Delayed-Enhanced Cardiovascular Magnetic Resonance in the diagnosis and management of Cardiac Sarcoidosis

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**Delayed-Enhanced Cardiovascular
Magnetic Resonance in the diagnosis and
management of Cardiac Sarcoidosis**

Jan-Peter Smedema

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Delayed-Enhanced Cardiovascular Magnetic Resonance in the diagnosis and management of Cardiac Sarcoidosis

Proefschrift/Dissertation

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert,
volgens het besluit van het college van Decanen,
in het openbaar te verdedigen op
donderdag 4 juli 2019 om 12.00 uur

to obtain the degree of Doctor at the University of Maastricht,
under the authority of the Rector Magnificus Prof. dr. Rianne M. Letschert,
according to the decision of the College of Deans,
to defend in public on Thursday, July 4, 2019 at noon.

door/by

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This dissertation is dedicated to Mrs. Specilene Francis, the first patient with cardiac sarcoidosis I encountered in Cape Town (1998). She presented with sustained monomorphic ventricular tachycardias, which originated from the lateral left ventricle. Delayed contrast-enhanced cardiovascular magnetic resonance revealed extensive patchy granulomatous infiltration and focal scar (19% of left ventricular mass), with involvement of the posterolateral papillary muscle resulting in severe eccentric mitral regurgitation. Her condition has remained stable on maximal medical treatment which initially included immune suppressive agents. A Cardioverter Defibrillator was implanted. After an initial electrical storm, she has remained free from sustained arrhythmias, device therapy and hospital admission. Specilene enjoys an active life with her husband of 37 years.

Follow up transthoracic echocardiography in mrs Francis (2005) demonstrated severe eccentric mitral regurgitation (panel A: 4 chamber view, arrow), secondary to papillary muscle dysfunction; tissue Doppler sampling of the longitudinal strain reveals normal deformation at the level of the lateral mitral annulus *, but impaired deformation of the basal $\circ$ and mid lateral $\diamond$ left ventricular segments, (panels B and C: respectively graphical and curved linear MMode representation); delayed contrast-enhanced cardiovascular magnetic resonance confirms the presence of extensive scarring of the mentioned segments (panel D: DECMR 4 chamber view, left sided arrow – contrast enhanced papillary muscle, right sided arrow – partly subendocardial, partly transmural lateral wall contrast enhancement i.e. myocardial scar tissue). (Smedema JP. Tissue Doppler Imaging in cardiac sarcoidosis. Eur J Echocard 2008;9:579-580. doi: 10.1093/ejchocard/jen073.)

Contents

Chapter 1	Introduction	9
Chapter 2	Review - Contrast-enhanced magnetic resonance in the diagnosis and management of cardiac sarcoidosis (submitted in abbreviated form)	11
Chapter 3	Cardiac involvement in patients with pulmonary sarcoidosis assessed at two University Medical Centres in The Netherlands (Smedema JP, Snoep G, van Kroonenburgh MPG, van Geuns RJ, Dassen WRM, Gorgels AP, Crijns HJGM. <i>Chest</i> 2005;128(1):30-5. doi: 10.1378/chest.128.1.30.)	97
Chapter 4	The additional value of gadolinium enhanced magnetic resonance imaging to standard assessment for cardiac involvement in patients with pulmonary sarcoidosis (Smedema JP, Snoep G, van Kroonenburgh MPG, Gorgels APM, Crijns HJGM. <i>Chest</i> 2005;128(3):1623-1628. doi: 10.1378/chest.128.3.1629.)	111
Chapter 5	Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis (Smedema JP, Snoep G, van Kroonenburgh MJPG, van Geuns RJ, Dassen WRM, Gorgels AP, Crijns HJGM. <i>J Am Coll Cardiol</i> 2005;45(10):1683-1690. doi: 10.1016/j.jacc.2005.01.047.)	129
Chapter 6	Contrast-Enhanced Cardiac Magnetic Resonance: Distinction between cardiac sarcoidosis and infarction scar (Smedema JP, van Geuns RJ, Truter R, Mayosi BM, Crijns HJGM. <i>Sarc Vasc Diff Lung Dis</i> 2017;34:307-314. http://www.mattioli1885journals.com/index.php/sarcoidosis/article/view/5715 .)	147
Chapter 7	Right ventricular involvement in cardiac sarcoidosis demonstrated with cardiac magnetic resonance (Smedema JP, van Geuns RJ, Ector J, Heidbuchel H, Ainslie G, Crijns HJGM. <i>ESC Heart Failure</i> 2017;4(4):535-544. doi: 10.1002/ehf2.12166.)	161

Chapter 8	Right ventricular involvement and the extent of left ventricular enhancement with magnetic resonance predict adverse outcome in pulmonary sarcoidosis <i>(Smedema JP, van Geuns RJ, Ector J, Heidbuchel H, Ainslie G, Crijns HJGM. ESC Heart Failure 2018;5(1):157-171. doi: 10.1002/ehf2.12201.)</i>	185
Chapter 9	General discussion	215
Chapter 10	Summary	225
Chapter 11	Valorisation	229
Chapter 12	Acknowledgements	231
Chapter 13	Curriculum Vitae	235

Chapter 1

Introduction

In 1998 we encountered a 40-year-old housewife in Cape Town who presented with sustained monomorphic ventricular tachycardia, and for the first time included Delayed Contrast-Enhanced Cardiovascular Magnetic Resonance (DECMR) in the diagnostic process. Endomyocardial biopsies confirmed cardiac sarcoidosis (CS). This experience introduced me to the world of cardiovascular magnetic resonance, and its potential to diagnose and help manage this intriguing condition. Apart from several case-reports no systematic research had been performed to determine the role of DECMR in the diagnosis, management and risk assessment of CS. Most experience in the management of CS and relevant published literature on this topic originated in Japan. The only existing Diagnostic Guidelines, which at that stage did not include DECMR, had been compiled in that country. After professor Dudley Pennell offered me accredited CMR training at the Royal Brompton Hospital, I was determined to formally study the role of DECMR in CS. This journey took me from Cape Town, and London, to Rotterdam, Maastricht and eventually back to Cape Town. The diagnostic tools available at that time were resting, exercise and ambulant electrocardiography, 2D echocardiography, as well as gallium, thallium and technetium-MIBI scintigraphy. These modalities were not sensitive or specific for the diagnosis of CS, and detected abnormalities frequently non-specific in nature. The prevalence and extent of CS remained underestimated, and detailed information on the myocardial distribution of inflammation and scarring was not provided. Postmortem studies in the United States suggested that 25-30% of sarcoidosis patients had either clinical or subclinical cardiac involvement. The prevalence of CS in The Netherlands was unknown. Diagnostic evaluation with the available armamentarium provided a substantially lower prevalence of CS. The first presentation of CS in some patients unfortunately was (aborted) sudden cardiac death. Clinicians needed a safe, accurate, robust and non-invasive diagnostic tool for CS, and DECMR held great promise.

The aim of our research was

1. To determine the prevalence of cardiac involvement in patients with pulmonary sarcoidosis in The Netherlands.
2. To determine the distribution and extent of myocardial sarcoidosis with DECMR.

3. To determine the diagnostic accuracy of DECMR for cardiac involvement in patients with pulmonary sarcoidosis compared to the gold-standard diagnostic Japanese Guidelines (1993) at that time (2005).
4. To determine the additional diagnostic value of DECMR for CS compared to the standard cardiac evaluation with resting 12-lead electrocardiography, 24-hour ambulant electrocardiography, transthoracic 2D Doppler echocardiography, and thallium or technetium-MIBI scintigraphy in patients with pulmonary sarcoidosis.
5. To determine the predictive value of DECMR for adverse cardiac outcome in patients with pulmonary sarcoidosis and cardiac involvement.

These research questions shaped the structure of this thesis. **Chapter 2** reviews the relevant clinical and pathophysiological background of CS, whilst introducing DECMR and detailing its role in the management of CS. The prevalence of CS, diagnostic accuracy and additional value of DECMR in addition to standard assessment in Dutch patients with pulmonary sarcoidosis at the University Hospitals of Rotterdam and Maastricht are detailed in **Chapters 3 and 4**. DECMR allows for the detection and quantification of focal scar and interstitial fibrosis. By 2016 numerous reports had been published on DECMR delineating left ventricular sarcoidosis, but relatively few studies reported on right ventricular involvement. **Chapter 5** describes the prevalence and distribution of right ventricular late gadolinium enhancement (LGE) in patients diagnosed with pulmonary sarcoidosis, and determines the relationship with pulmonary hypertension, ventricular volumes, mass and systolic function. The non-ischemic pattern of LGE in CS potentially distinguishes patients from those with LGE due to ischemic scar. In **Chapter 6** we describe the DECMR studies of 30 patients with CS, which were compared to those, performed in 30 consecutive myocardial infarct patients, who had been managed with primary coronary interventions. Blinded observers classified patients as either suffering from CS or ischemic heart disease by assessing the distribution of LGE. The prognostic value of DECMR is discussed in **Chapter 7**. **Chapter 8** puts the results obtained in this thesis in perspective.

Chapter 2

Review - Contrast-enhanced magnetic
resonance in the diagnosis and management of
cardiac sarcoidosis

Contents

Abbreviations	13
2.1 Introduction	15
2.2 Histopathology of cardiovascular sarcoidosis	15
2.3 Principles of Cardiovascular Magnetic Resonance and the application in cardiac sarcoidosis	17
2.4 Contrast agents and their application in the evaluation of cardiac sarcoidosis	19
2.5 Determining focal fibrosis (Tables 4, 5)	20
2.6 The measurement of extracellular volume and diffuse fibrosis with T1 mapping	21
2.7 CMR assessment of myocardial inflammation in sarcoidosis	23
2.8 The potential of Ultra Small Super paramagnetic and Nano particles in the assessment of mononuclear myocardial inflammation	24
2.9 Cardiovascular Magnetic Resonance in cardiac sarcoidosis: the first publications	25
2.10 The CMR diagnosis and differential diagnosis of cardiac sarcoidosis	25
2.11 Isolated cardiac sarcoidosis	26
2.12 The significance of evaluating for mediastinal lymphadenopathy in cardiomyopathy	26
2.13 Role of cardiovascular magnetic resonance in the guidelines and position papers	27
2.14 Atrial sarcoidosis	27
2.15 Right ventricular sarcoidosis	27
2.16 First-pass myocardial perfusion and perfusion reserve in sarcoidosis	29
2.17 Pericardial sarcoidosis	29
2.18 Macro granulomas	29
2.19 Can the distribution of LGE differentiate between different cardiomyopathies?	30
2.20 Prognostic value of DECMR - CMR as part of risk stratification	30
2.21 The relevance of screening for subclinical cardiac sarcoidosis	31
2.22 DECMR assists in clinical management of cardiac sarcoidosis	31
2.23 Improved outcomes with modern management	32
2.24 Conclusions	32
2.25 New and future applications of CMR in the management of cardiac sarcoidosis (Table 12)	33
2.26 Acknowledgements	33
References	34

Abbreviations

18F-FDG PET = 18F-

Fluorodeoxyglucose Positron Emission Tomography

67-Ga = Gallium-67

201-Th = Thallium-201

ACE = angiotensin converting enzyme

AIR = Arrhythmia-Insensitive-Rapid

ANGIE = Accelerated and Navigator-Gated look-locker imaging

ARCV = arrhythmogenic right ventricular cardiomyopathy

AVB = atrio-ventricular block

CID = cardiac implanted devices

CAD = coronary artery disease

CMR = cardiovascular magnetic resonance

CRT = cardiac resynchronization therapy

CS = cardiac sarcoidosis

CT = computed tomography

CU = cardiac ultrasound

DECMR = delayed contrast-enhanced cardiac magnetic resonance

DC = dendritic cells

ECG = electrocardiogram

ECV = extracellular volume fraction

EMB = endomyocardial biopsies

GBCA = Gadolinium-Based Contrast Agents

GraSE = Gradient-Spin-Echo

HASTE = Half-Fourier Acquisition Single-shot Turbo-spin-Echo

HCM = hypertrophic cardiomyopathy

HRS = Heart Rhythm Society

Ht = hematocrit

ICD = implantable cardioverter-defibrillator

ICS = isolated cardiac sarcoidosis

IGCM = giant cell myocarditis

IR-GRE = Inversion-Recovery Gradient Echo sequence

IR-FGRE = Inversion Recovery Fast Gradient Echo

JMHW = Japanese Ministry of Health and Welfare

LGE = late gadolinium enhancement

LV = left ventricle

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

MCLE = Multi-Contrast Late Enhancement Imaging

MDCT = multi-detector computed tomography

MGC = Multi-nucleated Giant Cells

MFR = myocardial flow reserve

MHC = Major Histocompatibility Complex

MOLLI = MODified Look-Locker Inversion recovery

MPS = myocardial perfusion scintigraphy

NICM = non-ischemic cardiomyopathies

NSF= nephrogenic systemic fibrosis

nsVT = non-sustained ventricular tachycardia

PAH = pulmonary arterial hypertension

PES = programmed electrical stimulation

PET = positron emission tomography

PH = pulmonary hypertension

PM = pacemaker

PSIR = Phase-Sensitive Inversion Recovery

RFA = radiofrequency ablation

RV = right ventricle

RVH = right ventricular hypertrophy

sVT = sustained ventricular tachycardia

SAP-T1 = Short Acquisition Period – T1 mapping

SAPPIRE = SATuration Pulse Prepared
heart-rate independent Inversion
REcovery

SASHA = SATuration recovery Single-
sHot Acquisition

SCD = Sudden Cardiac Death

SCMR = Society for Cardiovascular
magnetic Resonance

ShMOLLI = Shortened MOdified
Look-Locker Inversion recovery

SPECT = Single Photon Emission
Computed Tomography

SPIR = spectral presaturation with in-
version recovery

STONE = Slice-interleaved T1 mapping

SSFP = Steady-State-Free Precession

STIR = Short Tau Inversion Recovery

TWAaVR = T-wave amplitude in lead
aVR

TE = echo time

TI = inversion time

TR = repetition time

VT = ventricular tachycardia

VF = ventricular fibrillation

WASOG = World Association for Sar-
coidosis and Other Granulomatous
Disorders

2.1 Introduction

Sarcoidosis is a rare inflammatory condition, during which the deranged Th1 cellular immune response, triggered by a non-specific non-organic (insecticides, building dust, fumes, cosmetics) or organic particle (molds, tree pollen, viruses, *Propionibacterium*, *Mycobacteria*), forms the hallmark non-caseating granulomas and subsequent fibrosis. **(1-5)** In genetically predisposed individuals this condition can potentially affect any tissue or solid organ. Approximately 20% of patients suffer from concomitant autoimmune conditions such as inflammatory bowel, thyroid or thymal disease. **(1-3,5,7)** In 90% of patients the lungs and mediastinal lymph nodes are predominantly affected, which suggest that exposure to the agent generally occurs by inhalation. **(1-3,8)** Sarcoidosis originally received its name because of the “flesh like” skin lesions first described by Hutchinson in 1898 which macroscopically resembled “sarcoma”. **(9)** Bernstein et al (1929) were the first to report cardiac involvement in a 52 year-old Caucasian tailor, which resulted in congestive heart failure and death. **(10)** While 5-10% of sarcoidosis patients present with clinically manifest cardiac involvement, postmortem and imaging studies have revealed the heart to be affected in 20-30% of sarcoidosis patients. The basal left ventricular segments and right side of the interventricular septum are most frequently involved. **(11-23)** The distribution of cardiac involvement in sarcoidosis is demonstrated by **Figure 1 (24-41)** while the clinical presentation of cardiac sarcoidosis (CS) has been summarized in **Table 1. (12,13)** The incidence and severity of cardiac involvement differs between ethnic groups, with higher incidence in Scandinavians and more severe cardiac involvement in Japanese and African-Americans. **(3,23,43-44)** It is estimated that approximately 1-5% of sarcoidosis patients die of the condition, most commonly due to cardiac or pulmonary involvement. **(3)** The number of publications on CS has markedly increased over the last decades, largely due to the development of diagnostic imaging as well as the introduction of the cardiac implantable devices (CID), such as the pacemaker (PM) implantable cardioverter defibrillator (ICD) and catheter ablation of arrhythmias. **(Figure 2) Table 2 (Figures 3-8)** summarizes the contributions of the different relevant diagnostic modalities for CS. **(45-136)** The aim of this review is to provide relevant clinical and pathophysiological background on CS, whilst introducing cardiovascular magnetic resonance imaging (CMR) and detailing its role in the management of CS.

2.2 Histopathology of cardiovascular sarcoidosis

Inhaled antigens result in granulomatous alveolitis and activation of regional hilar and mediastinal lymph nodes. **(3,8,137,138)** Activated lymphocytes and macrophages from regional hilar, mediastinal lymph nodes, and spleen circulate, and enter the myocardial interstitium. Micro vascular infiltration of lymphocytes and macrophages occurs at capillary level, with degradation and lamellation of the basal membrane, deformation of endothelial cells, resulting increased permeability. **(139)** A recent Japanese CS study confirmed the predominance of M1 pro-inflammatory macrophages and myeloid dendritic cells, which capture antigens in peripheral tissues and stimulate naïve T cells and induce T1 or T2 dif-

ferentiation in the lymphocytic layer outside myocardial granulomas. **(77)** In addition antigens may enter the circulation with initial hematogenous spread followed by interstitial lymphogenic myocardial spread with local invasion. **(3,44,140)** Resident dendritic cells engulf the antigen, and present it to CD4 T1 helper cells via the Major Histocompatibility Complex (MHC) class II receptor, initiating a pro-inflammatory response, with release of interleukins (IL1 β , IL2, IL6, TNF α , IL12, IL18, and IFN γ), and chemokines. **(20,138,141)** At least 3 different resident cardiac macrophage/monocyte subsets exist in the human heart, two of which are innate, embryological in origin. The resident macrophage subsets originate from bone marrow and the embryonic yolk sac, have anti-inflammatory, pro-regenerative capabilities, and persist by in-situ self-renewal. **(142)** An abundance in macrophages exists in the distal atrio-ventricular node, where they play a role in immune surveillance, with removal of infectious particles and cellular debris, myocardial regeneration and repair, and have the ability to conduct electrical signal via the gap junction connexin 43. **(143)** Activation of these nodal macrophages in CS may in part explain the development of atrio-ventricular conduction disease. Activated macrophages turn into epithelioid cells, which merge and form multi-nuclear giant cells. **(138)** The basal septum, right-sided interventricular septum, lateral left ventricular (LV) wall and anterolateral papillary muscle have the most extensive lymphatic capillary network and are most frequently affected by granulomatous infiltration. **(Figure 9)** Obstruction of lymph drainage or retrograde lymphogenic spread of activated lymphocytes and macrophages from the right paratracheal lymph node, which drains the basal septum, right-sided interventricular septum, lateral left ventricular (LV) wall and anterolateral papillary muscle, may explain the predominance of myocardial involvement of these segments. **(Figure 10)** Activated macrophages produce lysozyme, angiotensin converting enzyme (ACE), bioppterin and osteopontin. **Figure 11** illustrates the progress through different stages of sarcoidosis involving the myocardium. Initially infiltration of CD4 lymphocytes causes interstitial edema, followed by migration of dendritic cells, and macrophages, which result in the formation of ill-defined interstitial granulomas. **(stages I and II– exudative stages, Figures 11A and B).** **(19,20)** Vascular involvement mainly consists of granulomatous infiltration of the media and adventitia of the small intramural coronary arteries and venules, whilst proliferation occurs of the intimal cells. **(144,145)** Resulting myocyte degradation with small amounts of central necrosis in granulomas may account for the elevated highly-sensitive troponin levels, which have been reported to respond to treatment with corticosteroids. **(8,18,59,63)** The activated pro-inflammatory macrophages turn into secretory epithelioid cells (activated macrophages resembling “epithelial cells” seen in intense immunological reactions – elongated in shape, with pale eosinophilic, finely granular, cytoplasm, and a central elongated nucleus). Fusion of epithelioid cells result in multi-nucleated giant cells (MGCs). MGCs are generally of the Langhans type, 4-50 μ m in diameter, with a large mass of cytoplasm, and a peripheral arrangement of at least 20 nuclei. MGCs may produce lysozyme and ACE. **(137,146)**

Stage III consists of relatively well defined non-necrotizing granulomas with abundant central epithelioid cells, MGCs, few central but plenty peripheral CD4 lymphocytes surrounded by a peripheral ring of CD4 and CD8 lymphocytes, plasma and mast cells. **(Figures 4 and 11C)** The peripheral CD4 lymphocytes demonstrate a shift towards Th2 cytokine profile with production of IL4, IL5, IL10, IL13 and TGF β , which are anti-

inflammatory and result in a fibro proliferative response with extracellular matrix deposition. (7,138,146) Non-specific intra-cytoplasmic inclusion bodies may be observed in some MGCs. Asteroid bodies are stellate shaped inclusion bodies, 5-25 μm in size, of filamentous micro tubular material. Schaumann or Conchoidal bodies are oval, concentrically laminated bodies, generally 25-200 μm in size, and consist of calcified proteins. Elongated birefringent crystalline cholesterol esters measure 1-20 μm in size. And lastly Hamazaki-Wesenberg bodies, which measure 3-15 μm in diameter, which are giant intra and extra cellular lysosomes. (8,20,137) Granuloma formation is a strategy during with the immune system aims to sequester particles, microbes, or pathogens which evade effective phagocytosis and killing. (20) **Table 3** summarizes the specific and differentiating characteristics of granulomatous myocarditis. (147-152)

The **final stages (IV)** of CS consist of peri-granulomatous fibro-hyaline replacement with deposition of collagen. (**Figure 11 C and D**) (7,19) Overt evidence of necrosis of the cardiomyocytes as seen in idiopathic giant cell myocarditis (IGCM) does not occur in CS. (7) Cardiomyocytes atrophy, loose striations, with electron microscopic evidence of mitochondrial disruption, swelling, and loss of mitochondrial enzymes. Hyaline sclerosis, mucoprotein and glycoprotein deposition usually starts at the periphery of the tubercle, and gradually replaces the epitheloid cells. (18,147,153)

2.3 Principles of Cardiovascular Magnetic Resonance and the application in cardiac sarcoidosis

Spinning atomic nuclei with odd numbers of protons, such as hydrogen (H), have magnetic momentum, and can be used for CMR. In the presence of a strong external magnetic field of a clinical CMR scanner (B_0 , 0.5-3 Tesla, 5000-50 000 fold the strength of the earth's magnetic field) the parallel and anti-parallel spinning H protons align along the bore (Z-axis) of the scanner. Slightly fewer align in the higher energy anti-parallel state, resulting in a net magnetization vector aligned to the external magnet. Individual nuclei precess around the direction of the external field in a phase that is different for each individual nucleus. When applied intermittent electromagnetic field pulses (pulse sequences) carry a radiofrequency which is identical to that of the H nuclei (Larmor frequency, 63.75 MHz at 1.5 Tesla), energy is transferred which causes them to jump to the antiparallel state, precess in phase, and flips them into the X-Y plane to a degree determined by the flip angle of the pulse sequence. When the radiofrequency current is switched off, the nuclei relax and realign to B_0 , generating a radio frequency (RF) signal, which is detected with receiver coils (a surface coil placed over or around the tissue or organ of interest or the magnet bore). The longitudinal, spin-lattice (surroundings) relaxation time (T_1) describes how quickly the net magnetization vector recovers to its ground state in the direction of the external static magnetization field B_0 . The T_2 or the spin-spin relaxation time relates to the decay of transverse magnetization (signal vector in the transverse Y axis/plane) after the resonance frequency pulse, and results from natural interactions at atomic and molecular levels. T_2^* (star) reflects the inhomogeneity's in the main magnetic field and field distortions produced by the tissue which cause the transverse magnetization to decay faster than predicted by

natural atomic and molecular mechanisms (T2). Three constantly changing orthogonal magnetic gradients allow for the spatial localization of emitted radio waves and the reconstruction of images of the human body. To create an image the magnetic resonance signal from the H-protons needs to contain information about where the protons are positioned. By adding a small magnetic gradient along the main magnetic field in caudal to cranial direction an imaging slice can be selected. Because the frequency of precession of the protons depends on the local field strength, a narrow band of frequencies will only excite a thin slice of spins through the body. With change in excitation frequency another parallel slice can be acquired later. By using a combination of gradients in all three directions, it is possible to acquire a slice in any direction through the body. Frequency and phase encoding are used to obtain information for the individual points within a slice, or pixels. For the phase encoding a short temporary change in the magnetic field is applied between the radiofrequency (RF) excitation pulse and the signal read out. This change will influence the frequency of precessing, resulting in a shift in the phase of precessing of the spins, dependent on the duration of this switch. By repeating this process with different duration of the temporary gradients, signals with different phase encoding are acquired. Frequency encoding is used to differentiate pixels with the same phase encoding. A magnetic gradient during read out of the signal results in a specific shift of the resonance frequency, likewise the effect of the slice-encoding gradient, for pixels with the same shift. Combining phase and frequency information allows the creation of a grid in which each pixel has a defined combination of phase and frequency codes. With a Fast Fourier Transform in both the frequency and phase encoding the raw digitized data are transformed into an image. The image resolution is determined by the obtained field of view (FoV, generally $240\text{--}400 \times 240\text{--}400$ mm), the number of frequency encodings (128–512 on the X-axis), the number of phase encoding steps (128–512 on the Y-axis), and the selected slice thickness (6–10 mm, with/without gaps). In practice the image resolution is not determined by the pixels (picture elements, $0.5\text{--}2 \times 0.5\text{--}2$ mm) or voxel sizes ($0.5\text{--}2 \times 0.5\text{--}2 \times 6\text{--}10$ mm), but signal-to-noise ratio (SNR). Decreases in voxel size are generally associated with decreases in SNR and increases in acquisition time. The operator will need to individualize the acquisition settings for each individual patient as to answer the clinical questions. Image contrast is determined by intrinsic tissue magnetic longitudinal (T1) and transverse (T2) relaxation times determined by the type and structure of the atoms. Protons in different tissues produce signal at different relaxation rates, resulting in unique imaging signatures of different tissues. The signal strength is determined by the strength of the external magnetic field B0. Most cardiovascular studies are performed with 1.5 Tesla scanners/magnets. Although 3T decrease the acquisition time, increase signal strength and SNR, these advantages may be off set by the higher susceptibility to artifacts. When one uses more than one RF pulse, a so-called pulse sequence, one can use pulses with different flip angles (90° or 180°). The flip angles of the pulses and the time between the pulses will determine the tissue signal. The time between the pulse sequences are called time to repeat (TR). TE is time to echo, which can be chosen by the operator, influencing the resulting signal and thus the image. The shorter the TE time, the stronger the signal, the better the signal-to-noise (SN) ratio, but the weaker the contrast. The longer the TE the more T2 weighted the study. By manipulating the number of pulses, their flip angles, the TR, and TE the CMR operator can

generate T1 weighted, T2 weighted or proton-weighted images. By altering the timing and strength of the alternating gradients, as well as the administration of external contrast agents, which alter the longitudinal relaxation times or spoil magnetization, differences in T1 and T2 values in tissues can be exploited to enhance and differentiate specific tissues of interest. Rapid imaging sequences allow for real time imaging, but most images requiring high spatial resolution and tissue contrast require electrocardiographical (ECG) timing to allow for the sampling of imaging data over several cardiac cycles. The large majority of investigations are performed with 2D imaging, with the acquisition of one slice of data in one breath-hold (generally lasting 11-20 seconds). Navigator triggered free breathing imaging may be considered in patients who are unable to hold their breath. CMR contrast agents predominantly alter the T1 relaxation time of the H nuclei resulting in stronger i.e. brighter signal. ECG triggered bright-blood sequences (b-SSFP) allow for functional assessment of myocardial segmental and global systolic left and right myocardial functions. **(153,154,155) Tables 4 (Figures 12-16) (38,57,99 132,134,158-171,175-179) and 5 (Figures 12-20) (27,28,31,32,33,35,36,38,39,161,163, 164,167,175, 180,181,183-185)** summarize the CMR sequences used in the evaluation of patients with suspected CS. The Society of Cardiovascular Magnetic Resonance (SCMR) has published protocols, which aim to optimize and standardize the evaluation of non-ischemic cardiomyopathies (NICM) and include recommendations for the assessment of patients with suspected CS. **(157,158)**

2.4 Contrast agents and their application in the evaluation of cardiac sarcoidosis

Contrasted CMR is mainly used to detect active granulomatous inflammation and chronic focal or diffuse interstitial scar. **(Figure 14) (168,171,183-188)** Although first-pass perfusion may be used to evaluate myocardial perfusion deficits due to coronary vasculitis or microcirculatory obstruction due to infiltrating granulomas, this is not generally used in clinical practice as it does not improve diagnostic or prognostic accuracy in CS. **(187)** The normal intra-cellular compartment contains approximately 75-80% of myocardial volume, with the remaining 25-30% representing the interstitial volume. Increased capillary permeability, interstitial expansion due to cellular, granulomatous inflammation, lymphatic obstruction and fibrosis due to collagen deposition result in an increased interstitial volume of distribution with decreased washout of the gadolinium-based contrast agents (GBCA). **(Figure 21) (130,131,156-158,167,170,185, 188,189) Table 6** summarizes the GBCA used in CMR. **(185)** GBCA consist of gadolinium, a biologically inert water soluble tracer obtained from rare earth, linked to different ligands such as diethylene- triaminepentaacetic acid (DTPA), which render it the capabilities to distribute freely in the intravascular and extra-cellular interstitial space. Gadolinium is the critical paramagnetic element responsible for the enhancement properties of GBCA, but the chemical structure of the ligand determines the degree of enhancement, half-life, distribution, pharmacokinetics and toxicity. GBCA do not cross the cell membrane unless damaged by ischemia, toxins, or as in CS, inflammation. Histopathological studies have revealed evidence of limited central cardiomyocyte necrosis in which case GBCA will accumulate intra-cellularly. **(165)** With the

clinically used intravenous dosages of 0.1-0.2 mmol/kg of GBCA the longitudinal (T1) relaxation time is shortened, with little effects on the T2 relaxation time. **(186)** Most investigators evaluating CS have used gadolinium-diethylenetriaminepentaacetic acid (Gd DTPA), gadopentetate dimeglumine, gadodiamide or gadoversetamide at 1.5 T field strength with dosages differing from 0.1-0.2 mmol/kg. Few have used gadobenate dimeglumine (BOPTA), with higher reported T1 signal. The myocardial T1 with BOPTA is 15 msec shorter without significant difference of the T1 relaxation time in the blood pool. This results in slightly greater extra-cellular volume (ECV) measurements with Gd-DTPA in the order of 0.01, greater T2 relaxivity in blood plasma and interstitial fluid, with higher contrast-to-noise (CNR) and signal-to-noise ratio (SNR) of LGE compared to remote normal myocardium. Lower dosages of BOPTA are needed compared to Gd-DTPA to deliver same diagnostic quality. Gd-BOPTA also prolongs the enhancement of blood, which can result in lower sensitivity for small subendocardial scars. The higher intra- and inter-observer variability with Gd-BOPTA, may however leave Gd-DTPA the preferred agent. **(191)** The use of GBCA carries a very low rate of adverse events (0.01-2.4%), lower compared to low osmolar non-ionic iodinated contrast agents for computed tomography. **(191-193)**

The most relevant safety issue is its restricted use to patients with preserved renal function. Nephrogenic systemic fibrosis (NSF) has been reported in a small subgroup of patients with an estimated glomerular filtration rate < 30 ml/min/1.73 m². The FDA has published guidelines for the use of GBCA in this population. **(194)**

2.5 Determining focal fibrosis (Tables 4, 5)

Until the introduction of inversion-recovery (fast) gradient echo (IR-GRE) sequences the delayed enhanced spin echo (SE) sequence was used to determine the presence, localization, distribution and amount of focal fibrosis i.e. LGE in ischemic and non-ischemic cardiomyopathies. **(161,163,164,195-197) (Figures 12,14,15)** IR-GRE sequences consist of a conventional SE sequence preceded by a 180° inverting pulse. The time between the inverting pulse and the 90° SE pulse is called the inversion time (TI). Ten to fifteen minutes after the administration of the GBCA the inversion pulse is administered. The function of the inverting pulse is to flip the initial longitudinal magnetization (M₀) of all tissues in the imaged slice or volume to the point opposite to the direction of the main magnetic field (B₀). During the TI interval these inverted tissues undergo T1 relaxation as they variably seek to re-establish magnetization along the Z-axis. At the 90° SE pulse the longitudinal magnetizations of different tissues are now separated based on their different intrinsic T1 relaxation times. Varying the TI parameter controls the degree of separation and thus image contrast. The TI is generally optimized on individual basis, ranging from 200-360 msec, and chosen as to suppress (“null”) signal from normal, un-enhanced, myocardium so that contrast with the bright, contrast-enhanced myocardium is optimal. The TI is time-dependent – as time lapses from administration the TI may need adjustment. The Phase-Sensitive Inversion Recovery (PSIR) acquisition sequence obviates the need for adjustment, it has been designed to null the myocardium over a range of inversion times. Generally two

separate phase encoding directions and two orthogonal DECMR views are generated confirm true LGE and to exclude artifact. **(Figure 22)** Diffuse interstitial inflammation (early stage of CS) or diffuse fibrosis will not be visualized by IR-GRE sequences, as the areas with little interstitial gadolinium will be nulled compared to the areas containing most gadolinium.

