for sarcoidosis including CS. All patients who were newly diagnosed with CS and subsequently treated with prednisone and/or

methotrexate between January 2010 and December 2017 were included. The investigation conforms with the principles outlined in the *Declaration of Helsinki.* Local institutional review board approval was obtained with registration number R&D/Z19.004, with a waiver of informed consent. This study was designed and reported in agreement with the criteria as defined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[17]

Study population and treatment protocol

Eligible patients were ≥18 years of age and diagnosed with CS by clinical consensus in a multidisciplinary team. Diagnosis was based on clinical findings, CMR and ^{18}F-FDG PET/CT findings and extracardiac sarcoidosis diagnosis.[18] All patients fulfilled either the 2014 Hearth Rhythm Society (HRS) or the 2016 Japanese Circulatory Society (JCS) diagnostic criteria for CS.[1,2] Other inclusion criteria were (1) baseline myocardial ^{18}F-FDG uptake, (2) a minimum of 6 months follow-up, and (3) immunosuppressive therapy with oral prednisone and/or methotrexate had to be initiated within 3 months after CS diagnosis. Patients treated with immunosuppressive therapies in the past 3 months before baseline were excluded.

Prednisone monotherapy typically consisted of a starting dose of 40 mg daily for 1 month, followed by taper to 20 mg daily at 3 months and 10 mg daily at 6 months. Methotrexate monotherapy and combination therapy started with a dosage of 10 mg weekly, which was increased to 15 mg weekly over a four-week period. All patients on methotrexate therapy received folic acid at a dosage of 5 mg weekly or biweekly. Patients with combination therapy typically received prednisone 20 mg daily for 1 month followed by prednisone taper to approximately 10 mg daily at 3 months. For all immunosuppressive regimens, doses were subsequently adjusted based on findings from clinical follow-up, ^{18}F-FDG PET/CT and side effects.

Clinical characteristics and outcome parameters

Data on baseline demographics, medical history, severity of disease, immunosuppressive treatment, side effects and serum biomarkers was collected by review of the electronic medical records. Baseline ^{18}F-FDG PET/CT was performed prior to CS diagnosis and before the initiation of immunosuppressive therapy. ^{18}F-FDG PET/CT protocol is described in supplementary S1. Serial ^{18}F-FDG PET/CT scans were performed at approximately 6 to 12 month intervals. Patients generally received CMR at baseline and CMR images were scored on both the presence of late gadolinium enhancement (LGE) and LVEF. Serum biomarkers included serum soluble interleukin-2 receptor (sIL-2R) and N-terminal pro brain natriuretic peptide (NT-proBNP).

The primary outcome parameter was the metabolic response based on visual interpretation and quantitative analysis of cardiac ^{18}F-FDG PET/CT within 12 months from initiation of treatment. ^{18}F-FDG PET/CT response was defined as a reduction in myocardial maximum standardized uptake value (SUVmax) ≥ 30.0%. Secondary outcomes included treatment patterns, major adverse cardiovascular events (MACE), change in LVEF, biomarkers and side effects during 24 months after treatment start. MACE was defined as cardiac death, heart transplantation, VA, new Mobitz type II second or third degree atrioventricular block (AVB), appropriate implantable cardioverter defibrillator (ICD) therapy and hospitalisation due to heart failure. In patients with and without MACE, SUVmax values and right ventricular (RV) ^{18}F-FDG uptake were compared. LVEF during follow-up was determined by transthoracic echocardiography using the biplane Simpson's method. Only side effects requiring dose reduction or permanent discontinuation of immunosuppressive therapy and side effects requiring medical treatment or hospitalisation were taken into account. Body weight was documented at baseline and at follow-up PET/CT.

Statistical analysis

Study data were collected and managed using the REDCap electronic data capture tool. Statistical analysis was performed with IBM SPSS 26.0 Statistics software (IBM, Armonk, New York, USA). Categorical variables are expressed as absolute numbers and percentages, continuous variables as means ± SD in case of normal distribution or as medians [25th – 75th percentile]. The normality of continuous variables was assessed visually by means of the frequency histogram and Q-Q plot and was tested using the Shapiro-Wilk test. The likelihood-ratio chi-square test or Fisher's Exact test was used to compare categorical variables. The independent-samples *t*-test or Mann-Whitney U test was used to compare mean or median values of two continuous variables. The one-way ANOVA or Kruskal Wallis test was applied to compare the means or medians of three continuous variables. The McNemar test was used to compare categorical variables of two related samples. The paired-samples *t*-test or Wilcoxon signed rank test was used to compare mean or median values of two related samples. Kaplan-Meier analysis was used for observed MACE free survival during follow-up with the Log-Rank test for comparison between curves. A two-tailed *p*-value of < 0.05 was considered significant.

RESULTS

Study population

Overall, 61 patients were included in this study (figure 1). One patient died from oesophageal cancer after 7 months since treatment initiation. One patients treated with

methotrexate was lost to follow-up after heart transplantation 12 months after treatment initiation, after being hospitalized due to heart failure after 7 months of treatment. This patient was included in the analysis of follow-up PET/CT and MACE.

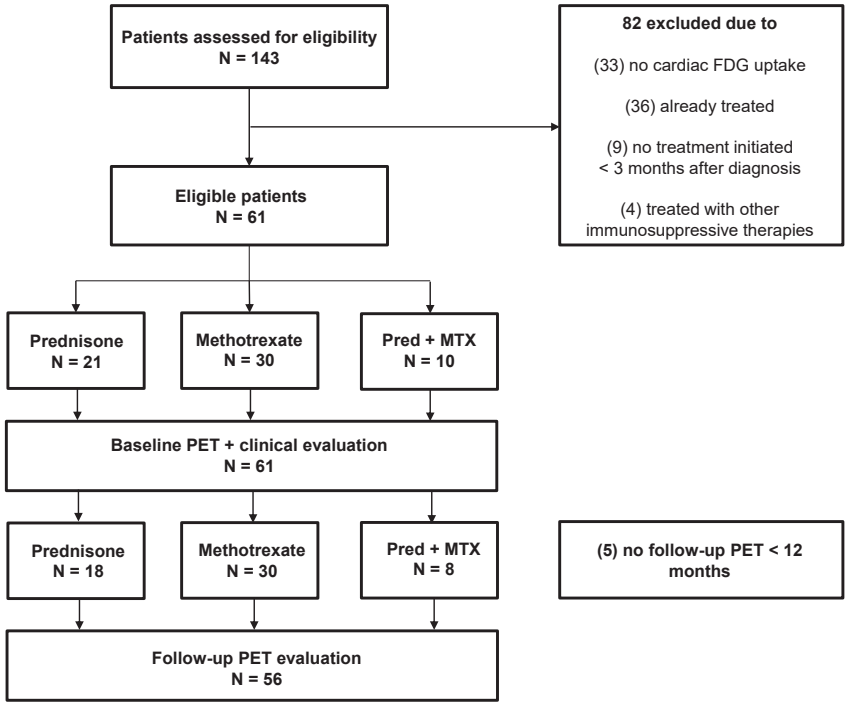

Figure 1. Patient disposition. MTX = methotrexate; pred = prednisone.

Immunosuppressive treatment was initiated with prednisone (n=21), methotrexate (n=30), or a combination (n=10). Initial monotherapy prednisone dose was 40 mg (n=18), 35 mg (n=2) or 20 mg daily (n=1), which was tapered to a median dose of 12.5 mg [10 - 15 mg] at 6 months. Methotrexate was dosed at 15 mg weekly for at least 6 months in all cases (both monotherapy and combination group). The initial combination therapy prednisone dose was 40 mg (n=2), 20 mg (n=6) or 10 mg daily (n=2). Of the combination group, 4 patients still used prednisone after 6 months, at a dose of 7.5 to 15 mg. Baseline characteristics were generally balanced between groups (table 1). BMI was higher and arterial hypertension was present more frequently in methotrexate treated patients. Importantly, prednisone treated patients more often had VA at baseline (p=0.04). Accordingly, ICD and pacemaker implantation and antiarrhythmic treatment occurred more frequently in the prednisone group.

Table 1. Baseline characteristics

Variable	Total (n = 61)	Prednisone (n = 21)	MTX (n = 30)	Pred + MTX (n = 10)	p-value
Age (years)	52.5±10.5	50.8±9.7	54.8±11.1	49.2±9.8	0.23
Male sex	46 (75.4)	17 (81.0)	21 (70.0)	8 (80.0)	0.63
Caucasian ethnicity	60 (98.4)	20 (95.2)	30 (100.0)	10 (100.0)	0.34
BMI (kg/m^2)	27.9±4.2	25.4±3.0	29.4±4.0	28.5±5.2	0.003*
Comorbidities					
Hypertension	19 (31.1)	2 (9.5)	14 (46.7)	3 (30.0)	0.012*
Diabetes mellitus	5 (8.2)	0 (0.0)	4 (13.3)	1 (10.0)	0.10
Coronary artery disease	2 (3.3)	0 (0.0)	2 (6.7)	0 (0.0)	0.23
Disease severity					
Extracardiac sarcoidosis					
- Pulmonary	52 (85.2)	19 (90.5)	24 (80.0)	9 (90.0)	0.52
- Neurologic	3 (4.9)	1 (4.8)	2 (6.7)	0 (0.0)	0.55
- Liver	11 (18.0)	6 (28.6)	3 (10.0)	2 (20.0)	0.23
- Ocular	5 (8.2)	1 (4.8)	3 (10.0)	1 (10.0)	0.76
Isolated cardiac sarcoidosis	2 (3.3)	1 (4.8)	1 (3.3)	0 (0.0)	0.67
Cardiac manifestations					
NYHA functional class					
- I	25 (41.0)	10 (47.6)	12 (40.0)	3 (30.0)	
- II	25 (41.0)	9 (42.9)	11 (36.7)	5 (50.0)	0.67
- III	11 (18.0)	2 (9.5)	7 (23.3)	2 (20.0)	
Ventricular arrhythmias	9 (14.8)	6 (28.6)	3 (10.0)	0 (0.0)	0.040
Second / third degree AVB	15 (24.6)	6 (28.6)	5 (16.7)	4 (40.0)	0.30
LVEF (%)	53.5 [46.8 – 60.0] (n=58)	52.0 [44.3 – 58.0] (n=21)	56.0 [47.0 – 60.0] (n=27)	56.0 [45.8 – 60.0] (n=10)	0.41
LGE on CMR	52 (89.7) (n=58)	19 (90.5) (n=21)	24 (88.9) (n=27)	9 (90.0) (n=10)	0.98
Treatment					
ICD or pacemaker implantation	35 (57.4)	16 (76.2)	13 (43.3)	6 (60.0)	0.059*
Antiarrhythmic treatment	25 (41.0)	12 (57.1)	12 (40.0)	1 (10.0)	0.030#
Biomarkers					
sIL-2R (pg/ml)	4940 [2768 – 7325]	4152 [3301 – 6104]	4851 [2354 – 6915]	7325 [3619 – 10085]	0.35
NT-proBNP (pg/ml)	190 [71 – 547] (n=45)	217 [116 – 1212] (n=13)	184 [68 – 504] (n=24)	141 [42 – 449] (n=8)	0.49

**p-value < 0.05 (prednisone vs MTX); #p-value < 0.05 (prednisone vs prednisone + MTX). AVB = atrioventricular block; BMI = body mass index; CMR = cardiac magnetic resonance imaging; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MTX = methotrexate; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; sIL-2R = soluble interleukin 2 receptor*

18F-FDG PET evaluation

At baseline, 48 of 61 patients (78.7%) showed focal cardiac ^{18}F-FDG uptake, while RV ^{18}F-FDG uptake was observed in 24 (39.3%) patients.

Follow-up ^{18}F-FDG PET/CT scans were available for 56 patients. Median intervals between baseline PET/CT and follow-up PET/CT in the prednisone, methotrexate and combination group, were respectively 8.5 [6.1 - 11] months, 9.4 [7.4 - 12] months and 8.7 [7.5 – 10] months (p=0.41) and median intervals from treatment start to follow-up PET/CT were 6.0 [4.5 – 6.9] months, 6.4 [5.8 – 7.7] months and 6.1 [6.0 – 7.0] months (p=0.31). Uptake pattern at follow-up differed significantly from baseline in all groups except for the prednisone group (table 2). Overall, 24 patients (42.9%) showed no cardiac ^{18}F-FDG uptake at follow-up. In the combination group, 7 of 8 patients (87.5%) showed no cardiac ^{18}F-FDG uptake, more frequent than in the prednisone group (p=0.005) and methotrexate group (p=0.042). At follow-up, myocardial SUVmax values were significantly reduced vs baseline in all treatment groups. Overall, myocardial SUVmax reduced from 6.9 [5.0 – 10.1] to 3.4 [2.1 – 4.7] (p<0.001), corresponding to a change of -47% [-69 – -25] (table 2). Reductions in normalised myocardial SUVmax were similar to the reductions in myocardial SUVmax (data not shown). Overall, 40 of 56 patients (71.4%) were ^{18}F-FDG PET/CT responder.

Table 2. Results from visual and quantitative FDG PET/CT evaluation

Visual PET evaluation					
	Total (n = 61)	**Prednisone (n = 21)**	**MTX (n = 30)**	**Pred + MTX (n = 10)**	**p-value**
Baseline FDG PET/CT	*n=61*	*n=21*	*n=30*	*n=10*	
Diffuse	13 (21.3)	3 (14.3)	8 (26.7)	2 (20)	0.56
Focal/focal on diffuse	48 (78.7)	18 (85.7)	22 (73.3)	8 (80)	
Follow-up FDG PET/CT	*n=56*	*n=18*	*n=30*	*n=8*	
No uptake	24 (42.9)	4 (22.2)	13 (43.3)	7 (87.5)	
Diffuse	9 (16.1)	3 (16.7)	6 (20.0)	0 (0.0)	0.019#,^
Focal/focal on diffuse	23 (41.1)	11 (61.1)	11 (36.7)	1 (12.5)	
	p<0.001	p=0.13	p< 0.001	p=0.016	
Quantitative PET evaluation					
	Total (n = 61)	**Prednisone (n = 21)**	**MTX (n = 30)**	**Pred + MTX (n = 10)**	**p-value**
Baseline FDG PET/CT	*n=61*	*n=21*	*n=30*	*n=10*	
Myocardial SUVmax	6.9 [5.0 – 10.1]	7.3 [5.4 – 11.3]	6.5 [4.7 – 9.0]	6.3 [4.5 – 9.7]	0.47
Follow-up FDG PET/CT	*n=56*	*n=18*	*n=30*	*n=8*	
Myocardial SUVmax	3.4 [2.1 – 4.7]	3.7 [2.7 – 5.4]	3.4 [1.9 – 4.8]	2.2 [1.8 – 2.7]	0.093#
	p<0.001	p=0.002	p<0.001	p=0.012	
Change SUVmax (%)	-47 [-69 – -25]	-47 [-70 – -26]	-38 [-66 – -12]	-67 [-72 – -56]	0.25
FDG PET/CT treatment responder	40 (71.4)	13 (72.2)	20 (66.7)	7 (87.5)	0.47

#p-value < 0.05 (prednisone vs prednisone + MTX); ^p-value < 0.05 (MTX vs pred + MTX).
FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; MTX = methotrexate; PET = positron emission tomography; pred = prednisone; SUV = standardized uptake value.

Treatment patterns

Before 2016, initial treatment of 27 patients consisted of prednisone (20), methotrexate (3) or combination treatment (4). From 2016 onwards, initial therapies in 34 patients were prednisone (1), methotrexate (27) or combination treatment (6). After 24 months of follow-up, 34 patients (55.7%) remained on methotrexate monotherapy or were switched to methotrexate monotherapy (figure 2). Three patients were on third line immunosuppressive therapies, such as infliximab.

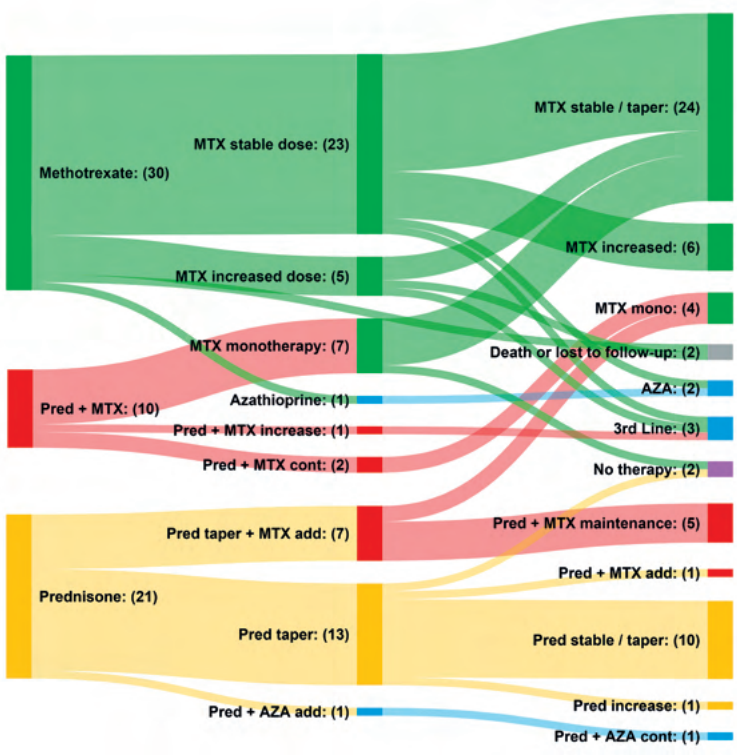

Figure 2. Treatment patterns at baseline, at 12 months and 24 months after treatment start. Add = addition; AZA = azathioprine; cont = continued; MTX = methotrexate; pred = prednisone.

Major adverse cardiovascular events and safety

During follow-up, 14 patients experienced at least one MACE, involving appropriate ICD therapy (n=10), hospitalisation due to heart failure (n=3) and new third degree AVB (n=1). One methotrexate treated patient underwent heart transplantation, however this patient was hospitalised due to heart failure earlier on. Another methotrexate treated patient developed new third degree AVB. Overall, 7 patients (33.3%) of the prednisone group, 6 patients (20.0%) of the methotrexate group and 1 patient (10.0%) of the combination

group experienced MACE (p=0.29*)* (figure 3). Importantly, 6 out of 10 patients experiencing appropriate ICD therapy during follow-up, already showed VA at baseline (p<0.001).

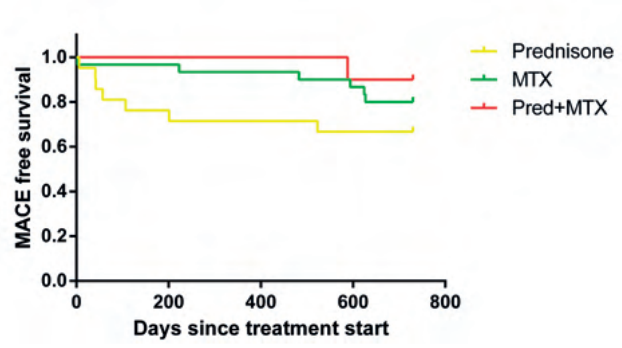

Figure 3. MACE free survival in prednisone, methotrexate and combined prednisone and methotrexate treated patients. MTX = methotrexate; pred = prednisone.

Patients with baseline RV ^{18}F-FDG uptake experienced MACE more often during follow-up: 11 out of 24 patients (45.8%) with RV uptake vs 3 out of 37 patients (8.1%) without RV uptake (p=0.001). Myocardial ^{18}F-FDG uptake was higher in patients experiencing MACE. In patients with and without MACE, myocardial SUVmax values were 10.4 [6.9 – 15.3] vs 5.9 [4.7 – 8.3] (p=0.003) at baseline and 4.7 [3.8 – 7.5] vs 2.8 [1.9 – 4.3] (p=0.002) at follow-up.

For 53 patients, LVEF measurements were available at a median of 16 [13 – 21] months since treatment start. Median follow-up LVEF measurements did not differ significantly from baseline values in all treatment groups (table 3).

Table 3. Results from LVEF analysis

	Total (n = 61)	**Prednisone (n = 21)**	**MTX (n = 30)**	**Pred + MTX (n = 10)**	**p-value**
Baseline LVEF (%)	*n=58* 53.5 [46.8 – 60.0]	*n=21* 52.0 [44.3 – 58.0]	*n=27* 56.0 [47.0 – 60.0]	*n=10* 56.0 [45.8 – 60.0]	0.41
Follow-up LVEF (%)	*n=53* 55.0 [50.0 – 60.0] p=0.67	*n=17* 50.0 [46.0 – 57.5] p=0.84	*n=26* 57.5 [50.0 – 60.0] p=0.81	*n=10* 60.0 [56.3 – 60.0] p=0.33	0.069
LVEF difference (follow-up vs baseline)	0.0 [-4.5 – 5.5]	3.0 [-7.0 – 7.5]	0.0 [-5.0 – 3.5]	2.5 [-1.0 – 5.3]	0.52

LVEF = left ventricular ejection fraction; MTX = methotrexate; pred = prednisone.

For 39 patients, NT-proBNP measurements were performed at a median of 21 [16 – 24] months after treatment start. Only in the combination treatment group, NT-proBNP

values were significantly decreased at follow-up (supplementary table S2). Follow-up sIL-2R values were available for 60 patients at a median interval of 22 [20 – 24] months since treatment start and were significantly lower compared to baseline in all groups (supplementary table S2).

Side effects occurred in 3 (prednisone), 7 (methotrexate) and 4 (combination group) patients. In prednisone treated patients, side effects were obstructive sleep apnea (OSA) (n=1), osteopenia (n=1) and Achilles tendon rupture (n=1). In methotrexate treated patients, abnormal liver function tests (n=2), hospitalisation for infection (n=1), complex partial seizures (n=1), OSA (n=1), erectile dysfunction (n=1) and hair loss (n=1) occurred. Hospitalisation for infection (n=2), new onset diabetes (n=1) and unacceptable weight gain (n=1) were observed in the combination group. Both patients developing new onset OSA, experienced significant weight gain (> 10% from baseline) during treatment. One patient experienced tinnitus after methotrexate addition to initial prednisone treatment, one patient was hospitalised for infection during methotrexate monotherapy after initial combination therapy. Between baseline and follow-up ^{18}F-FDG PET/CT, BMI increased significantly from 25.6±3.2 to 26.3±3.3 kg/m^2 in the prednisone group (p=0.020). In the methotrexate (29.4±4.0 to 29.9±4.6 kg/m^2; p=0.086) and combination group (28.2±3.6 to 29.7±5.0 kg/m^2; p=0.16) this increase was not statistically significant.

DISCUSSION

This is the first study comparing monotherapy prednisone, methotrexate and a combination of both in CS patients. This study showed significant suppression of cardiac inflammation measured by ^{18}F-FDG uptake after 6 months of treatment, irrespective of the immunosuppressive treatment regimen. During 24 months of follow-up, there were no significant differences in the occurrence of MACE or the preservation of LVEF between the three initial treatment strategies.

Few studies have reported on the effects of methotrexate in CS. In a prospective study by Nagai et al., treatment with glucocorticoids and a low dose of 6 mg methotrexate weekly resulted in a higher LVEF and lower NT-proBNP levels at 3-year follow-up compared to glucocorticoids alone, in a population with an average baseline LVEF of 51%.[19] Fussner et al. compared prednisone monotherapy with steroid sparing agents (including methotrexate) with or without prednisone and concluded that clinical presentation of CS had a larger impact on outcomes than the treatment regimen.[20] In a study of Ballul et al., patients treated with glucocorticoids and azathioprine or methotrexate showed lower

cardiac relapse rates than patients treated with glucocorticoids monotherapy.[21] Event rate was high in this cohort, with cardiac relapse in 36.1% of patients and a mortality rate of 8.3% during a median follow-up of 3.6 years. A treatment regimen of prednisone and methotrexate followed by prednisone taper was studied by Rosenthal et al.[22] Despite good initial suppression of myocardial ^{18}F-FDG uptake while using combination treatment or methotrexate maintenance therapy, a substantial number of patients required third line therapies due to persistent or recurrent myocardial ^{18}F-FDG uptake. Higher quality evidence is needed to compare the safety and efficacy of prednisone and methotrexate (combination) therapy, and the results of the CHASM CS-RCT are therefore highly anticipated.[15]

In our clinic, immunosuppressive treatment is initiated after a CS diagnosis with suspicious myocardial ^{18}F-FDG uptake, whether or not conduction abnormalities, VA or cardiomyopathy are present. Besides myocardial ^{18}F-FDG uptake, 90% of our population showed LGE on CMR, a combination that poses a higher risk of death, arrhythmia and decompensated heart failure.[7] We therefore aimed for early treatment, at a minimum of side effects. In 2016 and 2017, methotrexate monotherapy has been used in the majority of new CS diagnoses in our clinic. As of 2018 high risk patients are treated with methylprednisolone pulse therapy before methotrexate is started.