LGE by CMR has become the gold standard for assessing acute myocardial infarct scar (AMI), chronic myocardial infarct scar (CMI), and focal scar in NICM such as CS. **(Figures 20, 23)**

Although IR-GRE sequences have become the acquisition sequence of choice, there is currently no uniform approach for the CMR quantification of focal myocardial fibrosis in NICM.

Investigators have used different amounts of a variety of contrast agents (single vs. double dose 0.1- 0.2), different delays between administration of contrast agents and the acquisition of images, different inversion times – fixed or individual optimization, different slice thicknesses (thicker slices, higher SNR), magnetic field strengths (higher strength, higher SI, higher SNR, CNR), and different methods of quantifying the amount of LGE - visual interpretation with manual planimetry, semi-automated methods using signal intensity (SI) at a fixed number of standard deviations (SD, 2 - 6 SD) above remote unenhanced myocardium, subjective segmental scoring by independent experienced readers or the full-width at half-maximum method (FWHM) whereby the amount of LGE is delineated at 50% of the maximum SI in enhanced myocardium. **(57,134,198,199-201)** The reproducibility of LGE in NICM seems worse compared to ischemic scar, and LGE volume may vary substantially depending on the condition studied and quantification technique used. **(202)** The >2 SD technique generated LGE volumes up to two times higher compared to the manual planimetry, FWHM, and >6 SD methods. Regardless of the disease under study the FWHM method gives LGE volume similar to the manual quantification and seems most reproducible, reducing required sample size by half. **(200)**

Currently the recommended reporting of myocardial scar with > 2 SD above the signal of mean remote unenhanced myocardium in the same slice. **(203)** LGE of the relatively thin walled right ventricle (RV) was visually assessed by dividing the RV in 12 segments. **(204) (Figures 7,8,9, 12)**

2.6 The measurement of extracellular volume and diffuse fibrosis with T1 mapping

The normal extra cellular myocardial volume (ECV) measures approximately 23% and extra cellular matrix expansion by edema, interstitial fibrosis, deposition of iron, lipid, collagen, amyloid, or cellular infiltration as determined by the use of native and post-contrast T1 maps is diagnostic of myocardial dysfunction and an independent biomarker of poor outcome. **(Figure 21)** Native T1 mapping and the assessment of the ECV by the use of native and post-contrast T1 maps are currently considered as the most promising methods and may also detect myocardial ischemia, and myocyte necrosis due to ischemia in acute infarction. **(189,205-213,216,228)** T1 mapping refers to the pixel wise quantification of the

myocardial longitudinal relaxation time. Global T1 measurements can be determined either by analyzing the intensity of a group of pixels in a parametric T1 map, but also by deriving an exponential T1 recovery curve based on regions of interest (ROIs) from a number of SSFP images with varied inversion times i.e. (Shortened) MODified Look-Locker inversion-recovery sequences (MOLLI, ShMOLLI) and saturation recovery sequences SATuration recovery Single-sHot Acquisition (SASHA). Many widely used myocardial T1 mapping sequences use breath-hold acquisitions that limit precision – free breathing high-contrast SASHA (SASHA-HC) may provide accurate T1 maps with higher precision than MOLLI in acquisitions less than 30 seconds. Native (contrast-free) myocardial T1 mapping with MOLLI, ShMOLLI evaluates the whole myocardium, including capillaries, myocytes, and blood, and is able to detect and quantify myocardial ischemia, and extra-cellular expansion due to edema, collagen, amyloid, lipid or iron deposition on a pixel by pixel basis. **(Figures 15,16)** Since it obviates the need for contrast agents it can be applied in patients with renal impairment, is heart rate independent resulting in less image artifacts, and is less reliant on reference values. Standardization is however an issue, and locally derived normal values need to be determined in each patient population. Variability is introduced when determining ECV by different contrast agents and field strengths. Usually acquisition is obtained in end-diastole but systolic acquisitions, with lower T1 values, are more optimal in AF. Relatively fast breath-hold T1 mapping like MOLLI have made assessment of ECV a reality. Stable measurements are generated 5-10 minutes after a bolus of contrast agent.

The ECV fraction is derived from the ratio of changes in pre and post contrast signal in the extracellular myocardium and extracellular LV blood pool water (plasma). **(205,207,209,210, 212)** The conventional approach requires a blood test to determine hematocrit (Ht) and post-processing integrates the Ht in calculations of the ECV (%). The inverse linear relationship between the Ht and the native blood pool T1, allows for non-invasive estimation of the Ht. **(214)** Recently several investigators demonstrated the feasibility of estimating the ECV based on this synthetic, non-invasive, pre-contrast blood pool T1 based ECV, which allowed an immediate inline ECV map to be generated. **(215-217)** T1 and ECV measurements will likely very helpful in the diagnosis, management and prognostication of CS, due to its ability to evaluate focal or diffuse intra- and extracellular interstitial disease processes. **(112,171,173,218).**

This technique is based on the change in T1 values after injection of gadolinium DTPA, an extracellular contrast agent. ECV is estimated from repeated native T1 acquisitions at baseline and at 10 minutes after contrast administration. The change in $1/T1$ in tissue and blood pool is used to determine the contrast agent concentrations, the ratio of which is an estimation of ECV, followed by a correction of red cell concentration in the blood pool (hematocrit (Ht)). The Ht can be estimated from the native values of blood T1 precluding the need for laboratory tests.

Motion between the images will adversely impact T1 measurements, and should be corrected.

Relatively fast breath-hold T1 mapping like MOLLI have made assessment of ECV a reality stable measurement 5-10 minutes after bolus of contrast agent. Measuring the ECV is superior to native or post-contrast T1 mapping in determining collagen volume fraction

and risk assessment in large cohorts, and has been well-validated and highly reproducible across different vendors.

Confounders for post-contrast T1 mapping are renal clearance, contrast relaxivity, body weight, anemia, and the time between acquisition and administration of the contrast-bolus, (219,220)

2.7 CMR assessment of myocardial inflammation in sarcoidosis

Several case-reports and studies have reported on the value of SE T2 weighted, fat and blood suppressed T2 weighted (spectral presaturation with inversion recovery, SPIR; short tau inversion recovery, STIR), early relative and late post-contrast T1weighted imaging in patients with CS. (30,122,131,132,159-161,175,197,221-224) (Figure 13).

Due to the patchy distribution of the disease and lack of histological correlation the sensitivity and specificity of these sequences for the diagnosis of CS are unknown. T2 weighted imaging detects edema but is prone to low-signal-to-noise motion artifacts, imperfect blood suppression in areas of slow blood flow, and subjective visual interpretation. (174,224) Hypo intense lesions on T2 weighted imaging signify fibrosis, while LGE demonstrates both active inflammation as well as focal fibrosis. (38,165,189) (Figure 14) The concept of relative early enhancement (ERE) consists of comparing the signal intensities (SI) in regions of the left ventricle to skeletal muscle, such as the major pectoral or paraspinal muscles, 4 minutes after administering GBCA using SE black blood imaging. An increased regional global signal intensity (SI) in the myocardium signifies expanded interstitium reflecting inflammation by edema (relative SI ≥ 2) and hyperemia (relative SI ≥ 4) and, although no direct comparisons have been made, in all likelihood may be similar findings with T1 and T2 mapping. (38,165,175,189,224).

Regional myocardial T2 or transverse relaxation time mapping overcomes the challenges of image quality, reproducibility, and subjective assessment. Images are acquired with different echo times and are used to estimate the T2 values. Although the spatial resolution with T2-STIR is finer, allowing for more detailed subjective focal disease inspection, T2 mapping is heart rate independent, resulting in fewer artifacts, and less reliant on reference values. (224) A parametric image or map is generated with each pixel reflecting the calculated T2 relaxation time. Maps can be analyzed visually on a grey or color scale and regions of interest can be drawn for quantitative analysis. (Figure 16) At least three single-shot images are generated with increasing T2 preparation times to construct a relaxation curve, with long repetition times to prevent T1 longitudinal relaxation from distorting the images. Crouser used T2 mapping in a retrospective analysis comparing 50 suspected CS patients to healthy controls, whilst using a cut off value of 59 ms based on previous studies in viral myocarditis, and determined that mapping had a sensitivity of 54% and specificity of 100% for the diagnosis of CS. (171) In 41% of patients global T2 was prolonged in the absence of LGE, indicative its superior sensitivity.

The combination of these different sequences potentially helps distinguish inflammation from chronic sequelae. (38,164,165,171,174,189,213,216,222,224,225,228) The assessment of active granulomatous myocardial inflammation is important for diagnostic,

treatment and prognostic perspectives. Active granulomatous myocardial inflammation appears more arrhythmogenic and may potentially respond to immune-suppressive treatment. **(11,56,79,115,116,174,221,230,231)**.

Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and Single Photon Emission Computed Tomography Dual Isotope Scintigraphy have been demonstrated useful in CS, with FDG, Octreotide and ^{68}Ga -DOTA-TOC the most sensitive tracers. **(111,112,122,126,174,231,233)** **(Figures 6A,7B,8)** PET CT is currently considered the most sensitive modality for active CS. **(115,121,122,126,131,174,232,233)** Isotope scintigraphy is particularly useful when CMR is contra-indicated, but exposes the patients to ionizing radiation and is limited by image resolution. **(224,226)** The high sensitivity of FDG-PET for myocardial inflammation, and the superior image resolution, functional and structural information of modern CMR **(Table 2)** combined, make hybrid FDG PET/CMR the diagnostic and management tool of choice. **(124-130,234,235)** The relatively thin RV wall currently precludes breath-hold parametric mapping, but respiratory-gated techniques may provide a future solution. **(Figure 7,8,12)**

2.8 The potential of Ultra Small Super paramagnetic and Nano particles in the assessment of mononuclear myocardial inflammation

Ultra small super paramagnetic particles of iron oxide (USPIOs) consist of an iron oxide core surrounded by a carbohydrate or polymer coating, small (<20 to 250 nm) enough to extravasate through diseased microvasculature, where they may be engulfed by tissue resident macrophages.

Accumulation of USPIOs reduces the T2* decay time and creates signal deficits that can be visualized and quantified by T2*CMR. Thus the cellular inflammatory process can be imaged at tissue level. This technique can provide a non-invasive method for the diagnosis and monitoring of the tissue macrophage activity in the myocardium, and potentially allow for the evaluation of novel therapeutic interventions. **(236)** The current limited pre-clinical and clinical data confirm the potential of both magnetic and perfluorocarbon nano particles for the diagnosis of active myocarditis with histological correlation of imaging signal. **(237,238)** In addition to iron oxide particles, intravenous perfluorocarbon nano particles ^{19}F MRI may become useful in diagnosing and monitoring inflammatory cells – macrophages, dendritic cells, granulocytes - in the myocardium. In contrast to the regular ^1H NMR imaging fluorine particles are virtually absent in the human body, which means the absence of background noise –resulting in high specificity. Immune cell infiltration was successfully imaged in the pre-clinical beating mouse heart model of autoimmune myocarditis with a high field research magnet of 9.4T with simultaneous acquisition of ^{19}F and the matching ^1H images. This depicts hot spots of ^{19}F phagocytized by circulating macrophages, and creates the possibility of early detection and delineation of inflammation. Since these technologies are highly specific and have the ability to quantify they hold great promise for the diagnosis and management of sarcoidosis. **(174,239,240)**

A substantial percentage of CS receives treatment with (biventricular) pacemakers (PMs) or implantable cardioverter defibrillators (ICDs). **(95,96,241)** Off-label CMR scans in non-conditional pacemaker dependent patients and those with implantable cardioverter defibrillators for relevant diagnostic or management reasons can be safely performed with use of a strict protocol. **(239,240,244,245)** Since 2008 MRI compatible ('conditional') leads and pacemakers have become available, further reducing the extremely low risk of device interference (0,3%) by the radiofrequency energy and magnetic fields. **(244,245)**

2.9 Cardiovascular Magnetic Resonance in cardiac sarcoidosis: the first publications

The first case-reports describing the application of uncontrasted T1 and T2-weighted spin echo imaging were by Riedy et al in 1988 **(180)** **(Figure 17)** and Dupuis et al in 1994. **(245)** Chandra in 1996 were the first to report segmental LV dysfunction on bright blood ('cine') imaging and mediastinal lymphadenopathy in a patient with dilated cardiomyopathy secondary to CS. **(246)** The authors reported superior image quality and suggested CMR should be considered for diagnostic and therapeutic monitoring purposes in the each patient with suspected CS. In 2001 Shimada et al were the first to report the diagnostic findings and response to steroid therapy with gadolinium-enhanced CMR in 8 of 16 sarcoidosis patients. **(162)** Vignaux et al were the first to report the long-term response to steroid treatment with more comprehensive CMR imaging including cine imaging, and (un)contrasted T1 and T2 -weighted studies. **(159,160)**

2.10 The CMR diagnosis and differential diagnosis of cardiac sarcoidosis

The definite diagnosis of CS is based on histological confirmation by EMB, but due to the patchy, predominantly epicardial and mid-myocardial, LV distribution of granulomatous sarcoid infiltration, RVseptal EMBs suffer from sampling error and may be "false negative". **(75-77, 80,81,247,248)** **(Figure 24)** In the absence of diagnostic EMBs the current guidelines allow for the "clinical" ("at least probable", or "possible") diagnosis of CS to be made when ECG (conduction disease, supra/ventricular arrhythmias) and/or (non-invasive) diagnostic imaging (CU, PET/CT, Tc-MIBI, Thallium, Gallium, DECMR, delayed enhanced MDCT, invasive ventriculography) reveal abnormalities associated with CS (segmental myocardial motion abnormalities, hypertrophy, atrophy, focal scar, uptake, reversed perfusion defects) in the presence of histologically confirmed extra-cardiac sarcoidosis. Alternative conditions, such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), amyloidosis, Chagas disease, viral myocarditis, dilated cardiomyopathy (DCM), or coronary artery disease (CAD), need to be excluded. **(11,46,152,163,164,168,178,218,249-256)** **(Table 7)** **(Figures 23,24,25,26)** The diagnosis of CS is certain when the EMB demonstrates the histopathological hallmark of this condition, non-caseating granulomas in the absence of etiologic agents, microbes or fungi.

Although DECMR or electrophysiological endomyocardial mapping guided EMBs have decreased sampling error, the mid-myocardial or epicardial LV distribution of granulomas limits the diagnostic accuracy of trans venous EMBs. **(74) (Figure 20)** In the absence of diagnostic endomyocardial histology DECMR and PET have been demonstrated to be the most accurate diagnostic imaging test in patients with diagnostic extra-cardiac histopathology. **(11,12,257,258)** Table 2 describes the advantages and limitations of the different diagnostic modalities used until now. DECMR has rapidly developed as the most useful. Lately the number of (peer-reviewed) publications has steadily increased from 10-15/year to 100-150/year. **(Figure 2)**

2.11 Isolated cardiac sarcoidosis

Cardiac sarcoidosis without clinically apparent extra-cardiac disease so-called “isolated cardiac sarcoidosis” (ICS) has recently gained more attention and acceptance as a clinical entity. **(259,260,261,262)** Although the true prevalence of ICS is not known due to its inherent diagnostic challenge, estimates range from to 5.5-25% of CS. **(95,262)** ICS may be more prevalent amount Scandinavian (Finish) and Asian (Japanese) sarcoidosis patients. **(259,262,263)** A thorough clinical work-up of patients with suspected sarcoidosis including delayed enhanced CMR and whole-body F-18-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) guided sampling of (mediastinal/hilar) lymph nodes and right or left ventricular endomyocardial biopsies (EMB) markedly increases diagnostic accuracy for histologically confirmed CS. **(259,262,264,265)** The current HRS (2014) and JSSOGD (2006) guidelines do not provide for the diagnosis of ICS i.e. CS in the absence of histological evidence of extra-cardiac or cardiac sarcoidosis. The definite diagnosis of CS is based on histological confirmation by EMB, but due to the patchy, predominantly epicardial and mid-myocardial, LV distribution of granulomatous sarcoid infiltration, RV septal EMBs suffer from sampling error and may be “false negative”. **(11,266)** It is urgently necessary to formulate evidence based diagnostic criteria for “ICS”. Several recent publications included diagnostic guidelines for ICS based on imaging tests with major emphasis on contrasted CMR, whole body PET/CT, and hybrid PET/CMR. **(95,261,263,267-271)** When assessed with whole body 18FDG PET isolated CS was found to be rare, with only 1 of 31 CS patients without extra-cardiac uptake. PET and DECMR are the crucial diagnostic imaging tests used to diagnose CS in the absence of extra-cardiac or cardiac tissue diagnosis. **(95,262,267-271)**

2.12 The significance of evaluating for mediastinal lymphadenopathy in cardiomyopathy

Riedy et al (1988) were the first to report on CMR evidence of CS and mediastinal lymphadenopathy in a patient with CS. In patients diagnosed with idiopathic dilated cardiomyopathy and negative endomyocardial biopsies, computed tomography (CT) or PET/CT should be employed to assess for mediastinal lymphadenopathy. Due to sampling error

endomyocardial biopsies (EMB) may be negative in 50-70% of patients with CS. **(75)** Histological assessment of sampled mediastinal nodes may reveal underlying sarcoidosis as the potentially reversible etiology of the cardiac condition. **(264,265,274-276)** A thorough clinical work-up of patients with suspected sarcoidosis including delayed enhanced CMR and whole-body 18FDG-PET guided sampling of (mediastinal/hilar) lymph nodes and RV or LV EMBs markedly increases diagnostic accuracy for histologically confirmed CS. **(259,262,264,265)**

2.13 Role of cardiovascular magnetic resonance in the guidelines and position papers

Sofar CMR has been included in the Diagnostic and Management Guidelines of 5 professional Societies. **(11,46,251-254,266,277-279)** **(Table 8)** Since the first Diagnostic Guidelines by the the Japanese Ministry of Health and Welfare in 1993 (JMHW) the prominence of CMR has increased from being a minor to becoming a major contributor to the diagnosis of CS with prognostic relevance. **(11,46,254,277,278)**

2.14 Atrial sarcoidosis

Supraventricular arrhythmias occur in up to 32% of patients diagnosed with CS, with atrial fibrillation (18%) being most common and multifactorial in etiology. **(280,281)** Despite the limited image resolution due to the atrial wall thickness only measuring 4 mm, atrial infiltration and scarring can be demonstrated by T2 weighted and LGE CMR. Both have been reported to be the substrate of atrial fibrillation, flutter and sinus node dysfunction. **(24,282,283)** Though not yet studied in CS, atrial CMR strain analysis may potentially provide additional valuable information in patients with (suspected) CS. Impaired atrial booster function may carry valuable diagnostic and prognostic information, representing evidence of (sub)clinical (atrial) CS, myocardial fibrosis and non-compliance, as well as long-term risk of SVT. **(281-284)**

2.15 Right ventricular sarcoidosis

Until recently limited attention has been given to RV involvement in CS, its prevalence, relevance and prognostic value. **(285)** CMR is the preferred imaging tool to diagnose and delineate RV disease. **(286-288)** RV volumes, mass, and function can be quantified without geometric assumptions, with excellent intra- and inter-observer agreement and good inter-study reproducibility. **(133,189,289,291)** Although there are numerous reports on DECMR delineating LV sarcoidosis, relatively few studies have reported on RV involvement. **(204,285,291-293)** RV LGE is present in approximately 15% of patients diagnosed with pulmonary sarcoidosis, and in 38-49% of patients with left ventricular enhancement.

(29,30,285) (Figures 7,12) The presence of RV LGE correlates with pulmonary arterial hypertension (PAH), RV systolic dysfunction, hypertrophy and dilation. **(29,30)** RV sarcoid means more extensive and active CS, and also more active extra-cardiac i.e. mediastinal and hilar sarcoidosis **(29,30,292) (Figure 9)** Biventricular LGE at presentation may be the strongest, independent predictor of adverse outcome during long-term follow up of sarcoidosis patients. **(30,115,204,292,296)** Predominant or isolated RV involvement is rare, with the large majority of patients with RV LGE also suffering from LV disease. **(28-30)** More extensive LV LGE is associated with RV involvement. **(134,189,204,295,298)** RV LGE, and inflammation as demonstrated with FDG PET, have been associated with ventricular tachy-arrhythmias. **(134,204,230,241,298) (Figures 7,8)** The reported prognostic relevance of RV disease may at least partly reflect the extent of LV arrhythmogenic substrate. Several post-transplant and post-mortem studies in sarcoidosis patients have reported RV involvement to range from 6%, in patients dying from alternate causes, to as high as 65% in those dying sudden cardiac deaths. **(16,18,145,299,300)** Generally, patients with congestive failure were found to have extensive biventricular sarcoid, and in those who had died suddenly, active granulomatous infiltration and patchy scar were present. RV outflow tract involvement was rare. Eleven recent studies employing DECMR in the assessment of cardiac sarcoidosis, reported on RV disease in sarcoidosis. **(29,133,134,189,204,230,241,285,289,298, 301)** RV enhancement was reported in 6 of these studies, and ranged from 2% in unselected to 48% in high-risk populations. **(132,189,204,285,289)** The presence of RV LGE correlates with hypertrophy, dilation and systolic dysfunction. **(29)** RV LGE in sarcoidosis may be caused by direct granulomatous infiltration, but also be related to PAH. **(302)** RV hypertrophy, dilation, dysfunction and LGE may be secondary to PH, and are associated with worse prognosis. **(302,303) (Figure 20)** PH is found in 6-28% of the general sarcoidosis outpatient setting, and may be secondary to pulmonary fibrosis, angiitis and/or congestive heart failure. **(303) (Figure 27)** RV dilation and systolic impairment in sarcoidosis have been demonstrated to predict adverse outcome in sarcoidosis. **(105,134,204,231,241,298, 301,304)** In patients with predominant RV disease, CS needs to be differentiated from arrhythmogenic right ventricular cardiomyopathy (ARVC). **(Figure 25)** Distinguishing features favoring sarcoidosis consist of an older age of onset, a non-familial pattern, wider QRS complexes, septal involvement with atrio-ventricular conduction disease, multiple arrhythmogenic foci, particularly RV apical tachycardia, concomitant LV disease, and the presence of mediastinal lymphadenopathy. **(305)** LGE of the septum and insertion points may result from delayed wash-out of gadolinium due to altered myocardial fiber strain, fiber disarray, ischemia, and fibrosis, secondary to RV pressure or volume overload, and resulting septal shift. **(300,306,307) (Figure 27)** Ventricular insertion point enhancement has been reported in HCM, atrial septal defects, severe PAH, tetralogy of Fallot, transposition of the great arteries and even a proportion of healthy veteran endurance athletes. **(306-311) (Figure 23)** The amount of insertion point enhancement correlates with mean pulmonary arterial pressures, RV mass, volume and ejection fraction. **(300)** PH in sarcoidosis is associated with adverse outcome, particularly when accompanied by RV dysfunction, and/or lung fibrosis. **(302,303)**

2.16 First-pass myocardial perfusion and perfusion reserve in sarcoidosis

Bogabathina was the first to report non-specific first-pass perfusion defects and widespread patchy LGE with DECMR in a patient with severe active CS. **(169)** Only a single study has systematically evaluated myocardial stress perfusion CMR in 43 asymptomatic sarcoidosis patients, 34 of which had evidence of diffuse interstitial fibrosis and an impaired CMR myocardial perfusion reserve index (MPRI). **(312)** Follow up of 18/34 patients a year later revealed an increased T2 ratio and LGE in 6/9 patients with initial evidence of myocardial inflammation. Treatment with corticosteroids resulted in a normalized CMR scan at 6 months follow up, without any cardiovascular symptoms or events during this period.

Kruse et al demonstrated regional impairment of coronary circulatory function in segments with sarcoid-mediated myocardial inflammation with $^{18}\text{FDG}/^{13}\text{NH}_3$ PET/CT. Effective immune-suppression mediated decrease in inflammation was associated with preserved myocardial flow reserve (MFR) at follow-up whereas MFR significantly worsened in regions without changes or even increases in inflammation. **(313)** Previous studies with dipyridamole thallium and technetium perfusion scintigraphy had demonstrated similar reversible perfusion defects at rest redistribution and after dipyridamole. **(110,114,251,314)** These findings suggest a subclinical functional myocardial micro vascular perfusion disorder, which may be amenable to immune-suppressive treatment. The clinical and prognostic relevance of these findings is currently unclear.

2.17 Pericardial sarcoidosis

Sarcoidosis rarely affects the pericardium, with only a few case reports describing granulomatous pericarditis with effusion, tamponade and constrictive pericarditis as a chronic sequellae. **(39-42)** DECMR allows for the assessment of pericardial thickness, inflammation, fibrosis, fluid and septal motion. **(Tables 4 and 5)**

2.18 Macro granulomas

Granulomatous proliferation may result in large inflammatory masses, most frequently infiltrating the interventricular septum. DECMR delineates the inflammatory nature, precise localization, size and response to immune-suppressive treatment of the contrast-enhancing mass. **(33,180,183,184)** **(Tables 4,5)** **(Figure 17)**

2.19 Can the distribution of LGE differentiate between different cardiomyopathies?

A pattern-based approach to assessment with DECMR in cardiomyopathies

The distribution pattern of LGE in ischemic heart disease generally includes the sub-endocardium and may involve the mid- and epicardial layers, as ischemia and subsequent myocardial cell necrosis advances after occlusion of the perfusing epicardial coronary. **(168,315)** The focal scar pattern in NICM is not restricted to the distribution of coronary arteries and does not progress from endocardial to epicardial. **(168,178,315-318)** Dilated cardiomyopathy may be differentiated from specific infiltrative or inflammatory cardiomyopathies by the predominantly linear and patchy mid-myocardial LGE. **(168,178,315-318)** The pattern of LGE in CS is patchy, multi-segmental, not related to coronary artery territories, predominantly involving the mid myocardial and subepicardial layers. Near transmural scar is present in a minority of patients. **(99,132,168,183,197,316-328,320-327)** The pattern of LGE in CS needs to be distinguished from viral myocarditis, Anderson-Fabry and Chagas disease, which also predominantly affect the mid-myocardium and epicardium. **(168,316-322)** The clinical settings, symptomatology, (family) history, and geographical region will help determine the most likely etiology and differentiate between these conditions. In addition to LV enhancement RV dilation and LGE is present in up to 30% of CS patients, which may help differentiate CS patients from viral myocarditis, Anderson-Fabry and Chagas disease. **(29,30,168,316-322)** The junction of RV and LV and the right-sided interventricular septum are predominantly affected. **(29,30)** These findings may be explained by primary RV myocardial involvement, but alternatively the presence of PAH, resulting from extensive pulmonary sarcoidosis, has been considered a possible cause of RV fibrosis. **(318,330)** **(Figures 7,9,18,20)** Smedema et al compared the LGE distribution in 30 CS patients with subsequent patients with ischemic infarct scar in blinded fashion, and were able to differentiate between these conditions in 80% of cases. **(330)** In a number of infarct patients who underwent primary PCI the LGE was distributed in an atypical pattern more suggestive of NICM. **(328)** These findings suggest that DECMR is helpful in the non-invasive differentiation between CS and ischemic scar. In conclusion, the presence of sole mid-layer, epicardial and patchy three layer LGE with a non-vascular distribution, in patients with extra-cardiac sarcoidosis suggests cardiac involvement, and differentiates these patients from patients with coronary artery disease and a variety of other NICMs. **(330)**

2.20 Prognostic value of DECMR - CMR as part of risk stratification

Symptomatic CS carries a poor prognosis unless adequately managed with medical therapy, cardiac implantable devices (CID), arrhythmia ablation, or, in advanced irreversible heart failure, heart transplantation. **(11,12,95,99,204,230,238,328,329)** Apart from symptomatic presentation (CCF, syncope, palpitations), ECG (late potentials, Sylvester QRS score, nsVT or sVT on ambulatory rhythm monitoring), inducible sVT/VF with PES, impaired global

longitudinal LV strain, impaired systolic LV or RV functions (cardiac ultrasound, CMR, MDCT, myocardial perfusion scintigraphy (MPS)/SPECT), LV and/or RV LGE on DECMR, and LV and/or RV FDG uptake with PET are predictors of admission for CCF, PM implantation and/or cardiac death. **(11,14,29,29,35,5052,84,100,115,116,135,136,201, 226,301, 330-338)** The presence, amount, transmural extent, LV and particular RV LGE carry strong independent risk of adverse outcome. **Table 9** presents the baseline data of the 9 DECMR studies included in our meta-analysis, which have provided prognostic data. **(30,133,177,204,289,298,339-341)** We conducted our meta-analysis based on the methods published by Hulten et al. **(134)** Since Hulten's original publication, two additional studies were published, which fulfilled the inclusion criteria. **(30,341)** **Tables 10** and **11** provide detail on the prognostic relevance of any (LV, RV, biventricular) LGE or RV LGE for sVT, admission for CCF, PM implantation for high-grade AVB, cardiovascular death, or all cause death. **Figures 29-36** depict the respective pooled relative risk (RR) of any myocardial LGE or RV LGE for these adverse events. Myocardial LGE predicts future cardiovascular adverse events and death. RV LGE, inflammation and impaired systolic function have previously been associated with adverse outcome, particularly ventricular tachyarrhythmias. **(95,133,204, 230,238,301)** Biventricular LGE at presentation may be the strongest, independent predictor of adverse outcome during long-term follow up. **(30)** The significance of small asymptomatic myocardial scar needs further study. Several prospective studies have demonstrated a favorable long-term outcome in NICM, including CS, when LV scar was < 8% of LV mass. **(30,100,333,336,339,352)** LGE is the underlying pathophysiological substrate of myocardial dysfunction, conduction disease and ventricular arrhythmias. DECMR allows for direct quantification of focal scar, and as expected this parameter out-performs secondary markers of myocardial disease such as LVEDV and LVEF.

2.21 The relevance of screening for subclinical cardiac sarcoidosis

Approximately 5-10% of sarcoidosis patients present with symptoms of CS. Although routine DECMR has revealed small asymptomatic scar in 20-25% of sarcoidosis patients, the significance of these findings is uncertain. **(30,99,343)** The prognosis of small asymptomatic scar seems favorable. Current guidelines advise against routine evaluation with PET/CT and/or CMR in sarcoidosis patients without cardiovascular symptoms and normal ECGs and/or CUS, despite the fact that myocardial scar may remain undetected with this basic baseline assessment. **(11,46,252,254,278,343)** There is currently no consensus concerning the intervals of assessment with advanced imaging technology such as PET/CT and CMR in symptomatic patients.

2.22 DECMR assists in clinical management of cardiac sarcoidosis

DECMR guides the interventionalist in obtaining representative EMBs by the preprocedural delineation of the localization and extent of granulomatous inflammation. Preproce-

dural imaging will customize the approach to endocardial, epicardial, RV or LV. **(77,81)** In patients with newly diagnosed AVB and/or myocardial dysfunction DECMR will help diagnose and manage CS as the potential reversible cause. **(7,12,13,222,263,332,344)** **(Figures 6,19)** In PM patients with progressive systolic LV dysfunction DECMR helps differentiate progressive CS from pacing-induced cardiomyopathy. **(345)** In patients with LBBB, LV dyssynchrony and systolic dysfunction DECMR will help predict a favorable response to biventricular pacing, by localizing and quantifying LV scar. **(346,347)** DECMR assists the electrophysiologist in identifying and delineating the arrhythmic substrate and determine the optimal, endocardial, epicardial or hybrid, approach needed for successful ablation. **(226,348-354)** DECMR provides crucial information concerning the transmural distribution of scar which surface mapping cannot provide. **(351,352,354)** The amount, localization and distribution of LGE have been associated with the risk of VT and SCD. Mid-myocardial LGE involving 25-75% of the wall thickness predicts inducible VT at PES. **(30,100,351,353)** Asymptomatic CS patients with limited LGE (<8%), preserved LVEF and negative PES have a favorable prognosis **(30,100)** DECMR provides post-ablation feedback concerning the depth and distribution of the lesions are linked with ablation failure. Eventually real-time DECMR guided endomyocardial mapping and ablation will increase procedural success rates. **(354,355,356,357)** In addition to PET DECMR will help optimize immune-suppressive treatment for CS, and risk-stratify i.e. when to implant an ICD by evaluating systolic LV and RV functions, defining and quantifying myocardial scar. **(11,30,293,332,358)**

2.23 Improved outcomes with modern management

Long-term outcomes in pts with CS have remarkably improved due to accurate diagnostic imaging, modern medical heart failure treatment, the introduction of CIDs, arrhythmia ablation and transplantation in selected patients. **(11,12,25,27,28,98,230,331,335,336,361)** Five-year survival rates have improved from 41% to current 5 and 10-year survival rates of over 90%. **(30,98,263,328,329,358,359-361)** Current annual mortality rates range from 0-4.2/100 pts compared to 7.5-12/100 pts as previously reported by Yazaki (2001) and Fleming (1974). **(20,30,48,359,362)**

2.24 Conclusions

DECMR has become an important modality in the diagnosis, risk stratification and management of CS. In addition to accurately and reproducibly quantifying myocardial structure and functions, DECMR characterizes myocardial inflammation, infiltration, focal and interstitial fibrosis, thereby guiding management, resulting in improved outcomes.

2.25 New and future applications of CMR in the management of cardiac sarcoidosis (Table 12)

Ultra-high field CMR and compressed-sensing techniques will shorten scan times, improve image quality and spatial resolution. **(212)** Mapping multiple relaxation times simultaneously will similarly save time and remove confounders introduced by the interaction of relaxation times. Three-dimensional mapping allows for more complete characterization of disease distribution, so-called CMR fingerprinting of the myocardium, which implies the generation of structural, mechanical, functional as well as biochemical information. **(210,212,367)** DECMR is not accurate in detecting and quantifying RV scar. Additional RV CMR strain imaging will enhance the diagnostic accuracy for RV sarcoidosis, and may assist in increasing the success rate of RV ablation procedures. **(371)** Detailed information concerning focal scar and diffuse biventricular interstitial edema, fibrosis, as well as segmental and global systolic functions and myocardial strain, will improve risk stratification and help determine which patients will benefit from ICD implantation. Future, prospective research will determine whether management decisions based on parametric mapping will improve outcomes. Hybrid PET/CMR imaging which combines the advantages of DECMR (image resolution, scar imaging, high specificity) with those of PET (high sensitivity for inflammation), will reduce examination time and cost, while individualized treatment based on serial investigations may help improve outcome. **(125,126,235,278,377-380)** Recent advances have made real-time CMR guided EMB in patients with suspected isolated CS and ablations of (supra)ventricular arrhythmias a reality. **(368,370, 371)**

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Table 1. Symptoms of cardiac sarcoidosis

1. (aborted) sudden cardiac death may be the first presentation: VT/VF, AVB
2. palpitations: PAF, SVTs, (non-)sustained VTs
3. pre/syncopal episodes: SVTs, AVB, VT/VF, cor pulmonale
4. chest discomfort: compression of intramural coronary arteries by granulomas, pericarditis, rarely coronary vasculitis, pulmonary hypertension
5. dyspnea: arrhythmias, diastolic or systolic heart failure, pericarditis, tamponade, mitral regurgitation, pulmonary hypertension
6. pitting edema lower extremities: systolic or diastolic heart failure, tamponade

VT/VF- ventricular tachycardia/ventricular fibrillation

AVB – atrioventricular block

PAF – paroxysmal atrial fibrillation

SVT-supraventricular tachycardia

VT- ventricular tachycardia

Table 2. Overview of the diagnostic modalities for cardiac sarcoidosis.

Modality	Diagnostic accuracy	Prognostic accuracy	Strengths	Weaknesses	References
X chest (Figure 3)	poor	poor	low cost, lungs, nodes, cardiac size, device, leads	insensitive, non-specific	45
Cardiac ultrasound					
SWMA	poor	limited data		limited by imaging window,	47,48
SWT	poor	limited data		limited ability to detect focal disease	49,50
LoSWT	poor	limited data			51,52
diastolic dysf (E _s A)	poor	no data			53,54
LVEF	poor	relevant			55
LV, RV regional/global strain	poor	promising			49
longitudinal LV stain	sensitive				52,56,57
Laboratory					53, 58
ACE	poor	no data	non-invasive	limited data, non-specific	60,61
Lysozyme	poor, non-spec	no data	pulm disease activity		60,62,63
Highly sensitive troponins	promising	limited data	reflects active disease		59,60,64,65
NT-pro-BNP	high for CCF	limited data	monitoring of CCF	non-specific	49,65,66,67
Exosomal micro RNA	promising	no data		non-specific	68,69
Galectin-3	poor	no data		non-specific	58
Tenascin-C	poor	no data		non-specific	58
Neopterin	not	no data	reflects active disease	general dis activity	70,71
Soluble interleukin-2 receptor	limited	no data	reflects active disease	general dis activity	72
Interleukine 10	limited	no data	reflects active disease	general dis activity	62
U-8-OHdG	limited	promising	reflects active disease	general dis activity	73,74
Endo-Myocardial Biopsy (Figure 4)	Limited	limited data	definite, highest level of evidence	Invasive sampling error, but CMR or PES guided EMB more accurate	46,75,76,77,78,79,80, 81,82

Modality	Diagnostic accuracy	Prognostic accuracy	Strengths	Weaknesses	References
Resting ECG (Figure 5)	generally poor	strong when VT, AVB, Q's	widely available, low cost, first line		3,14,15,83,84
Selvester QRS score	promising	no data			85
Q waves	se 11%/sp100%	no data			86
fragmented QRS	se 100%/sp80%	no data			86,87
Microvolt T-wave alternans	91.4%	no data			88
SAECG	uncertain	no data		Schuller	89
QTc dispersion	limited data	no data			90
TWAa VR	poor				91
Exercise ECG	poor, limited data	poor, limited data	functional information on conduction, rhythm	influenced by respiratory and musculo-skeletal status	92
Exercise Echocardiography	limited data	limited data	functional information on systolic ventricular functions		93
Ambul Rhythm Monitoring				Soejima	95
Short term (1-7 days)	limited, sens 67%/spec 80%	limited			96,97,98
Long term (1CM)	high	high			99,100
PES		significant			14,101,102,103
Contrast-Enhanced MDCT	promising	no data	alternative to CMR in pts with devices	Radiation	104,105,106,107,108, 109
^{99m} Tc pyrophosphate SPECT	limited	limited data		poor resolution, non-specific	110
²⁰¹ Thallium SPECT	limited	limited data		poor resolution, non-specific	110,111,112,113
Tc ⁹⁹ MIBI SPECT (Figure 6A)	limited	limited data	superior to ²⁰¹ Thallium	limited resolution, non-specific	110,113,114
⁶⁷ Gallium SPECT	poor	Poor	predicts response to cortisone, cardiac and extra-cardiac involvement	limited resolution	111,112
⁶⁷ Gallium/ ^{Tc} ⁹⁹ MIBI SPECT					110
					46
					115

Modality	Diagnostic accuracy	Prognostic accuracy	Strengths	Weaknesses	References
PET/CT (Figure 8)	high	high	(extra-)cardiac involvement, monitoring of disease activity, available, limited resolution, alternative to CMR in pts with devices, diagnostic, prognostic value	cost, radiation, not widely particularly when evaluating the RV	116,117 110,118,111,112 46,118,119 46,120 121 122,123 124 124-130
F18-FDG (Figures 6A, 7B)					
F18-FDG/N13-NH3					
F18-FDG/Rb (Figure 8)					
Ocetreotide					
⁶⁸ Ga-DOTA-TOC					
¹¹ C-4DST					
PET/CMR	superior	superior	combined advantages of PET and CMR	cost, radiation	
¹¹¹ Inpentetreotide/ ^{99m} Tc-MIBI SPEDCT	limited data	no data	predicts response to cortisone	Radiation	131
DECMR (Figures 6B, 7A)	high	high	high resolution, free from ionizing radiation, structure, function, robust technology, diagnostic, prognostic value	cost, implanted devices may be contra-indication	29,30,132-136

CMR – Cardiovascular Magnetic Resonance
CT – Computed Tomography
DPECT – Dual injection Dual Photon Emission Computed Tomography
DECMR – delayed enhanced cardiac magnetic resonance imaging
ECG – Electrocardiography
ICM – rhythm monitoring by implanted cardiac devices
LoSWT – loss of segmental wall thickness
MDCT – Multi-Detector Computed Tomography
PES – Programmed Electrophysiological Stimulation
PET – Positron Emission Tomography
sc - sensitivity
sp - specificity
SWMA – segmental wall motion abnormality
SWT – segmental wall thickening
SPEDCT - Single Photon Emission Dual Isotope Computed Tomography
SPECT – Single Photon Emission Computed Tomography
TWAaVR- T wave amplitude in lead aVR
U-8-OHdG - urinary 8-Hydroxy-2'-Deoxyguanosin

Table 3. Differential diagnosis of (non-)caseating myocardial granulomas.

Condition	Presentation	Histopathology	Prognosis
Cardiac Sarcoidosis (147, 148, 149, 154)	generally subacute, syncope, AVB, palpitations, American, Japanese, Scandinavian	tight, naked, non-caseating epithelioid granulomas, interstitial and replacement fibrosis, cytoplasmic inclusion bodies	improved transplant free survival - > 70% at 5 years
Giant Cell Myocarditis (147, 148)	acute, progressive left-sided CCF	myocyte necrosis, edema, macrophages, MGC lymphocytes, plasma cells, eo's	poor transplant free survival -22% at 5 years
Chronic Berylliosis (149-152)	occupational exposure	non-caseating granulomas	determined by extent of pulmonary fibrosis
Tertiary Syphilis (149-152)	aortic aneurysm, coronary ostial stenosis	gumma, non-caseating granulomas, spirochetes,	favourable on penicillin
Polyarteritis Nodosa (149-152)	arthritis, nephritis	non-caseating granulomas	depends on extend of visceral, renal and CNS involvement
Hypersensitivity myocarditis (149-152)	rash, fever, arrhythmias	ill-defined non-caseating granulomas, eosinophils	favourable
Toxic myocarditis (149-153)	chest discomfort, heart failure, arrhythmias	neutrophils, lymphocytes, plasma cells, few eosinophils	guarded
Tuberculosis (150-152)	fever, night sweats, weight loss	caseating granulomas, larger rim of lymphocytes	favourable, depends on immune (in)competence and resistance of organism
Fungal infections (149-152)	fever, respiratory symptoms	non-caseating granulomas, neutrophilic microabscesses, necrosis, staining of fungus	determined by immune (in)competence
Rickettsial infections (149-152)	flu like symptoms, skin rash	small vessel vasculitis, thrombosis, necrosis	favourable on treatment
Parasitic/Protozoal infections (149-152)		eosinophils, lymphocytes, plasma cells	favourable on treatment
Foreign body reaction (149-152)	implanted device, catheter, lead in situ	non-caseating granulomas formed around foreign material	favourable
Churg-Strauss Vasculitis (149-152)	bronchial asthma, rash, arthralgia	non-caseating granulomas, marked eosinophilia	favourable on treatment
Wegener's Granulomatosis (149-152)	upper respiratory tract: epistaxis, sinusitis, nephritis	non-caseating granulomas	guarded, related to extent of baseline organ damage, drug toxicity, renal involvement
Takayasu Arteritis (149-151)	fever, arthralgia, large and medium arterial stenosis/occlusion, visual	non-caseating granulomas	favourable on treatment

Condition	Presentation	Histopathology	Prognosis
Erdheim-Chester disease (149-152)	bone, pituitary gland, eyes	foamy macrophages, occasional Touton type giant cells	high mortality rates
Oxalosis (149-152)	uroolithiasis, nephrocalcinosis	intra/extracellular oxalate crystals, necrosis	favourable on treatment
Rheumatoid Arthritis (149-152)	symmetric arthritis	necrosis surrounded by histiocytes/fibroblasts without giant cells	favourable on treatment
Rheumatic Carditis (149-152)	fever, rash, migrating polyarthritis, chorea	pancarditis, Aschoff bodies, Anitschkow cells, fibrinoid necrosis	guarded
Lupus Erythematosus (149-152)	butterfly rash, arthralgia, serositis, nephritis	non-casecting granulomas	determined by renal involvement

AVB – atrioventricular block, CCF – congestive heart failure, CNS – central nervous system, MCG - multinucleated giant cells

Table 4. CMR sequences used in cardiac sarcoidosis and their purpose.

CMR sequence	Spatial Resolution(mm)	Significance	Drawback	Reference
black blood SE T1, HASTE	1.7×2×8-10	structural information		99,132,160-165 (Figure 12)
black blood SE T2, double/triple IR, STIR	1.5-2×1.5-2 × 6-10	myocardial edema, with fat-suppression (STIR), blood pool suppression (double IR), both blood/fat suppression (triple IR)	sensitive to artifact, mapping superior	159,160,161,164 38,167,168 165,169 (Figure 13)
bSSFP	1.2-2.1×1.2-2.1×5-10 (temporal 25-49 msec)	functional information ie myocardial mass, ventricular volumes, ejection fractions		99,159-162,164,170,176
myocardial perfusion	1.4×1.4×10	not particularly helpful – should match LGE, when otherwise consider coronary vasculitis or CAD – compares to perfusion deficits on nuclear perfusion studies ie T1 and Tc ie granulomas impeding microcirculation		162,172,173,175,312
T1 mapping, ECV multiple single-shot bSSFP MOLL, ANGIE, STONE, AIR, SASHA, SAP-T1, SAPPPIRE		interstitial fibrosis, deposition, inflammation	promising, little data	171,172,173,205-217, 220,229 (Figures 15,16)
T2 mapping TSE with varying echo time bSSFP spoiled GRE GraSE		myocardial edema, inflammation	promising, little data	171-174,212,220,222-225,227,229 (Figures 14, 16)
ERE - black blood SE T1	1.5-2×1.5-2 × 6-10	increased ratio between myocardium/skeletal muscle suggests hyperemia/ capillary leakage capillary expansion, inflammation		162,175,183
Delayed Enhanced SE (until 2002) IR-GRE	0.7-2×0.7-2×8-10 0.9-1.8×0.9-1.8×6-10	focal myocardial scar	inconsistent image quality, reproducibility challenging, timing of image acquisition, lower accuracy in diagnosing myocarditis compared to T2 and LGE	160,161,162 99,164,176 (Figure 12) 132,134,168,178(Figure 14)
MCLE	1.5×1.5×6-10	increased sensitivity optimized inversion time		38
PSIR	0.9-1.8×0.9-1.8×6-10	likely inflammation, interstitial and scar	little data, unknown significance for now	164,177,178,183
strain analysis				179

Black blood sequences: anatomy, T1 weighted, inversion recovery prepulses to null the signal from blood - double IR - or both blood and fat triple IR; **ECV** - extracellular volume; **HASTE** - Half-Fourier Acquisition Single-shot Turbo-spin-Echo for anatomy; **PSIR** - Phase-Sensitive Inversion Recovery; **IR-GRE** - Inversion Recovery Gradient Echo; **IR-FGRE** - Inversion Recovery Fast Gradient Echo; **MCLE** - Multi-Contrast Late Enhancement Imaging; **SE** - Spin Echo; **Bright blood sequences:** **bSSFP** - balanced Steady-State Free Precession, to evaluate myocardial function, ventricular volumes and myocardial mass, high SNR; **STIR** - Short Tau Inversion Recovery - fat signal suppression, uses a short inversion recovery time, thus cannot be used with gadolinium since this agent also shortens T1 time, would result in ambiguous images; **FLAIR** - Fluid Attenuation Inversion Recovery - similar to suppress water signal; **ERE** - early relative myocardial enhancement.

Table 5. The application of CMR sequences in cardiac sarcoidosis.

Findings in CS	Sequences	Figure	Reference
asymmetric hypertrophy of the septum	HASTE, T1SE, bSSPF	17	33,53,180,181,185
loss of wall thickness	SSPF	18	53,99,159-162,164,165,170,176
inflammation, myocardial edema	T2-SE,	13	174,178,185,
	T2 STIR,	13	165,169
	T2 mapping,	14,16	165,171-174,212,222-225,227
	early relative contrast-enhancement (ERE)		162,175,183
pericardial fluid	bSSPF, T2-SE		41,42,162
contractive pericarditis	bSSFP, IR-GRE		39,40
segmental hypo-akinesia, LVEF	bSSFP	18	99,159-162,164,170,176
aneurysms	bSSFP, IR-GRE, PSIR		34,35,185
papillary muscle fibrosis, dysfunction, valvular regurgitation	IR-GRE, SSFP	12,18,19	37,38,164
focal scar	IR-GRE, PSIR, MCLE	12,13,18,19	38,132,134,164,168,177,178,183
interstitial fibrosis	T1-mapping, ECV	14,15	171-173,205-217,220,229
RVI, cor pulmonale, RVEF	bSSFP	20	28-32
large granulomas, valvular, myocardial, septal	T1 SE, T2 SE, SSFP, IR-GRE	17	33,180,181

Table 6. Properties of the gadolinium-based contrast agents used in CMR.

Generic name (Trade name)	Protein binding	Structure Charge	Type	elimination	Reported NSF
gadodiamide (Gd-DTPA-BMA) (Omniscan®)	none	linear non-ionic	extracellular	renal	yes- contra-indicated in renal failure
gadoversetamide (Gd-DTPA-BMEA) (OptiMARK®)	none	linear non-ionic	extracellular	renal	yes – contra-indicated in renal failure
gadopenetate dimeglumine (Gd-DTPA) (Magnevist®)	none	linear ionic	extracellular	renal	yes – contra-indicated in renal failure
gadobenate dimeglumine Gd-BOPTA (MultiHance®)	< 5%	linear ionic	extracellular	97% renal 3% bile	yes, higher T1/T2 relaxivity contrast agent, better for perfusion, MRA
gadoxetate disodium Gd-EOB-DTPA (Eovist/Primovist®)	< 15%	linear ionic	hepatobiliary	50% renal 50% bile	no
gadofosveset trisodium (Gd-DTPA) (Ablavar/Vasovist®)	> 85%	linear ionic	Bloodpool	91% renal 9% bile	no
gadoterate meglumine (Gd-DOTA) (Dotarem®)	none	macrocyelic ionic	extracellular	renal	no
gadobutrol (Gd-DO3A-butriol) (Gadavist/Gadovist®)	none	macrocyelic non-ionic	extracellular	renal	no
gadoteridol (Gd-HP-DO3A) (Prohance®)	none	macrocyelic non-ionic	extracellular	renal	no

DTPA - diethylenetriaminopentaacetic acid

DOTA – tetraazacyclododecanetetraacetic acid

NSF – nephrogenic systemic fibrosis

Table 7. CMR - differential imaging diagnosis of cardiac sarcoidosis.

Diagnosis	DECMR findings
Coronary Artery Disease	segmental edema/LGE subendocardial to transmural, coronary artery distribution, matched segmental LV/RV systolic dysfunction, impaired EF (Figure 20,23)
Viral Myocarditis	predominant segmental LV edema/LGE, epicardial to transmural, particularly lateral LV segments (Figure 23)
Giant Cell Myocarditis	predominant LV edema/LGE, with wall motion abnormalities, impaired LVEF
ARVC	predominant segmental or global RV dilation/systolic dysfunction, segmental RV dyskinesia, predominant RV LGE, segmental fatty RV infiltration/replacement (Figure 25)
Dilated Cardiomyopathy	globular, dilated LV/RV, global/multi-segment systolic dysfunction myocardial mid-layer LGE (Figure 23)
Amyloidosis	LVH, eventual dilation with systolic dysfunction, patchy, confluent or subendocardial LGE (Figure 23)
Hypertrophic Cardiomyopathy	SAM, segmental LVH with related focal LGE (Figures 22,23,26)
Chagas	segmental LV/RV systolic dysfunction – hypo-dyskinesia, LOWT, segmental edema/LGE subendocardial to transmural, non-coronary artery distribution

LGE – late gadolinium enhancement, LOWT – loss-of-wall-thickness, LV- left ventricle, RV – right ventricle, SAM – systolic anterior motion of the anterior mitral valve leaflet

Table 8. The role of CMR in the diagnostic Guidelines.

Organization	Country	Year	Role of CMR	Reference
Japanese Ministry of Health and Welfare	Japan	1993	None	277
Japanese Society of Sarcoidosis and Other Granulomatous Disorders	Japan	2006	Diagnostic minor criterium – myocardial LGE in a pattern compatible with CS Diagnostic major criteria – basal thinning of the interventricular septum	250,266
Japanese Society of Nuclear Cardiology Recommendations	Japan	2014	None, FDG guideline	279
New Japanese guidelines for the diagnosis and treatment of CS	Japan	2017	Diagnostic major criterium – 1.myocardial LGE in a pattern compatible with CS 2.thinning of the basal IVS 3.ventricular aneurysm 4.LVEF < 50%	250
WASOG	International	2014	Diagnostic: at least probable CS when LGE in a pattern compatible with CS and/or increased T2 signal on (DE)CMR indicative of CS	253
German Respiratory and Cardiac Societies	Germany	2014	Diagnostic: probable CS - in the presence of diagnostic biopsies of extracardiac tissue, CMR findings suggestive of CS (increased T2 signal, wall motion abnormalities, increased thickness, or loss of thickness, LGE) Diagnostic: certain CS - CMR findings of CS in the presence of 12-lead resting ECG, and/or Holter and/or TTE findings	252
HRS	International	2014	1.Diagnostic: probable CS - LGE in a pattern compatible with CS in pts with biopsy proven extra-cardiac sarcoidosis with either cardiac symptoms and/or abnormalities on 12-lead resting ECG, and/or TTE 2.Risk stratification: particularly in pts with LVEF > 35%, diagnosis in patients with extracardiac histology for sarcoidosis and cardiac LGE in a pattern which suggests CS	11
European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology.	Europe, USA	2017	1.Diagnostic value in suspected CS – symptomatic pts with biopsy proven extracardiac sarcoid and/or abnormal ECG and/or inconcl cardiac US – LGE/T2 2.Suspected relapse of CS 3.Prognostic value - LGE	46,275

Table 9. Baseline characteristics of the 9 studies included in the meta-analysis on the prognostic value of LGE in CS.