Our results suggest that in the first two years after diagnosis, methotrexate monotherapy results in a substantial suppression of myocardial inflammation and clinical stabilization. While more than a third of methotrexate treated patients required a dose increase during follow-up, only 4 from 30 patients switched to other second or third line therapies. Small patient numbers and imbalances in baseline characteristics warrant a cautious comparison of treatment regimens. Especially the higher occurrence of VA at baseline in the prednisone group, and some evidence of more frequent baseline AVB in the combination group seems to be relevant. This could indicate that these groups are at higher risk of MACE than the methotrexate group. Appropriate ICD therapy in VA was the most frequently observed event. In our cohort with generally normal or mildly reduced LVEF at baseline, LVEF was preserved in all treatment groups. This is consistent with a recent meta-analysis, in which immunosuppressive treatment was associated with preservation of LVEF in patients who presented with normal LVEF or mild to moderate LV dysfunction.[23] However, a possible confounder in the stabilization of LVEF might be the effect of heart failure therapy.

Glucocorticoids are considered first-line therapy, but they may lead to significant morbidity.[24] In a study by Kahn et al, the cumulative incidence of glucocorticoids associated toxicity kept increasing during the median follow-up of 101 months.[24] In a recent survey

of patient reported side effects in sarcoidosis, methotrexate gave fewer and less bothersome side effects than prednisone, although median treatment duration was longer in the prednisone group (24 vs 12 months).[16] In our study, methotrexate was not better tolerated than prednisone during the follow-up of 24 months.

Our observation that RV ^{18}F-FDG uptake is associated with the occurrence of MACE is in line with previous studies, reporting adverse cardiac events in 26-36% of patients with RV ^{18}F-FDG uptake compared to 3-7% in those without.[6,7,25,26] It has been suggested that RV involvement occurs in more advanced stages of the disease, and is associated with a broader distribution of sarcoid lesions in the LV.[26] We noted higher SUVmax values in patients with MACE, an association that has been found before.[7,8,27] In our cohort, adverse events primarily involved appropriate ICD therapy. Considering VA in CS can be either due to sarcoid granulomas or myocardial scarring, there is no uniform correlation between the extent of myocardial inflammation in imaging studies and VA.[28–30] In line with these findings are the results of a recent meta-analysis showing recurrence of VA in a wide range of 14-71% of CS patients treated with immunosuppressant therapy.[23] Based on the significantly higher SUVmax values, myocardial inflammation seems to be linked to VA in our population. Besides myocardial inflammation, pre-treatment VA, and the concomitant use of antiarrhythmic drugs need to be taken into account.

An important limitation of this study is the lack of a control group. Therefore the observed effect on myocardial inflammation could represent the natural course of the disease. Another limitation is the modest sample size of the study population, although our population is one of the largest compared to previous published studies. Finally, in our cohort, a small proportion of patients showed diffuse ^{18}F-FDG uptake with a physiologic pattern, considered as inadequate dietary preparation. It remains uncertain whether these patients did not have active cardiac inflammation, although none of these patients showed a focal on diffuse pattern.

CONCLUSION

In this cohort, significant suppression of cardiac 18F-FDG uptake was observed in CS patients after 6 months of monotherapy with prednisone, methotrexate or combination therapy. During a total follow-up of 24 months there were no significant differences in the occurrence of MACE or the preservation of LVEF. These results warrant further investigation of methotrexate treatment in CS patients.

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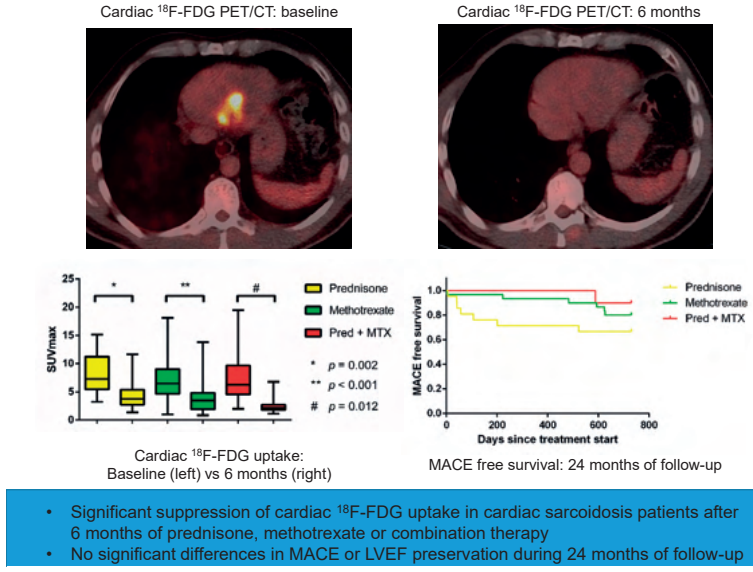
APPENDIX



Graphical abstract. Treatment naïve cardiac sarcoidosis patients commenced treatment with prednisone, methotrexate or a combination. Cardiac 18F-FDG uptake was significantly suppressed after 6 months of treatment. There were no significant differences between treatment groups in MACE or LVEF preservation during 24 months of follow-up.

Supplementary S1. ^{18}F-FDG PET/CT Protocol

^{18}F-FDG PET/CT was performed with a Philips Gemini Time of Flight PET/CT scanner (Philips Medical Systems, Eindhoven, The Netherlands). Serial ^{18}F-FDG PET/CT scans were performed at approximately six to twelve month intervals. Baseline PET scanning was performed prior to CS diagnosis and before the initiation of immunosuppressive therapy. Subsequent follow-up ^{18}F-FDG PET/CT scans were obtained while patients were on immunosuppressive therapy. All ^{18}F-FDG PET/CT scans were performed in accordance with the EANM guidelines. Patients were instructed to have a carbohydrate-restricted diet for 24 hours followed by a fast of at least 6 hours prior to ^{18}F-FDG injection. From October 2013 onwards, all patients received 50 IU/kilogram unfractionated heparin intravenously 15 minutes prior to the scan, to suppress physiologic myocardial uptake. Blood glucose level was measured in all patients prior to injecting ^{18}F-FDG. ^{18}F-FDG was administered when the plasma glucose level was <10 mmol·L^{-1}. Visual interpretation of cardiac ^{18}F-FDG-uptake was assessed as no uptake, diffuse uptake, focal uptake or focal on diffuse uptake.[1,2] Right ventricular (RV) ^{18}F-FDG-uptake was scored as yes or no. Quantitative assessment of ^{18}F-FDG uptake was performed by using the maximal standardized uptake value (SUVmax). Regions of interest (ROI) were drawn over the

visually affected part of the heart to measure the myocardial SUVmax. ROI was drawn at the same lesion/area at baseline and follow-up scan. Furthermore, a "normalized SUVmax" was determined by calculating the ratio between the myocardial SUVmax and the SUVmean of the bloodpool, measured in the descending thoracic aorta.[3,4] All ^{18}F-FDG PET/CT images were scored by a single experienced nuclear medicine physician (R.G.K.) blinded for treatment regimens and clinical outcomes.

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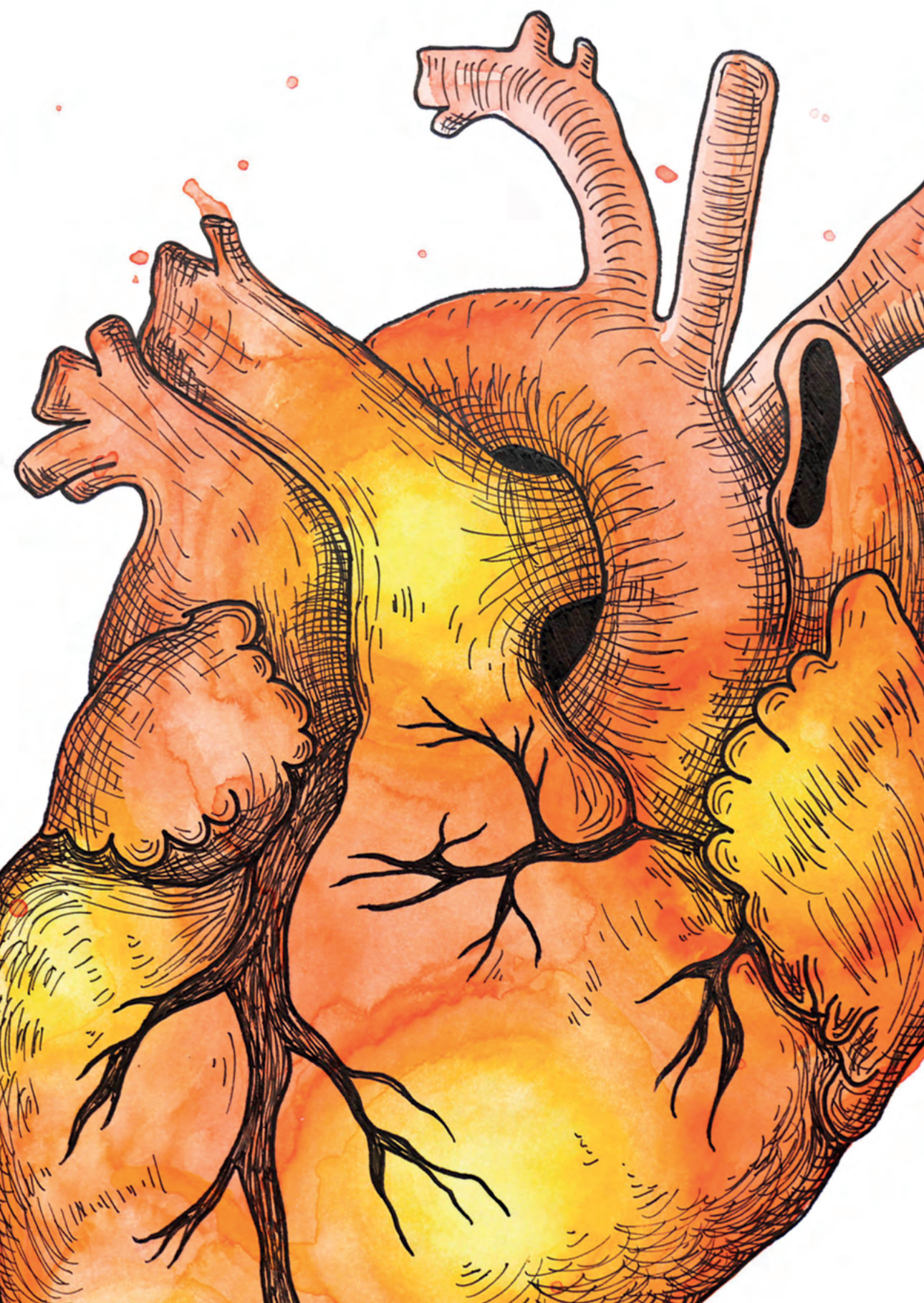
Supplementary table S2. Results from biomarker analysis

	Total (n = 61)	**Prednisone (n = 21)**	**MTX (n = 30)**	**Pred + MTX (n = 10)**	**p-value**
Baseline NT-proBNP (pg/ml)	*n=45* 190 [71 – 547]	*n=13* 217 [116 – 1212]	*n=24* 184 [68 – 504]	*n=8* 141 [42 – 449]	0.49
Follow-up NT-proBNP (pg/ml)	*n=39* 129 [43 – 414] p=0.094	*n=10* 150 [61 – 1072] p=0.80	*n=23* 129 [43 – 331] p=0.31	*n=6* 80 [8 – 325] p=0.028	0.42
Baseline sIL-2R (pg/ml)	*n=61* 4940 [2768 – 7325]	*n=21* 4152 [3301 – 6104]	*n=30* 4851 [2354 – 6915]	*n=10* 7325 [3619 – 10085]	0.35
Follow-up sIL-2R (pg/ml)	*n=60* 2542 [1706 – 3944] p<0.001	*n=20* 2290 [1213 – 2914] p<0.001	*n=30* 3114 [1821 – 4861] p=0.001	*n=10* 2533 [1524 – 3969] p=0.007	0.13

MTX = methotrexate; NT-proBNP = N-terminal pro brain natriuretic peptide; pred = prednisone; sIL-2R = soluble interleukin-2 receptor



8

Effectiveness and safety of infliximab in cardiac sarcoidosis

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ABSTRACT

Background: Immunosuppressive therapy in active cardiac sarcoidosis (CS) might prevent potential life-threatening complications. Infliximab (IFX) is a tumour necrosis factor alpha monoclonal antibody proven to be effective in refractory extracardiac sarcoidosis. It is sparsely used in CS, because of its association with worsening heart failure in prior studies. The goal of this study was to assess the effectiveness and safety of IFX in CS.

Methods: A retrospective, single centre cohort study was performed on sarcoidosis patients treated with IFX based on a cardiac indication between January 2016 and March 2019. Patients received IFX intravenously at a dose of 5 mg/kg at week 0, 2, and subsequently every 4 weeks. After every six months, treatment response was evaluated within the multidisciplinary team using FDG PET/CT, transthoracic echocardiography, biomarkers and device interrogation reports. Responder analysis definitions were based on; dosage of immunosuppressive drugs, improvement in functional class, left ventricular ejection fraction (LVEF) and maximum standardized uptake value (SUVmax).

Results: Twenty-two patients were included (mean age 51.0 ± 10.0 years, male 68.2%) with a mean follow-up of 18.9 months of whom 18 (82%) were classified as responders. Median SUVmax on FDG-PET/CT decreased from 5.2 [3.7 – 8.4] to 2.3 [1.4 –2.3], p=0.015. The target-to-background ratio decreased from 3.2 [2.1 – 5.1] to 1.0 [0.7 –2.4], p=0.002. The median left ventricular (LV) ejection fraction increased from 45.0% [34.0 – 60.0] to 55.0% [41.0 – 60.0], p=0.02. The majority of patients (73%) experienced no side effects and no patients had worsening of heart failure.

Conclusion: In this pilot study, patients with refractory CS treated with infliximab, on top of standard of care, had a reduction in inflammation on FDG-PET/CT and an improvement in LV function, without serious adverse events.

INTRODUCTION

Sarcoidosis is a multisystem disorder of unknown aetiology, typically affecting young individuals and characterized by the presence of noncaseating granulomas in involved organs. Cardiac involvement in sarcoidosis is an important cause of an inflammatory cardiomyopathy leading to conduction abnormalities, arrhythmias, congestive heart failure and sudden cardiac death.[1,2] Active myocardial inflammation is considered an indication for immunosuppressive treatment to prevent myocardial fibrosis in cardiac sarcoidosis (CS).[3–5] Up to now, there are no controlled studies available for the optimal treatment regimen.[6] In clinical practice, corticosteroids are the first-line therapy in CS, but steroid-sparing agents, e.g. methotrexate or azathioprine, are initiated early in the course of the disease to achieve long-term immunosuppressive treatment.[7,8] Tumour necrosis factor alpha inhibitors are sparsely used in CS, due to earlier reports on safety in patients with heart failure, high costs and lack of reimbursement in many countries.[9] In this study we evaluated the efficacy and safety of the tumour necrosis factor alpha inhibitor Infliximab (IFX) on cardiac function and inflammation in CS patients.

METHODS

Study design

We performed a retrospective database cohort study in patients treated with IFX for CS in the St. Antonius Hospital, Nieuwegein/Utrecht, a Dutch tertiary referral centre for sarcoidosis.

Study population

All sarcoidosis patients with initiation of IFX between January 2016 and March 2019 were evaluated by chart review. Patients with cardiac involvement as the main treatment indication were included. CS diagnosis was based on the diagnostic criteria from the Heart Rhythm Society consensus statement and WASOG criteria.[10,11] All patients were discussed in our multidisciplinary team (MDT) consisting of pulmonologists, cardiologists and nuclear medicine physicians. Only patients classified as definite or probable CS were included. All patients received IFX intravenously at a dose of 5 mg/kg at week 0 and 2, and subsequently every 4 weeks.

Data collection

All data were collected retrospectively by chart review. Demographics, medical history, comorbidities, sarcoidosis characteristics, laboratory tests (e.g. troponin T, N-terminal pro-brain natriuretic peptide (NT-proBNP), soluble interleukin-2-receptor (sIL-2R),

transthoracic echocardiography (TTE) results and fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) were collected. Device interrogation reports from implantable cardioverter defibrillator (ICD), pacemaker or internal loop recorder were screened for the occurrence of documented sustained ventricular tachycardia (VT), high degree atrioventricular block and ICD therapy (shocks and anti-tachycardia pacing). All reported side effects related to IFX were included in the database. Data were stored in the webbased-datamanager REDCap. The study was approved by the local institutional review board (R&D/Z19.004) with a waiver of informed consent.

FDG PET/CT

Sarcoidosis disease activity was objectified by FDG-PET/CT. FDG PET/CT examination was performed with a TF-64 combined PET/CT device (Philips Gemini, Eindhoven, The Netherlands). All patients were put on a carbohydrate restricted diet (only meat, fish, eggs, cheese, butter, oil, tea, coffee or water) for 24 hours and fasted 6 hours prior to the FDG PET/CT. Patients refrained from physical exercise in the 6 hours prior to the FDG PET/CT. Unfractionated heparin was injected intravenously 15 min prior to FDG administration to suppress physiologic uptake in the myocardium (50 IE/kg bodyweight, maximum 5000 IE). FDG dosage was based on body weight with a quadratic dose regimen. A focal or focal on diffuse pattern was interpreted as cardiac inflammation and diffuse uptake as physiologic uptake. FDG PET/CT results were interpreted by an experienced nuclear medicine physician. Inflammatory response on FDG PET/CT was classified as complete response, partial response, stable or progressive disease compared to the previous FDG PET/CT. For quantitative analysis of cardiac FDG uptake, maximum standardized uptake value (SUVmax) was measured in the myocardium. Subsequently, the target-to-background ratio (TBR) was reported (ratio of the cardiac SUVmax and the SUVmean of the bloodpool measured in the descending aorta at the level of the carina). The threshold for active inflammation is SUVmax >2.5 and the value must be higher than the SUVmean of the bloodpool.

Responders

Treatment response was evaluated every 6 months in the MDT after visit in the outpatient clinic, measurement of sIL-2R, NT-proBNP, TTE, FDG PET/CT, and cardiac device interrogation. In concordance with a recently published cohort of CS patients treated with IFX from Harper et al. we also performed a responder analysis classifying patients as “responders”, “stable” or “non-responders” modified to available outcome parameters.[12] In our study we added New York Heart Association (NYHA) class and FDG uptake on PET/CT in the analysis. These responder analysis definitions are in accordance with the criteria applied during re-assessment in our MDT. Patients were categorized as a

"responder" if at least one of the following occurred after 6 or 12 months of treatment, without worsening of other parameters:

1) Reduction of concomitant immunosuppressive medication to a prophylactic dose (prednisone<10mg, methotrexate<10mg, azathioprine<100mg, mycophenolate mofetil <1000mg).
2) NYHA functional class improvement of at least 1 class
3) Left ventricular ejection fraction (LVEF) improvement ≥10%
4) Reduction of cardiac SUVmax on FDG PET/CT >25% or complete cardiac response and reduction of extracardiac FDG uptake.

Patients were defined as "stable" if they had no significant change in all four categories. Patients were defined as a "non-responder" if they worsened in one or more of the four categories regardless of improvement in any of the other categories. A cut-off value for >25% reduction in SUVmax is in concordance with previous studies.[13–15]

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation, median with interquartile range or number with percentage. Change in NT-proBNP, sIL-2R, LVEF, SUVmax and TBR at baseline and the first re-assessment after at least 6 months of therapy were compared using the Wilcoxon signed rank test. If no results from 6 months were available, we used the 12 months data. Patients were excluded from the analysis, i.e. set to missing if specific responder analysis variables were missing. The ratio between change in SUVmax and LVEF was measured using the Pearsons correlation coefficient. Statistical analysis was conducted with SPSS Statistics (version 24.0 for Windows and Mac; Armonk, NY: IBM Corp).

RESULTS

Study subjects

Between January 2016 and July 2019, 50 consecutive patients started treatment for sarcoidosis with IFX. Chart review identified 22 patients (male 68.2%, mean age 51.0 ± 10.0 years) with CS as the main treatment indication: 19 patients had refractory CS with persistent inflammation on FDG PET/CT and three patients suffered from severe side effects from first or second-line therapies. Baseline characteristics are shown in table 1. Mean follow-up duration was 18.9 months (range 6 – 44 months) and five patients were treated more than two years. In nine patients concomitant immunosuppressive agents were administered in a therapeutic dose at baseline (prednisone ≥10mg, methotrexate ≥10mg or azathioprine ≥100mg). In all other patients, the concomitant medication

served as prophylaxis for antibody formation against IFX. This data is shown in supplementary table 1, together with data on previous immunosuppressive agents. All patients received IFX for at least 6 months.

Inflammation

The pattern of cardiac FDG uptake was focal in 77.3%, focal on diffuse in 13.6% and only extracardiac uptake in 9.1%. In the two patients with only extracardiac FDG uptake the cardiac treatment indication was based on granulomas in myocardial tissue and extensive cardiac lesions on cardiac magnetic resonance imaging, respectively.

Disease activity measured by SUVmax at baseline and after at least 6 months of treatment with IFX decreased from median 5.2 [3.7 – 8.3] to 2.3 [1.4 – 2.3], p=0.015. The target-to-background ratio decreased from 3.2 [2.1 – 5.1] to 1.0 [0.7 – 2.4], p=0.002 (figure 1). In 16 of 22 patients (72.7%) the SUVmax reduced >25%. In four patients (18.2%) the SUVmax was stable and in two patients (9.5%) the SUVmax increased >25%.

Table 1. Baseline characteristics

Variable	Value (n=22)
Age (years)	51.0 ± 10.0
Male sex	15 (68.2%)
Caucasian ethnicity	21 (95.5%)
Body mass index (kg/m^2)	28.3 ± 4.8
History	
Hypertension	6 (27.3%)
Diabetes mellitus	2 (9.1%)
Atrial fibrillation	5 (22.7%)
Prior or current tobacco use	8 (36.4%)
Cardiac parameters	
Left ventricular ejection fraction (%) • ≤50% • ≤35%	47.5 [34.5 – 60.0] 11 (50.0%) 7 (31.8%)
Prior ventricular tachycardia	5 (22.7%)
Prior 2nd or 3rd degree AV block	7 (31.8%)
Cardiac device (none/ ILR/ ICD/ CRT-P/ CRT-D)	1 / 7 / 9 / 1 / 4
NYHA functional class (I / II / III / IV)	9 / 9 / 4 / 0
NT-proBNP >300 pg/L	8 (44.4%)
Troponin T >0.014 ng/L	2 (11.1%)

Sarcoidosis parameters	
Presence of extracardiac sarcoidosis	
• Histologically confirmed	18 (81.8%)
• Consensus diagnosis	4 (18.2%)
Concomitant pulmonary treatment indication	2 (9.0%)
Concomitant neurologic treatment indication	1 (4.5%)
Disease duration of CS at initiation of IFX (years)	1.9 ± 1.5
Serum sIL-2R (pg/ml)	
• <3000	11 (50.0%)
• 3000 – 10000	9 (40.9%)
• >10000	2 (9.1%)
FDG PET/CT	
Uptake pattern	
• Focal uptake	17 (77.3%)
• Focal on diffuse uptake	3 (13.6%)
• No uptake	2 (9.1%)
Only cardiac uptake	6 (27.3%)
Cardiac SUVmax	5.1 [3.7-8.3]
Target-to-background ratio	2.9 [2.1 – 4.6]

AV = atrioventricular; CRT-D = cardiac resychronisation therapy with defibrillator; CRT-P = cardiac resychronisation therapy with pacemaker; CS = cardiac sarcoidosis; FDG PET/CT=fluorodeoxyglucose positron emission tomography with computed tomography; ICD = implantable cardiac defibrillator; IFX = infliximab; ILR = implantable loop recorder; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA= New York Heart Association; sIL-2R = soluble interleukin 2 receptor; SUVmax = maximum standardized uptake values

The median serum levels of sIL-2R also decreased significantly by 15.9% (3401 pg/ml to 2432 pg/ml, p=0.05). In five of nine patients (55.6%) with a therapeutic dose of concomitant immunosuppressive agents, the dose could be reduced to a prophylactic dose. One of the 'non-responders' continued IFX but started azathioprine in a therapeutic dose as concomitant medication. Six months later, FDG PET/CT showed complete metabolic response.