Authors	n	LGE+ (%)	RV LGE+ (%)	LGE mass (LV%)	LVEF LGE + LGE- LGE- LGE-	LVEDV($\bar{v}$) LGE + LGE- LGE- LGE-	RVEF LGE + LGE- LGE- LGE-	FU y	Age Y	F %	Ethnicity %	steroids %	CMR field strength Tesla
Murtagh (298)	205	41 (20)	...	8 $\pm$ 10	59 $\pm$ 5 61 $\pm$ 6	71 $\pm$ 15 72 $\pm$ 15	51 $\pm$ 9 52 $\pm$ 7	3.0	56 $\pm$ 7	69	AA 59	45	1.5
Patel (133)	81	21 (26)	14 (17)	6 (2,19)	45 median 57 median	...	...	1.8	46 $\pm$ 11	69	AA 73	91	1.5
Greulich (176)	153	39 (25)	'most'	4 (3,9)	55 [46-66] 65 [61-70]	140 [96-196] 125 [107-146]	...	2.6	50 $\pm$ 13	41	...	72	1.5
Nadel (289)	106	32 (30)	2 (2)	...	48 $\pm$ 11 60 $\pm$ 8	...	...	3.1	51 $\pm$ 12	40	...	58	...
Crawford (204)	51	32 (63)	13 (25)	15 $\pm$ 12	52 $\pm$ 10 52 $\pm$ 9	194 $\pm$ 45 143 $\pm$ 73	46 $\pm$ 13 45 $\pm$ 7	4.0	51 $\pm$ 10	68	AA 47	47	1.5
Nagai (339)	61	8 (13)	...	...	60 $\pm$ 3 64 $\pm$ 1	105 $\pm$ 9 105 $\pm$ 3	...	4.2	57 $\pm$ 15	79	J 100	16	1.5
Shafee (340)	37	26 (70)	...	...	56 $\pm$ 14 57 $\pm$ 8	...	...	3.8	57 $\pm$ 12	88	J 100	0	1.5
Smedema (30)	84	28 (33)	12 (14)	15 (6,33)	55 [49-72] 64 [50-70]	132 [92-172] 111 [91-131]	46 [36-56] 48 [42-54]	4.7	53 $\pm$ 10	64	C 75	71	1.5
Kouranos (341)	321	...	...	...	...	...	...	7	...	...	...	...	1.5
Overall	778	227	41										1.5

Columns represent absolute (% annualized incidence). Outcomes pooled by random effects meta-analysis are reported in the final row. Cardiovascular death reported by Crawford et al in the LGE – comparison group was not included because of uncertainty of the cause of death. Not all studies reported on heart failure admission, pacemaker implantations or cardiovascular (CV) mortality.

Table 10. Major adverse events according to the presence of any LGE.

Authors	N	FU, y	All cause mortality		Ventricular Arrhythmia		Death or Ventricular Arrhythmia		CV mortality		Pacemaker		Heart Failure Admission	
			LGE+ n=294 (%)	LGE- n=770 (%)	LGE+ n=320 (%)	LGE- n=781 (%)	LGE+ n=320 (%)	LGE- n=779 (%)	LGE+ n=253 (%)	LGE- n=586 (%)	LGE+ n=193 (%)	LGE- n=430 (%)	LGE+ n=161 (%)	LGE- n=311 (%)
Murtagh	205	3.0	6 (4.9)	2 (0.4)	4 (3.3)	0	10 (8.1)	2 (0.4)	...	...	...	...	...	...
Patel	81	1.8	4 (10.5)	2 (1.8)	2 (5.2)	0	6 (15.7)	2 (1.8)	4 (10.5)	1 (0.9)	...	...	...	...
Greulich	153	2.6	3 (3)	1 (0.3)	13 (12.8)	0	10 (9.9)	1 (0.3)	3 (3)	0	...	...	...	...
Nadel	106	3.1	4 (4.1)	8 (3.5)	8 (8.2)	0	12 (12.2)	8 (3.5)	3 (3.1)	1 (0.4)	2 (2)	2 (0.9)	15 (2.4)	3 (0.2)
Nagai	61	4.2	0	3 (1.4)	0	0	0	3 (1.4)	0	0	1 (0.1)	0	0	0
Crawford	51	4.0	2 (1.6)	1 (1.3)	13 (10.2)	0	14 (10.9)	1 (1.3)	1 (0.8)	...	1 (0.1)	0	...	...
Shafee	37	3.8	...	...	8 (8.1)	0	11 (11.3)	0	...	...	...	...	...	...
Snedema	84	4.7	1 (0.8)	3 (1.1)	6 (4.6)	1 (0.4)	7 (5.3)	4 (1.5)	1 (0.8)	0	0	1 (0.4)	1 (0.8)	0
Kouranos	321	7	9 (10)	4 (2)	7 (8)	0	16 (17)	4 (2)	7 (8)	1 (0.4)	...	...	3 (3)	0
Pooled	778	...	20 (3.6)	20 (1.4)	54 (6.6)	1 (0.1)	70 (9.2)	21 (1.3)	12 (2.3)	2 (0.3)	4 (0.5)	3 (0.3)	...	...

Columns represent absolute (%) annualized incidence). Outcomes pooled by random effects meta-analysis are reported in the final row.

Cardiovascular death reported by Crawford et al in the LGE – comparison group was not included because of uncertainty of the cause of death. Not all studies reported on heart failure admission, pacemaker implantations or cardiovascular (CV) mortality.

Table 11. Major adverse events according to the presence of right ventricular LGE.

Authors	n	FU, y	All cause mortality		Ventricular Arrhythmia		Death or Ventricular Arrhythmia		CV mortality		Pacemaker		Heart Failure Admission	
			RVLGE+ n=25 (%)	RVLGE- n=110 (%)	RVLGE+ n=25 (%)	RVLGE- n=110 (%)	RVLGE+ n=25 (%)	RVLGE- n=110 (%)	RVLGE+ n= (%)	RVLGE- n= (%)	RVLGE+ n= (%)	RVLGE- n= (%)	RVLGE+ n= (%)	RVLGE- n= (%)
Murtagh	205	3.0	...	...	...	...	...	...	...	...	...	...	...	...
Patel	81	1.8	...	...	...	...	...	...	...	...	...	...	...	...
Greulich	153	2.6	...	...	...	...	...	...	...	...	...	...	...	...
Nadel	106	3.1	...	...	...	...	...	...	...	...	...	...	...	...
Nagai	61	4.2	...	...	...	...	...	...	...	...	...	...	...	...
Crawford	51	4.0	1/13 (2)	1/38 (0.7)	10/13 (19)	4/38 (2.6)	11/13 (21)	5/38 (3)	0/38 (0)	...	...	...	...	...
Shafee	37	3.8	...	...	...	...	...	...	...	...	...	...	...	...
Snedema	84	4.7	2/12 (3.5)	2/72 (0.6)	4/12 (7.1)	4/72 (1.2)	6/12 (10.6)	6/72 (1.8)	1/12 (1.8)	0/72 (0)	0	0	1/12	0/72
Kouranos	321	7	...	...	...	...	...	...	...	...	...	...	...	...
Pooled	778	...	...	...	...	...	...	...	...	...	...	...	...	...

Columns represent absolute (% annualized incidence). Outcomes pooled by random effects meta-analysis are reported in the final row. Cardiovascular death reported by Crawford et al in the LGE – comparison group was not included because of uncertainty of the cause of death. Not all studies reported on heart failure admission, pacemaker implantations or cardiovascular (CV) mortality.

Table 12. Future imaging directions in the evaluation and management of cardiac sarcoidosis.

Modality	Principle	Novel benefit	Current status
SPIONs - superparamagnetic iron oxide nanoparticles (50-250 nm)	accumulation of USPIOs reduces the T2* decay time and creates signal deficits that can be visualized and quantified by T2*CMR.	non-invasive method for the diagnosis and monitoring of the tissue macrophage activity in the myocardium	proof-of-concept, ongoing clinical research
USPIOs - ultrasmall superparamagnetic particles of iron oxide (20-50 nm)			
VSPIOs - very small SPIONs (<20 nm)			
hybrid PET-CMR	combining the localization/quantification of radioactively labeled biological molecules and CBFA in the heart/chest	detecting, localizing, quantifying and matching inflammation and scar	available in selected centres
¹⁹ F MRI - intravenous perfluorocarbon	fluorine particles are virtually absent in the human body, which means no background noise	early detection and delineation of inflammation	preclinical studies
CMR-guided EMB	fusion of CECMR images with fluoroscopy and electro-anatomic mapping	increasing diagnostic accuracy of EMB	available
	real-time intra-bore MRI guided EMB		proof of concept, ongoing research, further technological advances needed
CMR-guided arrhythmia ablation	fusion of CECMR images with fluoroscopy and electro-anatomic mapping	improving ablation success by delineating myocardial scar	proof of concept, ongoing research, further technological advances needed
	real-time intra-bore MRI guided EMB

Figure 1. Distribution of cardiac involvement in sarcoidosis

1. Atrial infiltration and fibrosis resulting in atrial arrhythmias (AF, AFL, AT) (prevalence: frequent, post-mortem studies, case-reports) (15,23)
2. Coronary vasculitis (prevalence: rare, case-reports) (24,25)
3. Vasculitis of the aorta or pulmonary arteries (9,15,26)
4. Right ventricular infiltration and fibrosis (frequent, post-mortem series, case-reports) (27,28,29,30,31)
5. Granulomatous infiltration with asymmetrical hypertrophy and eventual fibrosis with loss of thickness of (the base of) the interventricular septum, resulting in atrio-ventricular conduction block (frequent, case-reports, post-mortem series) (15,16,32)
6. Cardiac aneurysm, associated with corticosteroid use (rare, case-reports) (15,33,34)
7. Granulomatous infiltration, fibrosis and secondary retraction of the papillary muscle(s) with tricuspid and/or mitral regurgitation (case-reports) (35,36,37)
8. Intraventricular thrombus, secondary to myocardial fibrosis, dysfunction and aneurysm formation (15)
9. Pericardial granulomatous infiltration, pericardial effusion, and rarely tamponade or constrictive pericarditis (38,39,40)

Figure 2. Number of publications on cardiac sarcoidosis included in Pub Med (1940-June 2017) related to the introduction of diagnostic methods and therapeutic interventions.

CUS-cardiac ultrasound, PM-pacemaker, EMB-endomyocardial biopsy, PES-programmed electrical stimulation; ICD-implantable cardioverter defibrillator, VT-ventricular tachycardia, CMR-cardiovascular magnetic resonance, TI – thallium, Ga-gallium, FDG PET-fluorodeoxyglucose positron emission tomography,

Figure 3. X chest (antero-posterior views) demonstrates mild cardiomegaly, bilateral reticulonodular changes predominantly affecting the upper lobes (stage 2 pulmonary sarcoidosis), and the presence of a single chamber implantable cardioverter defibrillator in a patient with cardiac sarcoidosis (left panel). The right-sided panel shows marked globular cardiomegaly in a patient with sarcoid cardiomyopathy, with a dual chamber pacemaker for third degree AVB in situ. He presented in cardiogenic shock with recurrent sustained VT (see 12 lead electrocardiogram below), was intubated (endotracheal tube in situ), ventilated and warranted recurrent electrical cardioversion (patches visible).

Figure 4. Endomyocardial biopsy demonstrates a sarcoid granuloma (arrow) consisting of giant cells, macrophages, CD4 lymphocytes, and hyaline sclerosis.

Figure 5. 12-lead electrocardiogram which demonstrates sustained monomorphic ventricular tachycardia (sVT).

Figure 6A. A 63 year-old man presented with recent onset symptoms secondary to third-degree atrio-ventricular block, for which a dual chamber pacemaker was inserted. MIBI-technetium SPECT demonstrated “reversed uptake” in the septal and apical segments (bull’s eye representation: A- rest image: apical and inferoseptal perfusion defects, B- stress image: apical perfusion defect decreased in size), suggestive of active granulomatous infiltration of these segments. FDG-PET showed increased nodular activity of the septum and anterolateral papillary muscle (E- horizontal long axis view, F- short axis view, equatorial slice; arrows point towards increased uptake). We diagnosed cardiac involvement according to the criteria published by the Japanese Ministry of Health (1996), and initiated treatment with oral steroids and methotrexate. Three months later his atrioventricular conduction had nearly recovered, with the percentage pacing being one. Follow up with MIBI-technetium SPECT revealed significant decrease of abnormalities, with small irreversible inferoseptal and apical defects remaining (C- rest image, D- stress image: small apical and inferoseptal perfusion defects). FDG-PET however still revealed increased nodular uptake in the inferior interventricular septum and papillary muscle (G- horizontal long axis view, H- short axis view, equatorial slice; arrows point towards increased uptake). Systolic ventricular function remained normal, without mitral valve regurgitation.

Figure 6B. DECMR study (Inversion-Recovery Gradient Echo sequence, end-diastolic frame, short axis view) in the same patient 3 months after the dual chamber pacemaker had been inserted. Ventricular insertion point enhancement is demonstrated (triangles). Pulmonary pressures were normal. (asteriks – artifact of right ventricular pace lead **B**: Seven years later DECMR demonstrates substantially more enhancement of the right-sided septum (arrow) and the insertion points (triangles). The percentage time pacing had increased from 5% to 15% of the time. (asteriks = artifact produced by right ventricular pace lead).

Figure 7A. Contrast-enhanced magnetic resonance study in a patient with biventricular congestive heart failure (left-sided panel, Inversion-Recovery Gradient Echo sequence, short axis view) demonstrates enhancement of the

right-sided interventricular septum and inferior right ventricular insertion point. The horizontal long axis view of the identical patient demonstrates enhancement of the RV free wall and right-sided interventricular septum. (right-sided panel, Inversion-Recovery Gradient Echo sequence)

Figure 7B. FDG PET of this patient demonstrates sarcoid lymphadenopathy (triangles) and active inflammation of the antero-apical LV segments and RV free wall (arrows).

Figure 8. Examples of focal inflammation of the RV due to sarcoidosis. **Example 1:** A 50 year-old female had pacemaker implantation for pre-syncope because of high degree block due to sarcoidosis. PET/CT for suspected CS identified a medium sized perfusion defect throughout the basal septum with increased FDG uptake (“mismatch pattern”). There was also FDG uptake involving the apex and RV free wall (arrow). Whole-body images show FDG uptake in the liver and spleen and in the paratracheal lymph nodes. EMBx identified the presence of granulomas consistent with the diagnosis of sarcoidosis. Interrogation of her ICD 3 month later identified the presence of rapid VT at a rate of 200 beats/min, which required anti-tachycardia pacing therapy. **Example 2:** 48-year-old male with pulmonary sarcoidosis who was referred for PET/CT for suspected cardiac involvement. He was found to have a perfusion defect associated with focal FDG uptake along the basal anterior and inferior septum as well as multiple focal areas of FDG uptake throughout the RV (arrows). Lymph node biopsy results confirmed the presence of sarcoidosis. Less than 1 month after ICD implantation he had an episode of VT (see rhythm strip). CT = computed tomography; PET = positron emission tomography. (Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, Kazemia P, Kwong RY, Tokuda M, Skali H, Padera R, Hainer J, Stevenson WG, Dorbala S, Di Carli MF. Cardiac Positron Emission Tomography Enhances Prognostic Assessments of Patients With Suspected Cardiac Sarcoidosis. *J Am Coll Cardiol* 2014;63(4):329-336. Reproduced with permission from the publisher)

Figure 9. Pattern of sarcoid involvement, apex to base. Often haphazard involvement of myocardium is present with variation from apex to base. However, a propensity was seen in this heart for posterior septal involvement, anterior subepicardial involvement, and right ventricular involvement, which in this heart, was anterior towards the base, and posterior throughout, merging with the septal disease. The apical tip demonstrates epicardial sarcoid. (Tavora F, Cresswell N, Li L, Ripple M, Solomon C, Burke A. Comparison of Necropsy Findings in Patients With Sarcoidosis Dying Suddenly from Cardiac Sarcoidosis Versus Dying Suddenly from Other Causes. *Am J Cardiol* 2009;104:571–577. Reproduced with permission from the publisher.)

Figure 10: Distribution of the cardiac lymph vessels and regional lymph nodes.

□ LGE ■ blood pool ■ unenhanced myocardium

Figure 13. T2 SE and T2 SE STIR demonstrate active cardiac sarcoidosis. **Panel A** reveals diffuse transmurular edema in the basal anterolateral LV, while **panel B** shows focal granulomatous infiltration in the interior interventricular septum.

□ myocardial edema/granuloma ■ blood pool ■ unenhanced myocardium

Figure 14. A 44 year-old male presented with non-specific systemic symptoms and dyspnea. T2 mapping shows prolonged T2 in the inferior and anterior segments (left upper panel). EMBs taken from the interventricular septum were diagnostic of CS. T2 The LGE in the inferior and anterior segments signified active granulomatous infiltration and cardiomyocyte degradation (left lower panel). Follow up mapping shows recovery of prolonged T2 in the inferior and anterior segments after treatment with corticosteroids for active CS (right upper panel). The LGE in the inferior and anterior has largely resolved. The remaining LGE suggest remaining focal scar (right lower panel). I kindly acknowledge support by dr Anna Herrey who managed this patient and provided the images.

Figure 15. CMR of a 44-year-old female presenting with palpitations and RBBB. Cine images revealed a preserved LVEF (51%) with hypokinesia in the anterior wall. LGE demonstrated a diffuse pattern of epicardial, intramural and transmural enhancement in the anterior wall, suggestive of CS. The native T1 map showed an increased T1 with 1040 ms (normal median 960 [942-986] ms), expanded ECV of 36% (25 [23-27]%), and decreased postcontrast T1 with 452 ms (526 [509 -552]ms). Coronary artery disease was ruled out, and EMB confirmed CS. Reproduced with the permission of the publisher.

Figure 16. CMR of a 27-year-old female with a history of pulmonary sarcoidosis since two months. She experienced recurrent chest pain. CMR revealed preserved LVEF with normal dimensions. DECMR did not demonstrate LGE. However, native T1 (1004 ms), ECV (26%) and T2 (53 ms) were increased, and post contrast T1 (483 ms) decreased compared with our control group (median native T1 960 ms, ECV 25%, postcontrast T1 526 ms, T2 49 ms). Reproduced with the permission of the publisher.

Figure 17. First ever published MR Images (0.5 T magnet, TR 750 msec, TE 10-100 msec, 12 mm slice thickness, matrix 256×256) of biopsy confirmed cardiac sarcoidosis, in a 30-year-old Caucasian male who presented with symptoms of a third degree atrio-ventricular block. (A: short axis image, B and C transverse images, arrows – signify focal areas of granulomatous infiltration resulting in hypertrophy and increased signal intensity; P = posterolateral papillary muscle, L= left ventricle, R= right ventricle)

From Riedy K, Fisher MR, Belic N, Koenigberg DI. MR Imaging of myocardial sarcoidosis. AJR 1988;151:915-916. Reproduced with the permission of the American Roentgenologic Society.

Figure 18: Cardiac ultrasound and DECMR study (SSFP and IR-GRE sequences, short axis views) in a patient without pulmonary hypertension demonstrate posterolateral loss-of-wall-thickness (LOWT) (A,B), hyperechoicity (C,D) and LGE of the ventricular insertion points (arrows), papillary muscles (asterisks) and postero-lateral LV segments (triangle).

□ LGE ■ unenhanced myocardium ■ blood pool

Figure 19: DECMR in a middle-aged female who presented with complete AVB and sVT demonstrates extensive transmural septal LGE (arrows) with papillary muscle involvement (triangle).

Figure 20. CMR study (Steady-State-Free Precession sequence, horizontal long axis view, end-diastolic frame), demonstrates dilation of the right ventricle (RV) and right atrium (RA), marked right ventricular hypertrophy, with displacement of the interventricular septum towards the left ventricle, both left ventricle and atrium are compressed (left-sided panel) (A) Contrast-enhanced CMR study (Inversion Recovery-Gradient Echo sequence, short axis view, end-diastolic frame) of the identical patient with pulmonary vascular sarcoidosis and resulting severe pulmonary arterial hypertension, demonstrates contrast-enhancement of the right ventricular hinge points (triangles) and free wall (arrows). (B) Two years later this patient presented with a subacute NSTEMI. The angiogram demonstrates stenosis with thrombus in segment two of the right coronary artery, and mid posterior descending artery. (arrows) (C) Follow-up contrast-enhanced CMR (Inversion-Recovery Gradient Echo sequence, short axis view, end-diastolic frame), demonstrates sub-endocardial enhancement in the distribution of the right coronary artery: the inferior right ventricular and left ventricular segments (arrows), different from the previously demonstrated ventricular insertion point enhancement (triangles). (right-sided panel) (D)

Figure 21. Schematic presentation of the LGE CMR principle – each box represents a voxel: **A.** normal myocardium before the administration of gadolinium, **B.** normal myocardium after the administration of gadolinium, distributed over the interstitial space, **C.** interstitial expansion due to infiltration by inflammatory cells and edema, **D.** followed by deposition of collagen, **E.** replacement fibrosis representing focal scar.

Figure 22. Delayed-enhanced three-dimensional breath-hold inversion-recovery gradient echo studies demonstrating confluent apical hyper-enhancement secondary to sarcoidosis (**A**: vertical long axis view, **C**: 4 chamber view) and apical patchy three-layer hyper-enhancement in a patient with coronary artery disease and myocardial infarction secondary to obstruction of the LAD (**B**: vertical long axis view, **D**: 4 chamber view).

Figure 23. Gadolinium CMR (inversion-recovery gradient echo sequence, 10 minutes after the administration of 0.1 mmol/kg gadolinium-DTPA) may help differentiate between ischemic heart disease (**A**- previous lateral myocardial infarct, **B** - ischemic cardiomyopathy, subendocardial septal and posterolateral infarcts), hypertrophic cardiomyopathy (**C**-scarring at the junctions of right and left ventricles), viral myocarditis (**D**- inferolateral epicardial LGE) and infiltrative cardiomyopathies (**E**-cardiac amyloidosis).

Figure 24. DECMR (IR-GRE, VLA and SA views) demonstrates antero-basal subepicardial, subepicardial inferior and mid-septal LGE in a middle-aged male who collapsed during a competitive field hockey game due to VT/VF.

☐ LGE ☒ unenhanced myocardium ☒ blood pool

Figure 25. DECMR (IR-GRE, end-diastolic frame, HLA view) in a patient diagnosed with arrhythmogenic right ventricular cardiomyopathy, demonstrates dilation of the RV with LGE of the RV free wall.

Figure 26. A 58-year-old male patient, previously diagnosed with pulmonary sarcoidosis, and asymmetric hypertrophy of the septum with systolic anterior motion (SAM), underwent a Morrow procedure for symptomatic LV outflow tract obstruction considered to be secondary to HCM. Histology of the resected basal septal tissue revealed non-caseating granulomas diagnostic of CS. (left-upper panel - 2 D TTE HLA demonstrating septal hypertrophy, right-upper panel -IRGRE patchy LGE in the interventricular septum and inferolateral LV segments, left and right lower panels – CMR SSFP, respectively diastolic and systolic VLA frames demonstrating severe hypertrophy of the basal interventricular septum) (Matsumori A, Hara M, Nagai S, et al Hypertrophic cardiomyopathy as a manifestation of cardiac sarcoidosis. Jap Circ J 2000;64(9):679-683. I kindly acknowledge the support of dr D van Kraaij who managed this patient and provided the images.

Figure 27. A patient with cardiac and pulmonary involvement by sarcoidosis. **A** The heart showed widespread fibrosis in association with granulomas (white patchy areas affecting the left and right ventricle (left side of the image) with right ventricular hypertrophy due to pulmonary arterial hypertension. **B** The pulmonary artery (left) shows a greater diameter than the aorta. *Respirology* 2010;16(1):69-77. Reproduced with permission by the publisher.

Figure 28. Delayed-enhanced CMR (horizontal long axis, IRGE) demonstrates multi-focal LGE in a non-ischemic pattern, which has been associated with an increased risk for ventricular tachycardia.
(204.Crawford T, et al.Magnetic Resonance Imaging for identifying patients with cardiac sarcoidosis and preserved or mildly reduced left ventricular function at risk of ventricular arrhythmias. Circ Arrhythm Electrophys 2014;7(6):1109-1115. doi: 10.1161/CIRCEP.113.000156.)

□ LGE ■ unenhanced myocardium ■ blood pool

Figure 29. Pooled relative risk (RR) of any myocardial LGE for all cause mortality in sarcoidosis. ($p = 0.005$)

Figure 30. Pooled relative risk (RR) of any myocardial LGE for sustained ventricular tachycardia in sarcoidosis. ($p < 0.001$)

Figure 31. Pooled relative risk (RR) of any myocardial LGE for all-cause death or sustained ventricular tachycardia in sarcoidosis. ($p < 0.001$)

Figure 32. Pooled relative risk (RR) of any myocardial LGE for cardiovascular mortality in sarcoidosis. ($p < 0.001$)

Figure 33. Pooled relative risk (RR) of any myocardial LGE for admission for congestive heart failure in sarcoidosis. ($p < 0.001$)

Figure 34. Pooled relative risk (RR) of any myocardial LGE for pacemaker implantation because of high degree atrio-ventricular block in sarcoidosis. ($p = 0.161$)

Figure 35. Pooled relative risk (RR) of RV LGE for sustained ventricular tachycardia in sarcoidosis. ($p < 0.001$)

Figure 36. Pooled relative risk (RR) of any RV LGE for all cause mortality in sarcoidosis. ($p = 0.048$)

Chapter 3

Cardiac involvement in patients with pulmonary sarcoidosis assessed at two University Medical Centres in The Netherlands

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Structured abstract

Study objectives: We aimed to determine cardiac involvement in patients with pulmonary sarcoidosis (PS) followed up at two University Medical Centres in The Netherlands.

Design: We reviewed the findings in consecutive patients who had been assessed by our departments during 1998 – 2004, and divided them in patients who had presented with symptoms of cardiac sarcoidosis (CS) (group A), and those who had been screened for this condition (group B).

Setting: Two University Medical Centers in the Netherlands.

Patients: 101 patients (69 males, mean age 47.6 years, 32 females, mean age 47.3 years) with biopsy proven pulmonary sarcoidosis.

Interventions: 12-lead ECG (101), ambulatory ECG (74), echocardiography (80), ²⁰¹ thallium SPECT (61), cardiac magnetic resonance imaging (87), coronary angiography to exclude coronary artery disease (17), and endo-myocardial biopsy (9).

Measurements: Electrocardiographic, structural and functional cardiac abnormalities according to the modified guidelines of the Japanese Ministry of Health and Welfare (1993).

Results: Sixteen of the 19 patients of group A and 3 of the 82 of group B were diagnosed with CS. During a mean follow up of 1.7 years (3 months - 4 years) 4 patients of group A died (20%), and 9 had a pacemaker and/or ICD implanted (47%), while the patients of group B had an uncomplicated course.

Conclusions: Once PS patients have developed symptomatic CS, their prognosis becomes very grim. In contrast, the prognosis in asymptomatic cardiac involvement in PS patients is good. Considering the poor prognosis of symptomatic CS, pulmonologists should consider regular screening of their PS patients for cardiac involvement with straightforward detection methods.

Contents

Structured abstract	98
3.1 Introduction	99
3.2 Patients and methods	99
3.3 Results	101
3.4 Discussion	102
3.5 Study limitations	103
3.6 Conclusions	103
3.7 Acknowledgements	104
References	105

3.1 Introduction

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology with symptomatic cardiac involvement in approximately five percent of patients. (1,2)

The clinical features of cardiac sarcoidosis (CS) include congestive heart failure, cor pulmonale, supraventricular- and ventricular arrhythmias, conduction disturbances, ventricular aneurysms, pericardial effusion and sudden death. (3) The diagnosis of CS is made in the co-existence of non-caseating granulomas on myocardial biopsy or biopsies of any extra-cardiac tissue (with the exclusion of other causes for granulomatous inflammation such as mycobacterial or fungal infection) and cardio-vascular abnormalities for which other possible causes have been excluded. The guideline from the Japanese Ministry of Health and Welfare provides an excellent diagnostic framework. (4) (Table 1) The prevalence of sarcoidosis in The Netherlands is estimated to be 20-30 per 100 000, while the prevalence of cardiac involvement is unknown. Postmortem studies revealed cardiac involvement in twenty to thirty percent of patients with sarcoidosis in the United States. (5,6) In Japan cardiac involvement is reported to be present in as many as 58% of patients, and is responsible for as many as 85 % of deaths from sarcoidosis. (7,8) We aimed to determine cardiac involvement in sarcoidosis patients followed up at two University Medical Centres in The Netherlands, and reviewed the findings in consecutive patients who had presented with symptoms of cardiac sarcoidosis, and those who had been screened for this condition.

3.2 Patients and methods

Study population

Between July 2000 and May 2004, 101 patients (69 males (33-71, mean 47.6 years), 32 females (29-72, 47.3 years), Caucasian: 87 (85%), African: 4, Asian: 9, Middle-Eastern: 1) with histologically proven pulmonary sarcoidosis underwent cardiac assessment in the cardiology departments of , the Erasmus Medical Centre (16) and University Hospital Maastricht (85). The diagnosis of sarcoidosis was confirmed if the clinical presentation and chest radiographic finding were supported by histological evidence of non-caseating granulomas by transbronchial biopsy, and the possibility of infection, environmental factors or hypersensitivity reaction to medication causing granulomatous inflammation, had been eliminated. Patients had either presented with symptoms suggestive of cardiac sarcoidosis (n=19), or had been screened for cardiac involvement (n=82). Patients underwent clinical assessment including determination of highest serum levels of angiotensin converting enzyme (SACE) (n=64), 12-lead electrocardiograms (n=101), ambulatory electrocardiographic monitoring (n=74), radiological chest stage by X-ray and/or High Resolution CT (n=101), transthoracic echocardiograms (n=80), ²⁰¹ thallium single-photon- emission-computed tomography (SPECT) (n=61), and gadolinium-DTPA cardiac magnetic resonance imaging (CMR) (87). Of the 88 CMR studies 5 were discarded because of insufficient image quality. Seventeen patients underwent diagnostic coronary angiography to exclude coronary artery disease, in six patients endo-myocardial biopsies

were taken, and three patients had a post-mortem examination. Because of the limited diagnostic yield of endomyocardial biopsies, and the invasive nature with an associated risk of morbidity, we felt not justified to systematically subject patients who were screened for CS to this procedure. For the purpose of the present study the Japanese guideline was modified by excluding endomyocardial biopsy as a diagnostic parameter. Since the guidelines were compiled before CMR had become integral part of cardiac assessment, we further modified our diagnostic scheme by incorporating CMR assessment of wall thickness and motion. The diagnosis of CS, according to the modified guideline (**Table 1**) was made in 19 of 101 patients included in the study.

Electrocardiography and ambulatory electrocardiography

A 12-lead surface electrocardiogram (ECG) was made (MAC, Marquette, Milwaukee, Wisconsin; paper speed 25 mm/sec) and the findings were classified as abnormal i.e. in keeping with the ECG criteria of the guidelines (**Table1**). Ambulatory ECGs (74) were performed for 24 -72 hours, and were considered abnormal when evidence of intermittent atrio-ventricular conduction delay or block, intermittent bundle branch blocks or ventricular arrhythmias such as frequent monomorphic and/or polymorphic PVCs > 100/24 hours, non-sustained VTs, and/or sustained VTs were found.

Echocardiography

Studies were performed with a Sonos 5500 phased array imaging system (Hewlett Packard) and considered abnormal when regional or global systolic dysfunction, wall thickening or thinning was found.

Thallium myocardial scintigraphy

After treadmill peak exercise, or during intravenous infusion of dipyridamol, ²⁰¹ thallium was administered and SPECT performed on a Siemens triple-detector gamma camera (MultiSPECT-3), equipped with low-energy, high resolution collimators. The images were made in a 64×64 matrix (60 frames/45 seconds). The thallium scan was considered suggestive of CS when areas with reversed uptake and/or irreversible perfusion defects were present, and/or reversible perfusion defects were found in patients with normal coronary arteries at angiography. Regional defects were localized according to the 17 segment 1model (**9**)

Cardiac Magnetic Resonance

Studies were performed using a 1.5 Tesla MRI scanner (Philips, Best, The Netherlands and General Electric, Milwaukee, Wisconsin, USA) with a cardiac-dedicated phased-array coil. The CMR studies were ECG triggered by standard software, and obtained in diastole to minimize artefact due to cardiac motion. Studies consisted of multislice-multiphase steady-

state-free precession (SSFP), spin echo (SE) and fat saturated T2 weighted breath hold sequences of the short axis (SA), vertical long axis (VLA) and four chamber (4CH) views. SSFP sequences were performed to assess regional wall motion abnormalities. T2 weighted studies were performed to assess the presence of myocardial inflammation. Ten minutes after the additional administration of 0.1-0.2 mmol/kg gadolinium-DTPA (Schering, Berlin), a SE (slice thickness 8 mm, gap .8 mm, matrix 512×512 , FOV 360 mm) and/or 3-D inversion recovery-gradient echo (IR-GRE) breath hold sequence (SA, VLA, 4 CH) (slice thickness 10 mm, no gap, matrix 256×256 , FOV 400 mm) was used to assess for the presence of contrast enhancing lesions. The inversion time (250-400 msec) was determined on an individual base to obtain optimal nulling of the un-enhanced myocardial signal. Regional differences in left ventricular wall enhancement were measured and localized according to the 17 segment model (9) (MASS suite post processing software, MEDIS, Leiden). The total time required for the investigation was 30-45 minutes.

The studies were independently evaluated by 4 blinded observers, 3 cardiologists and 1 radiologist, with experience in CMR. The studies were considered to be abnormal when at least 2 observers described identical abnormalities.

Coronary angiography

Diagnostic coronary angiography was performed when considered indicated by the managing physician, and was generally done in patients with symptoms and findings suggestive of significant coronary artery disease. One patient underwent diagnostic coronary angiography as part of the diagnostic work up before cardiac transplantation.

Statistical analysis

All statistical analyses were performed using the statistical software package SPSS version 11.5. Group data are expressed as mean $\pm$ SD. Continuous variables were assessed using the parametric *t* test for independent samples or Mann Whitney test were appropriate, and all categorical variables were assessed using the chi-square test. Statistical significance was defined as a *p* value less than 0.05.

3.3 Results

Patient characteristics

The demographic and clinical characteristics of group A and group B are presented in **Table 2**. Significantly more patients in group A were diagnosed with CS compared to group B. Pulmonary involvement based on radiological chest stage was significantly more extensive in group B, while the degree of functional impairment was significantly higher in group A.

Findings at cardiac assessment

The findings at cardiac assessment are presented in **Table 2**, with **Tables 3** and **4** presenting more detailed information on the findings in all patients diagnosed with CS. The ECGs, ambulatory ECGs, echocardiograms and CMR studies revealed significantly more conduction abnormalities, ventricular arrhythmias and regional loss of left ventricular wall thickness and function in group A. Of the diagnostic techniques, the ECG and CMR showed most abnormalities. The ECG demonstrated conduction abnormalities in 10 of the 16 patients (63%) diagnosed with CS. In 4 patients of group B electrocardiographic signs of right ventricular hypertrophy were present. CMR and/or echocardiography diagnosed decreased systolic left ventricular function (mean 35%, range 20-56%) with global or regional wall motion abnormalities in 12 (75%) of the CS patients. In 10 of the 16 CS patients CMR and SPECT were available. In 4 patients CMR and SPECT diagnosed defects, while CMR revealed small defects in 4 patients with normal SPECT studies. The findings with SPECT were not significantly different between group A and B. In 8 patients of group B small (ir)reversible perfusion defects were detected, which were mainly located in the inferior left ventricular (LV) wall. SPECT demonstrated reversible perfusion defects in the anterior wall in 2 patients with coronary artery disease (CAD) of group B and an irreversible perfusion defect in this region in 1 patient with CAD of group A. Coronary angiography was performed in 17 patients, and revealed significant coronary artery disease in 2 patients of group A. Two patients were diagnosed with hypertrophic cardiomyopathy, one of who was also diagnosed with CS.

Clinical data at follow up

The management, duration of follow up and outcome during follow up are presented in **Tables 3** and **4**. Of the 16 patients diagnosed with CS in group A, 9 received a pacemaker and/or implantable cardioverter/defibrillator (ICD). Three patients died of ventricular arrhythmias, one of treatment resistant VTs after implantation of an ICD, and one patient died of complications after cardiac transplantation. Nine patients were treated with immune-suppressive drugs, corticosteroids with methotrexate or azathioprine. None of the patients of group B had significant cardiovascular complications or died during follow up.

3.4 Discussion

Our study is the first to systematically evaluate cardiac involvement in patients with sarcoidosis in The Netherlands, and the largest to employ CMR. Earlier studies in the Sweden (86 patients), Ireland (50 patients), Israel (42 patients), the USA (88 patients), Japan (41 patients) and France (50 patients) used ECG, echocardiography, ²⁰¹thallium SPECT and CMR in prospective studies evaluating the prevalence of cardiac involvement in referred patients with sarcoidosis (**10-18**). Abnormalities were found in up to 23% of European and 63.4% of Japanese patients. In our study, depending on the technique used, abnormalities were found in 10 to 26% of patients without cardiac symptoms. SPECT detected small

irreversible perfusion defects in 13 patients, while gadolinium (Gd)-enhancing lesions were present in 12 patients. Both SPECT and CMR demonstrated lesions in 4 patients. Wagner et al. have previously demonstrated the ability of Gd-enhanced CMR to diagnose even small amounts of myocardial scar tissue not detected by SPECT in patients with coronary artery disease. **(19)** Histological assessment of gadolinium-DTPA (Gd) enhanced myocardium has been correlated with fibrosis and active myocarditis. **(20,21,22)** Since T2 weighted studies revealed increased signal, signifying inflammation, in only 1 patient, delayed enhancement in our patients suggest the presence of myocardial scar tissue. The favourable prognosis of abnormal SPECT studies in asymptomatic sarcoidosis patients was demonstrated by Kinney et al. in 52 similar patients in whom the presence of perfusion defects diagnosed with SPECT did not predict survival during a mean follow up of 89 months. **(23)** Since CMR is a relatively new diagnostic technique, and experience in evaluating patients with sarcoidosis limited, long-term follow up will have to determine the significance of small gadolinium-enhancing lesions in asymptomatic patients. The significantly poorer functional NYHA class in patients of group A, despite less radiological pulmonary involvement, is explained by more extensive LV involvement, resulting in a lower ejection fraction, heart failure and ventricular arrhythmias. When considering the study of Yazaki et al., who determined with multivariate analysis that the presence of higher NYHA class, increased left ventricular end-diastolic diameter and sustained VTs were independent predictors of death, we anticipated poorer outcome of group A. **(24)** Although the introduction of the ICD is expected to improve outcome in patients with CS, during a mean follow up of 15 months (3 to 54 months) in our population it delivered therapy in only 1 of 6 patients that had received the device. **(25)**

3.5 Study limitations

Theoretically bias was introduced by evaluating a pre-selected patient population that had been referred to tertiary centres. This however seems unlikely when considering the fact that only few of the patients who were screened for CS were actually diagnosed with this condition. It seems more likely that cardiac involvement may have been underestimated, since the diagnosis was based on the modified guideline of the Japanese Ministry of Health and Welfare. In the absence of diagnostic cardiac histology, CS could only be diagnosed in the presence of ECG abnormalities. As previously published by Silverman et al, and demonstrated by patients 1 and 3 (**Table 3**), cardiac involvement may well be present in the absence of diagnostic ECG abnormalities.

3.6 Conclusions

In our cohort of 101 pulmonary sarcoidosis patients, the rate of cardiac involvement in those screened for this condition was low (4%) and the prognosis was good. The CS patients who presented with cardiac failure or ventricular arrhythmias had significant morbidity and a mortality rate of 25% during a mean follow up of 15 months. Based on the

findings of our current study, we recommend regular electrocardiographic evaluation in patients with PS and early referral for additional cardiac assessment with echocardiography or CMR in patients with unexplained fatigue, dyspnoea, or palpitations.

3.7 Acknowledgements

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Table 1 Criteria for the diagnosis of cardiac sarcoidosis in this study: (modified after (4))

1. Histologic diagnosis group: endomyocardial biopsy demonstrates epithelioid granulomata without caseating granulomata.
2. Clinical diagnosis group: in patients with histologic diagnosis of extra-cardiac sarcoidosis, cardiac sarcoidosis is suspected when 'a' and at least one of criteria 'b' to 'd' are present:
a. Complete RBBB, LBBB, left-axis deviation, AV-block, VT, PVC, or pathological Q or ST-T change on resting- or ambulatory ECG.
b. Abnormal wall motion, regional wall thinning, or dilation of the left ventricle by echocardiography, magnetic resonance or SPECT.
c. Perfusion defect by ^{201}Tl -myocardial scintigraphy.
d. Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle.

Table 2 Summary of demographic and background medical data.

	cardiac presentation (group A, n = 19)	screened patients (group B, n = 82)	P value
Mean age (years)	48 $\pm$ 6	45 $\pm$ 10	ns
Gender (%)			ns
Male	14 (74%)	55 (67%)	
Race (%)			ns
Caucasian	17 (85%)	70 (85%)	
African	1	3	
Asian	1	8	
Middle Eastern	0	1	
Diagnosis			
Cardiac sarcoidosis	16 (84%)	3 (4%)	P < 0.0001
Hypertrophic cardiomyopathy	2	0	
Coronary artery disease	2	2	
Valvular heart disease	0	1	
Modified NYHA class 0 / I / II / III / IV	8 (42%) / 7 / 3 / 0 / 1	66 (94%) / 0 / 2 / 0 / 0	P < 0.0001
Time (years) since diagnosis of sarcoidosis	10 $\pm$ 9	6 $\pm$ 8	Ns
Pulmonary stage 0 / I / II / III / IV	0 / 5 / 9 / 4 / 1	10 / 21 / 7 / 25 / 9	P < 0.05
Steroid treatment	16 (84%)	47 (64%)	Ns
Hypertension	2 (11%)	11 (16%)	Ns
Palpitations	9 (47%)	23 (34%)	Ns
Syncope	5 (26%)	3 (9%)	Ns
SACE maximal (IU/l)	43 $\pm$ 39	31 $\pm$ 23	Ns
Abnormal ECG	17 (89%)	8 (10%)	P < 0.0001
Abnormal ambulatory ECG	12 (63%)	7 (13%)	P < 0.0001
Abnormal echocardiogram	15 (79%)	7 (11%)	P < 0.0001
Abnormal SPECT	5 (45%)	13 (26%)	Ns
Coronary angiography	14	3	Ns
Coronary artery disease	2	0	
CMR	14 (74%)	74 (90%)	
Poor image quality	0	5 (7%)	
Abnormal	12 (86%)	12 (16%)	P < 0.0001
Regional contrast enhancement	9 (64%)	12 (16%)	P < 0.0001
Decreased LVEF	9 (64%)	1 (1%)	P < 0.0001
Loss of wall thickness	2 (15%)	1 (1%)	ns
Increased T2 signal	1 (5%)	0	ns

Table 3 Findings in 19 patients presenting with symptoms of cardiac involvement.

pt	Age (years)	sex	diagnosis	symptoms	ECG	Holter	Echo	thallium	CMR	histology (biopsy/ postmortem)
1	53	M	CS	heart failure	Normal	0	LVEF ↓		CE, wall ↓, LVEF ↓	granuloma
2	39	M	CS	palpitations, SCD	Normal	VT	normal			granuloma
3	48	F	CS	heart failure	Δ ST-T	PVC's	LVEF ↓	normal	LVEF ↓	
4	52	F	CS	heart failure	Q's, Δ ST-T	nsVT	LVEF ↓	normal	CE, wall ↓, LVEF ↓	
5	42	M	CS	near-SCD	Q's, Δ ST-T	VT/VF	LVEF ↓ RWMD		CE, wall ↓, LVEF ↓ RWMD	
6	43	M	CS	palpitations	RBBB	PVC's	0	normal	CE	
7	55	F	CS	heart failure	LBBB	0	LVEF ↓	reversed uptake	CE, LVEF ↓	fibrosis
8	40	F	CS	heart failure	LBBB	VT	LVEF ↓			granuloma
9	47	M	CS	heart failure	LBBB	SSS	LVEF ↓	normal		
10	43	M	CS	heart failure	LBBB	nsVT	LVEF ↓		LVEF ↓	fibrosis
11	46	M	CS	heart failure, palpitations	LBBB	VF/VT	LVEF ↓			granuloma
12	42	M	CS	palpitations	RBBB, LAHB	PVC's	0	normal	CE	
13	50	M	CS	heart failure	3 rd AVB	nsVT	LVEF ↓			granuloma
14	54	M	CS	heart failure	3 rd AVB	0	LVEF ↓	normal	CE, LVEF ↓	
15	54	M	CS	heart failure	3 rd AVB	0	LVEF ↓	fixed perfusion defect	CE, LVEF ↓	
16	41	M	CS, HCM	palpitations	Δ ST-T	nsVT	L VH	fixed perfusion defect	CE, LVH	fibrosis, fiber disarray
17	62	F	HCM	palpitations	Δ ST-T	PAF	L VH	normal	L VH	
18	50	M	CAD	heart failure	LBBB	0	LVEF ↓ RWMD	fixed perfusion defect	CE, wall ↓, LVEF ↓ RWMD	
19	52	M	CAD	heart failure	Δ ST-T	0		reversible perfusion defect	normal	

CS = cardiac sarcoidosis, LBBB = left bundle branch block, RBBB = right bundle branch block, nsVT = non-sustained VT, VT = sustained ventricular tachycardia

Table 4 Findings in 3 asymptomatic pulmonary sarcoidosis patients diagnosed with cardiac involvement by screening.

pt	age (years)	Sex	diagnosis	ECG	Holter	Echo	thallium	CMR
1	72	F	CS	RBBB	0	RWMD	0	0
2	41	M	CS	RBBB	0	mitral valve prolapse	fixed perfusion defect	0
3	49	F	CS	Δ ST-T	0	0	reversed uptake	CE

Chapter 4

The additional value of gadolinium enhanced magnetic resonance imaging to standard assessment for cardiac involvement in patients with pulmonary sarcoidosis

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Abstract

Aim: To determine whether gadolinium enhanced magnetic resonance imaging (CMR) was of additional diagnostic value to standard assessment in patients with sarcoidosis who underwent evaluation for cardiac involvement.

Methods: We reviewed the findings in patients with pulmonary sarcoidosis who had been assessed with electrocardiography, Doppler-echocardiography, ²⁰¹thallium scintigraphy and CMR between 2002-2004.

Results: of the 55 patients evaluated standard evaluation diagnosed cardiac involvement in 13 while CMR diagnosed myocardial scarring (2.5 ± 1.9 segments) (all 6) and impaired systolic left ventricular function (1) in an additional 6 patients. The extent of delayed enhancement correlated with disease duration ($p < 0.05$), ventricular dimensions and function ($p < 0.001$), severity of mitral regurgitation ($p < 0.05$) and the presence of ventricular tachycardias ($p < 0.001$). Patients in whom cardiac involvement was only diagnosed with CMR had less myocardial scarring and functional impairment ($p < 0.05$) compared to patients diagnosed with standard assessment.

Conclusion: CMR provides an accurate estimation of the extent of cardiac involvement and may reveal signs of early infiltration that are not detected by standard assessment. The extent of late enhancement with gadolinium relates to severity of cardiac involvement and may therefore have prognostic implications.

Contents

Abstract	112
4.1 Introduction	113
4.2 Patients and methods	113
4.3 Results	116
4.4 Discussion	118
4.5 Conclusions	119
4.6 Acknowledgements	119
References	120

4.1 Introduction

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology with symptomatic cardiac involvement in up to 7% of patients. (1-3) Postmortem studies revealed cardiac involvement in twenty to thirty percent of patients with sarcoidosis in the United States. (4,5) In Japan cardiac involvement is even present in as many as 58% of patients, and is responsible for as many as 85% of deaths from sarcoidosis. (6,7) The clinical features of sarcoid heart disease include congestive heart failure, cor pulmonale, supra-ventricular- and ventricular arrhythmias, conduction disturbances, ventricular aneurysms, pericardial effusion and sudden death. (8) The diagnosis of cardiac sarcoidosis is made by the co-existence of non-caseating granulomas on myocardial biopsy or biopsies of any extra-cardiac tissue (with the exclusion of other causes for granulomatous inflammation such as mycobacterial or fungal infection) and cardiac abnormalities for which other possible causes have been excluded. Many tests have been used to diagnose and follow up on cardiac sarcoidosis, such as standard and ambulatory electrocardiography, echocardiography, gallium- and thallium scintigraphy. (9) More recently gadolinium-enhanced cardiac magnetic resonance imaging (CMR) has been used to demonstrate myocardial inflammation, wall motion abnormalities and fibrosis in patients with cardiac sarcoidosis. (10-12) Because of superior image resolution CMR may be able to demonstrate early signs of myocardial infiltration when scintigraphy or echocardiography fail to do so. (13) The additional value of CMR to currently employed techniques, electrocardiography, echocardiography and ²⁰¹thallium scintigraphy, remains to be determined. We aimed to evaluate the additional value of CMR in disclosing structural and functional cardiac abnormalities in patients with pulmonary sarcoidosis who underwent standard cardiac assessment either because of cardiac symptoms or for screening purposes, and correlated the findings with the techniques used in standard assessment.

4.2 Patients and methods

Study population

Between July 2002 and March 2004, 55 patients with histologically proven pulmonary sarcoidosis underwent cardiac assessment in the cardiology departments of the Erasmus Medical Centre (n=4) and the University Hospital Maastricht (n=51). The study group consisted of 38 men and 17 women, with a mean age of 48 and 47 respectively. Race was mainly Caucasian, 50 (91%), 4 were Asian, 1 African. The diagnosis of pulmonary sarcoidosis was confirmed if the clinical presentation and chest radiographic findings were supported by histological evidence of non-caseating granulomas by transbronchial biopsy, and the possibility of infection, environmental factors or hypersensitivity reaction to medication causing granulomatous inflammation, had been eliminated. The patients had either presented with symptoms of cardiac involvement (n=12), or were screened for cardiac involvement (n=43). Patients underwent a clinical assessment, and evaluation of the maximal serum angiotensin converting enzyme levels (n=43), 12-lead ECG (n=55), ambulatory ECG mon-

itoring (n=47), radiological chest staging by chest X-ray and/or High Resolution CT (55), Doppler-echocardiographic evaluation (n=55), ^{201}Tl thallium scintigraphy (51) and gadolinium-enhanced CMR (n=55). Diagnostic coronary angiography was done in 13 patients to exclude coronary artery disease. In four patients endo-myocardial biopsies were taken. In group A (standard assessment) the diagnosis of cardiac sarcoidosis (CS) was made when endomyocardial biopsy (EMB) demonstrated non-caseating, epithelioid granulomata, or when, after the exclusion of other causes, abnormalities were present on the resting or ambulatory ECG (LBBB, RBBB, LAHB, bifascicular block, atrio-ventricular-block, VT, PVC, or pathological Q waves or ST-T changes) and echocardiogram (abnormal wall motion, regional wall thinning, or dilation of the left ventricle) or ^{201}Tl -myocardial scintigram (irreversible perfusion defect, reversed distribution after exercise or administration of dipyridamol). In group B (CMR group) the diagnosis of cardiac sarcoidosis was based solely on abnormalities detected by CMR, and the exclusion of other conditions known to cause these abnormalities such as hypertension, coronary artery or valvular heart disease. CMR findings were considered suggestive of CS when impaired systolic LV function, loss of wall thickness or gadolinium enhancing left ventricular lesions were present and other explanations had been excluded. Group C consisted of patients in whom CMR abnormalities suggestive of CS were present, but in whom standard assessment revealed no abnormalities. Because of the limited diagnostic yield of EMB, and the invasive nature with an associated risk of morbidity, we considered it not justified to systematically subject patients who were screened for CS to this procedure.

Electrocardiography and ambulatory electrocardiography

A 12-lead surface ECG was made (MAC, Marquette, Milwaukee, Wisconsin; paper speed 25 mm/sec) and the findings were interpreted by two experienced cardiologists and assessed for the presence of abnormalities suggestive of cardiac involvement. Ambulatory ECGs were performed for 24-72 hours, and were considered suggestive of CS when evidence of intermittent atrio-ventricular conduction delay or block (disregarding nightly episodes with Wenckebach periodicity), intermittent bundle branch blocks or ventricular arrhythmias including PVCs > 100/24 hours or at least 1 ventricular tachycardia (VT) was found. VT was defined as a run of PVCs containing at least 3 beats with a rate > 100 beats per minute. Sustained VT was defined as VT with a rate > 100 beats per minute and lasting for at least 30 seconds.

Doppler-echocardiography

Studies were performed with a Sonos 5500 phased array imaging system (Hewlett Packard, S3 transducer). Two-dimensional, continuous wave, and colour flow Doppler echocardiography was performed from standard parasternal and apical windows in long and short axes. Pulsed Doppler echocardiography was performed from an apical four-chamber view with the sample volume placed at the level of the mitral valve leaflet tips with the cursor orientated parallel to an imaginary line bisecting the left ventricle from apex to mitral valve. Left ventricular internal dimensions and wall thickness were measured at end-diastole according

to the recommendations of the American Society of Echocardiography. **(14)** Left ventricular mass was calculated and indexed for body surface area. **(15)** Body surface area (m^2) was derived from the Dubois formula. **(16)** Left ventricular hypertrophy was considered present when LV mass index was $> 104 \text{ g/m}^2$ for women or $> 116 \text{ g/m}^2$ in men. **(17)** Left ventricular wall motion, thickness and thickening were determined according to the 17 segment model. **(18)** Thickness of the interventricular septum $> 13 \text{ mm}$, or wall thickness $< 7 \text{ mm}$ in any segment were considered abnormal. **(19)** Left ventricular diastolic function was evaluated by determining the iso-volumetric relaxation time, peak velocity of early (E) and late (A) left ventricular filling, E/A ratio, deceleration rate of early diastolic flow (DT), left atrial size, and flow patterns in the pulmonary veins. Diastolic function was assessed according to the Canadian Consensus Recommendations. **(20)** Left ventricular ejection fraction was calculated using a modified Simpson's rule. **(14)** The right ventricular size and function and the presence of pericardial fluid were assessed.

Thallium myocardial scintigraphy

After treadmill peak exercise, or during intravenous infusion of dipyridamol, ²⁰¹ thallium was administered and SPECT performed on a Siemens triple-detector gamma camera (MultiSPECT-3), equipped with low-energy, high resolution collimators. The images were made in a 64×64 matrix (60 frames/45 seconds). The thallium scan was considered suggestive of CS when areas with reversed uptake and/or irreversible perfusion defects were present, and/or reversible perfusion defects were found in patients with normal coronary arteries at angiography. Regional defects were localized according to the 17 segment model **(18)**

Cardiac Magnetic Resonance

Studies were performed using a 1.5 Tesla MRI scanner (Philips, Best, The Netherlands or General Electric, Milwaukee, Wisconsin, USA) with a cardiac-dedicated phased-array coil. The CMR studies were ECG triggered by standard software, and obtained in diastole to minimize artifact due to cardiac motion. Studies consisted of multislice-multiphase steady-state-free precession (SSFP) in 55 patients, spin echo (SE) in 54 patients and fat saturated T2 weighted breath hold sequences in 55 patients. Studies were obtained of the short axis (SA), vertical long axis (VLA) and four chamber (4CH) views. SSFP sequences were performed to assess regional wall motion abnormalities and T2 weighted studies were performed to assess the presence of myocardial inflammation. Ten minutes after the additional administration of 0.1 mmol/kg gadolinium-DTPA (Schering, Berlin), SA and 4 CH images were obtained with SE in 54 patients (slice thickness 8 mm , gap $.8 \text{ mm}$, matrix 512×512 , FOV 380 mm , voxel size $0.7 \text{ mm} \times 0.7 \text{ mm} \times 8 \text{ mm}$) and 3-D breath hold inversion recovery-gradient echo (IR-GRE) sequences (SA, VLA, 4 CH) in 15 patients (slice thickness 10 mm , no gap, matrix 256×256 , FOV 400 mm , voxel size $1.6 \text{ mm} \times 1.6 \text{ mm} \times 10 \text{ mm}$) to assess for the presence of gadolinium enhancing lesions (LGE). Fourteen patients had both SE and IR-GRE studies. The inversion time ($250\text{--}400 \text{ msec}$) was determined on an individual base to obtain optimal nulling of the un-enhanced myocardial sig-

nal. Regional differences in left ventricular wall enhancement were measured and localized according to the 17 segment model (18) The total time required for the investigation was 45-60 minutes. The studies were independently evaluated by 4 blinded observers, 3 cardiologists and 1 radiologist, all experienced in performing CMR. The studies were considered to be abnormal when at least 2 observers described identical abnormalities.

Coronary angiography

Diagnostic coronary angiography (n = 13) was performed when considered indicated by the managing physician, and was generally done in patients with symptoms and findings suggestive of coronary artery disease.

Statistical analysis

All statistical analyses were performed using the statistical software package SPSS version 11.5. Group data are expressed as mean $\pm$ SD. Continuous variables were assessed using the Student unpaired *t* test for independent samples or the Mann Whitney test were appropriate, and all categorical variables were assessed using the chi-square test. Statistical significance was defined as a *p* value less than 0.05.

4.3 Results

Findings at standard evaluation

Standard assessment diagnosed cardiac sarcoidosis in 13 patients. The demographic and clinical characteristics of the patients are presented in **Table 1**. During a mean follow up of 19 ± 7 months, of the patients diagnosed with CS with standard assessment 1 patient died suddenly, 2 received a DDD-R pacemaker because of 3rd degree atrio-ventricular block, and 4 received a pacemaker/implantable cardioverter defibrillator of ventricular tachyarrhythmias. The follow-up of patients diagnosed with CS solely because of CMR abnormalities (group C) was uneventful.

Findings with CMR

The findings with CMR are presented in **Table 1**. In 37 (67%) studies 4 out of 4 observers, in 12 (22%) studies 3 out of 4 observers, and in 6 (11%) studies 2 out of 4 observers agreed on the absence or the presence and localization of late enhancement. Late gadolinium enhancing lesions (LGE) were present in 17. Seven of 17 patients had evaluation with SE, 9 with SE and IR-GRE, and 1 patient had only IR-GRE. In 6 of the SE patients 2, and in 1 of the SE patients 3 observers agreed on the presence and localization of LGE, while in 4 of the 10 patients who had both SE and IR-GRE or only IR-GRE 3 observers, and in the remaining 6 all observers agreed on the presence and localization of LGE.

In 19 patients (group B), including all patients diagnosed by standard assessment (group A), the CMR examinations showed abnormalities that were suggestive of cardiac sarcoidosis. In 6 patients late enhancement, involving 1 - 6 segments (mean 2.5 ± 1.9), one of whom also had impaired systolic left ventricular (LV) function (LVEF 52%) was diagnosed by CMR, while standard assessment was normal. (**Figures 3 and 4**) The amount of myocardial enhancement in group A did not significantly differ from group C. The transmural extent of enhancement and number of enhancing segments both showed a negative correlation with LV function ($p < 0.05$). The presence of late enhancement correlated with a primary cardiac presentation ($p < 0.001$), and the duration of disease ($p < 0.05$). The presence of myocardial enhancement did not correlate with the extent of pulmonary disease. The bulls eye representation reflecting the distribution of LV enhancement is shown in **Figure 1**. Late enhancement predominantly involved the basal segments of the left ventricle (59%), with the anteroseptal and anterolateral segments most affected (43%). (Figures 5, 6 and 7)

Correlation of standard evaluation with the CMR findings

Figures 2A and B illustrate the correlations between the different investigations and CMR.