Cardiac function

At baseline eleven patients (50.0%) had a LVEF ≤50%. Eight out of eleven patients were on optimal medical treatment for heart failure according to current guidelines at least three months before initiation of IFX and four of these patients had cardiac resynchronisation therapy.[16] Three patients started heart failure therapy of whom one patient had a cardiac resynchronisation defibrillator implanted within three months of initiation of IFX. Follow-up on LV function was available in 21 of 22 patients: the median LVEF in these patients improved significantly from 45.0% [34.0 – 60.0] to 55.0% [41.0 – 60.0], p=0.02 (figure 1). After excluding the patients with newly initiated heart failure treatment, the LVEF improved from 46.5 [35.0 – 60.0] to 49.5 [43.0 – 60.0], p=0.042. None of the patients had a reduction of LVEF and four patients had an improvement of ≥10%. Improvement in

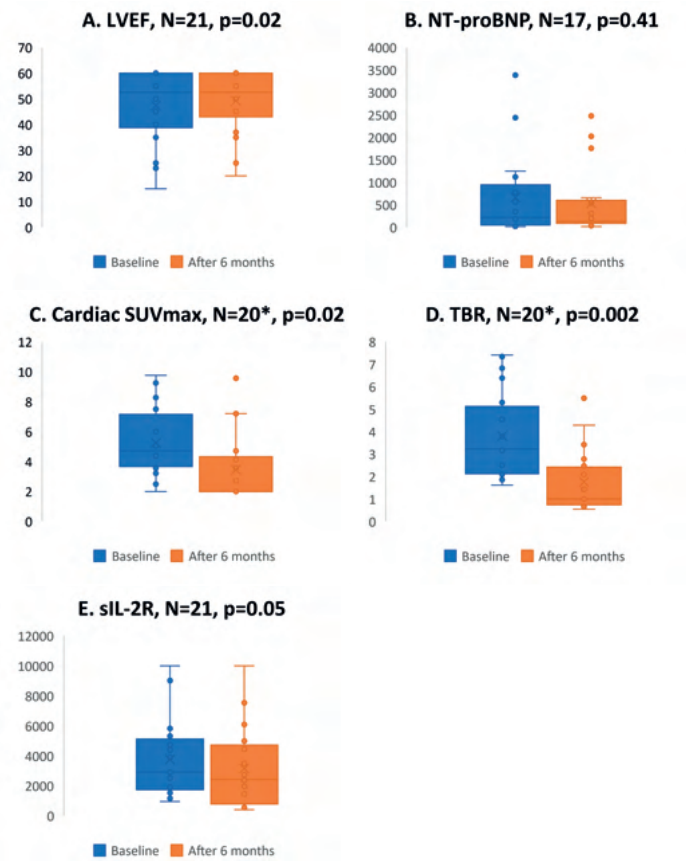

Figure 1. Treatment response in cardiac sarcoidosis at baseline and after at least 6 months of infliximab treatment. **A.** Left ventricular ejection fraction (LVEF). **B.** Level of NT-proBNP. **C.** SUVmax on FDG PET/CT of the myocardium. **D.** TBR (target to background ratio): cardiac SUVmax / SUVmean of the bloodpool. **E.** Serum sIL-2R * 2 patients with only extracardiac inflammation were excluded from this analysis.

NT-proBNP levels was not significant (p=0.41). The NYHA class improved in two patients; however, both patients discontinued IFX treatment due to major side effects. In all other patients the NYHA class remained stable. No significant correlation was found between the change in SUVmax and LVEF, $r = 0.16$ (figure 2).

Arrhythmias

A history of severe ventricular arrhythmias or high degree atrioventricular conduction disorder was present in respectively 23% and 32% of patients. However, none of the patients had started IFX treatment due to refractory arrhythmias. Two patients experienced an appropriate ICD shock after 6 months of therapy. Both patients showed a complete response on FDG PET/CT and an improvement of 5% in LVEF at the time of these events. Another patient had a history of refractory VTs and subsequent VT abla-

tion and started IFX 6 months afterwards. He was admitted 3 years after initiation of IFX because of an electrical storm provoked by a severe pneumonia. FDG PET/CT showed no cardiac inflammatory activity during this admission.

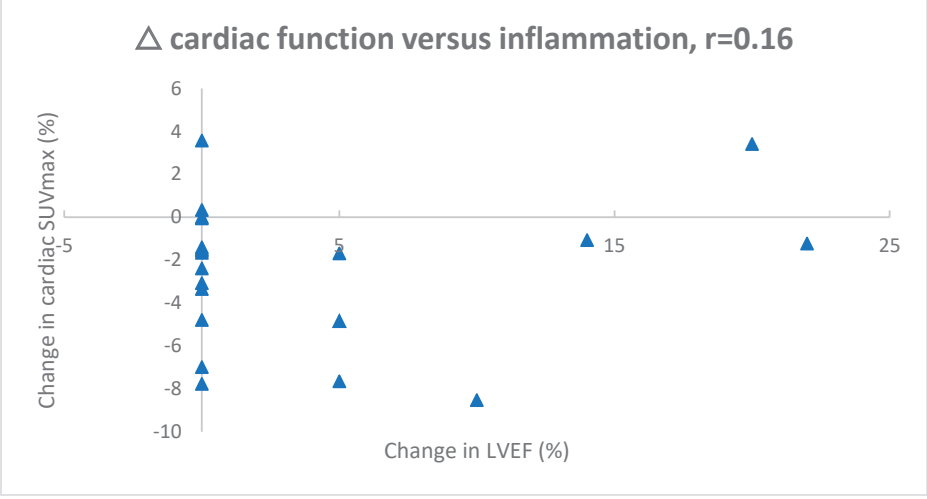

Figure 2. Correlation of change in myocardial inflammation (SUVmax) on FDG PET/CT versus change in cardiac function (LVEF). Pearson *rho* = 0.16.

Responder analysis

Eighteen of 22 patients (81.8%) were classified as responders to IFX treatment (figure 3); reduction in cardiac FDG uptake was the most common improving outcome parameter. Two patients (9.1%) had stable disease and two patients (9.1%) were non-responders. One responder discontinued therapy due to non-compliance; IFX infusions could not be combined with his work abroad. Three patients discontinued therapy due to major side effects, although the first two patients were considered responders. The first patient developed auto-immune hepatitis, which was thought to be induced by IFX. However, this could not be confirmed during follow-up, because liver function tests remained elevated more than 6 months after discontinuation. The second patient suffered from an allergic reaction during infusion due to auto-antibody formation to IFX. In both patients IFX was successfully switched to the tumour necrosis factor alpha inhibitor adalimumab. The third patient was hospitalized for several days due to recurrent fever of unknown cause, 6 months after initiation of IFX. FDG PET/CT showed increased cardiac but decreased extracardiac FDG uptake and TTE revealed LVEF improvement. IFX was withheld for two months. Three months after resuming treatment, he was re-admitted due to fever of unknown origin. Hypothetically the fever was related to IFX, therefore he was switched to high dose methotrexate in combination with high dose prednisone.

	Concomitant immunosupp.		LVEF		NYHA class		FDG PET/CT		Side effects / compliance	Overall
	6m	12m	6m	12m	6m	12m	6m	12m		
1				N/A	N/A	N/A		N/A	Musculo-skeletal pain	Responder
2				N/A		N/A				Responder
3			N/A			N/A		N/A		Responder
4				N/A			N/A		Pneumonia	Responder
5									Pneumonia	Responder
6			N/A							Responder
7										Responder
8										Responder
9								N/A		Responder
10		N/A		N/A		N/A		N/A		Responder
11				N/A				N/A		Responder
12		N/A		N/A		N/A		N/A		Responder
13			N/A					N/A		Responder
14		N/A		N/A		N/A		N/A		Responder
15		N/A						N/A		Responder
16		N/A		N/A		N/A		N/A	Non-compliance	Responder, %6m
17		N/A	N/A	N/A		N/A		N/A	Auto-antibodies	Responder, %6m
18									Auto-immune hepatitis	Responder, %12m
19				N/A		N/A		N/A		Stable
20										Stable
21		N/A		N/A		N/A		N/A	Fever eci	Non-responder, %9m
22										Non-responder

Definitions applied in responder analysis

	Improve	Stable	Worsen
Concomitant immunosup-pressive agents	Reduction to prophylactic dose (Prednison <10mg, methotrexate<10mg, azathioprine<100mg, mycophenolate <1000mg)	No change	Increase to therapeutic dose (Prednison ≥10mg, methotrexate≥10mg, azathioprine≥100mg, mycofenolate≥1000mg)
LVEF	Improvement ≥10%	Change <10%	Impairment ≥10%
NYHA class	Improvement of 1 class	No change	Worsening of 1 class
FDG PET/CT	No cardiac or reduced cardiac uptake > 25% of SUVmax AND reduced or stable extracardiac uptake	Stable cardiac or extracardiac uptake: <25% reduction of SUVmax or mixed response (reduced cardiac but progressive extracardiac FDG uptake)	Progressive cardiac uptake OR progressive extracardiac uptake.

Figure 3. Responder analysis.

Three other patients reported adverse events or side effects, but continued therapy: musculoskeletal complaints (n=1) and pneumonia (n=2). The majority of patients (73%) did not experience any side effects. Especially no device-related complications or worsening of heart failure were observed.

DISCUSSION

This study shows a high overall response rate of IFX in 82% of CS patients refractory to other immunosuppressive agents without worsening of cardiac function. Both cardiac SUVmax and LVEF improved significantly after 6 months of treatment with IFX. Reduction in inflammation on FDG PET/CT was the most common improving outcome parameter. Also, 9% showed stable disease, which can be an acceptable treatment goal after failure of multiple immunosuppressive agents. Our findings are in agreement with two recent observational studies.[12,17] Harper et al. found a response rate of 66% (24/36 patients) and stable disease in 8% (3/36 patients), based on three outcome parameters: reduction in steroid dose, LVEF and arrhythmia burden. Baker et al. observed clinical benefit in all 20 CS patients after initiation of infliximab or adalimumab assessed by LVEF and change in prednisone dose. In our study, concomitant immunosuppressive agents could be reduced from a therapeutic to a prophylactic dose in five of nine patients (55.6%). This is similar to the cohort from Harper et al. where prednisone dosage could be reduced more than 10mg in 20 patients (55.6%). Although tapering steroids is an important therapy goal in sarcoidosis, the decision is based on clinical findings and is therefore a less accurate outcome parameter for inflammation compared to cardiac FDG uptake.

This is the first cohort of IFX treated CS patients where treatmentresponse is evaluated by serial FDG PET/CT. The use of serial PET to guide immunosuppressive therapy is recommended by the European Society of Cardiovascular Imaging and the American Society of Nuclear Cardiology.[8,14,18,19] Nevertheless, no specific recommendations exist on frequency and quantification. Moreover, serial FDG PET/CT is not available in all countries due to a lack of insurance approval. Ning et al. retrospectively assessed findings from 128 cardiac FDG PET/CT scans in 34 CS patients; three of four scans contributed directly to a change in therapy.[20] They considered cardiac FDG PET/CT a valuable tool to evaluate response to therapy and to track disease burden. In our institution serial cardiac FDG PET/CT is routinely incorporated in the clinical management of CS; patients undergo FDG PET/CT every 6 months. The criteria used in the responder analysis for FDG PET/CT are comparable to the assessment of therapy in clinical practice during our MDT. Our treatment goal is to reduce cardiac inflammation and extracardiac inflammation. The extent of cardiac inflammation is the most important parameter in the re-assessment.

However, if extracardiac inflammation is worsening during treatment it might be the first sign of treatment failure. Unfortunately, there is no scientific data on this topic. It also depends on cardiac function and presence of arrhythmias if there is an indication to intensify immunosuppressive therapy. These decisions are made on an individual basis in our MDT. After tapering of immunosuppressive treatment, FDG PET/CT is repeated for early detection of inflammation recurrence.

SUVmax is a commonly used tool in inflammatory processes to quantify the degree of inflammation.[13,21–23] Several studies have shown the prognostic value of cardiac FDG uptake. Flores et al. evaluated 67 CS patients and found the SUVmax at time of diagnosis predictive for the occurrence of adverse events.[21] Larger cohorts from Muser et al. and Sperry et al. found metabolic activity on FDG PET predictive for future events, but other quantitative measurements as the lesion metabolic activity and the coefficient of variation, had a stronger predictive value than SUVmax.[13,22] However, we did not find a correlation between the change in SUVmax and change in LVEF. Osborne et al. reported a significant relationship between decrease in SUVmax and an increase in LVEF in 23 CS patients with serial FDG PET/CT; their model predicted a LVEF increase of 7.9% when SUVmax decreased by 10 ($p=0.08$).[19] These different results might be due to the stage of the disease. Patients in their cohort were newly diagnosed with CS and the largest change in LVEF was seen in the first 6 months of immunosuppressive treatment. In our study, most patients had refractory CS and a mean disease duration of almost 2 years before initiation of IFX. Patients are likely to have more myocardial scar or fibrosis and therefore less LVEF improval is suspected by reduction of inflammation. Unfortunately, in both studies numbers are too small to correct for potential confounding from concomitant heart failure therapy.

Treatment of CS with IFX was relatively safe in our study. None of the patients showed worsening of LVEF or NYHA functional class and 73% of patients did not report any side effects. In 14% of patients therapy was discontinued due to major side effects. Our results are in line with the results of Harper et al.; 83% did not report any side effects and 8% discontinued therapy due to major side effects.[12] However, the use of IFX >5mg/kg in heart failure patients is strongly discouraged by the American Food and Drug Administration, due to the ATTACH trial from Chung et al. in 2003. In their study, 150 patients with mainly ischemic heart failure and NYHA class III or IV were randomised to IFX 5 mg/kg, 10 mg/kg or placebo.[9] No clinical improvement was seen; furthermore the dosage of IFX 10 mg/kg was associated with an increased mortality and hospitalisation rate due to worsening heart failure. Previous studies already showed that IFX 5mg/kg in sarcoidosis results in adequate trough levels and that higher trough levels do not further increase efficacy.[24,25] This contributes to the discouragement of using a dose of 10 mg/kg in sar-

coidosis. Furthermore, in CS patients the rationale for IFX is different from the objective of the ATTACH trial, since inflammation of the myocardium is the primary cause of heart failure in CS patients. With the results from the present study, evidence is accumulating to support the safety and efficacy of IFX in patients with refractory CS.

In our cohort almost 23% of patients had a history of VT, but none of the patients started IFX due to refractory arrhythmias. Therefore, this parameter was not included in our responder analysis. However, this parameter is important to evaluate therapy in future studies, especially when refractory arrhythmias are the indication for intensifying immunosuppressive treatment.

Limitations of the current study are its retrospective design, the small number of patients, the single-centre experience. Also, due to the lack of a control group, the effect on inflammation could still be the natural course of the disease, although a benign course of the disease is less likely since the majority of patients were refractory to first- and second-line immunosuppressive therapy. A possible confounder in the improvement in cardiac function are the effects of heart failure therapy (i.e. angiotensin converting enzyme inhibitors, beta-blockers, cardiac resynchronization therapy). However, the LVEF significantly improved, even after excluding patients who started heart failure treatment at baseline. Another limitation might be the occurrence of selection bias. However, in our institution all patients with refractory CS and an indication for IFX therapy started treatment, irrespective of LVEF.

CONCLUSION

In this pilot study, patients with refractory CS treated with infliximab, on top of standard of care, had a reduction in inflammation on FDG PET/CT and an improvement in LV function, without serious adverse events. Future studies are needed to confirm the therapeutic value of infliximab in adequately powered double-blinded randomized clinical trials.

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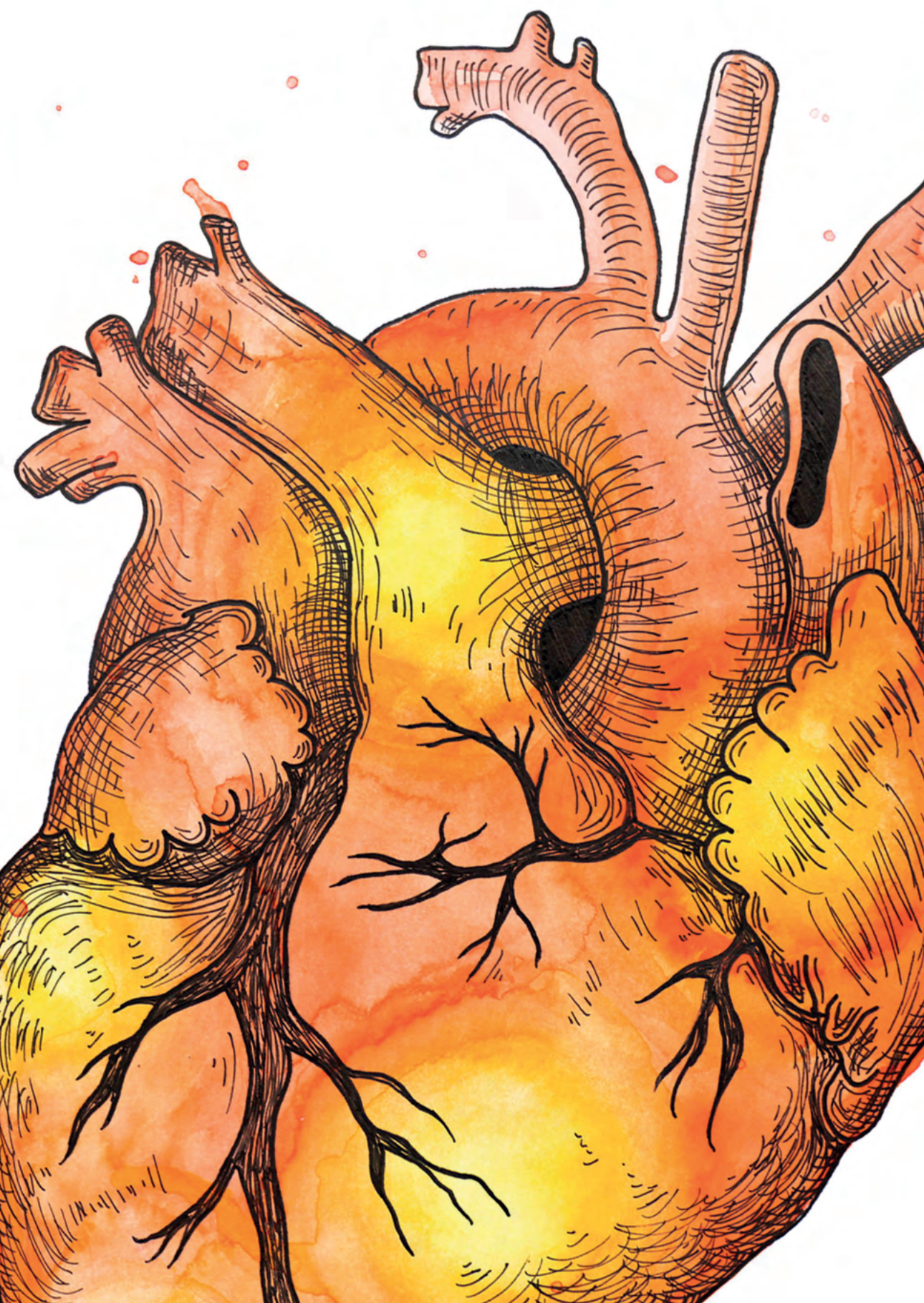
APPENDIX

Supplementary table 1. Baseline characteristics of prior and current immunosuppressive therapy

Immunosuppressive agents prior to IFX	Value (n=22)
Corticosteroids	12 (54.5%)
Methotrexate	10 (45.5%)
Azathioprine	6 (27.3%)
Mycophenolate mofetil	3 (13.6%)
Hydroxychloroquine	1 (4.5%)
None	0 (0.0%)
Concomitant medication	
Prednisone <10mg Prednisone ≥10mg	6 (27.3%) 5 (22.7%)
Methotrexate <10mg Methotrexate ≥15mg	8 (36.4%) 3 (13.6%)
Azathioprine <100mg Azathioprine >100mg	1 (4.5%) 1 (4.5%)
Mycophenolate mofetil 500mg	1 (4.5%)
Corticosteroids and immunosuppressant	4 (18.2%)
None	1 (4.5%)



9.1

Long-term monitoring of arrhythmias with cardiovascular implantable electronic devices in patients with cardiac sarcoidosis

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ABSTRACT

Background: Risk stratification for sudden cardiac death (SCD) in cardiac sarcoidosis (CS) is challenging in patients without overt cardiac symptoms. The purpose of this study was to determine the incidence of ventricular arrhythmias (VAs) and mortality after long-term monitoring with a cardiovascular implantable electronic device (CIED) in CS patients identified after systematic screening of patients with extracardiac sarcoidosis (ECS).

Methods: A retrospective study was performed in 547 predominantly Caucasian patients with ECS screened for cardiac involvement. If CS was diagnosed, risk stratification (high vs low-risk) for SCD was performed by a multidisciplinary team. The primary endpoint was defined as sustained VA, appropriate implantable cardioverter defibrillator (ICD) therapy, or cardiac death.

Results: In total, 105 patients were included (mean follow-up 33 ± 16 months). An ICD was implanted in 17 high-risk patients (16.2%), whereas 80 low-risk patients (76.1%) received an implantable loop recorder (ILR). Eight low-risk patients (7.6%) did not receive a device. The primary endpoint occurred in 4.8% (n=5) with an overall annualized event rate of 1.7%. The annualized event rate was 9.8% in high-risk patients and 0.4% in low-risk patients. Nine low-risk patients received an ICD during follow-up; in 7 patients as a result of the ILR recordings. None of these patients required ICD therapy.

Conclusion: In CS patients without overt cardiac symptoms at initial presentation the annualized overall event rate was 1.7%; 10% in high-risk patients, but only 0.4% in low-risk patients. In low-risk patients long-term arrhythmia monitoring with an ILR enabled early detection of clinically important arrhythmias, without showing impact on prognosis.

INTRODUCTION

Sarcoidosis is a multisystem disorder of unknown aetiology, characterized by the presence of noncaseating granulomas. Nearly every organ system can be affected, including the heart. Cardiac involvement is associated with increased risk for ventricular arrhythmias (VAs), atrioventricular conduction block (AVB), and sudden cardiac death (SCD). Cardiac involvement in sarcoidosis is often clinically silent and therefore underrecognized. Autopsy series have suggested cardiac involvement in up to 25% of patients, whereas clinically overt cardiac involvement was seen in 5-10% of cases.[1] Because patients with cardiac sarcoidosis (CS) are at increased risk for SCD, screening for CS and subsequent risk stratification for SCD is imperative.[2–5] An implantable cardioverter defibrillator (ICD) is recommended for patients with VA, third-degree AVB or left ventricular ejection fraction (LVEF) <35%.[2,6] Also, scar detected by cardiac magnetic resonance imaging (CMR) is strongly related to the occurrence of VA and SCD.[7–9] However, less is known about patients with a preserved ejection fraction, a small amount of scar tissue and no or mild cardiac symptoms.[2,6] Patients with extracardiac sarcoidosis (ECS) diagnosed with CS after screening for cardiac involvement often fulfill these criteria. In 2014 we routinely incorporated the use of implantable loop recorders (ILR) in our centre for continuous heart rhythm surveillance in CS patients without an ICD indication.[10] This regimen facilitates early detection of VA and other arrhythmias in all CS patients with a cardiovascular electronic implantable device (CIED). In this study, we report the incidence of important arrhythmias and mortality after long-term monitoring in a large, predominantly Caucasian population of CS patients identified after systematic screening in an ECS population.

METHODS

Study design

A retrospective single-centre cohort study was performed in the St. Antonius Hospital, a Dutch, tertiary referral centre for sarcoidosis. All patients with ECS who were referred to our CS multidisciplinary team (MDT) for CS diagnosis between January 2014 and January 2019 were retrospectively observed by chart review. The study was approved by the local institutional review board (R&D/Z19.004). No written informed consent was required. The research reported in this paper adhered to the Declaration of Helsinki as revised in 2013. Figure 1 shows the flowchart for patient selection. Diagnosis of ECS was based on current guidelines.[11,12]

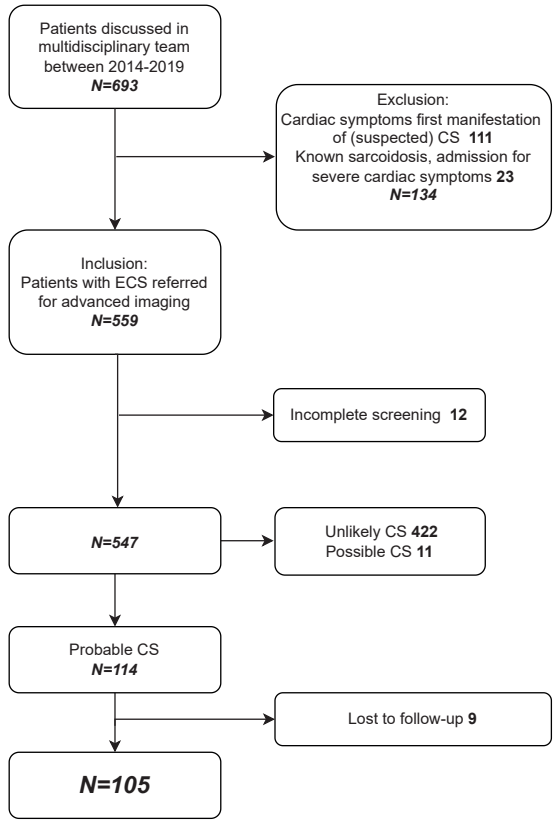

Figure 1. Flowchart for patient selection. CS = cardiac sarcoidosis; ECS = extracardiac sarcoidosis.

Patients with ECS who were referred after presentation in an emergency setting with severe cardiac symptoms (eg VA, AVB or heart failure) were excluded. Referral to our MDT was based on (1) abnormalities during initial assessment on the outpatient pulmonology clinic including cardiac symptoms, electrocardiogram (ECG) or cardiac biomarkers (troponin T and NT-proBNP) (2) cardiac abnormalities on full-body fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) (performed for ECS) or (3) abnormalities on echocardiography (performed for pulmonary hypertension screening). Patients with ECS and unremarkable findings on initial screening by the pulmonologists and without other coincidental findings on imaging were not assessed in the MDT. In total, 547 patients were referred to our MDT and underwent both CMR and FDG PET/CT. All data were collected by retrospective chart review, including demographic data; medical history; comorbidities; sarcoidosis characteristics; New York Heart Association functional class; results from ECG; FDG PET/CT, and CMR; immunosuppressive treatment and device interrogation. LVEF was determined by CMR.

CS diagnosis and SCD risk stratification

CS diagnosis was made by our MDT, which consisted of experienced pulmonologists, cardiologists, and nuclear physicians, after assessment of all relevant clinical data, including CMR and FDG PET/CT. Interpretation of both CMR and FDG PET/CT were based on visual assessment without further quantification of the extent of late-gadolinium enhancement (LGE) or FDG uptake, as no robust technique was available that could routinely and reliably quantify the percentage or mass of involved myocardium. The presence of 'extensive scar' was subjective based on the opinion of the imaging cardiologist(s). CS diagnosis was based on the 2014 Heart Rhythm Society (HRS) diagnostic criteria. CS was defined as a histologic diagnosis of CS or a clinical diagnosis of probable CS. After CS diagnosis, the MDT identified high and low-risk patients for SCD. This risk stratification was based on the recommendations of the HRS consensus statement, LVEF, and presence and extent of LGE on CMR (figure 2).

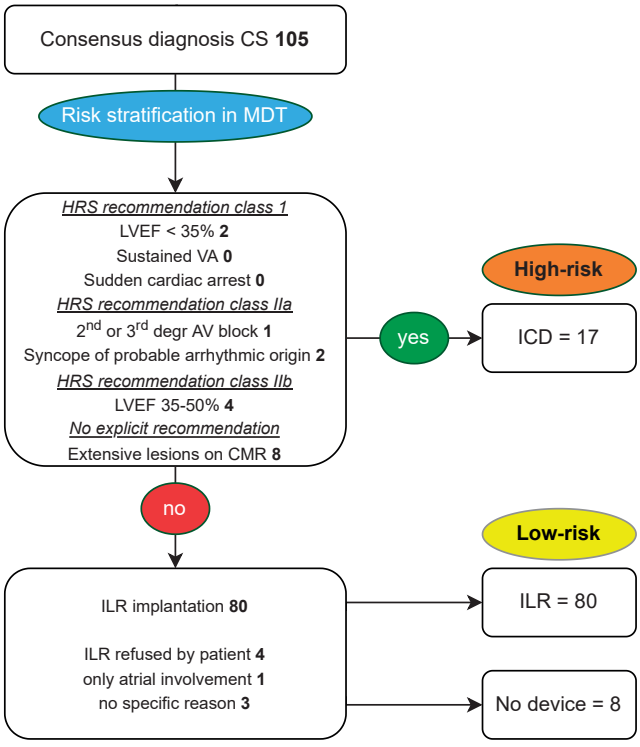

Figure 2. Risk stratification for sudden cardiac death in the multidisciplinary team. AV = atrioventricular; CMR = cardiac magnetic resonance; CS = cardiac sarcoidosis; degr = degree; HRS = Heart Rhythm Society; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; LVEF = left ventricular ejection fraction; VA = ventricular arrhythmia.

CIED implantation and follow-up

Patients considered at low-risk for SCD received an ILR for continuous heart rhythm monitoring. Patients considered at high-risk for SCD at baseline and patients who developed signs or symptoms suggesting high-risk during follow-up underwent placement of a single- or dual-chamber ICD. No patients had a cardiac resynchronization therapy-defibrillators or subcutaneous ICD. An ICD was implanted in accordance with current guidelines. ICD programming was at the discretion of the implanting and treating physicians.

All patients were revised at the outpatient pulmonology and cardiology clinic every 3 to 6 months. Device interrogation was performed every 3 to 6 months and during event-driven visits. Follow-up duration was calculated from the date of MDT diagnosis to the date of last visit. Minimal follow-up duration was 6 months.

Outcome

The primary outcome was defined as a composite of sustained VA, appropriate ICD therapy, or cardiac death. Sustained VA was defined as spontaneous ventricular tachycardia or fibrillation at a rate of ≥100 beats/min lasting >30 seconds or requiring termination due to haemodynamic compromise in <30 seconds.[6] Appropriate ICD therapy was defined as shocks or antitachycardia pacing due to sustained VA.

Secondary outcome included all-cause mortality, clinically important arrhythmias (second or third-degree AVB, nonsustained ventricular tachycardia (NSVT), implantation of an ICD during follow-up and device-related complications (eg inappropriate ICD therapy). NSVT was defined as ≥3 consecutive ventricular beats with a rate of >100 bpm lasting <30 seconds. Data on mortality were obtained from the national database of death registration. Inappropriate therapy was defined as ICD shocks resulting from supraventricular arrhythmias (including sinus tachycardia, atrial fibrillation and flutter), T wave oversensing or lead noise. The electrograms of all device therapies were checked by an experienced electrophysiologist to determine appropriateness. All other outcome measurements were collected by review of medical records and device interrogation reports.

Statistical analysis

Data were stored in the web-based datamanager REDCap. All statistical analyses were performed using SPSS Statistics (version 22.0 for Windows and Mac; IBM Corp, Armonk, NY). Patient characteristics are presented as mean ± SD or median (interquartile range) for continuous variables and as frequencies for categorical variables.

RESULTS

Study population

In total, 114 of 547 patients (21%) were diagnosed with CS. Nine patients were lost to follow-up. Table 1 lists the baseline characteristics of 105 included patients. Complete follow-up on arrhythmias was available in 97 CIED patients. LVEF at baseline was predominantly preserved with a mean LVEF of 57.6 ± 9.2%. In two patients, LVEF was <35%. In 91% of patients, LGE on CMR was present, and 70% showed active inflammation according to cardiac uptake on FDG PET/CT. At time of diagnosis, 39.0% of patients received immunosuppressive treatment. After CS diagnosis in the MDT, 64.8% of patients were treated with immunosuppressives. An ICD was implanted in 17 patients (16.2%) who were considered to be at high-risk for SCD (figure 2).[2] Eighty-eight patients (83.8%) were considered low-risk; 80 patients had an ILR implanted and 8 patients did not receive a device. Of these patients, four refused monitoring with an ILR, one had only atrial involvement on CMR and FDG PET/CT, and three patients had no documented reason for refraining from receiving an ILR.

Primary outcome

The primary outcome occurred in 4.8% (n=5) during 33 ± 16 months of follow-up (table 2). Sustained VA occurred in 3.8% (n=4) and cardiac death in 1.0% (n=1). All sustained VAs occurred in ICD patients (23.5%) and were successfully treated with ICD therapy (antitachycardia pacing in 3 and shock therapy in 1). The indications for an ICD in these patients were syncope of probable arrhythmic origin in 2 and extensive lesions on CMR in 2. One cardiac death occurred in the low-risk group; this patient with pulmonary hypertension died because of right-sided heart failure. Another low-risk patient died unexpectedly, but the cause of death was considered noncardiac. This patient was found dead at home. He had no active sarcoidosis for more than one year, a preserved ejection fraction, only mild involvement on CMR, and no conduction disorders. Postmortem interrogation of the ILR showed one recording with a paroxysm of junctional bradycardia lasting 34 seconds with a maximal R-R interval of 2.7 seconds. Autopsy was not performed. Based on this clinical information a noncardiac cause of his death seemed more likely, but the exact cause remains unclear. The overall annualized event rate for the combination of sustained VA, appropriate ICD therapy or cardiac death was 1.7%. The annualized event rate was 9.8% in high-risk patients versus 0.4% in low-risk patients.

Table 1. Baseline characteristics

Variable	All patients	High risk	Low risk	
		ICD	ILR	No device
Number	105	17	80	8
Patient characteristics				
Age (years)	54.7 ± 11.8	49.8 ± 10.4	55.7 ± 11.8	54.9 ± 13.1
Male sex	77 (73.3%)	10 (58.8%)	61 (76.3%)	6 (75.0%)
Caucasian ethnicity	96 (91.4%)	16 (94.1%)	73 (91.3%)	7 (87.5%)
Body mass index (kg/m2)	28.1 ± 4.6	28.0 ± 5.1	28.1 ± 4.5	28.1 ± 5.7
Comorbidities				
Hypertension	40 (38.1%)	6 (35.3%)	31 (38.8%)	3 (37.5%)
Diabetes mellitus	16 (15.2%)	1 (5.9%)	12 (15.0%)	3 (37.5%)
Coronary artery disease	8 (7.6%)	2 (11.8%)	5 (6.3%)	1 (12.5%)
Atrial fibrillation/flutter	11 (10.5%)	1 (5.9%)	9 (11.3%)	1 (12.5%)
Current or former smoking	42 (40.0%)	4 (23.5%)	36 (45.0%)	2 (25.0%)
Pulmonary function				
FEV1 (% of predicted)	86.6 ± 21.7	92.6 ± 16.4	86.6 ± 21.8	74.7 ± 27.4
DLCO (% of predicted)	75.8 ± 20.6	82.9 ± 16.2	74.8 ± 20.8	71.0 ± 25.7
Cardiac function				
LVEF (%)	57.6 ± 9.2	48.6 ± 12.0	59.7 ± 7.7	56.3 ± 4.4
NYHA functional class (I / II / III / IV)	42/34/18/0	8/6/1/0	31/25/15/0	3/3/2/0
Complete LBBB*	6 (5.7%)	3 (17.6%)	3 (3.8%)	0
Complete RBBB*	17 (16.2%)	4 (23.5%)	11 (13.8%)	2 (25.0%)
NT-proBNP (pg/mL)	86 (49 – 199)	284 (142 – 1178)	78 (38 – 158)	70 (54 – 150)
LGE on CMR	94 (91.3%)	14 (82.4%)	73 (91.3%)	6 (75.0%)
Cardiac FDG uptake on FDG PET/CT	73 (69.6%)	16 (94.1%)	55 (68.8%)	2 (75.0%)
Sarcoidosis characteristics				
Sarcoidosis duration (years)	2.7 (0.5 – 7.3)	2.9 (0.2 – 5.8)	2.9 (0.6 – 6.9)	7.7 (1.8 –28.5)
Biopsy-proven sarcoidosis	91 (86.7%)	16 (94.1%)	68 (85.0%)	7 (87.5%)
Extracardiac involvement				
• Lung	92 (87.6%)	15 (88.2%)	72 (90.0%)	6 (75.0%)
• Skin	10 (9.5%)	1 (5.9%)	10 (12.5%)	1 (12.5%)
• Liver	14 (13.3%)	3 (17.6%)	10 (12.5%)	1 (12.5%)
• Eye	15 (15.0%)	1 (5.9%)	8 (10.0%)	1 (12.5%)
• Nervous system	11 (10.5%)	0	10 (12.5%)	1 (12.5%)
• Other	34 (32.3%)	2 (11.8%)	30 (37.5%)	2 (25.0%)
Immunosuppressive treatment				
Before CS diagnosis	41 (39.0%)	6 (35.3%)	48 (60.0%)	4 (50.0%)
After CS diagnosis	68 (64.8%)	15 (88.2%)	51 (63.7%)	2 (25.0%)

CMR = cardiac magnetic resonance imaging; CS = cardiac sarcoidosis; DLCO=diffuse capacity of the lung for carbon monoxide (% of predicted); FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; FEV1 = forced expiratory volume in 1 second (% of predicted); ICD = implantable cardiac defibrillator; ILR = implantable loop recorder; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; RBBB = right bundle branch block. * Electrocardiogram available in 94 patients.

Table 2. Outcome parameters

Variable	All patients	High risk	Low risk	
		ICD	ILR	No device
Number	105	17	80	8
Mean follow-up duration (months)	33.4 ± 16.4	28.8 ± 17.4	35.4 ± 17.4	23.8 ± 4.6
Primary endpoint				
Sustained VA, appropriate ICD therapy or cardiac death.	5 (4.8%)	4 (23.5%)	1 (1.3%)	0
Cardiac death	1 (1.0%)	0	1 (1.3%)	0
Sustained VA	4 (3.8%)	4 (23.5%)	0	N/A
Appropriate ICD therapy	4 (3.8%)	4 (23.5%)	N/A	N/A
Appropriate ICD shock	1 (0.9%)	1 (5.9%)	N/A	N/A
Secondary endpoints				
Death due to any cause	7 (6.7%)	0	7 (8.8%)	0
Nonsustained VA	16 (15.2%)	5 (29.4%)	11 (13.8%)	N/A
AVB (second of third degree)	2 (1.9%)	0	2 (2.5%)	N/A
ICD implantation during follow-up	9 (8.6%)	N/A	9 (11.3%)	0
Device-related complications	7 (6.7%)	4 (23.5%)	3 (3.8%)*	N/A

AVB = atrioventricular conduction block; ICD = implantable cardioverter defibrillator; N/A = not applicable; VA = ventricular arrhythmias (ventricular fibrillation or sustained ventricular tachycardia). * 2 patients received an ICD and experienced a device related complication

Secondary outcomes

All-cause mortality was 6.7% (table 2). Twelve ILR patients (15.0%) showed clinically important arrhythmias on ILR: NSVT in 11, third-degree AVB in 1, and second-degree AVB in 1. One patient had both AVB and NSVT. Two ILR patients experienced near-syncope during NSVT. In seven ILR patients (6.7%) an ICD was implanted during follow-up due to ILR recordings (symptomatic NSVT in 6 and third-degree AVB in 1). Clinical data of these seven patients are given in table 3. The two patients with near-syncope due to NSVT are shown in detail in figure 3. Only two of seven patients had active cardiac inflammation based on focal FDG uptake on PET/CT at the time of the event. In one patient (case 1), pulse therapy with methylprednisolone was initiated because of symptomatic NSVT. The other patient (case 3) already had a recent upscale in methotrexate because of cardiac FDG uptake on PET/CT two weeks before the NSVT. Two ILR patients received an ICD for other reasons: a decline in LVEF in one and inducible VA at electrophysiology study (EPS) during pulmonary vein isolation for atrial fibrillation in one. None of the 9 ILR patients with an upgrade to an ICD received appropriate ICD therapy during a mean follow-up of 23 ±20 months. Device-related complications occurred in 6.7%; inappropriate shock due to atrial fibrillation (n=2), atrial lead dislodgement (n=1), ICD pocket infection (n=1), deep venous thrombosis (n=1), frozen shoulder (n=1) and mild ILR pocket infection (n=1).

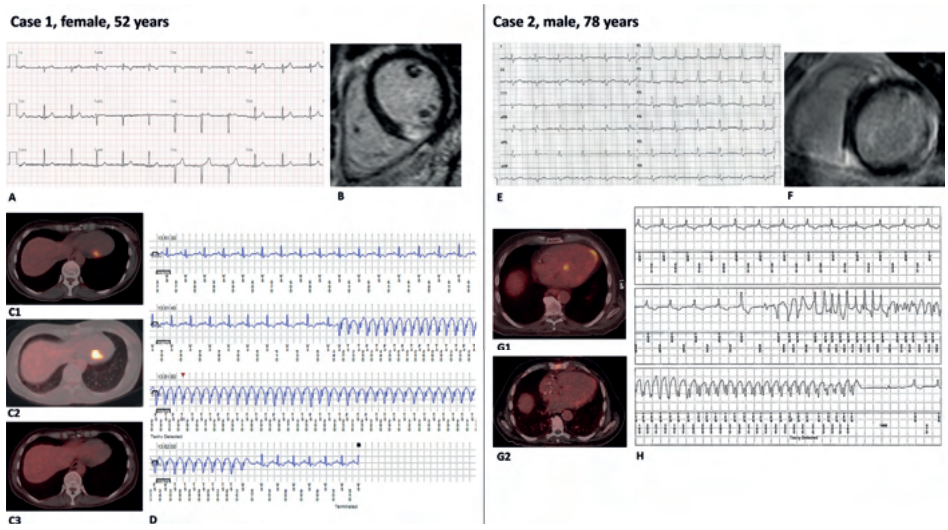

Figure 3. Clinical details on two low-risk patients with near-syncope due to nonsustained ventricular tachycardia on ILR recordings.

Case 1: Female, 52 years. Six months after an initial diagnosis of pulmonary sarcoidosis, clinical suspicion of cardiac sarcoidosis was raised due to symptoms of palpitations. A: Her ECG showed a RSr' in V1-V2 without conduction delay. Ambulatory 24-hour ECG monitoring was normal. B: Cardiac magnetic resonance imaging showed normal biventricular function and LGE in two myocardial segments: basal inferior and mid antero-septal. C: FDG PET/CT showed cardiac FDG uptake in the corresponding segments (C1). CS was diagnosed, and risk assessment was performed by the MDT: she was considered low-risk for SCD. She underwent implantation of an ILR and was treated with methotrexate 15mg weekly. Five months later, she experienced a near-syncope during hiking. D: ILR revealed a broad complex tachycardia of 222 bpm during 16 seconds, classified as NSVT. An ICD was inserted several days after this event. A new FDG PET/CT showed increased cardiac FDG uptake in the same two segments (C2). Immunosuppressive treatment was intensified with two pulses of high-dose intravenous methylprednisolone and increase of methotrexate to a dosage of 25mg weekly. In addition, metoprolol was started at 25mg daily. After 6 months, FDG PET/CT showed complete remission of cardiac and extracardiac FDG uptake (C3). No ICD therapy was required during 13 months of follow-up.

Case 2. male 78 years, known with Scadding stage IV pulmonary sarcoidosis. E: the patient was referred for advanced cardiac imaging because of a trifascular AV nodal block on ECG. He experienced no specific cardiac symptoms. Ambulatory 24-hour ECG monitoring revealed no arrhythmic events. F: CMR showed LVEF of 50% and epicardial and midmyocardial LGE uptake in five segments: basal and mid lateral, basal anteroseptal, basal inferoseptal and apical. G1: FDG PET/CT showed moderate FDG uptake in the lateral and apical wall. He was diagnosed as having CS by the MDT and considered low risk for SCD. An ILR was implanted, and monotherapy methotrexate 15mg once weekly was initiated. G2: Six months later, FDG PET/CT showed an almost complete remission of both cardiac and extracardiac FDG uptake. Methotrexate was continued at the same dosage. Twenty-three months after ILR implantation, he was hospitalized due to near syncope. H: Interrogation of the ILR showed an episode of fast, polymorphic NSVTs at 282bpm. A new FDG PET/CT showed no cardiac FDG uptake. Coronary angiography showed severe coronary artery disease. Coronary artery bypass grafting was performed, and an ICD was implanted. No ICD therapy was required during a follow-up of 14 months. The patient died of severe pneumonia.

Table 3. Clinical data of patients with an ICD implantation due to recorder arrhythmias on ILR

	Sex, age (y)	ECG	Events	Specification	Symptoms	LV function*	CMR abnormalities	Cardiac FDG PET/CT*	Therapy*
1	F, 52	Sinus rhythm, RSr' V1-V2	NSVT	59 beats Monomorphic 222 bpm	Near-syncope	Normal	Intense signal of LGE in 2 segments: mid anteroseptal , basal inferior	Focal cardiac FDG uptake, corresponding with CMR	Methotrexate 15mg/wk
2	M, 79	Sinus rhythm, trifascicular block	NSVT	41 beats Polymorphic 282 bpm	Near-syncope	Mildly reduced (45-50%)	Intense signal of LGE in 5 segments: basal lateral, mid lateral, basal anteroseptal, basal inferoseptal, apical	Mild, diffuse FDG uptake	Methotrexate 25mg/wk
3	M, 78	Sinus rhythm, RBBB	NSVT	29 beats Monomorphic 250 bpm	Dizziness	Normal	Intense signal of LGE in 2 segments: basal anteroseptal, basal inferoseptal	Focal cardiac FDG uptake, corresponding with CMR	Methotrexate 25mg/wk
4	F, 50	Sinus rhythm	NSVT 2nd degree AVB	19 beats Monomorphic 222 bpm 2nd degree AVB	Palpitations	Normal	Moderate signal of LGE in 3 segments: mid anteroseptal, mid anterior, mid lateral	No cardiac FDG uptake	None
5	M, 40	Sinus rhythm	NSVT	10 beats Monomorphic 193 bpm	Palpitations	Normal	Mild signal of LGE in 4 segments: basal anteroseptal, basal lateral, mid inferoseptal, apical	No cardiac FDG uptake	None
6	M, 64	Sinus rhythm	NSVT	21 beats Monomorphic 200 bpm	Palpitations	Normal	Mild signal of LGE in 2 segments: basal anteroseptal, right ventricular free wall	Mild cardiac FDG uptake basal right ventricular wall	Methotrexate 25mg/wk
7	M, 67	Atrial fibrillation	3rd degree AVB	4-second pause	Dizziness	Moderate (40%)	No LGE	No cardiac FDG uptake	Methotrexate 25mg/wk

AVB = atrioventricular conduction block; LV = left ventricular; NSVT = non sustained ventricular tachycardia; RBBB = right bundle branch block. * closest to event.

DISCUSSION

This is the first study reporting the use of CIED for long-term monitoring of arrhythmias in patients with CS diagnosed after systematic screening in an ECS population. Regular 24-hour Holter recording might miss clinically important arrhythmias. Therefore, the use of ILR for continuous heart rhythm surveillance was incorporated in our daily practice in patients with CS considered low-risk for SCD.

In this study of CS patients without overt cardiac symptoms at initial presentation, the combination of sustained VA, appropriate ICD therapy or cardiac death occurred in 4.8% with an annualized event rate of 1.7%. Earlier studies in ECS populations screened for CS reported an annualized event rate between 0 and 14%. In accordance with our study, low event rates were reported in a large study by Kouranos et al. CS was detected in 96 of 321 Caucasian ECS patients (30%) screened for cardiac involvement with CMR according to the HRS criteria.[13] During a median follow-up of 84 months, severe cardiac events occurred in 4.7%. Whether these events occurred in CS patients was not described, but if this is assumed, the annualized event rate would be <2.3%. Much higher event rates were reported by Patel et al. and Murtagh et al.[14,15] Both studies were also performed in ECS patients screened for cardiac involvement. They reported an annualized event rate of 13.6% in 21 CS patients and 8.1% in 41 CS patients, respectively. Of interest, in both studies about 70% of patients were black. Moreover, in the study by Murtagh et al. all cardiac events and death occurred in black patients. This finding suggests an increased risk for cardiac events in this group and might explain the different outcome compared to the predominantly Caucasian population in the present study and the study by Kouranos et al.

In our CS population with a presumed low-risk of SCD, the annualized event rate was 0.4%. However, in 15% of low-risk patients who received an ILR, clinically important arrhythmias were detected, and in 9% the recorded arrhythmias led to ICD implantation. Remarkably, none of these patients received appropriate ICD therapy after implantation. In six patients the MDT decided to implant an ICD due to symptomatic NSVT, although no evidence on the predictive value of NSVT for SCD in CS exists. In five other ILR patients NSVT were asymptomatic, short in duration, and infrequent and therefore considered benign. Only two ILR patients (case 4 and 7) experienced a second or third degree AVB. This is less frequent than expected, as this is a common symptom in patients with CS. Overall, the diagnostic impact of monitoring with ILR seems good, but no impact was seen on prognosis. Based on our current data, an implantation of an ILR in all low-risk patients still is not recommended, as continuous arrhythmia monitoring with an ILR is

costly, only 9% of patients were reclassified as high-risk and, most importantly, none of these patients received appropriate ICD therapy.

The use of ILR in our institutional protocol differs from the HRS consensus statement in which EPS is recommended for risk stratification in CS patients with LVEF>35%. Initially, the electrophysiologists in our center considered long-term monitoring with ILR of more prognostic value because there was little evidence for the use of EPS at the time of the study. However, more recent studies support the HRS recommendation.[16,17] Zipse et al. describe a high negative predictive value for future VAs and SCD after a negative EPS but emphasize that EPS cannot predict fatal VAs related to new cardiac involvement or disease progression. An advantage of monitoring with ILR is that new onset of arrhythmias can be detected in case of disease progression during long-term follow up. Overall, monitoring with an ILR should be applied in more selected patients. Future, prospective studies should focus on a risk stratification model categorizing low, intermediate and high risk for SCD based on more predefined selection criteria, such as localization and extent of scar tissue or inflammation on CMR and FDG PET/CT. ILR implantation might be indicated in patients carrying an intermediate risk.

Despite the low overall incidence of the primary endpoint, the annualized event rate of almost 10% in high-risk patients was high. In a recent meta-analysis, Halawa et al. reported even higher event rates of appropriate ICD therapy in 39% of 585 CS patients during a mean follow-up of 25 months (annualized event rate 18.7%).[7] In our cohort, the decision to implant an ICD was based on the HRS consensus statement and the best evidence available at that point in time. During the time frame of the present study, evidence for the predictive value of LGE on CMR for risk stratification, irrespective of LV function, was accumulating and applied in clinical practice. In 2016, a meta-analysis by Coleman et al. of 760 sarcoidosis patients with a (near)normal LVEF showed a significant association between LGE on CMR and all-cause mortality or VA.[4] They found an annualized event rate of 11.9% for patients with LGE vs 1.1% in patients without LGE. Based on these data, the 2017 American Heart Association / American College of Cardiology Guideline also recommended an ICD for CS patients with LVEF > 35% who experienced syncope and/or evidence of “extensive” myocardial scar by CMR or FDG-PET (class IIa recommendation).[6] These recommendations are in accordance with our clinical risk stratification. Although this retrospective study was not designed to assess a prediction model for SCD, the risk stratification in the MDT performed well in identifying high-risk patients.