Electrocardiography

The findings with the resting ECGs are presented in **Table 2**. The presence of regional wall motion abnormalities ($p < 0.001$), impaired LV function ($p < 0.001$) and the segmental extent ($p < 0.05$) of late enhancement all correlated with the ECG abnormalities. The transmural extent and distribution of late enhancement did not determine the presence of conduction abnormalities on the ECG. Transmural enhancement ($p < 0.001$) and segmental extent of enhancement ($p < 0.05$) correlated with the presence of Q waves. The presence of impaired LV function ($p < 0.05$) and regional wall motion abnormalities ($p < 0.001$) correlated with the abnormalities found with ambulatory ECG mentioned in **Table 2**. The extent of segmental enhancement ($p < 0.001$) and transmural enhancement correlated with the presence of (non)sustained ventricular arrhythmias.

Doppler Echocardiography

The findings with Doppler echocardiography are presented in **Table 3**. The segmental and transmural extent of enhancement correlated with regional wall motion abnormalities ($p < 0.05$), mitral regurgitation ($p < 0.001$), LV dimensions ($p < 0.05$), and impaired diastolic and systolic left and systolic right ventricular function ($p < 0.05$).

Thallium scintigraphy

²⁰¹Thallium scintigraphy demonstrated reversed distribution or irreversible perfusion defects in 6 patients. The presence of perfusion defects correlated with late enhancement and impaired systolic LV function ($p < 0.05$). The localization of perfusion defects and late enhancement matched in 4 of the 6 patients. In 1 patient reversed distribution was present in the apex, while ECG, echocardiography and CMR were normal.

4.4 Discussion

The diagnostic potential of CMR for detecting cardiac sarcoidosis has been demonstrated by several case-reports and single-centre patient series. **(10-12,21-28)** Patel et al assessed 58, mainly african american, sarcoidosis patients without cardiac symptoms and reported a two-fold higher rate of cardiac involvement with gadolinium-enhanced CMR compared to evaluation with ECG and echocardiography. **(28)** Sköld et al. recently reported on 18 subsequent patients with pulmonary sarcoidosis who had had been systematically evaluated for cardiac involvement with ECG, Doppler-echocardiography and CMR. **(29)** Our study is the first to evaluate the value of comprehensive CMR assessment in addition to resting and ambulatory ECGs, Doppler-echocardiography and ²⁰¹thallium scintigraphy. We found CMR to be highly sensitive in detecting abnormalities that suggest cardiac involvement in patients with histologically confirmed pulmonary sarcoidosis. Our findings demonstrate a strong correlation between electrocardiographic and echocardiographic abnormalities and the amount of left ventricular enhancement with CMR. The distribution of enhancement correlates well with the localization of inflammation and fibrosis reported in postmortem studies of patients with CS. **(4,5)** Limited, non-transmural or patchy myocardial scar tissue, frequently found at postmortem evaluation of CS patients, may remain undetected by electrocardiography, ultrasound or scintigraphy, but be detected by CMR due to its high image resolution and inversion-recovery gradient echo sequences that increase signal intensity differences by almost 500%. **(13,30)** The additional value of CMR to standard assessment was demonstrated in 6 patients (11%) in whom left ventricular involvement was only diagnosed by CMR. Since disease in this group was of shorter duration in comparison to the group diagnosed with standard assessment, and myocardial involvement limited, the findings in these patients may well reflect early involvement. The follow up of this group, though uneventful, may be too short (21 ± 7 months) to draw firm conclusions concerning the prognostic relevance of the CMR findings. Electrocardiography is considered an appropriate screening test for cardiac sarcoidosis, however, in 25% of patients with gross cardiac infiltration at postmortem assessment ECG abnormalities had not been present during life. **(4,31,32)** Ambulatory electrocardiography is reported to have a sensitivity of 67% and specificity of 80% for the diagnosis of cardiac sarcoidosis. **(33)** Abnormalities on 2-D echocardiograms, increase or loss of wall thickness, ventricular dilation, functional impairment, mitral regurgitation, or the presence of pericardial effusions, have been detected in 14 - 41% of patients with sarcoidosis, even in the absence of ECG abnormalities and clinical symptoms. **(34-39)** Impaired diastolic function was found in 14 - 56% of patients.

(27,37) In our study population unexplained diastolic relaxation abnormalities were present in 19 (35%) patients without evidence of cardiac involvement. CMR did not reveal scar tissue in this group and, unlike a previous study, its presence did not correlate with disease duration. (29,39) ²⁰¹Thallium scintigraphy has been most extensively studied and revealed perfusion defects diagnostic of myocardial fibrosis or granulomatous infiltration in 13 – 32% of sarcoidosis patients. (40,41). Both electrocardiography and echocardiography have demonstrated prognostic value in patients with CS. The presence of sustained ventricular tachycardias, NYHA functional class and left ventricular dilation were found to be strong independent predictors of mortality. (42) The correlation between the presence of non-sustained and sustained VTs on Holter and the extent of left ventricular enhancement with CMR in sarcoidosis has not been reported before. Myocardial scar tissue is considered to be the substrate for ventricular tachyarrhythmia's due to electrical reentry. (43) In our study population the presence of VTs did not correlate with substrate in a particular myocardial layer, since delayed enhancement involved parts of all three myocardial layers in most patients. Further study is needed to elucidate the diagnostic and prognostic relevance of CMR in the management of this condition.

4.5 Conclusions

CMR is a useful technique for the assessment of cardiac involvement in sarcoidosis, since the findings correlated strongly with standard assessment, and the diagnosis of CS according to accepted guidelines. CMR may be able to demonstrate disease at an early stage, when standard assessment fails to do so. In addition, extent of late enhancement with gadolinium correlated with ventricular dilatation, functional impairment, and the presence of ventricular arrhythmias, all known markers of sudden death. CMR based early detection and monitoring of cardiac sarcoidosis may represent a useful strategy to determine optimal timing of medical intervention.

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Table 1: Summary of the clinical and demographic patients characteristics and findings with CMR.

Abnormal CMR studies	cardiac sarcoidosis standard assessment (group A, n = 13)	cardiac sarcoidosis only with CMR (group C, n = 6)	P value
Mean age (years)	49 ± 6	50 ± 10	ns
Gender (%) male/female	9(69%)/4	4(67%)/2	ns
Time (years) since diagnosis	9 ± 8	5 ± 2	ns
Follow up (months) since cardiac assessment	18 ± 10	21 ± 7	ns
Modified NYHA class 0 (no complaints) / I / II / III / IV	7/5/0/0/1	6/0/0/0/0	ns
Pulmonary stage 0/ I / II / III / IV	0/3/4/6/0	1/3/0/1/1	ns
Palpitations	4 (31%)	4 (67%)	ns
Maximal serum ACE (IU/l) mean ± SD	49 ± 40	31 ± 12	ns
LVEF (%) mean ± SD	45 ± 17	60 ± 6	?
Number of patients with late enhancement	11	6	
Number of segments per patient			
Range	0-12	1-6	
Mean ± SD	4.1 ± 4.2	2.5 ± 1.9	ns
Localization of gadolinium enhancement (%):			
Basal segments (1-6)	30 (57%)	10 (67%)	ns
Equatorial segments (7-12)	19 (36%)	5 (33%)	ns
Apical segments (13-16)	4 (7%)	0	ns
Transmural distribution of gadolinium enhancement (%):			
Subendocardial layer (%)	9 (82%)	6 (100%)	ns
Middle layer (%)	9 (82%)	5 (67%)	ns
Subepicardial layer (%)	9 (82%)	2 (33%)	ns
All three layers (%)	9 (82%)	2 (33%)	ns
Confluent transmural (%)	3 (27%)	0	ns
Regional wall motion abnormalities	7	0	P < 0.05
Loss of wall thickness < 7 mm	2	0	ns

Table 2: Summary of electrocardiographic findings.

Findings with 12-lead electrocardiogram	cardiac sarcoidosis standard assessment (group A, n = 13)	cardiac sarcoidosis only with CMR (group C, n = 6)	P value
Normal	1 (7%)	6 (100%)	P < 0.001
Abnormal	12	0	
LBBB	2	0	
RBBB	1	0	
Bifascicular block	1	0	
LAHB	1	0	
Grade III atrio-ventricular block	2	0	
Pseudo-infarct pattern	2	0	
ST-T segment abnormalities	3	0	
Findings with ambulatory electrocardiography			
Abnormal	6 (46%)	0	ns
PVC > 100/24 hrs	2	0	
Non-sustained VT	3	0	
Sustained VT	1	0	
Paroxysmal atrial fibrillation	0	0	
Atrioventricular nodal reentrant tachycardia	0	0	

Table 3: Summary of echocardiographic findings.

Echocardiographic findings	cardiac sarcoidosis standard assessment (group A, n = 13)	cardiac sarcoidosis only with CMR (group C, n = 6)	P value
Diastolic dysfunction			
Relaxation abnormalities	2	1	ns
Pseudonormalization	1	1	ns
Restrictive filling pattern	3	0	ns
LVH	1	1	ns
LVEF (%)			
Mean $\pm$ SD	47 $\pm$ 16	62 $\pm$ 4	P < 0.05
LVEF $\leq$ 55%	8	0	P < 0.05
Regional wall motion abnormalities	7	0	P < 0.05
Regional wall thinning	2	0	ns
Mitral regurgitation			ns
Grade 1	1	0	
Grade 2	3	0	
Grade 3	0	0	
Grade 4	2	0	
Tricuspid regurgitation	1	0	ns
Pulmonary hypertension	2	1	ns
Range (mm Hg)	30 – 55	30	
Right ventricular hypertrophy	3	1	ns
Right ventricular dysfunction	6	0	P < 0.05
Pericardial effusion	0	0	ns

Figure 1. Bulls eye plots demonstrating left ventricular segmentation (left) (18) and the distribution of late enhancement per segment in 19 sarcoidosis patients (right).

Figure 2A. Bar diagram showing the distribution of abnormal test results and correlation with late enhancement at magnetic resonance imaging.

Figure 2B. Bar diagram showing the distribution of abnormal findings at Doppler echocardiography and correlation with late enhancement at magnetic resonance imaging.

Figure 3. CMR study (spin echo (SE) sequence, short axis view (SA)) demonstrates late enhancement (segments 1, 4 and 5) in a patient in whom standard assessment had not revealed abnormalities.

Figure 4. CMR study (spin echo (SE) sequence, short axis view (SA)) demonstrates late enhancement (segments 7 and 12) in a patient in whom standard assessment had initially not revealed abnormalities.

Figure 5. CMR study (left: 3 D breath-hold inversion recovery fast gradient echo IR-FGRE, short axis view; right: SSFP, 4 chamber view) demonstrates loss of wall thickness and late enhancement (segments 11 and 12) in a patient who survived out of hospital cardiac arrest secondary to ventricular fibrillation.

Figure 6. CMR study (spin echo (SE) sequence, short axis (SA) view) demonstrates left ventricular dilation and late enhancement (segment 6) in a patient who presented with heart failure and left bundle branch block.

Figure 7. CMR study (3 D breath-hold inversion recovery fast gradient echo (IR-FGRE), left: short axis (SA), and right: vertical long axis (VLA) views) demonstrates late enhancement (segments 2,8,10,12) in a patient who presented with sustained monomorphic VT, originating from the inferolateral left ventricular wall.

Chapter 5

Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis

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Structured abstract

Objectives: This study analyzed the accuracy of gadolinium-enhanced cardiovascular magnetic resonance (CMR) for the diagnosis of cardiac sarcoidosis (CS).

Background: The diagnosis of CS is made according to the guidelines of the Japanese Ministry of Health and Welfare (1993). CMR has not been incorporated in the guidelines, and the diagnostic accuracy of CMR for the diagnosis of CS has not yet been evaluated.

Methods: We performed an analysis of the 12-lead ECGs, 24-hours ambulatory ECGs, echocardiograms, thallium scintigrams and gadolinium-enhanced CMR studies in 58 biopsy proven pulmonary sarcoidosis patients assessed for CS. The diagnostic accuracy of CMR for CS was determined with modified Japanese guidelines as gold standard.

Results: The diagnosis of CS was made in 12 of 58 patients (21%). CMR revealed late gadolinium enhancement (LGE), mostly involving basal and lateral segments (73%), in 19 patients. In 8 of the 19 patients scintigraphy was normal, while patchy LGE was present. The sensitivity and specificity of CMR were 100% (95% CI, 78-100%) and 78% (95% CI, 64-89%) the PPV and NPV 55% respectively 100%, with an overall accuracy of 83 %.

Conclusions: In patients with sarcoidosis CMR is a useful diagnostic tool to determine cardiac involvement. New diagnostic guidelines should include CMR.

Contents

Structured abstract	130
Abbreviation list	130
5.1 Introduction	131
5.2 Patients and methods	131
5.3 Results	133
5.4 Discussion	134
5.5 Conclusions	135
5.6 Study limitations	136
5.7 Recommendations for further study	136
5.8 Acknowledgements	136
References	137

Abbreviation list

ECG	electrocardiogram
CMR	Cardiovascular Magnetic Resonance
CS	cardiac sarcoidosis
LGE	late gadolinium enhancement
VT	ventricular tachycardia

5.1 Introduction

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology with symptomatic cardiac involvement in up to seven percent of patients. **(1-3)** Postmortem studies reveal cardiac involvement in twenty to thirty percent of patients with sarcoidosis in the United States. **(4,5)** In Japan cardiac involvement is present in as many as 58 % of patients, and is responsible for as many as 85 % of deaths from sarcoidosis. **(6,7)** The clinical features of sarcoid heart disease include congestive heart failure, cor pulmonale, supra-ventricular- and ventricular arrhythmias, conduction disturbances, ventricular aneurysms, pericardial effusion and sudden death. **(8)** The diagnosis of cardiac sarcoidosis (CS) is made in the co-existence of non-caseating granulomas on myocardial biopsy and/or biopsies of any extra-cardiac tissue (with the exclusion of other causes for granulomatous inflammation such as mycobacterial or fungal infection) and cardiovascular abnormalities for which other possible causes have been excluded. The guideline from the Japanese Ministry of Health and Welfare provide an excellent frame work. **(9)** **(Table 1)** The guideline combines the results of various diagnostic tests such as tissue biopsy, electrocardiography, echocardiography, and myocardial scintigraphy to either exclude or diagnose CS. Most diagnostic tests, including endomyocardial biopsy, suffer of low sensitivity, low specificity or both. The most accurate diagnostic strategy for this condition is currently unknown. We aimed to assess the accuracy of gadolinium-enhanced cardiovascular magnetic resonance (CMR) in the diagnosis of cardiac sarcoidosis (CS) with a modified guideline of the Japanese Ministry of Health and Welfare (1993) as gold standard. Because of the limited diagnostic yield and invasive nature of the procedure with an associated risk of morbidity, we felt not justified to systematically subject patients who were screened for CS to endo-myocardial biopsy. **(10)** For the purpose of the present study the Japanese guideline was modified by excluding endomyocardial biopsy as a diagnostic parameter **(Table 1)**.

5.2 Patients and methods

Study population

Between July 1998 and May 2004 , 58 patients with histologically proven pulmonary sarcoidosis underwent cardiac assessment in the cardiology departments of Tygerberg Hospital (1), Medical Centre Haaglanden (1), the Erasmus University Medical Centre (3) and the University Hospital Maastricht (53). The diagnosis of sarcoidosis was confirmed if the clinical presentation and chest radiographic finding were supported by histological evidence of non-caseating granulomas by transbronchial biopsy, and the possibility of infection, environmental factors or hypersensitivity reaction to medication causing granulomatous inflammation, had been eliminated. The patients had either cardiac symptoms (16), or were screened for cardiac involvement in the absence of cardiac symptoms (42). All patients underwent clinical assessment, 12-lead electrocardiography, ambulatory electrocardiographic monitoring, transthoracic echocardiography, ²⁰¹ thallium SPECT, and CMR. Patients underwent diagnostic coronary angiography to exclude coronary artery disease in patients

with a (partially) reversible perfusion defect on SPECT and decreased left ventricular ejection fraction and regional wall motion abnormalities. Cardiac histology was obtained in five patients by cardiac biopsy, and three patients who had a post-mortem examination. The diagnosis of CS, according to the modified guideline of the Japanese Ministry of Health and Welfare (**Table 1**), was made in 12 of 58 patients included in the study.

Electrocardiography and ambulatory electrocardiography

A 12-lead surface ECG was made (MAC, Marquette, Milwaukee, Wisconsin; paper speed 25 mm/sec) and the findings were interpreted by two experienced cardiologists and classified as abnormal i.e. in keeping with the ECG criteria of the Japanese guideline (complete RBBB or LBBB, bifascicular block, third degree atrio-ventricular block, ventricular tachycardia, or pathological Q or ST-T abnormalities) or normal. Ambulatory ECGs were performed for 24-72 hours, and were considered abnormal when intermittent atrio-ventricular conduction delay or block, intermittent bundle branch blocks or ventricular arrhythmias such as frequent monomorphic and/or polymorphic PVCs > 100/24 hours, non-sustained VTs, and/or sustained VTs were found.

Echocardiography

Studies were performed with a Sonos 5500 phased array imaging system (Hewlett Packard) and considered abnormal when regional or global systolic dysfunction, wall thickening or thinning was found. Regional differences in left ventricular wall enhancement were measured and localized according to the 17 segment model (**10**)

Thallium myocardial scintigraphy

After treadmill peak exercise, or during intravenous infusion of dipyridamol, ²⁰¹ thallium was administered and SPECT performed on a Siemens triple-detector gamma camera (MultiSPECT-3), equipped with low-energy, high resolution collimators. The images were made in a 64×64 matrix (60 frames/45 seconds). The thallium scan was considered suggestive of CS when areas with reversed uptake and/or irreversible perfusion defects were present, and/or reversible perfusion defects were found in patients with normal coronary arteries at angiography. Regional defects were localized according to the 17 segment model (**11**)

Cardiac Magnetic Resonance

Studies were performed using a 1.5 Tesla MRI scanner (Philips, Best, The Netherlands and General Electric, Milwaukee, Wisconsin, USA) with a cardiac-dedicated phased-array coil. The CMR studies were ECG triggered by standard software, and obtained in diastole to minimize artifact due to cardiac motion. Studies consisted of steady-state-free precession (SSFP) in 58 patients, spin echo (SE) in 57 patients, and fat saturated T2 weighted breath

hold sequences in 58 patients. Short axis (SA), vertical long axis (VLA) and four chamber (4CH) views were obtained. SSFP sequences were performed to assess regional wall motion abnormalities. T2-weighted studies were performed to assess the presence of myocardial inflammation. Ten minutes after the additional administration of 0.1mmol/kg gadolinium-DTPA (Schering, Berlin), SA and 4 CH images were obtained with SE in 57 patients (slice thickness 8 mm, gap .8 mm, matrix 512×512 , FOV 380 mm, voxel size $0.7 \text{ mm} \times 0.7 \text{ mm} \times 8 \text{ mm}$) and 3-D breath hold inversion recovery-gradient echo (IR-GRE) sequences (SA, VLA, 4 CH) in 16 patients (slice thickness 10 mm, no gap, matrix 256×256 , FOV 400 mm, voxel size $1.6 \text{ mm} \times 1.6 \text{ mm} \times 10 \text{ mm}$) to assess for the presence of gadolinium enhancing lesions (LGE). Fifteen patients had both SE and IR-GRE studies. The inversion time (250-400 msec) was determined on an individual base to obtain optimal nulling of the unenhanced myocardial signal. Regional differences in left ventricular wall enhancement were measured and localized according to the 17 segment model (10) (MASS suite post processing software, MEDIS, Leiden, The Netherlands). The total time required for the investigation was 30-45 minutes. The studies were evaluated independently by 4 blinded observers, 3 cardiologists and 1 radiologist, with experience in ceCMR. The studies were considered to be abnormal when at least two independent observers described identical abnormalities.

Statistical analysis

All statistical analyses were performed using the statistical software package SPSS version 11.5. Group data are expressed as mean $\pm$ SD. Continuous variables were assessed using the parametric *t* test for independent samples or Mann Whitney test were appropriate, and all categorical variables were assessed using the chi-square test. Statistical significance was defined as a *p* value less than 0.05.

5.3 Results

Patient characteristics

A total of 58 patients were assessed. Twelve of the patients were diagnosed with CS according to the modified guidelines. The demographic, clinical and diagnostic findings in the group with CS and without CS are shown in **Tables 2 and 3**. The ages, gender, race, the time between cardiac evaluation and the diagnosis of sarcoidosis, and pulmonary stage did not differ significantly between the groups. Functional class was significantly poorer in the patient group with CS compared to the group without CS due to heart failure.

Cardiac Magnetic Resonance

Table 4 summarizes the findings of the CMR studies. In 40 (69%) studies 4 out of 4 observers, in 13 (22%) studies 3 out of 4 observers, and in 5 (9%) studies 2 out of 4 observers

agreed on the absence or the presence and localization of LGE. Late gadolinium enhancing lesions were present in 19 patients (mean 3.6 segments/pt, range 1-12). Nine of 19 patients had evaluation with SE, 9 with SE and IR-GRE, and 1 patient had only IR-GRE. In 5 of the SE patients 2, and in 3 of the SE patients 3 observers agreed on the presence and localization of LGE, while in 9 of the 10 patients who had both SE and IR-GRE or only IR-GRE all observers agreed on the presence and localization of LGE. Most enhancing lesions were located in the basal and lateral left ventricular segments (segments 1-7,11,12,16; 60/71 enhancing segments (73%)). **(Figure 1)** In 10 patients a significantly reduced left ventricular systolic function (LVEF 20-51%, mean 36%) was reported, 7 (54%) with CS, one patient with dilated cardiomyopathy, one with valvular heart disease, and 1 with coronary artery disease. In 3 patients regional loss of wall thickness was found, 2 patients with CS and one with coronary artery disease. Twelve of the 22 patients with abnormal CMR studies were diagnosed with CS according to the modified guideline. Overall the diagnosis of cardiac sarcoidosis according to the modified guideline was made in 12 of 58 sarcoidosis patients (21%). The sensitivity and specificity of ceCMR was 100% (one sided 95% CI, 78-100%) and 78% (95% CI, 64-89%) the PPV and NPV 55% respectively 100%, with an overall accuracy of 83%. CMR showed one to six contrast-enhancing myocardial lesions in 6 patients, who had not been diagnosed with CS according to the modified guideline. In 8 patients CMR (5 with SE, 3 with SE and IR-GRE) diagnosed LGE, while ¹²³thallium scintigraphy was normal. In 6 of the 8 patients LGE involved only 1 or 2 segments, while in 2 patients respectively 6 and 8 segments were involved. In 3 patients LGE involved 1 myocardial layer, sub-endocardial or mid-myocardial, in 1 patient both sub-endocardial and mid-myocardial layers were involved, and in 4 patients patchy involvement of all 3 myocardial layers was present, without confluent transmural involvement.

5.4 Discussion

The prognosis of sarcoidosis is mainly determined by pulmonary and cardiac involvement. **(12,13)** Multivariate analysis identified New York Heart Association functional class, LV enddiastolic diameter and the presence of sustained ventricular tachycardias as independent predictors of mortality. **(14)** It is important to accurately diagnose cardiac involvement. The guideline published by the Japanese Ministry of Health and Welfare (1993) provides us with an excellent frame work for the diagnosis, but the techniques utilized lack sensitivity and specificity in the absence of a diagnostic endo-myocardial biopsy. Magnetic resonance imaging is a robust imaging technique that enables us to evaluate cardiac structure, function, and tissue characteristics with high image resolution. It may guide the cardiologist when taking endo-myocardial biopsies and increase the sensitivity of this technique. **(15,16)** Serial CMR studies are possible because of the absence of exposure to ionizing radiation, and may evaluate disease activity and extent in response to therapy. Postmortem studies in sarcoid patients have revealed the presence of varying amounts of myocardial scar tissue, which is considered to be the substrate for lethal ventricular arrhythmias. **(4,5,12,13,14)** Gadolinium-DTPA (Gd-DTPA) is an extra-cellular CMR contrast agent. Histological assessment of Gd-DTPA enhanced myocardium has been correlated with local fibrosis and

active myocarditis. **(16,17,18)** Wagner et al. have demonstrated the superior ability of Gd-enhanced CMR to diagnose even small amounts of myocardial scar tissue in patients with coronary artery disease when compared to myocardial scintigraphy. **(19)** Several case-reports and small single-centre patient series have demonstrated the diagnostic potential of CMR in cardiac sarcoidosis. **(20-28)** So far no study has systematically evaluated the diagnostic accuracy of CMR for the presence of CS, with the diagnostic Japanese guideline as gold standard. The current study is part of a prospective initiative that aims to evaluate the prevalence of cardiac involvement in patients with sarcoidosis, and determine the most accurate and cost-effective diagnostic strategy for CS. The diagnostic accuracy of CMR compares well to the techniques employed in the diagnostic framework of the Japanese guideline. The fact that the combination of ECG and CMR saves valuable time at equal cost compared to our previously employed diagnostic pathway of ECG, echocardiography and SPECT (cost in The Netherlands respectively €222,- and €205,-) makes it an attractive alternative. The low PPV of 55% reflects the superior spatial resolution of CMR. CMR is able to detect small myocardial lesions which have not resulted in conduction delay, repolarization abnormalities, or regional changes in wall thickness or function, and hence are not detected by ECG, echocardiography or SPECT. Unfortunately even small myocardial scars may result in arrhythmias, and the follow up of this patient population will determine the significance of our findings. For this reason, CMR may become very important for the early detection of cardiac involvement and for identifying pulmonary sarcoidosis patients at risk of sudden death. Most of the enhancing lesions (73%) were localized in the basal and lateral left ventricular wall. These findings correlate with the findings at postmortem assessment of sarcoidosis patients, where most lesions were found in the mentioned segments. **(4,5)** Although in some patients LGE was transmural, resulting in loss of wall thickness and regional wall motion abnormalities, lesions in most patients were patchy, affecting several myocardial layers. The presence of patchy LGE has also been reported in patients with dilated cardiomyopathy, but our findings clearly differ from the distribution of LGE in patients with coronary artery disease. **(29)** Considering the diagnostic limitations of electrocardiography, 25% of patients with extensive cardiac involvement in Roberts study had normal ECGs, and the superior spatial resolution of CMR compared to scintigraphy, new diagnostic guidelines need to be compiled that include CMR

5.5 Conclusions

In patients with sarcoidosis CMR is a useful, cost-effective diagnostic tool to determine cardiac involvement. The combination of ECG with CMR was as accurate but more time- and cost-effective compared to ECG, ambulatory ECG, echocardiography and SPECT for the diagnosis of CS. CMR diagnosed small myocardial lesions, not diagnosed by ECG, echocardiography or SPECT, that might be of prognostic relevance.

5.6 Study limitations

Ideally CMR findings should be correlated with CMR guided EMB i.e. myocardial histology. In our study CMR findings were compared to clinical guidelines. In only four patients myocardial histology was obtained.

5.7 Recommendations for further study

There is a need for multi-centre studies that will determine the diagnostic accuracy of CMR and studies into the prognostic implications of ceCMR detected CS not detected by conventional methods. Early treatment may possibly prevent sudden death and deterioration of ventricular function and result in improved prognosis.

5.8 Acknowledgements

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Table 1: Modified guidelines for the diagnosis of cardiac sarcoidosis based on the study report on diffuse pulmonary diseases from the Japanese Ministry of Health and Welfare, 1993. (9)

1. Histologic diagnosis group: endomyocardial biopsy demonstrates epithelioid granulomata without caseating granulomata.
2. Clinical diagnosis group: in patients with histologic diagnosis of extra-cardiac sarcoidosis, cardiac sarcoidosis is suspected when 'a' and at least one of criteria 'b' to 'd' are present, and other etiologies such as hypertension and coronary artery disease have been excluded:
a. Complete RBBB, LBBB(<i>included by the authors</i>), left-axis deviation, AV-block, VT, PVC, or pathological Q or ST-T change on resting- or ambulatory ECG.
b. Abnormal wall motion, regional wall thinning, or dilation of the left ventricle.
c. Perfusion defect by ^{201}Tl -myocardial scintigraphy or abnormal accumulation by ^{67}Ga -citrate or $^{99\text{mTc}}$ -PYP myocardial scintigraphy.
d. Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle.
<i>(the original guidelines mentioned: c. Interstitial fibrosis or cellular infiltration over moderate grade, even if the findings are non-specific)</i>

Table 2: Summary of demographic and background medical data.