Limitations

The potential limitations of retrospective observational research must be taken into account. Nine patients were lost to follow-up, and in eight low-risk patients follow-up on arrhythmias was lacking because they did not receive a CIED. There is a risk for referral bias, as the study was conducted in a tertiary referral centre. Finally, we did not apply strict criteria to quantify the extent of LGE or FDG uptake on both CMR and FDG PET/CT. The amount of LGE as percent of LV mass was not assessed. The presence of extensive scar was based on visual assessment by the imaging cardiologist(s) who participated in the MDT. If the extent of LGE was decisive in the risk assessment for SCD, this could reliably be extracted from the MDT report. Final interpretation has always been performed by the MDT, leading to consensus on the final diagnosis and risk stratification for SCD.

CONCLUSION

Overall, the annualized event rate of VA and cardiac death in predominantly Caucasian CS patients without overt cardiac symptoms at initial presentation is 1.7%. Within the high-risk group the annualized event rate is almost 10%. In low-risk patients, long-term arrhythmia monitoring with ILR enabled early detection of arrhythmias, without showing impact on prognosis. Future, prospective studies should focus on a risk stratification model based on predefined selection criteria, including pattern and quantification of involved myocardium on CMR and FDG PET/CT.

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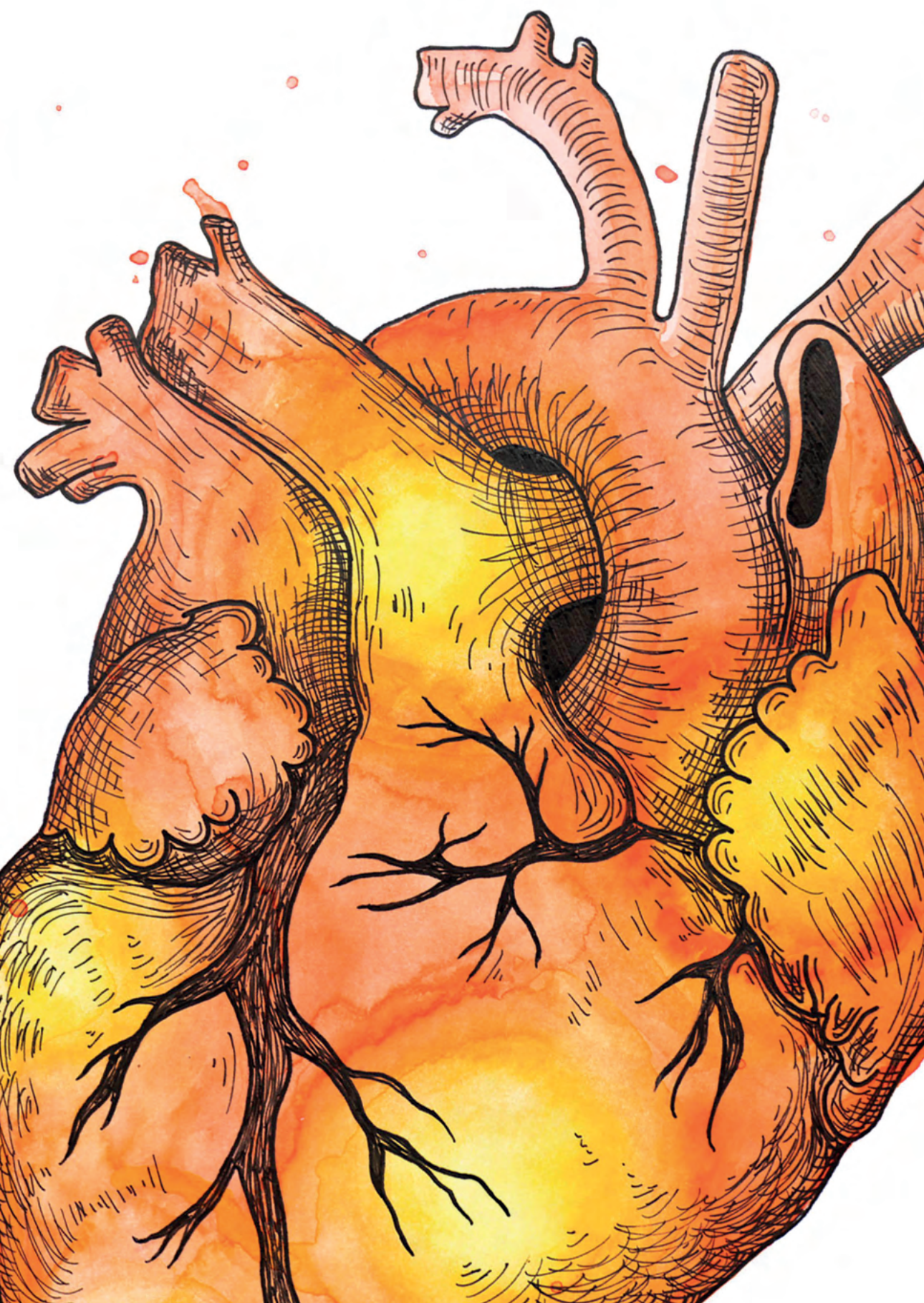

9.2

How to risk-stratify cardiac sarcoidosis patients with normal or near-normal ventricular function?

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EDITORIAL

It is estimated that 20%–25% of sarcoidosis patients have asymptomatic or minimally symptomatic cardiac involvement. This was established initially from autopsy studies[1] and confirmed using late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR).[2] These patients usually have normal or near-normal ventricular function but seem to have some risk of ventricular arrhythmia (VA). Hence, key clinical questions are how should we assess these patients for risk of VA and which patients should we recommend for implantable cardioverter-defibrillator (ICD) implantation? In this issue of Heart Rhythm Journal, Bakker et al.[3] present some novel observations to inform the debate. The first key point is the existence of clear-cut data that cardiac sarcoidosis (CS) patients with advanced conduction system disease and normal ventricular function have a substantial risk of VA and should receive an ICD.[4] These patients were not studied by Bakker et al.[3]

Otherwise it is clear that CS may not behave the same as other cardiomyopathies with regard to risk of VA and sudden death. For example, CS patient cohorts seem to have more frequent ICD therapies than other populations, and patients with mildly impaired or normal ventricular function had a risk of arrhythmia.[5,6] In 2014, an international group of CS experts published guidelines for ICD implantation.[7] In 2017, the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) produced largely similar guidelines for the use of ICDs in CS patients.[8] However, there were key differences between the 2 documents with regard to patients without significant systolic dysfunction. A summary of the relevant recommendations is given in Table 1 . Of note, none of the CS experts who wrote the 2014 HRS document were involved in the 2017 guideline.

Table 1. Comparison of recommendations for primary prevention ICD in CS patients with near-normal or normal ventricular function

2014 HRS expert consensus statement[7]		2017 AHA/ACC/HRS guideline[8]	
LVEF 36% - 49% and/ or RVEF <40%	ICD implantation (class IIb recommendation)	LVE >35%	ICD implantation (class IIa recommendation) in patients with evidence of extensive myocardial scar by cardiac MRI or PET scan * Extensive not defined
LVEF normal	Consider CMR, and if LGE is positive then do EP study. If EP study is positive, then ICD implantation (class IIa recommendation) ICD implantation is not recommended in patients with normal LVEF/ RVEF and negative EP study, regardless of LGE on CMR		

AHA/ACC/HRS = American Heart Association/American College of Cardiology/Heart Rhythm Society; CMR = cardiac magnetic resonance; CS = cardiac sarcoidosis; EP = electrophysiology; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET = positron emission tomography; RVEF = right ventricular ejection fraction.

Bakker et al.[3] studied a consecutive series of patients with extracardiac sarcoidosis referred for screening for cardiac involvement. Patients with clinically manifest CS (ie, having one or more of sustained VA, important heart block, or heart failure) were excluded. Of 557 patients, 547 underwent both CMR and fluorodeoxyglucose positron emission tomographic scanning. Of these patients, 114 were classified by the multidisciplinary team as having probable CS. Nine of the patients were lost to follow-up. Of the remaining 105 patients, 17 were classified as having higher risk for VA; the others were classified as having lower risk. These patients were classified partly based on the 2014 guideline document,[7] although importantly electrophysiological (EP) testing was not part of the risk algorithm.[3] The 17 higher-risk patients were implanted with an ICD. During mean follow-up of 33 months, 4 of these 17 patients had appropriate ICD therapy. Most of the lower-risk patients (80/88) were implanted with an implantable loop recorder, and during follow-up none of these patients had sustained VA. Seven of the lower-risk patients underwent ICD implantation because of either nonsustained VA or heart block during follow-up. One cardiac death in the low-risk group occurred as a result of right heart failure secondary to pulmonary hypertension. Of note, among the-low risk patients, 73 of 80 patients (91.3%) had LGE on CMR.[3]

These are important and unique data, and Bakker et al.[3] are to be congratulated. However, there are 2 important limitations to the study. First, there was selection bias in how the cohort was constructed. Specifically, the clinician had a reason (symptoms and/or investigation findings) to refer the patient for screening for cardiac involvement. Second, Bakker et al did not quantify LGE on magnetic resonance imaging, so there is no clear definition of what was used to define high risk and trigger ICD implantation (hopefully the authors can do so in a future study).

These findings suggest that there are patients with CS and some degree of LGE on CMR who have a very low risk of sustained VA during follow-up. Looking to the future, we suspect there will be 3 main areas of research focus. First, to further explore the extent of LGE, and we believe, our field can learn from similar research in hypertrophic cardiomyopathy. A recent meta-analysis of 2993 patients showed that, after adjustment for baseline characteristics, there was a clear "dose–response" relationship between the extent of LGE and sudden death risk.[9] Recent studies have shown similar observations in CS, with the majority of events occurring in patients with more extensive LGE (expressed as percent left ventricular mass) (>21.4%[10]; >20%[11]; >8%[12]). Second, to continue to explore the utility of EP testing for risk stratification. Indeed, since the publication of the 2014 guideline document, additional data supporting EP testing have been reported.[13] It is intriguing to speculate that although EP testing has been shown to be of no incremental benefit for risk stratification in most disease substrates, CS may be the exception, per-

haps because of its unique patchy substrate. In support of this concept are observations that, during ablation, consistently more morphologies of VA are induced in CS patients than all other substrates of nonischemic cardiomyopathy.[14] Third, research will continue to examine the role of right ventricular disease on risk.[15]

Bakker et al.[3] have provided important data, but clearly much more data are required to inform recommendations about ICD placement. In the meantime, at our institution we will continue to follow the 2014 guideline document and will contribute all data to a prospective research registry (CHASM-CS NCT01477359).

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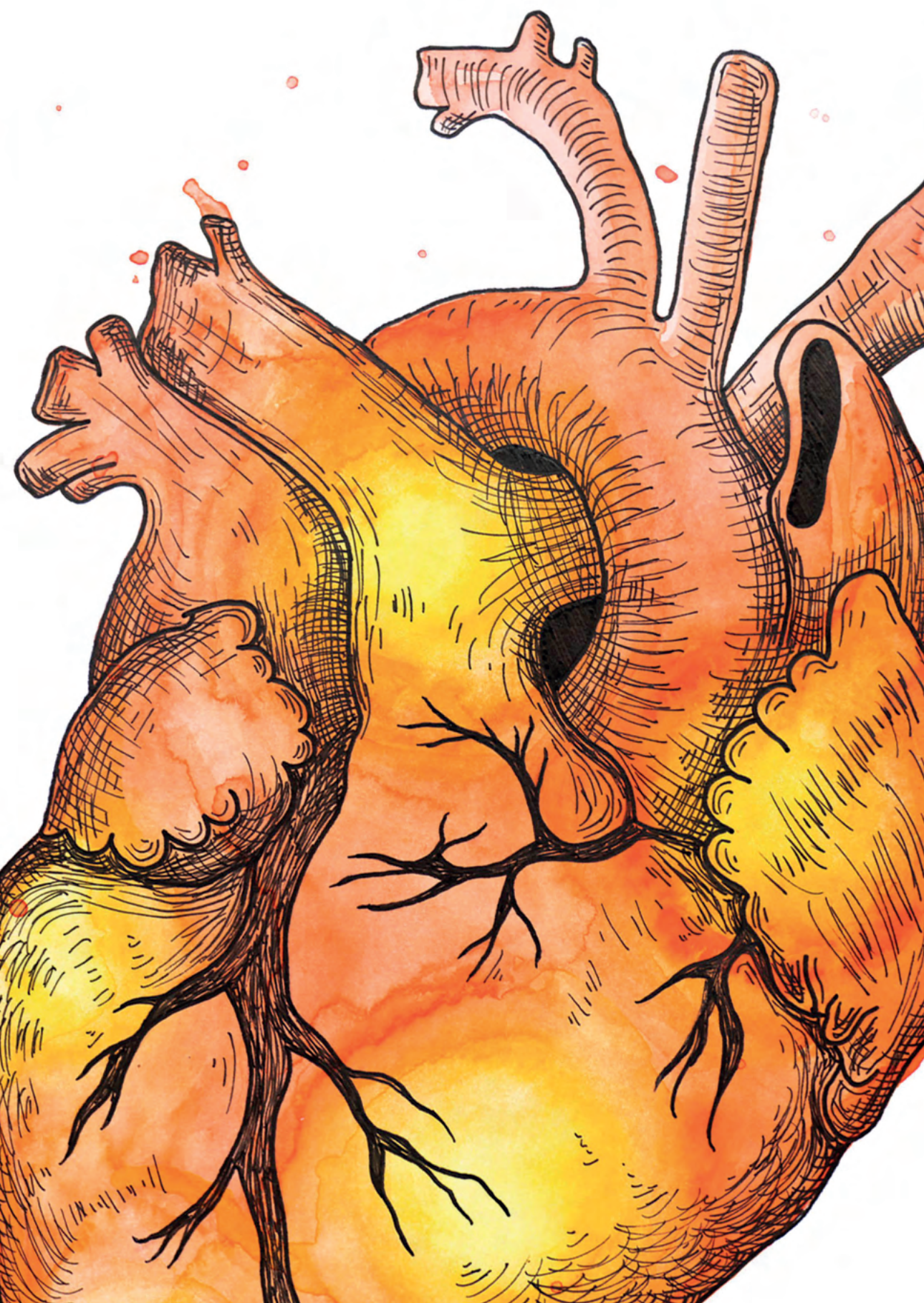

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Predictors of appropriate implantable cardiac defibrillator therapy in cardiac sarcoidosis

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ABSTRACT

Background: Cardiac sarcoidosis (CS) is associated with an increased risk for sudden cardiac death. An implantable cardiac defibrillator (ICD) is recommended in a subgroup of CS patients. However, the recommendations for primary prevention differ between guidelines. The purpose of the study was to evaluate the efficacy and safety of ICDs in CS and to identify predictors of appropriate therapy.

Methods: A retrospective cohort study was performed in CS patients with an ICD implantation between 2010 and 2019. Primary outcome was appropriate ICD therapy. Independent predictors were calculated using Cox proportional hazard analysis.

Results: 105 patients were included. An ICD was implanted for primary prevention in 79%. During a median follow-up of 2.8 years, 34 patients (32.4%) received appropriate ICD therapy of whom 24 (22.9%) received an appropriate shock. Three patients (2.9%) received an inappropriate shock due to atrial fibrillation. Independent predictors of appropriate therapy included prior ventricular arrhythmias (hazard ratio (HR): 10.5 [95% CI 5.0–21.9]) and right ventricular late gadolinium enhancement (LGE) (HR: 3.6 [95% CI 1.7–7.6]). Within the primary prevention group, right ventricular LGE (HR: 5.7 [95% CI 1.6–20.7]) was the only independent predictor of appropriate therapy. Left ventricular ejection fraction did not differ between patients with and without appropriate therapy (44.4% vs. 45.6%, p=0.70).

Conclusion: In CS patients with an ICD, a high rate of appropriate therapy was observed and a low rate of inappropriate shocks. Prior ventricular arrhythmias and right ventricular LGE were independent predictors of appropriate therapy.

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology. Cardiac involvement is found in up to 25% of patients in autopsy series, while clinically overt cardiac involvement is seen in approximately 5% of cases.[1,2] Cardiac sarcoidosis (CS) presentation can range from asymptomatic to life-threatening ventricular arrhythmias (VA), atrioventricular block (AVB) and heart failure. Also, CS is associated with an increased risk for sudden cardiac death (SCD).[3] Therefore, implantable cardiac defibrillators (ICD) are recommended in subgroups of CS patients for both primary and secondary prevention of SCD. A high incidence of both appropriate and inappropriate ICD therapy are reported in these patients.[4–7] However, it remains a challenge to identify those patients with CS who will benefit from ICD implantation. Current guidelines differ in recommendations.[8,9] Furthermore, up to now studies did not well define which CS patients should receive an ICD for primary prevention. The purpose of this study is to evaluate the efficacy and safety of ICD implantation, predominantly for primary prevention, in a cohort of CS patients.

METHODS

Study design

A retrospective single-centre cohort study was conducted in the St. Antonius Hospital, a tertiary referral centre for both sarcoidosis and CS. Local institutional review board approval was obtained with a waiver of informed consent. All patients diagnosed with CS between January 2010 and January 2019 whom had an ICD implanted within 6 months after CS diagnosis or whom already had an ICD before CS diagnosis were included. Minimal follow-up duration was three months.

CS diagnosis

Patients were diagnosed with CS after discussion in our multidisciplinary team (MDT), which consisted of experienced pulmonologists, imaging cardiologists, nuclear physicians and specialized nurses. Using the 2016 Japanese Circulation Society (JCS) diagnostic criteria all but three patients fulfilled the diagnostic criteria for CS.[10] These three patients had biopsy proven extracardiac sarcoidosis and a 3rd degree AVB without abnormalities on cardiac magnetic resonance imaging (CMR) and full body fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT). These three patients did fulfil the 2014 Heart Rhythm Society (HRS) diagnostic criteria and were diagnosed with CS.[8] At time of diagnosis, CMR and FDG PET/CT were performed. CMR was performed in 99 patients (94.3%). In six patients no CMR was performed due to

a non-MRI conditional intra-cardiac device. Late gadolinium enhancement (LGE) images were obtained 12-20 minutes after intravenous administration of 0.4 ml/kg gadolinium. All CMR images were retrospectively analysed by two experienced observers (F.A. and H.E.) blinded for clinical outcomes. Both observers evaluated each CMR exam as a team and agreed to a given result. All CMR images were scored on left ventricular ejection fraction (LVEF), presence of LGE (by visual assessment) and localization of LGE (septum, lateral wall, inferior wall, anterior wall and right ventricle). FDG PET/CT was performed in all patients. PET/CT images were scored for myocardial FDG uptake and pattern. FDG uptake patterns were classified as: none, diffuse, focal and focal on diffuse.

ICD implantation

All patients underwent ICD implantation using standard techniques and preoperative antibiotics. The indication for implantation was obtained using the MDT report or implantation procedure report. Secondary prevention indications included: sudden cardiac arrest, history of sustained VA, or syncope of probable tachyarrhythmic origin. In all other cases the indication was classified as primary prevention. Primary prevention indications were a reduced LVEF (both LVEF <35% and LVEF 35-50%, with other causes excluded), 2nd or 3rd degree AVB or extensive LGE on CMR (as determined by the MDT). Some patients had multiple primary prevention indications, such as LVEF <35% and a 3rd degree AVB. ICD programming was at the discretion of the implanting and treating physicians. All patients received routine wound and device check within the first 14 days after implant. Device interrogation was performed every 3-6 months and during event-driven visits.

Outcomes

The primary outcome was appropriate ICD therapy. Secondary outcome parameters included mortality, heart transplantation or left ventricular assist device placement, inappropriate ICD therapy and device related complications. Appropriate ICD therapy was defined as shocks or anti-tachycardia pacing (ATP) due to sustained VA. Nonsustained VA, lasting <30 seconds, were excluded from analysis. Inappropriate therapy was defined as ICD shocks resulting from supraventricular arrhythmias (including sinus tachycardia, atrial fibrillation and atrial flutter), T wave oversensing or lead noise. An experienced electrophysiologist (J.B.) checked all device interrogation reports of all device therapies to determine appropriateness. Electrical storm was defined as ≥3 appropriate ICD therapies in a 24-hour period. Death was classified as cardiac and non-cardiac death. Data on mortality were obtained from the national database of death registration. Device related complications, defined as early (≤30 days after implantation) or late (>30 days), were obtained by chart review. Baseline was defined as the date of CS diagnosis in the MDT. LVEF at baseline was determined by CMR. If CMR was not performed, LVEF was based on

echocardiography using the biplane Simpson's method (n=6). As some patients already had received an ICD before CS diagnosis, follow-up duration was calculated from the date of ICD implantation to the last date of device interrogation.

Statistical analysis

Data were stored in the web-based data manager REDCap. Patient characteristics are presented as mean ± standard deviation or median [interquartile range] for continuous variables and as frequencies (percentage) for categorical variables. The Student's t-test or Mann-Whitney U test was used to compare mean or median values of continuous variables. The chi-squared test or Fisher's Exact Test was used to compare categorical variables. Kaplan-Meier analysis was used for observed event rates during follow-up with the Log-Rank test for comparison between curves. Predictors of appropriate ICD therapy were analysed using Cox proportional hazard analysis. All variables with a p-value <0.10 in the univariate analyses were entered into the multivariate analysis. After backward stepwise selection, variables associated with a p-value <0.10 were retained in the multivariate model. Hazard ratios (HR) are presented with 95% confidence intervals (CI). Statistical analyses were performed using SPSS Statistics version 26.0 for Windows (Armonk, NY: IBM Corp). A two-tailed p-value of <0.05 was considered significant.

RESULTS

In total, 105 CS patients were included (63.4% male, mean age 52 ± 10.0 years). Baseline characteristics are shown in table 1.

CS diagnosis and cardiac imaging

CS diagnosis was based on the presence of cardiac granulomas on biopsy in 2.9%, while 76.2% had biopsy proven extracardiac sarcoidosis. In 17.1% of patients a clinical diagnosis of extracardiac sarcoidosis was made based on clinical, laboratory and radiological findings.[11] Only 2.9% of patients had isolated CS (table 1). Of the 99 patients who underwent CMR, 89 patients (89.9%) showed LGE; located in the septum (76.8%), lateral wall (62.6%), inferior wall (64.6%), anterior wall (49.5%), and right ventricle (40.4%). All patients with right ventricular (RV) LGE also showed left ventricular LGE. Mean LVEF was 45.2% ± 14.0%. FDG PET/CT showed focal or focal on diffuse cardiac uptake in 75.2%, diffuse uptake in 6.7% and no uptake in 18.1% of patients. Extracardiac FDG uptake was present in 82.9%.