	Group with cardiac sarcoidosis (n = 12)	Group without cardiac sarcoidosis (n = 46)	P value
Mean age (years)	49±6	47±10	ns
Functional class			P < 0.01
No complaints	9 (69%)	40 (87%)	
Modified NYHA (class 0 – IV)	0.9 ± 1.6	0.2 ± 0.5	
NYHA I	0	1	
NYHA II	2	3	
NYHA III	0	0	
NYHA IV	2	0	
Time (years) since diagnosis of sarcoidosis	9±8	6±9	ns
Pulmonary stage (I-IV)	1.8 ± 1	2.2 ± 1.2	ns
Steroid treatment	12 (92%)	31 (67%)	ns
Hypertension	0	10 (23%)	P < 0.05
Palpitations	4 (31%)	13 (30%)	ns
Syncope	1 (8%)	2 (5%)	ns
ACE maximal (IU/l)	35±40	30±17	ns
Abnormal ECG	13 (100%)	3 (7%)	P < 0.0001
Abnormal ambulatory ECG	7 (58%)	6 (13%)	P < 0.01
Abnormal echocardiogram	6 (46%)	3 (7%)	P < 0.01
Abnormal thallium scintigram	3 (43%)	5 (11%)	ns
CMR			
Regional contrast enhancement	12 (92%)	8 (17%)	P < 0.0001
Number of enhancing segments	3.3± 3.6	0.5±1.3	P < 0.0001
Decreased LVEF	7 (54%)	3 (7%)	P < 0.0001
Mean LVEF (%)	48 ± 15	59 ± 5	P < 0.0001
Loss of wall thickness	2 (15%)	1 (2%)	ns

Table 3: 12 patients with cardiac sarcoidosis (modified Japanese guideline).

pt	age (yrs)	sex	time since diagnosis of sarcoidosis (yrs)	symptoms	thallium	echo	CMR	ECG	Holter	EMB
1	53	M	10	heart failure		1	1,2	Δ ST-T	0	non-caseating granulomas
2	50	F	4	palpitations		1	1	Δ ST-T	VT	
3	52	F	30	heart failure	normal	1	1,2	pseudo-infarct	nsVT	fibrosis
4	55	F	7	heart failure	abnormal	1	1,2	LB BBB	0	
5	41	M	1	palpitations	abnormal	1	1,3	Δ ST-T	nsVT	fibrosis
6	42	M	5	palpitations	normal	0	1	bifasc block	0	
7	43	M	14	heart failure		1	2	LB BBB	nsVT	fibrosis
8	43	M	6	palpitations	normal	0	1	RBBB	0	
9	54	M	15	heart failure	normal	1	1,2	3 rd AV block	0	
10	54	M	5	heart failure	normal	0	1,2	3 rd AV block	0	
11	41	M	10	none	abnormal	1	1	Δ ST-T	0	
12	52	M	4	syncope		1	1,2,3	pseudo-infarct	nsVT	

Tabel 4: Abnormal findings with CMR.

pts	age years	sex	CMR segments	diagnosis	ECG	Holter	echo	thallium segments
1	53	M	LGE: 1,3,4,6,8,9,10,11,12,15, all layers, some confluent transmural lesions; regional wall motion abnormalities; LVEF 50% (Figure 2)	CS (guideline)	ΔST-T	0	LVEF 50%	
2	41	M	LGE: 5,12, all layers	CS (guideline)	ΔST-T		mild MVP	irreversible, 10,15
3	50	F	LGE: 2,3,6, all layers	CS (guideline)	ΔST-T	VT	hyperechoicity	
4	52	F	LGE: 1,2,3,5,6,7,8,9,13,14,15,16, all layers, some confluent transmural lesions; regional wall motion abnormalities; LVEF 30% (Figure 3)	CS (guideline)	pseudo-infarct	nsVT	LVEF 30%	
5	55	F	LGE: 1,6, involving all layers; LVEF 51%	CS (guideline)	LBBB	0	LVEF 30%	reversed uptake, 1,6,7,12
6	41	M	LGE: 11,16,17, all layers, some confluent transmural lesions; loss of wall thickness, regional wall motion abnormalities	CS (guideline)	ΔST-T	nsVT	HCM	partly reversible, 13,14,16,17
7	42	M	LGE: 7, mid- myocardial layer	CS (guideline)	bifasc block	PVC's	0	0
8	43	M	LVEF 20%	CS (guideline)	LBBB	nsVT	LVEF 20%	
9	43	M	LGE: 2,3, involving all layers	CS (guideline)	RBBB	0	0	0
10	54	M	LGE: 1,2,3,4,7,8,9,10, all layers; regional wall motion abnormalities; LVEF 35% (Figure 4)	CS (guideline)	3 rd AV block	0	dilated RV+LV, LVEF 46%	0
11	54	M	LGE: 2,6, involving all layers; LVEF 56%	CS (guidelines)	3 rd AV block	0	0	0
12	52	M	LGE: 5,6,11,12, all layers, some confluent transmural lesions; loss of wall thickness, regional wall motion abnormalities; LVEF 40% (Figure 5)	CS (guidelines)	pseudo-infarct	nsVT	hypokinesia, 4,5,10,11,15,16 LVEF 40%	
13	47	M	LGE: 7, mid- myocardial layer	undetermined	0	0	0	0
14	39	M	LGE: 2, sub-endocardial layer	undetermined	0	0	0	irreversible, 10,15
15	49	F	LGE: 1,2,9,11,12, all layers	undetermined	0	0	0	reversed uptake, 1,2,7,8
16	48	M	LGE: 3,4,5,6,9,10, all layers	undetermined	0	0	0	0
17	44	F	LGE: 1,5, sub-endocardial layer (Figure 6)	undetermined	0	0	0	0
18	67	F	LGE: 2,4, sub-endocardial layer	undetermined	0	0	0	0

pts	age years	sex	CMR segments	diagnosis	ECG	Holter	echo	thallium segments
19	50	M	LGE: 13,14,15,17, sub-endocardial and transmural, loss of wall thickness, LVEF 20%	CAD	LBBB	0	apical dyskinesia, LVEF 34%	irreversible, 1,6,7,12
20	58	M	LGE: 2,3, sub-endocardial layer	CAD	0	0	0	reversible inferior
21	39	M	LVEF 50%	aortic valve regurgitation	0	0	LVEF 50%	0
22	69	F	LVEF 30%	DCM	RVH	0	LVEF 30%	0

Figure 1. Bulls eye plots demonstrating left ventricular segmentation (left) (11) and the distribution of late enhancement per segment in 19 sarcoidosis patients (right).

Figure 2A: CMR study (IR-GRE, SA view, 10 minutes after administration of 0.1 mmol/Gd-DTPA) of patient 1, a 53-year old man with a history of stage 2 pulmonary sarcoidosis, who presented with congestive cardiac failure. Arrows point towards the enhanced myocardial segments (10, 11 and 12).

Figure 2B: The end-systolic frame (SSFP, SA view) of this slice demonstrated regional loss of wall thickness and hypokinesia of the Gd- enhanced segments (10, 11 and 12).

Figure 3: CMR study (IR-GRE, SA view, 10 minutes after administration of 0.1mmol/Gd-DTPA) of patient 4, demonstrated extensive late gadolinium enhancement, involving 33% of the left ventricle.

Figure 4: CMR study (IR-GRE, 4CH view, 10 minutes after administration of 0.1 mmol/Gd-DTPA) of patient 10, a 54-year old man with a history of stage 3 pulmonary sarcoidosis, who was referred with grade III atrio-ventricular block. Arrows point towards the Gd-DTPA enhanced myocardial segments (2,8).

Figure 5A: CMR study (3 D breath-hold IR-FGRE, SA view, 10 minutes after administration of 0.1 mmol/Gd-DTPA) of patient 12 demonstrated loss of wall thickness and late gadolinium enhancement (segments 11 and 12). This patient survived out of hospital cardiac arrest secondary to ventricular fibrillation.

Figure 5B: CMR study (SSFP, 4 chamber view) of patient 12 demonstrated loss of wall thickness and late gadolinium enhancement (segments 11 and 12). This patient survived out of hospital cardiac arrest secondary to ventricular fibrillation.

Figure 6: CMR study (SE, SA view) of patient 17 demonstrated late gadolinium enhancement (segments 1,4) in a patient in whom standard assessment had not revealed abnormalities.

Chapter 6

Contrast-Enhanced Cardiac Magnetic Resonance: Distinction between cardiac sarcoidosis and infarction scar

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Abstract

Objectives: To review the value of delayed contrast-enhanced cardiac magnetic resonance (CECMR) in differentiating patients with cardiac sarcoidosis (CS) from those with coronary artery disease and recent myocardial infarctions.

Background: Late gadolinium enhancement (LGE) accurately delineates myocardial necrosis or fibrosis. The pattern of LGE in ischemic and non-ischemic myocardial disease is different, and might be helpful in distinguishing CS from ischemic disease.

Methods: The CECMR studies of 30 patients with CS were compared to those performed in 30 consecutive infarct patients, who had been managed with primary coronary interventions, and 10 healthy controls. Two experienced blinded observers classified patients by assessing the distribution of LGE.

Results: LV LGE was present in 29/30 CS (mean 3.8 segments, range 0 – 12), all infarct (mean 4.3 segments, range 0 – 9), and none of the patients in the control group. The amount of LV LGE did not differ significantly between CS and infarct patients ($19 \pm 11\%$ and $19 \pm 12\%$, $P = 0.8$). The CS group exhibited a predominantly patchy, 3 layer LGE ($P = 0.01$), whereas confluent transmural LGE ($P = 0.04$) with a vascular distribution ($P < 0.001$) was prevalent in the infarct group. Significantly more RV LGE ($P = 0.01$) and dilation ($P = 0.02$) were found in the CS group. The two observers classified patients correctly as CS in 72% and 83% of cases, as ischemic in nature in 77% and 80% of cases, and as normal in 90% and 100% respectively.

Conclusions: Gadolinium CMR was helpful in differentiating patients with CS from patients with ischemic heart disease and previous myocardial infarctions. In a subgroup of ischemic patients the pattern of LGE was atypical, and suggestive of non-ischemic etiology.

Contents

Abstract	148
6.1 Introduction	149
6.2 Patients and methods	149
6.3 Results	151
6.4 Discussion	152
6.5 Conclusion	153
References	154

6.1 Introduction

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology with cardiac involvement in approximately twenty to thirty percent of patients. **(1)** The clinical features of sarcoid heart disease include congestive heart failure, cor pulmonale, supraventricular and ventricular arrhythmias, atrioventricular and intraventricular conduction disease, ventricular aneurysms, pericardial effusion and sudden death. **(1)** The diagnosis of cardiac sarcoidosis (CS) is made in the co-existence of non-caseating granulomas on myocardial biopsy or biopsies of any extra-cardiac tissue (with the exclusion of other causes for granulomatous inflammation such as mycobacterial or fungal infection) and cardiovascular abnormalities for which other possible causes have been excluded. **(2)** The value of gadolinium-enhanced cardiac magnetic resonance (CMR) in the diagnosis and management of this condition has been demonstrated. **(2-4)** Late gadolinium enhancement (LGE) by CMR is the most accurate non-invasive method to evaluate myocardial necrosis or fibrosis caused by acute myocardial infarction, chronic myocardial infarction or non-ischemic myocardial disease. **(5)** The distribution of LGE was valuable in differentiating between ischemic and non-ischemic myocardial scarring. **(6-9)** Since a significant number of patients with CS present with symptoms of heart failure or chest pain, similar in nature to those in patients with coronary artery disease, we aimed to determine whether CMR, and specifically the pattern of MDE, would allow us to distinguish the CS patients from patients with coronary artery disease and recent myocardial infarcts.

6.2 Patients and methods

Patient population

Between July 1998 and November 2004 thirty patients were diagnosed with CS according to modified guidelines, based on the Study Report on Diffuse Pulmonary Diseases of the Japanese Ministry of Health and Welfare (1993). **(2)** We compared the CMR findings in the CS patients with those of 30 consecutive patients who had presented with myocardial infarcts, and who had CECMR studies during the study period. We included CECMR studies of 10 healthy control subjects. All patients in the infarct group had recently been diagnosed with myocardial infarction as defined by the European Society of Cardiology and American College of Cardiology, and underwent coronary angiography with (primary) percutaneous coronary interventions. **(10)** Twenty patients had myocardial infarction in the distribution of a single coronary artery (right coronary artery: 6 patients, left anterior descending artery: 7 patients, left circumflex artery: 7 patients), while ten patients had infarcts in the distribution of two coronary arteries (right coronary artery and left anterior descending artery: 4 patients, left anterior descending artery and left circumflex artery: 4 patients, right coronary artery and left circumflex artery: 2 patients). Since the study concerned retrospective analysis of clinical data in the CS and infarct groups, the Institutional Review Board waived the need for consent according to Dutch legislation. The Board approved the CMR studies in the control subjects, and all controls provided written informed consent.

CMR protocol

Studies were performed using a 1.5 Tesla MRI scanner [(Philips, Best, The Netherlands (53 patients) , Siemens, Erlangen, Germany (3 patients, 10 controls) and General Electric, Milwaukee, Wisconsin, USA (4 patients)] with a cardiac-dedicated phased-array coil. The CMR studies were ECG triggered by standard software. All patients underwent steady-state-free precession studies of short axis, vertical long axis and four chamber views, to assess regional wall motion abnormalities. Before and ten minutes after the administration of 0.1 mmol/kg gadolinium-DTPA (Schering, Berlin), short axis, vertical long axis and 4 chamber images were obtained with Spin Echo in 5 patients (slice thickness 8 mm, gap .8 mm, matrix 512×512 , FOV 380 mm, voxel size $0.7 \text{ mm} \times 0.7 \text{ mm} \times 8 \text{ mm}$), and 3-D breath hold inversion recovery-gradient echo (IR-GRE) sequences, obtained in diastole to minimize artifact due to cardiac motion, in the remaining 55 patients and 10 controls (slice thickness 10 mm, no gap, matrix 256×256 , FOV 400 mm, voxel size $1.6 \text{ mm} \times 1.6 \text{ mm} \times 10 \text{ mm}$) to assess for the presence of LGE. The inversion time (250-400 msec) was determined on an individual basis to obtain optimal nulling of the unenhanced myocardial signal. The total time required for the investigation was 30-45 minutes.

CMR Analysis

CMR studies were analyzed off-line using commercially available software (CAAS MRV 3, Pie Medical Imaging, Maastricht, The Netherlands). Ventricular parameters were assessed in a standard way. **(11)** Regional wall motion abnormalities, loss of wall thickness and left ventricular (LV) LGE were localized according to the standard 17 segment model. **(12)** After delineating the endocardial and epicardial LV contours manually, the hyper-enhanced myocardium was depicted by changing the threshold setting for signal intensity. Signal intensities of LV and right ventricular (RV) LGE, and remote unenhanced LV and RV myocardium were measured in the short axis slice with the highest level of enhancement. The cut off signal intensity value for LGE was two times the standard deviation of remote unenhanced myocardium. The absolute and relative amounts of LV LGE were computed by the post-processing software. RV LGE was considered to be present when seen in both the short axis and four chamber views. The distribution of LV LGE was classified as sub-endocardial, mid-wall, sub-epicardial, patchy three-layer involvement, or confluent transmural involvement. Two blinded, independent observers (RT, BMM) were asked to differentiate between the three groups based on the presence and distribution of LGE. To test for intraobserver variability, one observer (RT) repeated the assessment after a month, while blinded to previous results.

Statistical analysis

All statistical analyses were performed with a commercially available statistical software program (SPSS for Windows, version 21; SPSS, Chicago, Ill). Group data were expressed as mean $\pm$ SD. Continuous variables were assessed using the parametric *t* test for independent samples or Mann Whitney test where appropriate, and all categorical variables were as-

essed using the chi-square test. Statistical significance was defined as a p value less than 0.05. Bland-Altman analyses and intra-class correlation coefficients were used to determine intra-observer variability in the assessment of ventricular masses, volumes, ejection fractions, and the amount of LGE. We used kappa values to assess interobserver variability in determining the presence and localization of LGE, the diagnostic accuracy of the observers and the intra-observer variability in diagnosing CS and infarcts by LGE CMR.

6.3 Results

Patient characteristics

The demographic and background medical data are summarized in **Table 1**. The patients suffering from coronary artery disease were significantly older, had more cardiovascular risk factors, and pathological Q-waves on their 12-lead ECG's.

Cardiac Magnetic Resonance

The CMR findings are summarized in **Table 2**. The LV ejection fraction and LV end-diastolic volume index differed significantly between the CS and infarct groups, with more loss of regional LV wall thickness ($P = 0.009$) and wall motion abnormalities ($P = 0.008$) resulting in poorer systolic function ($P = 0.047$) and larger ventricles ($P = 0.01$) in the latter group. LGE of the LV was present in 29/30 CS patients (mean 3.8 segments/patient, range 0 – 12), 30/30 infarct patients (mean 4.3 segments/patient, range 0 – 9), and none of the control group. The amount of LGE did not significantly differ between the CS and infarct groups ($P = 0.8$). Most enhancing lesions in the CS group were located in the basal and anterolateral LV (segments 1-6, 12 and 16; 74 out of 117 enhancing segments (64%), compared to 58/127 (46%) for the MI group). In the majority of CS patients (19/30, 63%) patchy LGE involved all three myocardial layers. In 2/30 (7%) confluent transmural LGE was present, suggesting co-existing coronary artery disease. (**Figure 1A**) But coronary angiography showed unobstructed epicardial coronary arteries. In 25/30 (83%) patients of the infarct group the distribution of LGE was suggestive of underlying coronary artery disease, since hyper-enhancement started at the subendocardium and involved segments restricted to the vascular territory of specific coronary arteries. Sole mid-layer involvement was only seen in patients with CS, while LGE involving both the subendocardial and mid myocardial layers was predominantly seen in infarct patients. When considering sole mid layer, patchy subendocardial and three layer LGE to be diagnostic of CS, 26/30 (87%) would have been correctly classified. (**Figure 2A, C, E**) Significantly more RV LGE (8 (27%) versus 3 (7%) patients, $P = 0.01$) and RV dilation (10 (33%) versus 2 (7%) patients, $P = 0.02$) was found in the CS group. (**Figure 3**) The observers correctly diagnosed CS in 21/29 (72%), 24/29 (83%), 21/29 (72%), ischemic heart disease in 23/30 (77%), 23/30 (77%), 24/30 (80%) and normal controls in 9/10 (90%), 10/10 (100%), 10/10 (100%). The kappa values for interobserver agreement in differentiating between CS, infarcts and normal controls by assessing the LGE CMR studies were 0.91 (0.86, 0.95), and 0.86 (0.81,

0.92). The kappa value for intra-observer agreement in differentiating between CS, infarcts and normal controls by assessing the LGE CMR studies was 0.86 (0.81, 0.92). There was excellent intra- and interobserver correlation for ventricular volumes, masses, and ejection fractions. The intra-class correlation coefficient for LV LGE was 0.989 [0.981-0.993] ($p=0.001$).

6.4 Discussion

Our study is the first to systematically compare the distribution of LGE in CS with the findings in patients with coronary artery disease. Our findings suggest that CECMR is helpful in the non-invasive differentiation between patients with CS and patients with coronary artery disease and previous myocardial infarcts. However, in approximately a third of patients with coronary artery disease, subepicardial or patchy, three layer LGE was found, a pattern that was suggestive of a non-ischemic etiology such as CS. **(6,7,8)** Additional angiographic information was needed to correctly classify 11 patients with coronary artery disease and 3 with CS.

LGE results from the sustained presence of gadolinium in the myocardium, secondary to expansion of the interstitial space or impaired microvascular wash out (“no-reflow phenomena”), and has been reported in a variety of conditions, such as coronary artery disease, cardiomyopathies, myocarditis, and myocardial infiltration, that are characterized by necrosis, fibrosis or inflammation. **(2-9)** In CS the presence of active, granulomatous inflammation and the resulting myocardial fibrosis are considered to be the underlying histopathological substrate resulting in the accumulation of gadolinium. **(2-4)** Recent studies have determined subendocardial and transmural LGE to be diagnostic of underlying coronary artery disease, while sole mid-layer and epicardial LGE were predominantly seen in patients with non-ischemic cardiomyopathies. **(2-9)** Although sole subepicardial myocardial fibrosis is considered rare in coronary artery disease, both our patients with epicardial LGE happened to be infarct patients. **(13)** **(Figure 3)** Early presentation and primary percutaneous interventions may have resulted in smaller, myocardial scars with an atypical mural distribution. **(14)** **(Figure 2B, D, F, 4B, D)**

The pattern of LGE in CS has been reported to be patchy, multi-segmental, not related to coronary artery territories, while predominantly involving the mid myocardial and subepicardial layers. **(2-4)**. When considering sole mid-layer, and patchy subendocardial or patchy transmural LGE to be diagnostic of CS, and confluent subendocardial or confluent transmural LGE diagnostic of coronary artery disease, the sensitivity, specificity and overall accuracy of LGE CMR for these conditions respectively would be 87%, 70%, 78%, and 63%, 90% and 77%. The significantly higher number of patients with loss of regional wall thickness, wall motion abnormalities, and generally poorer systolic LV function in the infarct group is explained by more extensive, confluent, transmural LGE in this group. **(15)**

RV LGE and dilation was present in a substantial number of CS patients. These findings may be explained by primary RV myocardial involvement, but alternatively the presence of pulmonary arterial hypertension, resulting from extensive pulmonary sarcoidosis, has been considered a possible cause of RV fibrosis. **(16)** The junction of right and left

ventricle and right-sided interventricular septum seemed to be predominantly affected. **(Figure 4)** However, further studies are needed to elucidate the underlying mechanisms and significance of RV LGE in patients with sarcoidosis. The absence of LGE in one patient with CS, with a dilated, globally hypokinetic LV, may be explained by the presence of diffuse myocardial fibrosis, which is not detected with the IR-GRE technique.

IR-GRE is the current gold standard technique in the assessment of myocardial fibrosis, and we may have underestimated the amount of myocardial scar tissue by relying on Spin Echo sequences in 5 patients. The distribution of LGE in these particular patients was however strongly suggestive of CS, in that it concerned patchy subendocardial or three layer hyperenhancement. Since the majority of patients were not assessed with first-pass myocardial perfusion studies, we did not include these data. The presence of flow limiting coronary artery disease in the infarct group might have improved the diagnostic accuracy of CMR in this group.

6.5 Conclusion

The presence of sole mid-layer, and patchy, subendocardial or three layer LGE with a non-vascular distribution, in patients with extra-cardiac sarcoidosis suggests cardiac involvement, and differentiates these patients from patients with coronary artery disease.

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Table 1: Summary of demographic and background medical data.

	Coronary Artery Disease (n = 30)	Cardiac Sarcoidosis (n = 30)	Controls (n = 10)	p value*
Mean age (years)	62 ± 13	49 ± 8	39 ± 14	p < 0.001
Sex (M/F)	27/3	19/11	9/1	p = 0.02
Body Surface Area (m ²)	1.93 ± 0.11	1.89 ± 0.19	1.89 ± 0.22	p = 0.3
Functional class				p = 0.2
NYHA I	10	14	10	
NYHA II	17	10	0	
NYHA III	3	4	0	
NYHA IV	0	2	0	
Angina	30	0	0	p < 0.001
Palpitations	4	19	0	p < 0.001
Syncope	2	4	0	p = 0.7
Hypertension	10	2	0	p = 0.02
Diabetes Mellitus	8	1	0	p = 0.03
12-lead ECG				
Atrial Fibrillation	0	0	0	
Bundle Branch Block	5	7	0	p = 0.5
RBBB	0	1	0	
LBBB	4	3	0	
LAFB	1	1	0	
Bifascicular block	0	2	0	
Atrio-ventricular Block	0	4	0	p = 0.1
Grade II AV Block	0	2	0	
Grade III AV Block	0	2	0	
Q wave	11	2	0	p = 0.01

* P values concern the comparison between the groups with coronary artery disease and cardiac sarcoidosis

Table 2: Summary of the findings with gadolinium-enhanced cardiac magnetic resonance.

	Coronary Artery Disease (n = 30)	Cardiac Sarcoidosis (n = 30)	Controls (n = 10)	P value
Left Ventricular mass (gram)	122 ± 28	129 ± 61	97 ± 40	p = 0.6
Left Ventricular mass index (gram/m ²)	64 ± 16	68 ± 26	51 ± 18	p = 0.5
Left Ventricular Hypertrophy (pts)	4 (13%)	7 (23%)	0	p = 0.5
Regional LGE (pts)	30 (100%)	29 (97%)	0	p = 1.0
Number of Left Ventricular segments with LGE	127/510 (25%)	117/510 (23%)	0	p = 0.4
Range per patient	0 - 9	0-12		
Mean	4.3	3.8		
Sub-endocardial LGE (pts)	6 (20%)	5 (17%)	0	p = 1.0
Confluent, coronary artery distribution	6 (20%)	0		p = 0.02
Patchy	0	5 (17%)		p = 0.01
Sub-endocardial + Mid-wall LGE (pts)	5 (17%)	1 (3%)	0	p = 0.2
Mid-wall MDE (pts)	0	2 (7%)	0	p = 0.5
Sub-epicardial + Mid-wall LGE (pts)	2 (7%)	0	0	p = 0.5
Patchy LGE of all 3 Left Ventricular layers (pts)	9 (30%)	19 (63%)	0	p = 0.01
Transmural confluent Left Ventricular LGE (pts)	8 (27%)	2 (7%)	0	p = 0.04
One focus of LGE (pts)	21	10	0	p = 0.02
Multiple foci of LGE (pts)	9	19	0	p = 0.02
Vascular segmental distribution of LGE (pts)	25	3	0	p < 0.001
Left Ventricular LGE (gram)			0	p = 0.8
Min - Max	jul-68	0 - 73		
Mean	26 ± 14	27 ± 21		
Left Ventricular LGE (%)				p = 0.8
Min - Max	jun-47	0 - 38		
Mean	19 ± 11	19 ± 12		
Left Ventricular End-Diastolic Volume (ml)				p = 0.08
Min - Max	103 - 573	74 - 308	107 - 229	
Mean ± SD	194 ± 84	160 ± 58	154 ± 33	
Left Ventricular End-Diastolic Volume index (ml/m ²)				p = 0.01
Min - Max	57 - 311	36 - 148	64 - 102	
Mean ± SD	101 ± 47	75 ± 29	81 ± 101	
Left Ventricular Ejection Fraction (%)				p = 0.005
Min - Max	jun-63	21 - 70	52 - 73	
Mean ± SD	37 ± 14	49 ± 14	62 ± 6	
Dilated Left Ventricle (pts)	15 (50%)	9 (30%)	1(10%)	p = 0.1
Left Ventricular Ejection Fraction < 55% (pts)	25 (83%)	17 (57%)	1(10%)	p = 0.047
Loss of Left Ventricular wall thickness (pts)	20 (67%)	9 (30%)	0	p = 0.009
Left Ventricular wall motion abnormalities (pts)	23 (77%)	12 (40%)	0	p = 0.008
Right Ventricular LGE (pts)	3 (7%)	8 (27%)	0	p = 0.01
Dilated Right Ventricle (pts)	2 (7%)	10 (33%)	0	p = 0.02
Right Ventricular Ejection Fraction < 45% (pts)	19 (63%)	12 (40%)	1 (10%)	p = 0.1
Right Ventricular End-Diastolic Volume (ml)				P = 0.7
Min - Max	94 - 258	79 - 260	94 - 169	
Mean ± SD	162 ± 38	157 ± 48	123 ± 28	
Right Ventricular End-Diastolic Volume index (ml/m ²)				p = 0.9
Min - Max	53 - 147	40 - 138	55 - 87	
Mean ± SD	85 ± 20	85 ± 26	65 ± 10	
Right Ventricular Ejection Fraction (%)				p = 0.5
Min - Max	15 - 60	18 - 64	46 - 69	
Mean ± SD	43 ± 12	46 ± 12	58 ± 6	

* P values concern the comparison between the groups with coronary artery disease and cardiac sarcoidosis; LGE = myocardial delayed enhancement

Figure 1. Delayed-enhanced three-dimensional breath-hold inversion-recovery gradient echo studies (short axis views) demonstrating multi-focal transmurular hyper-enhancement involving the inferior and lateral LV segments in a patient with sarcoidosis (A), and patchy (B) respectively confluent (C) transmurular inferior LV (arrows) and RV (arrowheads) wall late gadolinium enhancement secondary to infarctions in patients with coronary artery disease of the RCA.

Figure 2. Delayed-enhanced three-dimensional breath-hold inversion-recovery gradient echo studies (short axis views) of three patients with cardiac sarcoidosis, demonstrating: focal (A) and patchy, multi-segmental three layer hyper-enhancement (C and E), and three patients with coronary artery disease demonstrating: focal sub-epicardial infarctions in the distribution of respectively the LCX (B) and RCA (D), and two-vessel disease (F) involving the LAD (subendocardial infarction) and RCA (mid-layer infarction).

Figure 3. Delayed-enhanced three-dimensional breath-hold inversion-recovery gradient echo studies (A: 4 chamber view; B, D: short axis views) demonstrating multi-segmental, patchy three layer hyper-enhancement in a patients with sarcoidosis (A,B) and confluent transmural hyper-enhancement in the vascular distribution of the RCA (D). The delayed-enhanced spin echo study (C: short axis view) shows patchy, three layer involvement of the lateral LV segments. Transmural right ventricular enhancement secondary to sarcoidosis (C) and coronary artery disease (D) is demonstrated by the arrowheads.

Figure 4. Delayed-enhanced three-dimensional breath-hold inversion-recovery gradient echo studies demonstrating confluent apical hyper-enhancement secondary to sarcoidosis (A: vertical long axis view, C: 4 chamber view) and apical patchy three-layer hyper-enhancement in a patient with coronary artery disease and myocardial infarction secondary to obstruction of the LAD (B: vertical long axis view, D: 4 chamber view).

Chapter 7

Right ventricular involvement in cardiac sarcoidosis demonstrated with cardiac magnetic resonance

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Abstract

Aims: Cardiac involvement in sarcoidosis is reported in up to 30% of patients. Left ventricular involvement demonstrated by contrast-enhanced cardiac magnetic resonance has been well validated. We sought to determine the prevalence and distribution of right ventricular late gadolinium enhancement in patients diagnosed with pulmonary sarcoidosis.