Table 1. Baseline characteristics

Variable	All (n=105)	Primary prevention (n=83)	Secondary prevention (n=22)	p-value
Age (years)	52.3 ± 10.0	52.4 ± 10.0	51.9 ± 10.1	0.85
Male sex	67 (63.8%)	49 (59.0%)	18 (81.8%)	0.08
Body mass index (m^2/kg)	27.2 ± 4.2	27.4 ± 4.3	26.4 ± 4.1	0.32
Caucasian ethnicity	99 (94.3%)	78 (94.0%)	21 (95.5%)	1.00
Sarcoidosis diagnosis				
Biopsy proven CS	3 (2.9%)	1 (1.2%)	2 (9.1%)	0.11
Biopsy proven ECS	80 (76.2%)	66 (79.5%)	14 (63.6%)	0.12
Clinical diagnosis ECS	18 (17.1%)	14 (16.9%)	4 (18.2%)	1.00
Clinical diagnosis isolated CS	4 (3.8%)	2 (2.4%)	2 (9.1%)	0.19
Sarcoidosis localization and manifestation				
Isolated CS	4 (3.8%)	2 (2.4%)	2 (9.1%)	0.19
ECS localization • Pulmonary • Spleen • Liver • Neurologic	101 (96.2%) • 93 (88.6%) • 20 (19.0%) • 11 (10.5%) • 2 (1.9%)	81 (97.6%) • 76 (91.6%) • 17 (20.5%) • 9 (10.8%) • 2 (2.4%)	20 (90.9%) • 17 (77.3%) • 3 (13.6%) • 2 (9.1%) • 0 (0.0%)	0.19 • 0.06 • 0.56 • 1.00 • 1.00
CS was first manifestation of sarcoidosis	63 (60.0%)	48 (57.8%)	15 (68.2%)	0.38
2^{nd} or 3^{rd} degree AVB	46 (43.8%)	42 (50.6%)	4 (18.2%)	0.01
Ventricular arrhythmias	19 (18.1%)	0 (0.0%)	19 (86.4%)	<0.001
LVEF (%) • LVEF <35% • LVEF <50%	45.2 ± 14.0 • 23 (21.9%) • 61 (58.1%)	44.5 ± 15.2 • 22 (26.5%) • 49 (59.0%)	47.7 ± 7.4 • 1 (4.5%) • 12 (54.5%)	0.17 • 0.04 • 0.70
Comorbidities				
Hypertension	23 (21.9%)	19 (22.9%)	4 (18.2%)	0.78
Diabetes mellitus	7 (6.7%)	4 (4.8%)	3 (13.6%)	0.16
Atrial fibrillation or -flutter	9 (8.6%)	8 (9.6%)	1 (4.5%)	0.68
Treatment				
Immunosuppressive treatment	97 (92.4%)	76 (91.6%)	21 (95.5%)	1.00
Corticosteroids	76 (72.4%)	61 (73.5%)	15 (68.2%)	0.62
Non-steroid therapy • Methotrexate • Azathioprine • Infliximab • Other	69 (65.7%) • 65 (61.9%) • 3 (2.9%) • 2 (1.9%) • 3 (2.9%)	55 (66.3%) • 51 (61.4%) • 3 (3.6%) • 2 (2.4%) • 3 (3.6%)	14 (63.6%) • 14 (63.6%) • 0 (0.0%) • 0 (0.0%) • 0 (0.0%)	0.82 • 0.85 • 1.00 • 1.00 • 1.00
Antiarrhythmic drugs • Beta-blocker • Sotalol • Amiodarone • Other	62 (59.0%) • 50 (47.6%) • 8 (7.6%) • 5 (4.8%) • 8 (7.6%)	41 (49.4%) • 34 (41.0%) • 5 (6.0%) • 0 (0.0%) • 4 (4.8%)	21 (95.5%) • 16 (72.7%) • 3 (13.6%) • 5 (22.7%) • 4 (18.2%)	<0.001 • 0.008 • 0.36 • <0.001 • 0.06
ACE-inhibitors or ARBs	48 (45.7%)	38 (45.8%)	10 (45.5%)	0.98

AVB = atrioventricular block; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CS = cardiac sarcoidosis; ECS = extracardiac sarcoidosis; LVEF = left ventricular ejection fraction

ICD indication

Eighty-three patients (79.0%) received an ICD for primary prevention and twenty-two patients (21.0%) for secondary prevention. As shown in table 1, patients who received an ICD for primary prevention had a higher prevalence of 2nd or 3rd degree AVB and LVEF <35% at baseline and were less often treated with antiarrhythmic drugs including beta-blockers and amiodarone. There were no significant differences between the primary- and secondary prevention group regarding presence and localization of LGE and cardiac FDG uptake on PET/CT (supplementary table S1). Further specification of the indication for ICD implantation is shown in table 2. In the primary prevention group, second or 3rd degree AVB was the most common indication (50.6%) for ICD implantation. Of these 42 patients, 18 (17.1%) had a reduced LVEF <50%, while 24 patients (22.9%) had an AVB with a preserved LVEF. Nine patients (8.6%) neither showed a reduced LVEF or AVB, but had an ICD implanted because of extensive LGE on CMR.

Table 2. ICD indication and therapy

Variable	All (n=105)	Primary prevention (n=83)	Secondary prevention (n=22)	p-value
Time between ICD implantation – CS diagnosis (months)	2.2 ± 8.2	0.6 ± 3.1	8.3 ± 15.8	0.03
Primary prevention • Severely reduced LVEF (<35%) • Reduced LVEF (35-50%) • 2nd or 3rd degree AVB • Extensive LGE on CMR without LVEF reduction or AVB	83 (79.0%) • 21 (20.0%) • 29 (27.6%) • 42 (40.0%) • 9 (8.6%)	83 (100%) • 21 (25.3%) • 29 (34.9%) • 42 (50.6%) • 9 (10.8%)	0 (0.0%)	-
Secondary prevention • Documented VA • Syncope of probable arrhythmic origin	22 (21.0%) • 19 (18.1%) • 3 (2.9%)	0 (0.0%)	22 (100%) • 19 (86.4%) • 3 (13.6%)	-
Upgrade from pacemaker to ICD	11 (10.5%)	8 (9.6%)	3 (13.6%)	0.70
Cardiac resynchronization therapy	15 (14.3%)	13 (15.7%)	2 (9.1%)	0.73
Appropriate ICD therapy	34 (32.4%)	16 (19.3%)	18 (81.8%)	<0.001
Appropriate ICD shock	24 (22.9%)	12 (14.5%)	12 (54.5%)	<0.001
Time to first appropriate therapy (months)	7.7 [2.0 – 18.0]	12.8 [5.7 – 21.7]	3.9 [1.7 – 14.9]	0.04
Number of appropriate therapies per person (only patients with appropriate therapy)	4.0 [1.0 – 17.3]	5.0 [1.0 – 17.5]	4.0 [1.8 – 21.8]	0.83
Number of appropriate shocks per person	2.0 [1.0 – 5.0]	2.0 [1.0 – 4.5]	2.5 [1.0 – 19.0]	0.51
Electrical storm	11 (10.5%)	6 (7.2%)	5 (22.7%)	0.04
Inappropriate ICD shock	3 (2.9%)	0 (0.0%)	3 (13.6%)	0.01
Follow-up duration (years)	2.8 [1.8 – 4.6]	2.7 [1.8 – 4.5]	3.3 [1.6 – 5.7]	0.74

AVB = atrioventricular block; CMR = cardiac magnetic resonance imaging; CS = cardiac sarcoidosis; ICD = implantable cardiac defibrillator; LGE: late gadolinium enhancement; LVEF = left ventricular ejection fraction; VA = ventricular arrhythmias

Primary outcome: appropriate ICD therapy

As shown in table 2, over a median follow-up of 2.8 [1.8–4.6] years, 34 patients (32.4%) received appropriate ICD therapy and 24 of 34 patients (22.9%) received appropriate shocks. In total, 16.2% received both shock and ATP, 6.7% only shock and 9.5% only ATP. Figure 1 shows the number of ICD therapies per person. Patients with appropriate ICD therapy received a median of 4.0 [1.0–17.3] therapies. Annualized event rate was 11.6% for ATP and shock and 8.2% for shock only. Patients in the secondary prevention group received more appropriate therapies (81.8% vs. 19.3%, p <0.001) and more appropriate shocks (54.5% vs. 14.5%, p <0.001). Figure 2 shows the Kaplan Meier curves for appropriate ICD therapy and appropriate ICD shock in the primary and secondary prevention group which differed significantly (p<0.001). Supplementary table S2 shows the rate of appropriate ICD therapy per indication for ICD implantation. In a subgroup of 25 patients who did not meet the HRS criteria for an ICD implantation (no VA, no syncope, no 2nd or 3rd degree AVB and LVEF >35%) six patients received appropriate ICD therapy.

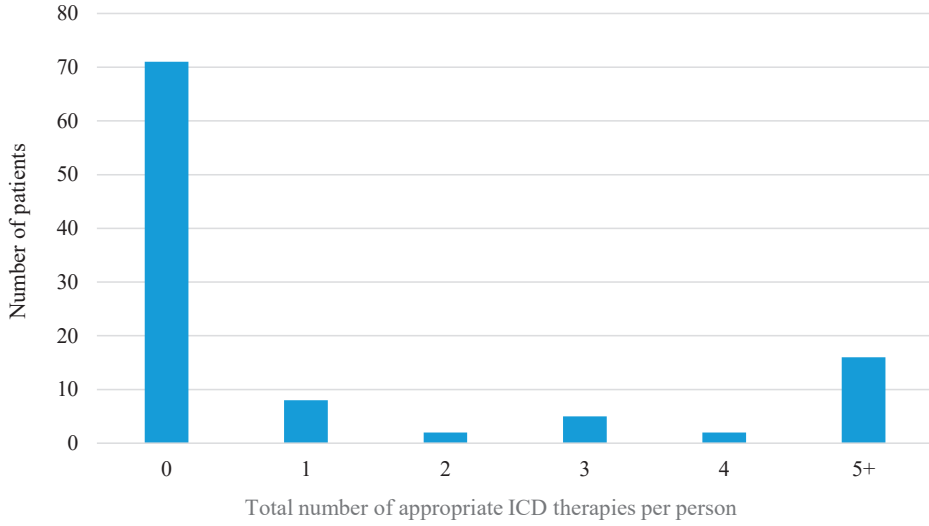

Figure 1. Frequency of appropriate ICD therapy per person including ATP and shocks.

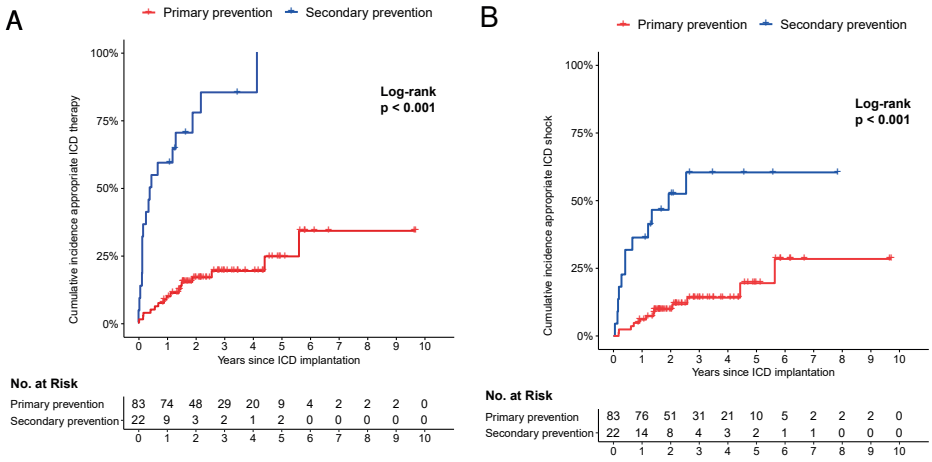

Figure 2. Kaplan-Meier curves comparing the cumulative incidence of appropriate ICD therapy (ATP and shock) (A) and only appropriate ICD shocks (B) in patients with a primary prevention indication (red line) and a secondary prevention indication (blue line). Each vertical tick on the curves displays a censored patient.

Predictors of appropriate ICD therapy

All patients with appropriate ICD therapy showed LGE on CMR and all ten patients without LGE did not receive appropriate ICD therapy. LVEF between patients with and without appropriate therapy did not differ significantly (44.4% vs. 45.6%, p=0.70). When applying a cut-off value for the LVEF of 35%, appropriate therapy occurred in 26.1% with LVEF <35% vs. 34.1% with LVEF ≥35% (p=0.62). When comparing the groups based on LVEF of 50% as cut-off, appropriate therapy occurred in 34.4% with LVEF <50% and in 29.5% with LVEF ≥50% (p=0.68).

Table 3 shows Cox proportional hazard analysis results for appropriate ICD therapy in all patients and the primary prevention group. Male sex, 2nd or 3rd degree AVB, prior VA, inferior wall LGE, anterior wall LGE and RV LGE were significant univariate predictors of appropriate ICD therapy in all patients. After multivariate analysis both prior VA (hazard ratio (HR): 10.5 [95% CI 5.0 – 21.9], p <0.001) and RV LGE (HR: 3.6 [95% CI 1.7 – 7.6], p=0.001) were significant independent predictors. Analysis of the group of patients who received a CMR at baseline (n=99) resulted in similar univariate and multivariate predictors (data not shown). In the primary prevention group (n=83), anterior wall LGE (HR: 3.3 [95% CI 1.0 – 10.6], p=0.04) and RV LGE (HR: 6.3 [95% CI 1.7 - 22.5], p=0.005) were the only significant univariate predictors (table 3). Lateral wall LGE (HR: 4.5 [95% CI 1.0 – 20.5], p=0.05) was also included into multivariate analysis. After multivariate analysis, only RV LGE was an independent predictor of appropriate ICD therapy in the primary prevention group (HR: 5.7 [95% CI 1.6 – 20.7], p=0.008). Supplementary table S3 shows univariate

Cox proportional hazard analysis results of all baseline characteristics in the primary prevention group.

Table 3. Predictors of appropriate ICD therapy in all patients and in the primary prevention group

	All patients (n=105)			
	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	2.33 (1.02 – 5.36)	0.046		
2nd or 3rd degree AVB	0.38 (0.17 – 0.84)	0.017		
Prior VA	9.60 (4.73 – 19.51)	<0.001	10.45 (5.00 – 21.86)	<0.001
Inferior wall LGE	2.30 (0.94 – 5.60)	0.067		
Anterior wall LGE	3.03 (1.40 – 6.56)	0.005		
Right ventricular LGE	3.36 (1.61 – 6.99)	0.001	3.62 (1.72 – 7.59)	0.001
	Primary prevention group (n=83)			
	Univariate analysis		**Multivariate analysis**	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
Lateral wall LGE	4.48 (0.98 – 20.49)	0.053	4.25 (0.80 – 22.49)	0.089
Anterior wall LGE	3.32 (1.04 – 10.64)	0.043		
Right ventricular LGE	6.27 (1.74 – 22.54)	0.005	5.70 (1.57 – 20.68)	0.008

AVB = atrioventricular block; CI = confidence interval; HR = hazard ratio; LGE: late gadolinium enhancement; VA = ventricular arrhythmias

Secondary outcomes

Four patients (3.8%) died during follow-up, of whom two of the primary prevention group (2.4%) and two of the secondary prevention group (9.1%). Three patients died due to heart failure and one due to lymphoma. Supplementary figure 1 shows the Kaplan Meier curve for survival. Survival did not differ between the primary- and secondary prevention groups (p=0.22, Log Rank test). Two patients (1.9%), both of the primary prevention group, received a left ventricular assist device and no heart transplantation was performed. Three patients (2.9%) received 10 inappropriate shocks, all due to atrial fibrillation. All three patients had an ICD for secondary prevention and had previously received appropriate therapy. One patient underwent VT ablation during follow-up. Figure 3 shows an overview of the device related complications. Twenty-three complications occurred in nineteen (18.1%) patients, with early and late device-related complications in 13.3% and 7.6%, respectively. Most common complications were lead fracture of dislodgement (n=7), wound- or pocket infection (n=5), deep venous thrombosis (n=4) and pneumothorax (n=3). One patient had two early complications (pocket hematoma and lead perforation). Three patients showed both early and late device related complications. None of the patients had a serious device infection requiring device explantation.

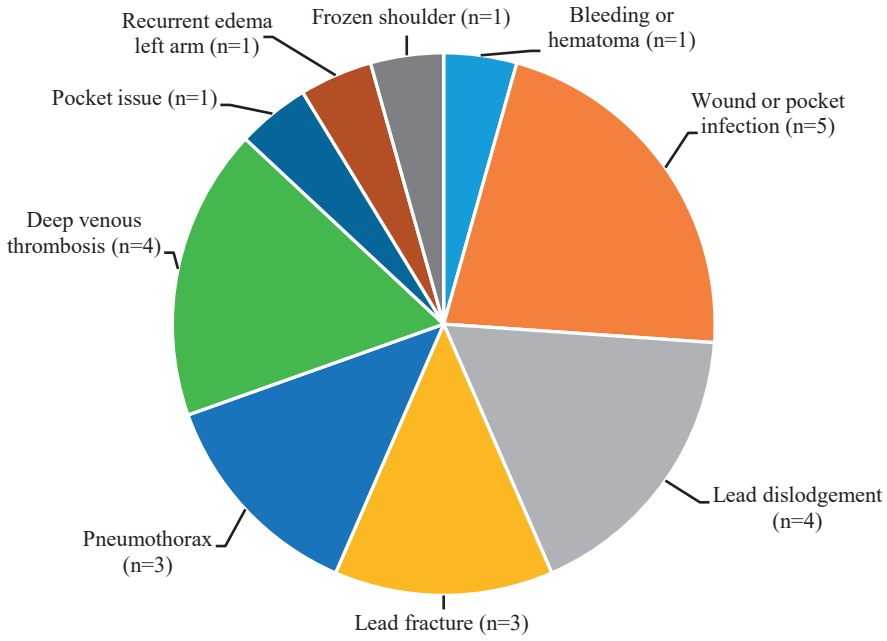

Figure 3. Device-related complications for ICD in CS patients.

DISCUSSION

The main finding of the present study is that appropriate ICD therapy is frequently reported in CS patients, with an annualized event rate of 11.6%. When comparing the primary and secondary prevention group, appropriate therapy was significantly higher in the secondary prevention group. Using multivariate analysis, prior VA and RV LGE were independent predictors of the primary outcome. Reduced LVEF was not associated with higher rates of appropriate ICD therapy.

The rate of appropriate ICD therapy in our study is largely comparable with existing literature. A recent meta-analysis reported appropriate ICD therapy in 39% of CS patients. A high degree AVB was the only predictor of appropriate ICD therapy.[7] In the largest retrospective study to date, Kron et al. included 235 patients with a clinical CS diagnosis. Appropriate ICD therapy was observed in 36.2% of patients, while 29.7% of patients also received an appropriate shock. However, multivariate analysis was not performed and thus independent predictors of ICD therapy were not described.[4] Schuller et al. observed appropriate ICD therapy in 36 of 112 patients (32.1%) during a mean follow-up period of 2.4 years. RV dysfunction, LVEF <55% and symptomatic heart failure symptoms were independent predictors of worse outcome. In both studies, CMR was

not performed routinely and therefore CMR results could not be analysed as possible predictors of adverse outcome. Furthermore, primary prevention subgroups were not defined and CS diagnosis was not based on MDT consensus.

Currently, two guidelines address the implantation of ICD in CS: the American Heart Association (AHA)/American College of Cardiology (ACC) guideline and the HRS consensus statement.[8,9] Both recommend ICD implantation in patients with a LVEF <35% (class I) or with an AVB requiring permanent pacing (class IIa). However, there are differences between both guidelines as the HRS document states that an ICD may be considered in patients with LVEF in the range of 36-49%, while the AHA/ACC guideline recommends an ICD (class IIa) in patients with LVEF>35% in case of extensive scar on CMR or FDG PET/CT, syncope or when permanent pacing is indicated. These differences are largely based on the accumulating evidence of the predictive value of LGE on CMR. In our cohort, the decision to implant an ICD was based on the HRS consensus statement and the best evidence available at that point in time. During the time frame of the present study, evidence for the predictive value of LGE for risk stratification was increasing and applied in clinical practice. We found no significant differences in LVEF between patients with and without appropriate therapy, even in the primary prevention group. Conversely, in the study by Schuller et al. LVEF <55% was a significant independent predictor of appropriate therapy. Also, no patients in the primary prevention subgroup with normal RV- and LV function received appropriate therapy, while the mean LVEF was comparable to our study (44.9% vs. 45.2%).[5] A possible explanation is the large difference in the prevalence of 2nd or 3rd degree AVB, which was significantly higher in our population (43.8% vs. 15.2%). Previous studies have shown that the presence of AVB is associated with VA, even in patients with a preserved LVEF.[12,13] It is thought that advanced conduction system disease could be a surrogate marker for more extensive granulomatous infiltration of the myocardium. In our study, the presence of high degree AVB was associated with appropriate ICD therapy in univariate Cox proportional hazard analysis, but not in multivariate analysis. This cannot be explained by the presence of RV LGE as the prevalence of 2nd or 3rd degree AVB was not higher in patients with RV LGE vs. no RV LGE (p=0.95). An explanation for the association between AVB and VA in prior studies might be the delay in CS diagnosis in patients who present with lone AVB and preserved LVEF. We did not find such association as the mean delay between ICD implantation and CS diagnosis in the primary prevention group was only 0.6 ± 3.1 months. Further research is warranted to investigate the relationship between conduction system disease and VA in CS patients.

It should be noted that, in concordance with the results of the present analysis, a more recent study by Rosenthal et al. showed no association between LVEF and worse out-

comes in CS patients. In this study, LVEF was not associated with an increased risk of VA or SCD in 110 CS patients.[14] The authors recommend investigating arrhythmia risk in all patients with CS, even in the setting of an otherwise normal LVEF. Our study suggests that CMR, especially the presence of RV LGE, can be an important tool for VA risk assessment. In the current literature, LGE presence has been associated with worse outcome in CS patients.[15,16] Therefore the AHA/ACC guideline recommends ICD implantation in patients with extensive scar on CMR, without further defining the term extensive.[9] Our study supports this recommendation, since only patients with LGE received appropriate ICD therapy and RV LGE was a strong independent predictor of appropriate therapy. RV LGE was always accompanied with left ventricular LGE, which could imply more profound disease with a larger scar burden. The association between RV LGE and adverse outcomes in CS has been reported earlier.[16,17] More recently, Velangi et al. showed that RV LGE was independently associated with a composite endpoint of SCD or VA (HR: 5.4, p=0.024).[18] Our study adds to the growing body of evidence that the presence of RV LGE should be used as a marker of extensive LGE to meet the recommendation for ICD implantation.[18] Some studies have shown that LGE as % of left ventricular mass can also be used as a marker for 'extensive scar', although different methods for LGE quantification have been used and these methods have not been validated in other CS cohorts.[16,18,19] The extent of LGE could not be determined in this study as the included patients received their CMR in different hospitals with different MRI vendors and there was no robust technique available that could routinely and reliably quantify the percentage or mass of involved myocardium.

Inappropriate shocks and device-related complications in CS

We found a very low number of inappropriate shocks (2.9%) in our study. These findings are in contrast with earlier published studies in which the rate of inappropriate therapy ranged between 11-30%.[4–7] However, some studies reported only the total number of inappropriate shocks and ATP. One of the highest rates was observed by Kron et al. with 24.3% receiving inappropriate shocks, mostly due to supraventricular tachycardia and lead failure.[4] This even prompted an editorial questioning whether an ICD is a savior or sinner in CS patients.[20] Our study shows that the benefits outweigh the risks. The differences between both studies could be explained by several factors. First, as the authors stated: the timing of their study corresponded with the peak implantation of Medtronic Sprint Fidelis leads, with high failure rates and subsequent risk for inappropriate shocks.[21] Also, our follow-up duration is shorter (median 2.8 years vs. mean 4.2 years). Furthermore, in the past years the usage of device interrogation by home monitoring has been increasingly used in our hospital. This could result in an earlier detection of supraventricular tachycardia's and lead issues. Finally, ICD programming in our hospital has evolved significantly over the last years with better supraventricular

tachycardia discrimination algorithms, higher VA zones and delayed therapy.[22] As supraventricular tachycardia is the most prevalent cause for inappropriate shock, improved discrimination and prolonged delay in therapy could have a large effect. In our study, device-related complications were observed in 18.1%, with the majority due to lead dislodgement or lead dysfunction (6.7%). Kron et al. were the first to report the incidence of ICD complications in CS and found a comparable rate of 17.4%, with more than half due to lead dislodgement or fracture. The high rate of this specific complication might be explained by the younger age of most CS patients with a more active lifestyle.

Limitations

The potential limitations of retrospective, single centre observational research must be taken into account. An important limitation is the sample size of the study population. Therefore, multivariate analysis is limited by large 95% confidence intervals and the risk of an overfitted model. Only parameters with a p-value <0.10 were taken into account for multivariate analyses, creating the risk of missing clinically important variables in multivariate analysis. Our results might not be applicable to all CS patients, as the indication for ICD implantation was not standardized in our cohort. Extensive LGE was not further defined by the MDT and LGE as % of left ventricular mass was not determined. In addition, all CMR exams were interpreted by two observers and interobserver variability could not be assessed as the interpretation was performed as a team. Furthermore, not all patients underwent a dedicated cardiac FDG PET/CT as patients were included since 2010. Therefore, the exact localization of FDG-uptake in the different left ventricular walls could not be reliably assessed. The impact of immunosuppressive treatment might be underestimated due to the time difference between ICD implantation and CS diagnosis. Sarcoidosis was not biopsy proven in 20.9% of patients; however, CS diagnosis was based on the MDT discussion using the experience of imaging cardiologists, pulmonologists and nuclear physicians. Earlier studies have shown that no distinction should be made regarding treatment and follow-up of patients with definite or probable CS.[6,23]

CONCLUSION

In our cohort of CS patients with an ICD, predominantly for primary prevention, a high rate (32%) of appropriate ICD therapy was observed, with a low rate of inappropriate shocks (3%). Independent predictors of appropriate therapy include prior VA and RV LGE. Patients in the secondary prevention group received more appropriate therapy and shocks than patients in the primary prevention group. LVEF was no predictor of

appropriate ICD therapy. Prospective, multicentre studies are needed to further define predictors of appropriate ICD therapy in CS patients.

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APPENDIX

Supplementary table S1. CMR and FDG PET/CT results at baseline

Variable	All (n=105)	Primary prevention (n=83)	Secondary prevention (n=22)	p-value
Focal or focal on diffuse FDG uptake on PET/CT	79 (75.2%)	64 (77.1%)	15 (68.2%)	0.39
LGE on CMR (n=99)	89 (89.9%)	67 (80.7%)	22 (100%)	0.11
Septal wall LGE	76 (76.8%)	57 (74.0%)	19 (86.4%)	0.27
Lateral wall LGE	62 (62.6%)	49 (63.6%)	13 (59.1%)	0.70
Inferior wall LGE	64 (64.4%)	48 (62.3%)	16 (72.7%)	0.37
Anterior wall LGE	49 (49.5%)	35 (45.5%)	14 (63.6%)	0.13
Right ventricular LGE	40 (40.4%)	30 (39.0%)	10 (45.5%)	0.58

CMR = cardiac magnetic resonance imaging; FDG PET/CT = fluorodeoxyglucose glucose positron emission tomography with computed tomography; LGE: late gadolinium enhancement

Supplementary table S2. Appropriate ICD therapy per indication

Variable	Value
Primary prevention:	
• Severely reduced LVEF (<35%)	6 (28.6%)
• Reduced LVEF (35-50%)	5 (17.2%)
• 2nd or 3rd degree AVB	6 (14.3%)
• Extensive LGE on CMR without LVEF reduction or AVB	3 (33.3%)
Secondary prevention:	
• Documented VA	16 (84.2%)
• Syncope of probable arrhythmic origin	2 (66.7%)

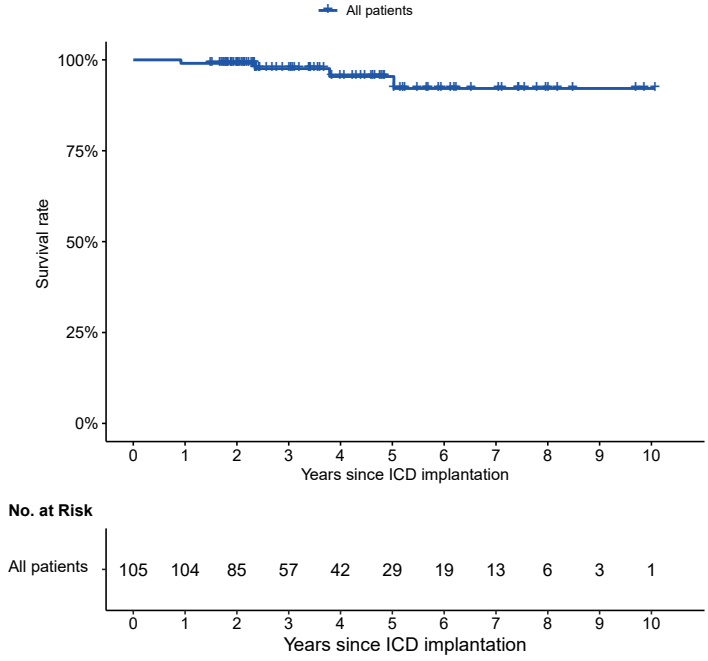
AVB = atrioventricular block; CMR = cardiac magnetic resonance imaging; LGE: late gadolinium enhancement; LVEF = left ventricular ejection fraction; VA = ventricular arrhythmias

Supplementary table S3. Univariate Cox proportional hazard analysis for appropriate ICD therapy in the primary prevention group (n=83)

Variable	Patients without ICD therapy (n=67)	Patients with ICD therapy (n=16)	Hazard ratio (95% CI)	p-value
Age (years)	52.4 ± 10.4	52.2 ± 8.2	0.99 (0.94 – 1.04)	0.69
Male sex	37 (55.2%)	12 (75.0%)	0.50 (0.16 – 1.54)	0.23
Body mass index (m^2/kg)	27.3 ± 4.2	27.6 ± 4.6	1.00 (0.88 – 1.12)	0.94
Caucasian ethnicity	62 (92.5%)	16 (100%)	22.0 (0.01 – 369469)	0.53
Sarcoidosis diagnosis				
Biopsy proven CS	1 (1.5%)	0 (0.0%)	0.05 (0.01 – 1112265)	0.76
Biopsy proven ECS	53 (79.1%)	13 (81.3%)	0.99 (0.28 – 3.49)	0.99
Clinical diagnosis ECS	11 (16.4%)	3 (18.8%)	1.47 (0.41 – 5.21)	0.55
Clinical diagnosis isolated CS	1 (1.5%)	0 (0.0%)	0.05 (0.01 – 3518)	0.71
Sarcoidosis localization and manifestation				
Isolated CS	2 (3.0%)	0 (0.0%)	0.05 (0.01 – 5462)	0.61
ECS localization	65 (97.0%)	16 (100%)	21.87 (0.01 – 261065)	0.61
• Pulmonary	• 61 (91.0%)	• 15 (93.8%)	• 1.87 (0.24 – 14.9)	• 0.55
• Spleen	• 13 (19.4%)	• 4 (25.0%)	• 1.31 (0.42 – 4.08)	• 0.64
• Liver	• 7 (10.4%)	• 2 (12.5%)	• 1.20 (0.27 – 5.26)	• 0.82
• Neurologic	• 2 (3.0%)	• 0 (0.0%)	• 0.04 (0.01 – 1066)	• 0.54
CS was first manifestation of sarcoidosis	38 (56.7%)	10 (62.5%)	0.65 (0.23 – 1.80)	0.40
2^{nd} or 3^{rd} degree AVB	36 (53.7%)	6 (37.5%)	0.55 (0.20 – 1.53)	0.25
LVEF (%)	40.2 ± 15.1	45.6 ± 15.2	0.98 (0.94 – 1.01)	0.13
• LVEF <35%	• 17 (25.4%)	• 5 (31.3%)	1.48 (0.51 – 4.34)	0.47
• LVEF <50%	• 38 (56.7%)	• 11 (68.8%)	1.92 (0.64 – 5.74)	0.25
Comorbidities				
Hypertension	15 (22.4%)	4 (25.0%)	0.99 (0.32 – 3.08)	0.99
Diabetes mellitus	4 (6.0%)	0 (0.0%)	22.00 (0.01 – 508409)	0.55
Atrial fibrillation or -flutter	7 (10.4%	1 (6.3%)	1.76 (0.23 – 13.4)	0.58
Treatment				
Immunosuppressive treatment	61 (91.0%)	15 (93.8%)	1.50 (0.20 – 11.4)	0.70
Corticosteroids	47 (70.1%)	14 (87.5%)	2.56 (0.58 – 11.3)	0.22
Non-steroid therapy	46 (68.7%)	9 (56.3%)	0.94 (0.32 – 2.73)	0.91
Antiarrhythmic drugs	30 (44.8%)	11 (68.8%)	2.27 (0.79 – 6.54)	0.13
ACE-inhibitors or ARBs	30 (44.8%)	8 (50.0%)	1.17 (0.43 – 3.13)	0.76
FDG PET/CT and CMR results				
Focal or focal on diffuse FDG uptake on PET/CT	52 (77.6%)	12 (75.0%)	0.90 (0.29 – 2.79)	0.85
LGE on CMR (n=77)	53 (84.1%) (n=63)	14 (100%) (n=14)	25.0 (0.03 – 21393)	0.35
Septal wall LGE	44 (69.8%)	13 (92.9%)	4.57 (0.60 – 34.9)	0.14
Lateral wall LGE	37 (58.7%)	12 (85.7%)	4.48 (0.98 – 20.5)	0.05
Inferior wall LGE	36 (57.1%)	12 (85.7%)	3.41 (0.76 – 15.3)	0.11
Anterior wall LGE	25 (39.7%)	10 (71.4%)	3.32 (1.04 – 10.6)	0.04
Right ventricular LGE	19 (30.2%)	11 (78.6%)	6.27 (1.74 – 22.5)	0.005

AVB = atrioventricular block; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CMR = cardiac magnetic resonance imaging; CS = cardiac sarcoidosis; ECS = extracardiac sarcoidosis; FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction

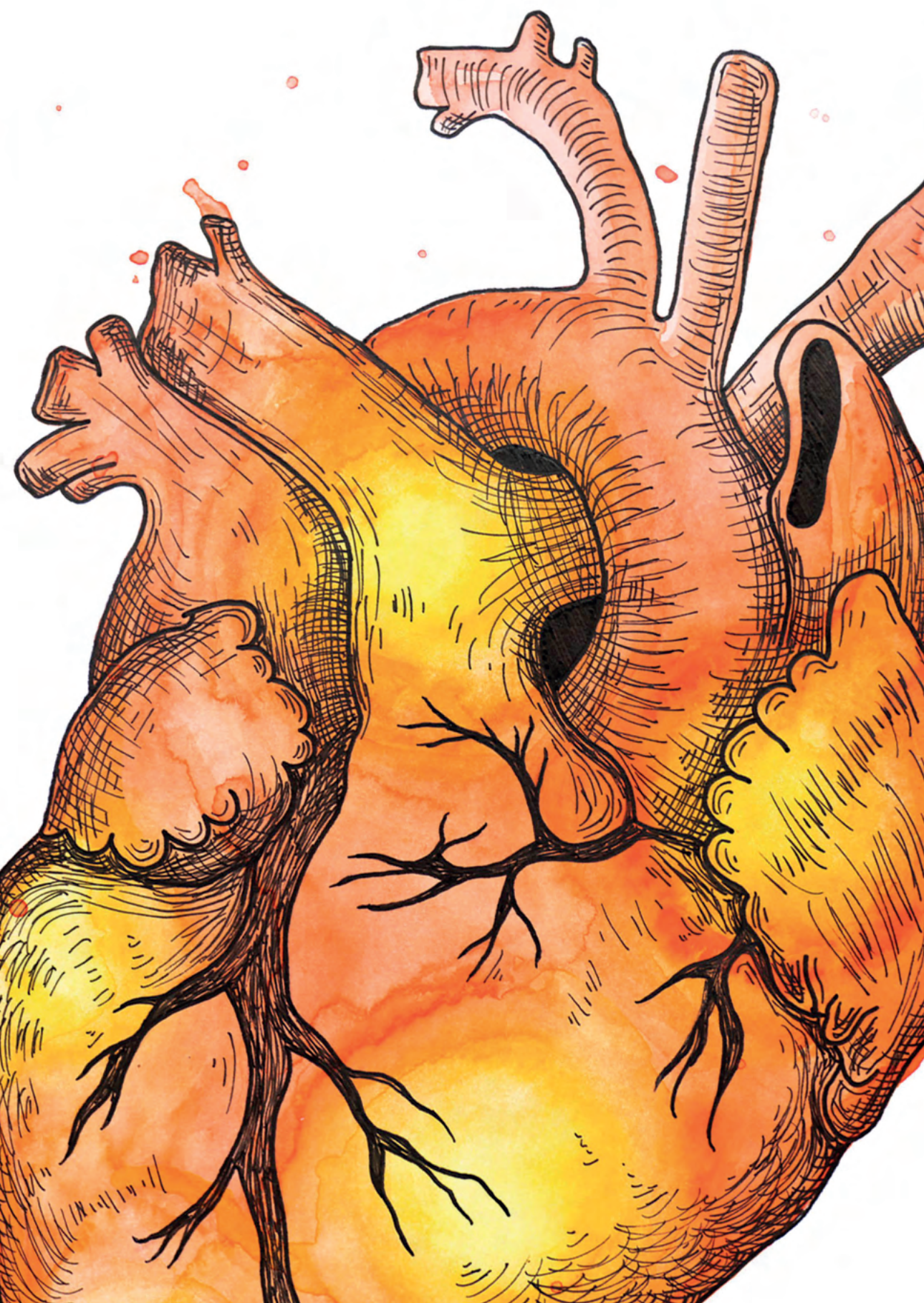
Supplementary figures



Supplementary figure 1. Kaplan-Meier curves showing all cause survival in the total population (n=105). Each vertical tick on the curves displays a censored patient.

PART C

SUMMARY AND GENERAL DISCUSSION



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SUMMARY AND GENERAL DISCUSSION

The research conducted in this thesis aimed to elaborate the current knowledge on both pulmonary hypertension (PH) and cardiac involvement in sarcoidosis. To properly treat patients afflicted with these diseases, one needs to have adequate knowledge of the underlying pathophysiology and diagnosis. Moreover, further insight in the prognosis of both disease entities is essential to compose treatment goals.

PART A

Sarcoidosis-associated pulmonary hypertension (SAPH) is most commonly due to destruction of pulmonary vasculature by fibrosis and subsequent hypoxemia. However, this cannot account for all. A variety of pathophysiologic mechanisms have been described that could impact treatment and prognosis.[1–5] Nonetheless, current data are of limited quality and more insight is warranted. **Chapter 2** describes a novel clinical phenotyping system of 40 SAPH patients after extensive assessment of different pathophysiological mechanisms including vascular compression and chronic pulmonary emboli.[6] Our study shows that post-capillary PH is uncommon (7.5%), while the parenchymal phenotype is most common (72.5%). Remarkably, there are large differences in pulmonary haemodynamics in this phenotype, despite a largely comparable pulmonary disease severity. This indicates that the difference in pulmonary haemodynamics is probably driven by the severity of the pulmonary vasculopathy. Unfortunately, it is very difficult to assess vasculopathy in patients with chronic lung disease, such as sarcoidosis, as the spectrum of severity of both the pulmonary vascular and parenchymal lung disease is most likely a continuum. There is a need for clear-cut diagnostic criteria to determine the dominant cause of PH in patients with parenchymal lung disease, because this might have therapeutic consequences. PH patients in World Health Organization (WHO) group I (pulmonary arterial hypertension e.g. vasculopathy) have an indication for treatment with PH-targeted therapies, while patients with chronic lung disease (WHO group III) do not.[7] Although, a recently published study did show a beneficial effect of PH-targeted therapies in patients with interstitial lung disease and PH.[8] Nevertheless, 21% of the included patients discontinued the trial prematurely, so careful patient selection is essential. Future studies should therefore focus on diagnostic criteria for vasculopathy, and their subsequent therapeutic and prognostic implications. For example, should a pulmonary vascular resistance >3.0 Wood Units be used as a surrogate for vasculopathy? Should these patients receive a trial treatment with PH-targeted therapies? Furthermore, are other haemodynamic parameters such as the pulmonary arterial compliance or the mean pulmonary artery pressure more meaningful?

Another important observation made in **chapter 2** is the very good clinical and haemodynamic response of immunosuppressive treatment in patients with compression of pulmonary vasculature by active inflammatory lung disease.[6] This suggests that PH in these patients could be (partially) reversible, which is a very important prognostic finding.[2,9] Whether patients with compression by fibrosis or calcified lymph nodes could benefit from interventional therapies like pulmonary arterial stenting[10,11], needs to be explored in future studies. A recently published World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) Task Force statement on SAPH recommended to identify a dominant cause for SAPH on an individual basis, as it is likely to have treatment implications.[12] Clinical phenotyping can be a first step towards identifying this dominant cause and towards personalized therapeutic decision-making.

Right ventricular (RV) dysfunction in sarcoidosis is associated with adverse outcomes and prevalence of PH, but its assessment by conventional transthoracic echocardiography (TTE) is challenging. **Chapter 3** explores the usage of the novel technique knowledge-based reconstruction (KBR) for imaging the right heart.[13] This technique was compared with the gold standard cardiac magnetic resonance imaging (CMR). There was a strong correlation with good agreement for RV end-diastolic volume, but poor agreement for the RV end-systolic volume, stroke volume, and ejection fraction. These findings are in contrast with the usage of TTE-KBR in congenital heart disease or PH populations.[14–16] Remarkably, the incongruity with the aforementioned studies could not be explained by the image quality, presence of PH nor time between TTE-KBR and CMR. Nonetheless, the usage of TTE-KBR in this population does not provide additional value over TTE or CMR. New technologies for the assessment of the RV such as 3D-echocardiography are highly anticipated.

Chapter 4 assesses the usage of the endothelin receptor antagonist (ERA) macitentan in a case-series of six SAPH patients.[17] Pulmonary haemodynamics and functional outcome improved in three, respectively four patients, while one patient had to stop therapy due to side-effects. Our results underline that some, but not all, SAPH patients might benefit from PH-targeted therapies. These therapies target underlying pulmonary vasculopathy via different pathways, but can worsen ventilation/perfusion mismatch in chronic lung disease patients, probably due to reduced physiologic vasoconstriction. Adverse results have been shown in earlier trials in pulmonary fibrosis populations using the ERAs ambrisentan and bosentan.[18,19] Therefore, caution is advised when treating SAPH patients with these therapies. Only patients with a suspected vasculopathy should be considered for a trial treatment on a case-by-case basis after multidisciplinary discussion, and only with close monitoring of side-effects and assessment of functional improvement. Current literature does not provide sufficient data to prefer one specific

therapy.[20–23] It must be noted that, as illustrated in chapter 2, PH-targeted therapies should be tailored, based on the specific mechanisms involved in the development of PH, the severity of PH, and the severity of the underlying parenchymal lung disease. Thus, better patient selection is necessary in order to determine which patients will benefit from PH-targeted therapies, and endeavours should be made to unveil why some patients do not. Furthermore, it is important to realize that no survival benefit of PH-targeted therapies has yet been established in SAPH.

Chapter 5 describes a 4-year survival of 94.6% in a large single-centre pulmonary sarcoidosis population[24], which was significantly better compared to previous studies.[2,25,26] The impact of SAPH on prognosis in pulmonary sarcoidosis patients has been described earlier, but mostly in small populations with more advanced disease. Our study was the first to perform prospective cardiac evaluation including extensive PH screening, showing a high PH probability on echocardiography as predictor for mortality with a hazard ratio of 8.7. Multivariate analysis could not be performed due to the low mortality rate. The cause of death was highly variable and one could argue whether SAPH patients are succumbing in the presence of PH or because of PH. The SAPH task force of the WASOG has argued the latter, which was partly based on two multi-regression analyses.[12,25,27] Therefore, extensive PH screening in sarcoidosis patients could prove to be beneficial for prognosis as early recognition can warrant treatment to prevent further deterioration.

Future directions

As SAPH is rare disease entity, both multidisciplinary collaboration and multicentre collaboration are imperative. As many different diagnostic modalities are used, multidisciplinary team meetings with pulmonologists, cardiologists and radiologists are necessary to establish diagnosis, to determine the underlying pathophysiology, and to optimize treatment. The ReSAPH registry is a first example of an international, multicentre collaboration between sarcoidosis expertise and PH expertise centres to create a large SAPH cohort.[26,28] This will lead to increased understanding regarding the epidemiology, pathophysiology, and prognosis of SAPH. In addition, this might facilitate multinational, placebo-controlled trials for PH-targeted therapies in sarcoidosis.

Furthermore, research is needed to optimize patient selection for right heart catheterisation. Conventional TTE plays a pivotal role in the screening of SAPH, but its utility in determining RV dimensions and function is limited. New techniques such as 3D echocardiography allow a more complete assessment of RV structural and regional abnormalities, but have not yet been investigated in SAPH.[29] Furthermore, RV strain analysis showed promising results in pulmonary arterial hypertension patients.[30,31] Future studies have to determine whether these new techniques correlate with right

heart catheterisation and CMR data, and whether these techniques can replace or complement conventional TTE in the screening for SAPH. After SAPH diagnosis, imaging results, haemodynamics, comorbidities, and functional status have to be integrated into (clinical) phenotypes, as described in chapter 2. Phenotyping can aid clinical trials to compose a tailored treatment for each patient, including immunosuppressive treatment, interventional therapies, and PH-targeted therapies.

PH-targeted therapies have shown promising results in small studies, but we are far behind in our knowledge compared to other PH groups such as pulmonary arterial hypertension. This is partly due to adverse results of trials in chronic lung disease patients and consequential hesitation to start PH-targeted therapies in SAPH patients. Hopefully, we can bridge this gap with the use of phenotyping. Better selection of patients with a suspected pulmonary vasculopathy is needed before new trials using PH-targeted therapies in SAPH are initiated. This might put an end to the discussion whether SAPH patients benefit from PH-targeted therapies. Moreover, future trial end-points should incorporate patient-related outcome measurements. The recently published WASOG task force statement is a first step towards unifying the international sarcoidosis community regarding the screening, diagnosis, and treatment of SAPH.[12]

PART B

Since its first description in 1929, many questions remain regarding the diagnosis, treatment, and prognosis of cardiac sarcoidosis (CS). Its diagnosis is often based on the presence of extracardiac granulomas on biopsy combined with clinical or imaging results suggestive of CS. However, artefacts, interpretation bias, and the experience of the assessing physician impair imaging results. Therefore, in some patients the diagnosis of CS can neither be confirmed nor excluded and is deemed 'possible'. In **chapter 6** the repeated usage of advanced cardiac imaging with CMR and fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) is assessed in patients with possible CS.[32] In 25 of 35 patients (71.4%) a CS diagnosis could be established or rejected after repeated imaging. Remarkably, two patients showed new late gadolinium enhancement (LGE) on CMR at re-evaluation, while no LGE on CMR was seen at baseline. Both patients did show focal cardiac FDG-uptake at baseline and were treated with immunosuppressive therapies for extracardiac sarcoidosis. Some studies and reviews have recommended CMR as primary diagnostic tool for CS and limited the usage of FDG PET/CT to patients with established LGE, to determine myocardial inflammation.[33–35] In contrast, our findings imply that CMR alone is not sufficient to fully exclude the diagnosis of CS. Future research should further elaborate the diagnostic and prognostic

value of FDG-uptake in the absence of LGE. We observed a large number of FDG PET/CT scans with diffuse uptake at baseline due to inadequate suppression of physiological myocardial uptake. We should create awareness that in these patients, only FDG PET/CT should be repeated with adequate dietary preparation, as none of these patients showed LGE at repeated CMR. This thesis illustrates that adequate dietary preparation is of the utmost importance in all sarcoidosis patients undergoing FDG PET/CT. Unfortunately, physiologic myocardial FDG-uptake does not entail diffuse FDG-uptake only as lateral wall uptake can also be seen[36–38], which is shown in chapter 6. Besides, LGE can be seen in many different cardiac diseases such as hypertrophic cardiomyopathy, ischemic cardiomyopathy, and myocarditis.[33,39] Thus, both imaging modalities complement each other and have to be used in conjunction and not in separation. Furthermore, it is of incremental value to discuss and diagnose patients in a multidisciplinary team setting with experience in diagnosing and treating CS. One should be very careful to diagnose CS in the absence of such a team and should refer patients to an expertise centre.

The treatment of CS is evaluated in **chapters 7** and **8.** In **chapter 7**, prednisone monotherapy, methotrexate monotherapy, and prednisone / methotrexate combination therapy are compared. These therapies are considered first- and second line treatment for sarcoidosis and both resulted in a significant decrease in myocardial FDG-uptake, while the prevalence of adverse cardiac events was comparable. There was a trend towards a larger myocardial FDG-uptake reduction in the combination therapy group, although numbers were small. In contrast with other CS expertise centres, methotrexate monotherapy has been frequently used in the St. Antonius hospital for the treatment of (low-risk) CS patients. This has been debated, as some experts believe that one should strike 'hard and fast' with prednisone to establish adequate suppression of myocardial granulomatous inflammation.[33,40,41] However, long-term prednisone treatment has a large number of side-effects, which increase with a higher cumulative dosage.[42] It has already been shown that a starting dosage >40mg/day does not provide additional value over a starting dosage <40mg/day.[43] Furthermore, there has been increasing attention to the usage of second line therapies as steroid-sparing strategy.[44–46] It is unclear whether these therapies should be started simultaneously, or separately after first reassessment with FDG PET/CT. Our study shows that it is safe to start methotrexate simultaneously with prednisone and we report a shift from prednisone therapy towards methotrexate monotherapy after 24 months. Notwithstanding these results, the usage of methotrexate monotherapy should be limited to patients with preserved left ventricular function (LVF) without any severe arrhythmias. In patients with impaired LVF, severe conduction disorders or ventricular arrhythmias (VA), corticosteroids are essential for an immediate anti-inflammatory response and the benefits will outweigh the potential side-effects.

Future, randomised, controlled trials are necessary to confirm our findings and the results of the CHASM-RCT are highly anticipated.[47]

In patients with refractory disease, with persistent cardiac FDG-uptake or with severe side-effects, third line therapies should be considered. One of these third line therapies is the TNF-alpha inhibitor infliximab, which is assessed in **chapter 8**.[48] Overall, infliximab was well tolerated and 82% of patients were considered a responder to therapy. Also, 9% showed stable disease, which can be an acceptable treatment goal after failure of multiple immunosuppressive agents. The usage of infliximab in CS patients is controversial due to a warning of the American Food and Drug Administration (FDA). Based on the 2003 ATTACH trial by Chung et al. the usage of infliximab >5mg/kg in heart failure patients was strongly discouraged by the FDA.[49] However, this study predominantly included patients with ischemic heart disease in whom an inflammatory pathophysiology is not the dominant cause of heart failure, in contrast to CS patients. Our study adds to the growing body of evidence that infliximab is safe and effective in refractory CS patients to stabilize or improve disease activity.[50,51] On the other hand, attention should be paid to the optimal dosage, especially in patients with heart failure or with little inflammatory activity.

The last two chapters of this thesis report the prognostic outcomes of implantable loop recorders (ILR) and implantable cardioverter defibrillators (ICD) in CS patients. In **chapter 9,** long-term arrhythmia monitoring was conducted in a predominantly low-risk population using both ICD and ILRs.[52] Remarkably, none of the 80 low-risk patients with an ILR showed sudden cardiac death or sustained VA. Nine low-risk patients received an upgrade to an ICD during follow-up, mostly due to non-sustained VA, but none of them received appropriate ICD therapy. Furthermore, 91% of all patients showed LGE on CMR at baseline, which has been associated with poor outcomes in previous studies.[53–55] This is the first study to describe the usage of ILR for long-term arrhythmia monitoring in CS and overall, the diagnostic impact of monitoring with ILR seems very good, but no impact was seen on prognosis. Nevertheless, our study showed some very valuable information. First, not all patients with LGE on CMR are at high risk for VA during follow-up. Second, non-sustained VA is not necessarily a precursor of sustained VA. Finally, ILR implantation should not be recommended in all low-risk CS patients. We have to be aware that our results are limited by the fact that only patients without overt cardiac symptoms were included.

In **chapter 10** a large group of CS patients who received an ICD for primary or secondary prevention is examined.[56] A very high rate of appropriate ICD therapy was observed, ranging from 19.3% in the primary prevention group to 81.8% in the secondary prevention

group. RV LGE and prior VA were independent predictors for appropriate ICD therapy. RV LGE was the only independent predictor in the primary prevention group. In contrast to previous studies, LVF did not predict appropriate ICD therapy and we found a very low rate of inappropriate shocks.[57,58] These findings illustrate the pivotal role of LGE in the occurrence of VA, as all patients who received appropriate therapy had LGE on CMR. Not all patients with LGE, however, are at risk for VA, as chapter 9 makes abundantly clear. So LGE needs to be further assessed, but how? Some propose to assess the extent of LGE, as is the clinical standard in hypertrophic cardiomyopathy.[59–62] However, CS is an active disease with flare-ups and it is difficult to distinguish inflammation and fibrosis with CMR. Moreover, up to now no robust and reliable method is available to assess this extent in CS patients. Could the localisation of LGE be the answer? Our results add to the increasing evidence that RV LGE is associated with adverse events in CS, even after adjustment for other factors like LVF or FDG-uptake. Perhaps certain LGE patterns (unifocal or multifocal, endocardial or epicardial involvement) are associated with better outcomes, which should be assessed in future studies. In conclusion, the decision to implant an ICD should not be taken lightly, given the fact that 18.1% of patients had a device related complication. So risk stratification is crucial and clinical status, electrocardiography, echocardiography, FDG PET/CT, and CMR results have to be incorporated. Furthermore, the decision to implant an ICD should be made in a multidisciplinary setting and the pros and cons should be discussed with each patient individually.

Future directions

As mentioned before, many questions remain unanswered regarding the treatment and prognosis of CS, since its first description in 1929. The optimal treatment strategy has not been found yet and the rate of adverse events during follow-up varies greatly between CS patients. Thus, risk stratification is essential. By using risk stratification, the treatment of CS patients with immunosuppressives, heart failure therapies, antiarrhythmics, and device therapy can be tailored. Our results have shown the presence of a ‘low-risk’ group in whom an ICD is not recommended. This group is characterized by the absence of severe arrhythmias or conduction disorders at baseline, a preserved LVF, and no or little LGE on CMR. The question remains whether these patients require corticosteroid therapy, heart failure therapy, or antiarrhythmic drugs. As shown in chapter 9, the implantation of an ILR or ICD in this population is also not recommended. Moreover, patients with prior VA, 2nd or 3rd degree AV-block, severely impaired LVF, or RV involvement (on CMR or FDG PET/CT) should be considered ‘high-risk’, as shown in chapter 10. ‘High risk’ patients should be treated with corticosteroids, heart failure therapy, antiarrhythmic drugs, and of course an ICD. However, there is also a group of patients who do not fulfil the criteria for either ‘low risk’ or ‘high risk’ and this group can be considered ‘intermediate risk’. For example, should patients with non-sustained VA receive an ICD? Or patients with

less severe conduction disorders such as a first-degree AV-block or left bundle branch block? Do these patients require corticosteroid treatment or will methotrexate therapy suffice? Ideally, this thesis would have provided an answer to these questions, but future research is necessary. Perhaps ILR can be meaningful in monitoring this 'intermediate risk' population. Also, LGE will play a pivotal role in the risk stratification of these 'intermediate risk' patients and the presence and extent of LGE should be further specified. Larger trials are necessary and (inter)national collaboration is imperative.

Complete suppression of myocardial inflammation is still seen as the therapeutic goal in all CS patients. However, the burden of immunosuppressive treatment can outweigh its benefits. Is complete remission of cardiac FDG-uptake necessary to achieve better clinical outcomes? Or is stabilization of cardiac inflammation sufficient to prevent future adverse events? The role of (second-line) immunosuppressive therapies as 'cardioprotective medicine' should be elaborated in future research. It is important to realize that cardiac FDG-uptake is not a surrogate for heart failure or arrhythmias. We also have to be aware that baseline characteristics such as extensive LGE and prevalence of VA are better predictors of adverse events than myocardial FDG-uptake or remission of FDG-uptake, as is shown in chapters 7, 9, and 10. Therefore, one might speculate whether prevention of extensive LGE should be the treatment goal as extensive LGE is associated with adverse outcomes?[53,55] However, it is challenging to assess LGE in patients with an ICD due to artefacts. Finally, as in SAPH, patient-related outcome measurements need to be assessed in future studies regarding the treatment of CS. As (cardiac) sarcoidosis is a chronic disease, the effects of long-term immunosuppressive therapies on daily activities and associating side-effects have to be examined. The optimal treatment for CS is likely not a one-size-fits-all solution.

CONCLUDING REMARKS

In conclusion, all the aspects mentioned above show the complexity of both SAPH and CS, the heterogeneity of the populations, and the need for multidisciplinary and specialised care. Clinicians should be aware of the diverse underlying pathophysiological mechanisms of SAPH and subsequent prognosis and treatment options. In CS, advanced cardiac imaging and again multidisciplinary discussion is crucial for adequate diagnosis. The optimal medical therapy of CS is still not determined, but immunosuppressive treatment should be initiated in symptomatic patients and should be considered in patients with cardiac inflammation. Finally, risk stratification has to be performed in each CS patient incorporating clinical status and different diagnostic / imaging results. Hopefully, further investigations and global collaboration will lift SAPH and CS treatment towards evidence based and personalised medicine.

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PART D

APPENDIX

NEDERLANDSE SAMENVATTING

Sarcoïdose is een systeemziekte van onbekende oorzaak. De ziekte wordt gekenmerkt door ophopingen van ontstekingscellen in de organen, ook wel granulomen genoemd. Deze kunnen in alle organen in het lichaam voorkomen, maar ontstaan vooral in de longen ('pulmonale sarcoïdose') en de lymfeklieren. De oorzaak van sarcoïdose is tot op heden onbekend, maar men denkt dat de oorzaak een combinatie van erfelijke- en omgevingsfactoren is. Sarcoïdose komt voornamelijk voor bij patiënten tussen de 25 en 60 jaar. De ziekte is vaak zelflimiterend en verdwijnt in de meeste patiënten spontaan binnen 2 tot 5 jaar. Echter bij een deel van de patiënten is er sprake van progressie en kan verlittekening van het longweefsel ontstaan, oftewel longfibrose. Bij deze patiënten moet er vaak worden gestart met medicijnen die het immuunsysteem onderdrukken, zogenaamde immunosuppressiva. Het falen van het ademhalingssysteem door ernstige longfibrose is de meest voorkomende doodsoorzaak bij sarcoïdosepatiënten.

DEEL A: SARCOÏDOSE GEASSOCIEERDE PULMONALE HYPERTENSIE

Het eerste deel van dit proefschrift (**deel A**) gaat over sarcoïdose-geassocieerde pulmonale hypertensie (SAPH). Bij patiënten met ernstige vormen van sarcoïdose, met name in de longen, kan er sprake zijn van een verhoogde bloeddruk in de longslagader, ook wel pulmonale hypertensie (PH) genoemd. Dit is een ernstige complicatie met een hoger risico op sterfte en afname van de levenskwaliteit. PH komt voor in 3 tot 21% van de sarcoïdosepatiënten en wordt momenteel gedefinieerd als een gemiddelde bloeddruk ≥25mmHg gemeten in de longslagader via een rechterhart katheterisatie. De eerste casus van SAPH werd al in 1949 beschreven, maar nog altijd is er veel onbekend over dit ziektebeeld. SAPH wordt veroorzaakt door meerdere mechanismen, maar ernstige longschade door fibrose en daarbij horend zuurstofgebrek is het meest voorkomend. SAPH komt echter ook voor bij patiënten zonder ernstige longschade. Er zijn ook andere mechanismen als oorzaak van de PH beschreven zoals linkszijdig hartfalen, longembolieën en uitwendige compressie van de longslagader. Het is belangrijk om het achterliggende mechanisme van SAPH vast te stellen, omdat dit van invloed kan zijn op de verdere behandeling en de prognose. Bij patiënten met het vermoeden op PH wordt een echocardiogram verricht. Bij dit echocardiogram wordt gekeken of er sprake is van een verhoogde systolische druk in de rechterhartkamer. Dit is geassocieerd met een hoger risico op PH. De reden om sarcoïdosepatiënten te screenen op aanwezigheid van PH is erg divers en loopt uiteen van symptomen van benauwdheid of flauwvallen tot afwijkende bloeduitslagen, longfunctietesten of CT-scan van de longen. Zodra de PH diagnose is gesteld, moet worden nagedacht over de behandeling. De meeste studies die

de behandeling van SAPH hebben onderzocht zijn kleine retrospectieve studies en de resultaten kunnen niet zomaar op de hele SAPH populatie worden toegepast. Mogelijke behandelingen zijn immunosuppressiva, PH-specifieke medicatie en endovasculaire stenting. PH-specifieke medicatie heeft bewezen effect bij andere PH-populaties (zoals pulmonale arteriële hypertensie), maar het effect bij patiënten met PH en ernstig longlijden (zoals longfibrose of COPD) is wisselend. Daarom kunnen deze therapieën niet zomaar worden gestart bij patiënten met sarcoïdose en is een goede patiëntenselectie belangrijk.

Zoals gezegd is de achterliggende oorzaak van SAPH erg divers en zijn er verschillende mechanismen waardoor PH kan ontstaan. In **hoofdstuk 2** wordt het gebruik van klinisch fenotyperen in een SAPH populatie onderzocht. Patiënten werden onderverdeeld in fenotypes op basis van het (vermoedelijke) onderliggende mechanisme van de PH. In drie patiënten was er sprake van PH door linkszijdig hartfalen, ook wel post-capillaire PH genoemd. De overige patiënten hadden pre-capillaire PH en hiervan waren 29 patiënten ingedeeld in het 'parenchymaal fenotype' waarbij het longlijden (voornamelijk longfibrose) de PH veroorzaakt. Andere fenotypes waren 'vasculopathie', 'chronische longembolieën' en 'compressie van de longslagader'. Fenotyperen is een eerste stap naar een geïndividualiseerde behandeling van SAPH patiënten.

Het slechter functioneren van de rechterhartkamer bij sarcoïdosepatiënten is geassocieerd met slechtere uitkomsten en een hogere kans op PH. In **hoofdstuk 3** wordt een nieuwe echocardiografie techniek geëvalueerd in pulmonale sarcoïdosepatiënten. Deze techniek genaamd 'knowledge based reconstruction' werd gebruikt in aanvulling op het standaard echocardiogram voor het bepalen van de afmetingen en functie van de rechterkamer. Dit werd vergeleken met de gouden standaard: de cardiale MRI. Helaas was er alleen sprake van een goede overeenkomst met de MRI voor het eind-diastolisch volume van de rechterkamer, terwijl de andere waarden (eind-systolisch volume, slagvolume en ejectiefractie) niet goed overeenkwamen. Deze nieuwe techniek lijkt dus niet bruikbaar in pulmonale sarcoïdosepatiënten voor het bepalen van de afmetingen en functie van de rechterhartkamer.

Hoofdstuk 4 beschrijft het gebruik van de endotheline receptor antagonist macitentan in een case-series van zes patiënten met SAPH. Dit medicijn wordt succesvol gebruikt voor de behandeling van patiënten met pulmonale arteriële hypertensie, maar het gebruik was nog niet eerder beschreven in SAPH patiënten. Van de zes behandelde patienten toonden er vier een verbetering van hun functionele status, terwijl drie patiënten een verbetering lieten zien van de bloeddruk in de longslagader. Eén patiënt moest de behandeling na enkele dagen staken vanwege bijwerkingen, de andere vijf patiënten

konden de therapie voortzetten. Macitentan lijkt dus veilig en is misschien effectief in een geselecteerde populatie SAPH-patiënten, maar verder (gerandomiseerd) onderzoek is noodzakelijk.

In **hoofdstuk 5** wordt de overleving beschreven van een grote populatie pulmonale sarcoïdosepatiënten die middels een echocardiogram werden gescreend op PH. In totaal werden 399 patiënten gevolgd en de 4-jaars overleving was 96%. De oorzaak van overlijden was erg divers, maar het falen van het ademhalingsstelsel was de meest voorkomende doodsoorzaak. Uit analyse blijkt dat een verhoogde kans op PH op basis van het echocardiogram, en een verhoogde systolische druk in de rechterhartkamer, allebei geassocieerd zijn met een hoger risico op overlijden. Ook patiënten met ernstige vormen van longlijden (bijv. meer longfibrose) hadden een hoger risico op overlijden. Screening op pulmonale hypertensie leidt hopelijk tot een vroege behandeling en daarmee een verbetering van de prognose.

DEEL B: CARDIALE SARCOÏDOSE

In **deel B** van dit proefschrift wordt verder ingegaan op cardiale sarcoïdose (CS), oftewel sarcoïdose in het hart. Cardiale betrokkenheid is een belangrijke doodsoorzaak in sarcoïdosepatiënten. Het komt voor in 5 tot 20% van de sarcoïdosepatiënten en kan leiden tot levensbedreigende geleidingsstoornissen, ritmestoornissen en hartfalen. Door de granulomen in het hart ontstaat littekenweefsel (fibrose) en de klachten van CS hangen sterk af van de locatie en de ernst van deze fibrose. Het stellen van de diagnose CS is moeilijk doordat de granulomen in het hart alleen aangetoond kunnen worden via een hartbiopt. Deze procedure heeft een laag slagingspercentage en hoog risico op complicaties. De diagnose wordt daarom vaak gesteld op basis van de aanwezigheid van granulomen in andere organen in combinatie met tekenen van CS, zoals klachten of afwijkende beeldvorming. De patiënten met een verdenking op CS kunnen worden onderverdeeld in twee groepen: 1) patiënten met bekende sarcoïdose buiten het hart die worden gescreend vanwege klachten of andere tekenen van CS, en 2) patiënten die zich presenteren met ernstige cardiale klachten zoals ritme- of geleidingsstoornissen, waarbij CS de eerste uiting is van de ziekte sarcoïdose.

Bij de diagnose van CS zijn twee onderzoeken belangrijk: de cardiale MRI en fluorodeoxyglucose positron emissie tomografie (FDG PET). Bij de cardiale MRI wordt gekeken naar de aanwezigheid van ‘late gadolinium enhancement’ (LGE). De aanwezigheid hiervan in het hart kan namelijk wijzen op ontsteking of fibrose. De FDG PET is een nucleair onderzoek waarbij de opname van radioactief gelabeld glucose een aanwijzing is voor

een actieve ontsteking. Het nadeel van dit laatste onderzoek is dat een voorbereiding middels een uitgebreid dieet noodzakelijk is om de natuurlijke opname van glucose in het hart te onderdrukken.

De behandeling van CS bestaat uit immunosuppressiva en eventueel medicatie voor hartfalen en/of ritmestoornissen. Helaas zijn veel studies die de behandeling van CS hebben onderzocht erg kleinschalig. Het is gebruikelijk om immunosuppressiva te starten in symptomatische patiënten met tekenen van actieve ontsteking in het hart op basis van de FDG PET. Echter, er is minder bekend over de behandeling van asymptomatische patiënten met een actieve ontsteking. Corticosteroïden, zoals prednison, worden gezien als de eerste stap van de behandeling, gevolgd door methotrexaat en azathioprine als tweedelijnsbehandeling. In patiënten waarbij eerdere therapie onvoldoende heeft gewerkt of bij patiënten met veel bijwerkingen, wordt steeds vaker gestart met derdelijnsbehandelingen zoals het medicijn infliximab. De beste strategie om CS te behandelen is tot op heden niet duidelijk.

Omdat CS patiënten een hoger risico hebben op levensbedreigende ritme- en geleidingstoornissen, krijgt een deel van de patiënten (preventief) een ICD geïmplanteerd. Dit is een implanteerbare cardioverter defibrillator, oftewel een apparaat dat bij levensbedreigende ritmestoornissen kan ingrijpen met een schok of door te 'pacen'. Het plaatsen of hebben van een ICD is niet zonder risico, waardoor het belangrijk is om de juiste patiënten hiervoor te selecteren. Helaas is het niet geheel duidelijk welke patiënten hier nu het meeste baat bij hebben. Patiënten met eerdere levensbedreigende ritmestoornissen hebben al een indicatie voor een ICD, maar het voorspellen welke patiënten een dergelijke ritmestoornis krijgen is moeilijk. Uit eerdere studies blijkt dat de eerder genoemde LGE op de cardiale MRI een rol speelt, maar ook een relatie met de pompfunctie van de linkerhartkamer is beschreven. Het is dus belangrijk om voor iedere CS-patiënt het individuele risico in te schatten.

Hoofdstuk 6 evalueert het gebruik van herhaalde MRI en FDG PET in patiënten met een 'mogelijke' CS diagnose. Dit zijn patiënten bij wie een CS diagnose zowel niet aangetoond als uitgesloten kon worden. Na gemiddeld 6 maanden werd een nieuwe MRI en FDG PET verricht en in 71.4% van de patiënten kon de diagnose worden aangetoond of uitgesloten. Opvallend was dat drie patiënten alleen bij de tweede MRI fibrose hadden in het hart, terwijl er wel FDG-opname was op de eerste FDG PET. Mogelijk dat de ontsteking bij deze patiënten heeft geleid tot fibrose, wat te zien was op de MRI. Verder had geen van de patiënten met een diffuse opname van FDG in het hart bij de tweede MRI tekenen van fibrose. Het herhalen van de MRI en FDG PET lijkt dus nuttig in het uitsluiten of aantonen van CS bij een initiële onzekere diagnose.

In **hoofdstuk 7** wordt de behandeling van CS door middel van immunosuppressiva onderzocht. Prednison is normaliter de eerste lijn van de behandeling, maar geeft veel bijwerkingen. Methotrexaat wordt beschouwd als de tweedelijns behandeling, maar het gebruik hiervan als monotherapie voor CS is internationaal niet gebruikelijk. In deze studie werden drie behandelingen met elkaar vergeleken in 61 patiënten: prednison monotherapie, methotrexaat monotherapie en prednison + methotrexaat combinatietherapie. Alle behandelingen leidden tot afname van de ontstekingsactiviteit in het hart na gemiddeld 6 maanden (gemeten via de cardiale FDG-opname op de FDG PET). Het optreden van ernstige complicaties tijdens de follow-up was laag en vergelijkbaar tussen de groepen. Verder viel het op dat het merendeel van alle patiënten na 24 maanden werd behandeld met methotrexaat monotherapie. Concluderend zijn alle drie de behandelingen effectief in het verminderen van de cardiale ontstekingsactiviteit door sarcoïdose en zijn er geen significante verschillen in het ontstaan van ernstige adverse events.

Hoofdstuk 8 beschrijft het gebruik van het derdelijnsmiddel infliximab. Dit is een TNF-alfa remmer en wordt al gebruikt in de behandeling van andere vormen van sarcoïdose. In 22 CS patiënten die onvoldoende reageerden op eerdere behandelingen of last hadden van ernstige bijwerkingen werd gestart met infliximab. Na een gemiddelde behandelduur van 19 maanden reageerde 82% van de patiënten goed op de therapie. Dit bleek uit: afname van de dosering van andere immunosuppressiva (n=5), afname van ontstekingsactiviteit op de FDG PET (n=16), verbetering van de pompfunctie van het hart (n=4) of door verbetering van de functionele status (n=2). Zes patiënten (27.3%) hadden last van bijwerkingen, waardoor drie patiënten (13.6%) de behandeling moesten staken. Geen enkele patiënt had toename van hartfalen. In deze kleinschalige studie was infliximab dus effectief in het onderdrukken van de ontstekingsactiviteit én in het verbeteren van de pompfunctie van het hart.

In **hoofdstuk 9** wordt het risico op levensbedreigende kamerritmestoornissen geëvalueerd in een grote populatie CS patiënten. Hierbij wordt gebruik gemaakt van monitoring door ICD's (in hoog-risicopatiënten) en implanteerbare looprecorders (in laag-risicopatiënten). In de 80 patiënten met een looprecorder werden geen langdurige kamerritmestoornissen of acute hartdood geobserveerd. Wel kregen 9 patiënten een upgrade naar een ICD, voornamelijk vanwege kortdurende kamerritmestoornissen. Geen van deze 9 patiënten kreeg terechte ICD therapie tijdens de follow-up. Daarentegen kregen 4 van de 17 patiënten met initieel een ICD een terechte behandeling via deze ICD voor een kamerritmestoornis. Patiënten met een geschat laag risico hebben dus daadwerkelijk ook een lage kans op langdurige kamerritmestoornissen en looprecorders zijn nuttig in het vroegtijdig detecteren van deze ritmestoornissen. Er lijkt echter geen effect te zijn

wat betreft de prognose, want in geen enkele patiënt met een ICD upgrade heeft de ICD moeten ingrijpen in een later stadium.

In het laatste hoofdstuk, **hoofdstuk 10**, werd de veiligheid en effectiviteit van ICD's in CS patiënten beschreven. In totaal kregen 105 patiënten een ICD, hiervan had 21% al eerder een levensbedreigende kamerritmestoornis gehad (secundaire preventie groep). Na gemiddeld 2.8 jaar follow-up, hadden maar liefst 34 patiënten (32.4%) terechte ICD therapie gehad vanwege een kamerritmestoornis. Tevens hadden 24 patiënten (22.9%) ook een ICD schok gehad. Drie patiënten kregen een onterechte ICD schok i.v.m. boezemfibrilleren. Patiënten met een ICD voor secundaire preventie hadden een significant hoger risico op terechte ICD therapie dan patiënten met een ICD in het kader van primaire preventie. Onafhankelijke voorspellers voor terechte ICD therapie zijn: fibrose en/of ontsteking in de rechterkamer op de MRI en eerdere kamerritmestoornissen. In de primaire preventiegroep was alleen fibrose in de rechterkamer op de MRI een onafhankelijke voorspeller voor terechte ICD therapie.

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Lydwien en Lars, ik vergeet nooit dat ik vlak na de start van m'n PhD aan jullie mocht gaan uitleggen wat ik nou eigenlijk aan het onderzoeken was. De regels waren simpel: iedere onnodige medische term was een shotje en als het te lang duurde om alles uit te leggen, gingen jullie wat anders doen. Zussie, ik denk dat heel veel broers en zussen jaloers zijn op de band die wij hebben en de hoeveelheid dingen die we samen doen. Onze band is de afgelopen jaren alleen maar sterker geworden en nu je eindelijk weer terug bent uit de USA kunnen we nog meer gaan doen. Ik prijs mezelf gelukkig dat ik je altijd kan bellen, no matter what. Thanks voor al je steun!

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was. Dit maakte je niets uit, want je vierde alle successen mee en stimuleerde me om door te zetten in moeilijke tijden. Je brengt me tot rust als ik weer eens hyperactief thuis kom en je weet me altijd weer te verassen met je creativiteit. Hoe geweldig is het dat je de kaft van mijn proefschrift hebt ontworpen. Lieverd, je bent mijn steun en toeverlaat en we kunnen altijd bij elkaar terecht. De afgelopen jaren zijn voorbij gevlogen en samen kunnen we nog zoveel nieuws ontdekken. Dus, wat gaan we morgen doen?

CURRICULUM VITAE / ABOUT THE AUTHOR

Harold Mathijssen was born on the 16th of July 1994 in Veenendaal, the Netherlands. He attended high school at the Rembrandt College in Veenendaal and graduated with distinction in 2012. In the same year he started his medical training at Maastricht University. During his medical training he became increasingly interested in the field of Cardiology. Therefore, he did an elective rotation at the St. Antonius Hospital in Nieuwegein during his final year. There, he discovered his fascination for the field of pulmonary hypertension and sarcoidosis and came into contact with prof. dr. Marco Post. After obtaining his medical degree with distinction, he started with a combined clinical and PhD trajectory at the St. Antonius Hospital under supervision of dr. J.J. Mager, dr. F. Akdim, prof. dr. J.C. Grutters and prof. dr. M.C. Post. The results of this PhD trajectory are presented in this thesis. In April 2022, he started his residency in Cardiology (AIOS) at the St. Antonius Hospital under supervision of dr. M.C.E.F. Wijffels. He's is currently working at the department of Internal Medicine under supervision of dr. P.C. de Jong.