Methods and results: We prospectively evaluated 87 patients diagnosed with pulmonary sarcoidosis with contrast-enhanced cardiac magnetic resonance for right ventricular involvement. Pulmonary artery pressures were non-invasively evaluated with Doppler echocardiography. Patient characteristics were compared between the groups with and without right ventricular involvement, and right ventricular enhancement was correlated with pulmonary hypertension, ventricular mass, volume, and systolic function. Left ventricular late gadolinium enhancement was demonstrated in 30 patients (34%). Fourteen patients (16%) had right ventricular late gadolinium enhancement, with sole right ventricular enhancement in only two patients. The pattern of right ventricular enhancement consisted of right ventricular outflow tract enhancement in 1 patient, free wall enhancement in 8 patients, ventricular insertion point enhancement in 10 patients, and enhancement of the right side of the interventricular septum in 11 patients. Pulmonary arterial hypertension correlated with the presence of right ventricular enhancement ($p < 0.001$). Right ventricular enhancement correlated with systolic ventricular dysfunction ($p < 0.001$), hypertrophy ($p = 0.001$), and dilation ($p < 0.001$).

Conclusion: Right ventricular enhancement was present in 16% of patients diagnosed with pulmonary sarcoidosis, and in 48% of patients with left ventricular enhancement. The presence of right ventricular enhancement correlated with pulmonary arterial hypertension, right ventricular systolic dysfunction, hypertrophy and dilation.

Contents

Abstract	Error! Bookmark not defined.
7.1 Introduction	Error! Bookmark not defined.
7.2 Methods	Error! Bookmark not defined.
7.3 Results	Error! Bookmark not defined.
7.4 Discussion	Error! Bookmark not defined.
7.5 Conclusions	Error! Bookmark not defined.
7.6 Limitations	Error! Bookmark not defined.
7.7 Future focus of development	Error! Bookmark not defined.
7.8 Acknowledgements	Error! Bookmark not defined.
References	Error! Bookmark not defined.

7.1 Introduction

Sarcoidosis is a rare, inflammatory condition, resulting from an uncontrolled cellular inflammatory response in genetically predisposed individuals, which affects the heart in approximately a third of patients. **(1)** Left ventricular involvement demonstrated by contrast-enhanced cardiac magnetic resonance has been well validated. **(2)** Until recently limited attention has been given to right ventricular involvement in cardiac sarcoidosis, its prevalence, relevance and prognostic value. **(3)** Cardiac magnetic resonance imaging is the preferred imaging tool to evaluate the healthy and diseased right ventricle. **(4,5)** Right ventricular volumes, mass and function can be quantified without geometric assumptions and excellent intra- and inter-observer agreement and inter-study reproducibility. **(4,5,6)** Delayed contrast-enhanced magnetic resonance allows for the detection and quantification of focal scar and interstitial fibrosis. Although there are numerous reports on delayed contrast-enhanced cardiac magnetic resonance delineating left ventricular sarcoidosis, relatively few studies have reported on right ventricular involvement. **(3,7,8,9,10)** We sought to determine the prevalence and distribution of right ventricular late gadolinium enhancement in patients diagnosed with pulmonary sarcoidosis, and determine the relationship with pulmonary hypertension, ventricular volume, mass and systolic function.

7.2 Methods

Patient selection

Between July 2001 and March 2014, we enrolled 87 consecutive patients with histologically proven pulmonary sarcoidosis. Cardiac evaluation was performed because of symptoms or routine screening to exclude cardiac involvement. Patients were excluded when the standard contra-indications for contrast-enhanced cardiac magnetic resonance existed. Institutional Review Board approval was obtained for this study.

Baseline investigations

Baseline investigations included 12-lead electrocardiography, Doppler echocardiography, and contrast-enhanced cardiac magnetic resonance. Pulmonary artery systolic pressure was estimated from the tricuspid regurgitant velocity plus an estimate of right atrial pressure derived from the inferior vena cava. **(11)** Right-sided heart studies (26) were performed in patients with pulmonary hypertension, congestive heart failure and in patients in whom automated cardioverter defibrillators were implanted. Coronary angiography was performed to exclude underlying coronary artery disease in patients with documented ventricular tachy-arrhythmias, pathological Q-waves, impaired systolic function, regional wall motion abnormalities, and/or late gadolinium enhancement.

CMR protocol and analysis

Studies were performed using a commercial 1.5Tesla scanner with a cardiac-dedicated phased-array coil. The cardiac magnetic resonance studies were electrocardiographically triggered by standard software. Studies consisted of multi-phase multi-slice steady-state-free precession, and fat-saturated T2-weighted (69) breath-hold sequences of the short axis, vertical long axis and horizontal long axis views. Outflow tract views were generated in patients with right ventricular abnormalities. The short-axis images covered the left ventricle from base to apex. The steady-state-free precession sequences (typical repetition time: 3.5 msec; echo-time 1.4 msec; flip-angle 55°, temporal resolution 50 msec, voxel size 1.6×1.6×10 mm, no gap) were performed to assess regional wall-motion abnormalities, left and right ventricular masses, volumes and ejection fractions. Papillary muscles were included when determining right ventricular mass, and excluded when determining volumes. Contrast-enhanced and T2 weighted images were obtained in diastole to minimize artifact due to cardiac motion. Ten minutes after the additional administration of 0.1mmol/kg gadolinium-diethylenetriaminepenta-acetic acid. (Schering, Berlin, Germany), a two-dimensional segmented inversion recovery-gradient echo breath-hold sequence (short axis, vertical long axis, horizontal long axis, and right ventricular outflow tract in selected patients, voxel size 1.6×1.6×10 mm, without gap), was used to assess for late gadolinium enhancement. The inversion time (250 to 400 msec) was determined on an individual basis to obtain optimal nulling of the unenhanced myocardial signal. Two experienced, blinded, and independent observers used commercially available software (CAAS MRV 3.4, Pie Medical Imaging, Maastricht, The Netherlands) to determine the standard parameters delineated in **Table 1**. The distribution of right ventricular late gadolinium enhancement was determined by consensus and characterized as free wall, apical, outflow tract, right-sided interventricular septal, and/or including the ventricular insertion points. Late ventricular gadolinium enhancement was considered present only if confirmed on both short-axis and matching long-axis myocardial locations. Late left ventricular gadolinium enhancement was quantified by a semiautomatic detection method using the signal intensity threshold of ≥ 2 SD above a remote reference region. The intra- and interobserver variability's were determined by calculating the variability coefficients and intra-class correlations for each parameter in 18 randomly selected studies.

Variables and definitions

Peak systolic right ventricular pressures over 35 mm Hg were considered to represent pulmonary hypertension. Right ventricular hypertrophy was defined as right ventricular weight exceeding normal values as published by Maceira et al and/or right ventricular end-diastolic wall thickness over 5 millimeters. **(6)** Right ventricular systolic dysfunction was defined as an ejection fraction below 45%. **(12)**

Statistical analysis

All statistical analyses were performed using statistical software (Version 21.0, SPSS; Chicago, IL). Continuous normal distributed variables were expressed as mean $\pm$ SD, and between group comparisons were made using the parametric *t* test for independent samples or the Mann-Whitney test when appropriate. In the non-normally distributed continuous data the median and interquartile range were determined, and between group correlations were made with the Wilcoxon test. Categorical variables were assessed using the chi-square or Fischer Exact test when appropriate. Statistical significance was defined at $p < 0.05$.

7.3 Results

Patient characteristics

Table 1 demonstrates the baseline characteristics in the included 87 patients. Twenty-seven (31%) patients presented with cardiac symptoms, while the remaining 60 either suffered from non-specific symptoms or were routinely screened for cardiac sarcoidosis. According to the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities, an implantable cardioverter defibrillator or pacemaker was implanted in respectively 14 and 3 patients after the baseline cardiac magnetic resonance study. **(13)** All had late gadolinium enhancement and suffered of cardiac symptoms. When applying the recently published Heart Rhythm Society expert consensus criteria we diagnosed 31 patients (36%) with cardiac involvement. **(14)**

CMR analyses

Thirty patients (34%) had left ventricular and 14 patients (16%) right ventricular enhancement, with enhancement limited to the right ventricle in only 2 patients (2%). The group of patients with right ventricular enhancement had significantly more extensive left ventricular enhancement compared to those without. (**Table 1**, $p = 0.007$) **Table 2** describes the distribution of right ventricular enhancement. Right ventricular enhancement correlated with early-diastolic left-sided septal displacement ($p=0.002$), systolic right ventricular dysfunction ($p<0.001$), hypertrophy ($p<0.001$), and dilation ($p=0.009$). Fifteen patients had pulmonary hypertension, 8 of which had right ventricular enhancement. The presence of ventricular insertion point enhancement ($p=0.007$), right-sided septal ($p<0.001$) and right ventricular free wall enhancement ($p=0.016$) correlated with the presence of pulmonary hypertension. Right ventricular hypertrophy correlated with the presence of ventricular insertion point enhancement ($p=0.004$) and right-sided septal ($p=0.001$), but not with free wall enhancement ($p=0.076$). In 5 patients early-diastolic septal displacement towards the left ventricle was observed, 2 of which had insertion point enhancement ($p=0.099$), and 3 of which had right-sided septal enhancement ($p=0.013$). Neither the chronicity of pulmonary sarcoidosis, as determined by the time since diagnosis, nor the extent of lung disease as determined by high-resolution computed tomography, correlated with pulmonary hyper-

tension, right ventricular systolic function or myocardial enhancement. The right ventricular end-diastolic volume index in patients with pulmonary Stage 4 (fibro-cystic disease), was significantly larger compared to the earlier disease Stage 1 (hilar nodes only) ($p = 0.027$). The T2-weighted studies suggested active, granulomatous disease in only 10/69 (14%) of patients. The intraobserver variability for right ventricular end-diastolic volume was 2%, end-systolic volume 3.4%, ejection fraction 3.4%, and mass 4%. The interobserver variability for right ventricular end-diastolic volume was 1.6%, end-systolic volume %, ejection fraction 3.2%, and mass %.

7.4 Discussion

This is the first prospective cardiac magnetic resonance study to specifically report on the prevalence, and distribution of right ventricular involvement in cardiac sarcoidosis. Predominant or isolated right ventricular involvement is rare, with nearly all patients suffering from left ventricular disease. **(15)** With Murtagh et al, Crawford et al, and Cheong et al we found more extensive left ventricular enhancement to be associated with right ventricular involvement. **(8,10,16)** Previous studies reported a correlation between the presence and extent of left ventricular enhancement, impaired left and right ventricular systolic function, and higher adverse event rates. The direct relationship between right ventricular enhancement, its size and systolic function, as previously demonstrated in left ventricular sarcoidosis, has not been reported before.

Right ventricular enhancement, inflammation and impaired systolic function have been associated with adverse outcome, particularly ventricular tachy-arrhythmias. **(10,16,17,18,19)** However, the localizations of the arrhythmogenic foci were not reported on. Since right ventricular sarcoidosis occurs in patients with more extensive left ventricular disease, the reported prognostic relevance of right ventricular disease may at least partly reflect the extent of left ventricular arrhythmogenic substrate.

Several post-transplant and post-mortem studies in sarcoidosis patients have reported right ventricular involvement to range from 6%, in patients dying from alternate causes, to as high as 65% in those dying sudden cardiac deaths. **(20-24)** Generally, patients with congestive failure were found to have extensive biventricular sarcoid **(Figure 1)**, and in those who had died suddenly, active granulomatous infiltration and patchy scar were present. Right ventricular outflow tract involvement was rare. **(Figure 2)**

Ten recent studies employing contrast-enhanced magnetic resonance in the assessment of cardiac sarcoidosis, reported on right ventricular disease in sarcoidosis. **(Table 3)** **((3,7,8,9,10,16,17,18,19,25))** Our findings in an unselected population with pulmonary sarcoidosis compare. Right ventricular enhancement was reported in 5 of these studies, and ranged from 2% in unselected to 48% in high-risk populations, which compares to our 47% of patients with left ventricular sarcoidosis. **(3,7,8,9,10)** Similar to our findings, nearly all patients with right ventricular enhancement had left ventricular enhancement. Samar et al, Patel et al and Crawford et al were the only to report on right ventricular enhancement in more detail. **(3,7,10)** Contrary to our and other studies, Samar et al reported that right ventricular enhancement did not correlate with a difference in left ventricular ejection

fraction. His data were included in a poster presentation, which precluded detail, while relevant data were not available in 19% of patients. **(3)** Crawford reported multi-focal right ventricular enhancement in nearly half of those with left ventricular enhancement, basal, mid or apical right ventricular segments being equally involved. **(10)** Similar to Crawford et al, the large majority of our patients (70%) had multi-focal right ventricular enhancement. However, most of our patients had right-sided septal enhancement, similar to Patel's findings. **(7)** Right-sided septal and insertion point enhancement were related to pulmonary hypertension in 8 of our patients. Crawford et al and Patel et al did not include data on right ventricular or pulmonary pressures. Compared to Crawford's population, our patients with right ventricular enhancement had on average poorer systolic function, and more extensive left ventricular enhancement.

The presence of right ventricular enhancement correlated with hypertrophy, dilation and systolic dysfunction. The relationship between pulmonary hypertension, right ventricular hypertrophy, dilation, systolic dysfunction, septal displacement and septal and insertion point enhancement has been demonstrated before. **(26) (Figure 3)** Right ventricular enhancement in sarcoidosis may be caused by direct granulomatous infiltration, but also be related to pulmonary hypertension. **(26) (Figures 1 and 3)** Right ventricular hypertrophy, dilation, dysfunction and enhancement may be secondary to pulmonary hypertension, and are associated with worse prognosis. **(26,27)** Pulmonary hypertension is found in 6-28% of the general sarcoidosis outpatient setting, and may be secondary to pulmonary fibrosis, angiitis and/or congestive heart failure. **(27)**. The fact that pulmonary hypertension in our population did not correlate with disease extent as determined by computed tomography, illustrates the variety in pathophysiology of this condition in sarcoidosis. **(28)** Right ventricular dilation, systolic impairment, and inflammation, as demonstrated with positron emission tomography, in sarcoidosis have been demonstrated to predict adverse outcome in sarcoidosis. **(10,12,16,17,18,25,29)**

In patients with predominant right ventricular disease, cardiac sarcoidosis needs to be differentiated from arrhythmogenic right ventricular cardiomyopathy. Distinguishing features favoring sarcoidosis consist of an older age of onset, a non-familial pattern, wider QRS complexes, septal involvement with atrio-ventricular conduction disease, multiple arrhythmogenic foci, particularly right ventricular apical tachycardia, concomitant left ventricular disease, and the presence of mediastinal lymphadenopathy. **(30)** Electro-anatomic mapping, contrast-enhanced magnetic resonance and/or positron emission tomography may guide endomyocardial biopsies needed to obtain histological confirmation of the diagnosis.

We report on ventricular insertion point enhancement, a distribution pattern not specifically mentioned in the other studies. Late enhancement of the septum and insertion points may result from delayed wash-out of gadolinium due to altered myocardial fiber strain, fiber disarray, ischemia, and fibrosis, secondary to right ventricular pressure or volume overload, and resulting septal shift. **(26,32,33)** Ventricular insertion point enhancement has been reported in hypertrophic cardiomyopathy, atrial septal defects, severe pulmonary hypertension, tetralogy of Fallot, transposition of the great arteries and even a proportion of veteran healthy endurance athletes. **(31,32,33,34,35) (Figures 2, 3, 4 and 5)** The amount of insertion point enhancement correlates with mean pulmonary arterial pressures,

right ventricular mass, volume and ejection fraction. (26) Pulmonary hypertension in sarcoidosis is associated with adverse outcome, particularly when accompanied by right ventricular dysfunction, and/or lung fibrosis. (26,27) Recently Swift et al reported septal extension of insertion point enhancement in pulmonary hypertension to mark more severe disease, with associated right ventricular dilation, but found it not to be an independent predictor of overall mortality. (26)

Late gadolinium enhancement includes active, potentially reversible, granulomatous inflammation as well chronic focal scar. (8,19,36) Immune suppressive treatment, currently a work in progress, may potentially improve systolic function and decrease arrhythmogenic substrate. (10,19,36) The T2-weighted Spin Echo-based assessment used in our study to evaluate for active granulomatous infiltration and associated edema is rather insensitive. (8) T2 mapping and positron emission tomography have shown promise, and will be included in future projects. (28,37)

7.5 Conclusions

Approximately 30% of an unselected patient population with pulmonary sarcoidosis had left ventricular involvement, half of which had right ventricular involvement. More extensive left ventricular enhancement correlated with right ventricular involvement. Right ventricular enhancement may result from direct infiltration and resulting scar, or pulmonary hypertension. Previous studies associated impaired systolic right ventricular function and right ventricular enhancement with ventricular tachy-arrhythmias. We demonstrate right ventricular enhancement with cardiac magnetic resonance to be mostly multi-focal, involve the septum and correlate with increased right ventricular volumes, hypertrophy and impaired systolic function.

7.6 Limitations

Pulmonary pressures were routinely determined non-invasively in the majority of our patients, and we may have under-estimated the pulmonary pressures. Our imaging protocol was not primarily adapted to evaluate the right ventricle, our slice thickness, and potentially sub-optimal myocardial nulling may have resulted in an underestimation of the presence and extent of right ventricular infiltration and scarring. Since T2 mapping was not performed, we likely underestimated active granulomatous inflammation. The relatively small number of patients included limits our findings and conclusions.

7.7 Future focus of development

Customized hybrid approaches including electrocardiography, ultrasound, positron emission tomography and contrast-enhanced magnetic resonance will provide us with more

sensitive, accurate and comprehensive information on hemodynamic, electrical, mechanical, and inflammatory characteristics of the atriae and ventricles.

7.8 Acknowledgements

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Conflicts of interest

None declared.

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Table 1: Characteristics of patients with and without RV Late Gadolinium Enhancement

	Pts without RV LGE n = 73	Pts with RV LGE n = 14	P Value
Male	48 (66)	9 (64)	0.779
Caucasian	58 (79)	8 (57)	0.074
Age (years)	52.8±10.2	55.7±9.1	0.460
Cardiac presentation	18 (25)	10 (71)	< 0.001
Syncope	4 (5)	1 (8)	0.564
Palpitations	7 (10)	3 (21)	0.167
Clinical congestive heart failure	4 (5)	6 (43)	0.001
Sustained Ventricular Tachycardia	6 (8)	4 (29)	0.039
Chest discomfort	2 (3)	1 (8)	0.388
Dyspnea			
NYHA 0-2	72 (98)	12 (86)	0.388
NYHA 3-4	2 (3)	1 (7)	0.388
Diabetes Mellitus	3 (4)	0	1.000
Hypertension	7 (10)	0	0.588
Medication at any time	51 (70)	12 (86)	0.102
Steroids	5 (7)	2 (14)	0.280
Methotrexate	5 (7)	5 (36)	0.006
Loop diuretics	5 (7)	6 (43)	0.001
Spironolactone	5 (7)	7 (50)	< 0.001
Ace inhibitors/ATIIIRB	7 (9)	7 (50)	0.001
Beta blockers	9 (12)	6 (43)	0.008
Amiodarone			
Abnormal ECG	18 (25)	10 (71)	< 0.001
Pulmonary Hypertension	5 (7)	9 (64)	< 0.001
CMR imaging parameters			
LVEF %	60 [54-66]	50 [42-58]	0.015
LVEF ≤ 50%	8 (11)	5 (36)	0.039
LVEDV ml	113 [90-136]	134 [81-187]	0.261
LVEDV index ml/m ²	58 [47-69]	75 [70-100]	0.142
LV mass	112 [72-152]	122 [83-161]	0.550
LV mass index gr/m ²	64 [44-84]	65 [38-92]	0.780
LVH	20 (27)	3 (23)	0.747
LV dilation	5 (8)	4 (29)	0.035
LV LGE	18 (25)	12 (86)	p<0.001
LV LGE%	12 [4-20]	28 [18-38]	0.002
RVEF %	49 [43-55]	33 [24-42]	0.001
RVEDV ml	148 [108-188]	188 [141-235]	0.034
RVEDV index ml/m ²	78 [58-98]	96 [68-124]	0.018
RVESV	72 [47-97]	102 [70-134]	0.05
RVESV index ml/m ²	37[26-48]	58 [38-78]	0.046
RVH	5 (7)	6 (43)	0.001
RV mass gr	42 [34-50]	53 [35-71]	0.068
RV mass index gr/m ²	21 [17-25]	28 [22-34]	0.075
RV dilation	3 (4)	6 (43)	< 0.001
RVEF ≤ 45%	6 (8)	10 (71)	< 0.001
T2 positive	7/60 (12)	3/9 (33)	0.112

Values are n (%), median [IQR], or mean ±SD. * Values are for all patients with sarcoidosis (87). CI = confidence interval; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; LGE = late gadolinium enhancement; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVH = right ventricular hypertrophy.

Table 2: Characteristics of patients with RV Late Gadolinium Enhancement

Enhanced segments	Patients (n=14)	Combination of enhanced segments	Patients (n=14)	Patients with pulmonary hypertension	Patients with end-systolic septal shift (n=5)
RV septal	11	RV septal VIP RV free wall RVOT	1	1	0
VIP	10	RV septal VIP RV free wall	3	2	1
RV free wall	8	RV septal VIP	4	1	0
RVOT	1	RV septal RV free wall RV septal RV free wall VIP RV free wall VIP	2 1 1 1 1 1	2 1 0 1 0	1 1 1 1 0

RV – right ventricular; RVOT – right ventricular outflow tract, VIP – ventricular insertion points

Table 3: CMR studies reporting on right ventricular involvement in cardiac sarcoidosis.

Authors	Type of study	Patients	Conclusion
Cheong BYC et al. (2009) (8)	prospective, single-centre	31 pts asymptomatic biopsy proven systemic sarcoidosis, 8(26%) LV LGE of whom 2 (25%) with RV LGE, inferobasal RV LGE in pts with most LV LGE	asymptomatic small amount of LGE (average 3.2% of LV) in 26%, no cardiac events after 1 yr
Patel MR, et al. (2009) (7)	prospective, single-centre	81 pts with extra-cardiac sarcoidosis, 21(26%) with LV LGE (average 6 grams), 14 (67%) had right-sided septal LGE incl 4 RV free wall/outflow tract/anterobasal segments	pts with LGE had 9 fold higher rate of adverse events
Patel AR, et al. (2011) (18)	retrospective, single-centre	152 pts extra-cardiac sarcoidosis, LVEF $\geq$ 50%, 29(19%) LV LGE, no data on RV LGE	pts with LV LGE had lower RVEF, either because of presumed biventricular disease and/or pulmonary hypertension
Schuller JL, et al. (2012) (17)	retrospective, multi-centre	112 CS pts with ICD's for primary or secondary prevention, no data on LGE	impaired systolic LV and RV function correlates with more ICD therapy
Samar HY et al. (2014) (poster) (3)	retrospective, single-centre	122 sarcoidosis pts, 37(22%) LV LGE, 18 (49%) of these also RV LGE	LVEF, LVEDV, RVEDV similar in groups with/without RV LGE
Crawford T, et al. (2014) (10)	retrospective, multi-centre	52 CS pts, all LVEF > 35% 32(62%) with LV LGE of which 13 (41%) also had RV LGE	multi-focal LGE correlated with VT/VF, pts with RV LGE had more extensive LV LGE
Nadel J, et al. (2015) (9)	retrospective, single-centre	106 sarcoidosis pts, 32 CS-defined by CMR LGE - 32 LV LGE, 2 (6%) RV LGE	LGE only independent predictor of adverse outcome
Muser D, et al. (2015) (19)	prospective, single-centre	31 CS pts with VTs pre-ablation, 23 had CMR, 21(68%) LV LGE, 11 (35%) RV LGE, no data on RV distribution or extent	LGE extent predicted VT-free survival
Ekström K, et al. (2016) (25)	retrospective, single-centre	50 CS pts, 48 (96%) with LV LGE, not reported on RV LGE	LV extent of LGE and RVEF, correlated with adverse outcome
Murtagh G, et al. (2016) (16)	retrospective, single-centre	205 pts extra-cardiac sarcoidosis, LVEF $\geq$ 50%, 41(20%) LV LGE, $\geq$ 4 pts with VIP LGE, no specific data on RV LGE	for every 1% in LGE burden the hazard for an event increased by 8%; mild impaired RV dysfunction correlated with increased event rate

CS – cardiac sarcoidosis, LGE – late gadolinium enhancement, LV – left ventricle, LVEF – left ventricular ejection fraction, RV – right ventricle, RVEF – right ventricular ejection fraction

Figure 1A: Contrast-enhanced magnetic resonance study in a patient with biventricular congestive heart failure (Inversion-Recovery Gradient Echo sequence, horizontal long axis view) demonstrates enhancement of the right ventricular free wall and right-sided interventricular septum.

Figure 1B: Short axis view in the same patient demonstrates enhancement of the right-sided interventricular septum and inferior right ventricular insertion point.

Figure 2: Contrast-enhanced magnetic resonance study (Inversion-Recovery Gradient Echo sequence, end-diastolic frame, short axis view) demonstrates enhancement of the right ventricular free wall (arrow), ventricular insertion points (triangles) and right-sided septum (arrow).

Figure 3A: Magnetic resonance study (Steady-State-Free Precession sequence, horizontal long axis view, end-diastolic frame), demonstrates dilation of the right ventricle (RV) and right atrium (RA), marked right ventricular hypertrophy, with displacement of the interventricular septum towards the left ventricle, both left ventricle and atrium are compressed.

Figure 3B: Contrast-enhanced magnetic resonance study (Inversion Recovery-Gradient Echo sequence, short axis view, end-diastolic frame) of the identical patient with pulmonary vascular sarcoidosis and resulting severe pulmonary arterial hypertension, demonstrates contrast-enhancement of the right ventricular hinge points (triangles) and free wall (arrows).

Figure 4: Contrast-enhanced magnetic resonance study (Inversion-Recovery Gradient Echo sequence, short axis view) in a patient without pulmonary hypertension demonstrates enhancement of the ventricular insertion points (arrows), papillary muscles (asterisks) and postero-lateral left ventricular segments (triangle).

Figure 5A: Contrast-enhanced magnetic resonance study (Inversion-Recovery Gradient Echo sequence, end-diastolic frame, short axis view) in a patient diagnosed with a high degree atrio-ventricular block secondary to active cardiac sarcoidosis. A dual chamber pacemaker had been inserted. Ventricular insertion point enhancement is demonstrated (triangles). Pulmonary pressures were normal. (asterisk – artifact of right ventricular pace lead)

Figure 5B: Contrast-enhanced magnetic imaging study (Inversion-Recovery Gradient Echo sequence, end-diastolic frame, short axis view) in the identical patient when reassessed 7 years later demonstrates substantially more enhancement of the right-sided septum (arrow) and the insertion points (triangles). The percentage time pacing had increased from 5% to 15% of the time. (asterisk = artifact produced by right ventricular pace lead)

Chapter 8

Right ventricular involvement and the extent of left ventricular enhancement with magnetic resonance predict adverse outcome in pulmonary sarcoidosis

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Abstract

Objectives: To determine whether delayed right ventricular (RV) gadolinium enhancement (LGE) with cardiovascular magnetic resonance (CMR) predicts adverse events in addition to left ventricular LGE during long-term follow up of pulmonary sarcoidosis patients.

Background: Cardiac involvement is the main determinant of poor outcomes in sarcoidosis. Right ventricular dysfunction and LV LGE were reported to be predictive of adverse outcome in non-ischemic cardiomyopathies.

Methods: 84 consecutive biopsy proven pulmonary sarcoidosis patients were followed for a median of 56 months [38-74] after baseline DECMR. The composite primary end-point consisted of admission for congestive heart failure, sustained VT, appropriate ICD therapy, pacemaker implantation for high degree atrio-ventricular block, or cardiac death. The composite secondary end-point included all cause mortality in addition to the primary end-point.

Results: RV and LV LGE were demonstrated in respectively 12 and 27 patients. Five of ten events included in the primary end-point occurred in the group with RV LGE. RV LGE, LV or biventricular LGE yielded Cox hazard ratios of 8.71 (95% CI 1.90-23.81), 9.22 (95% CI 1.96-43.45), and 12.09 (95% CI 3.43-42.68) for the composite primary end-point. In a multi-variate model the predictive value of biventricular LGE for the composite primary and secondary end-points was strongest. Kaplan Meier event-free survival curves were most significant for RV LGE and biventricular LGE (log rank with $p < 0.001$).

Conclusions: Biventricular LGE at presentation is the strongest, independent predictor of adverse outcome during long-term follow up. Asymptomatic myocardial scar $< 8\%$ of LV mass carried a favorable long-term outcome.

Contents

Abstract	186
8.1 Introduction	187
8.2 Methods	187
8.3 Results	189
8.4 Discussion	191
8.5 Study limitations:	193
8.6 Conclusions	193
8.7 Perspectives	193
8.8 Acknowledgements	194
Disclosures	194
References	195

8.1 Introduction

Sarcoidosis is a rare inflammatory condition of unknown etiology, which results in granulomatous infiltration and focal myocardial scar in approximately a third of patients. Major cardiac morbidity or mortality have been reported in approximately five to ten percent of sarcoidosis patients. **(1)** Diagnosing cardiac sarcoidosis (CS) can be challenging and several non-invasive diagnostic imaging modalities have been used over the years. Recently delayed contrast-enhanced cardiac magnetic resonance (DECMR) and positron electron tomography (PET) showed most diagnostic and prognostic promise. **(2-15)** DECMR has become the gold standard test for detecting and quantifying focal myocardial scar, a predictor of high degree atrio-ventricular block (AVB), heart failure (CCF), ventricular tachycardia (VT), and sudden cardiac death (SCD) in CS. **(2-8,10-15) (Table 1)** Systolic right ventricular (RV) impairment and multi-focal RV late gadolinium enhancement (LGE) on CMR, and active RV granulomatous inflammation on PET have been associated with adverse outcomes in retrospective studies. **(2,7,11,12,21,22,24)** We previously demonstrated the diagnostic accuracy of DECMR for CS, and reported on RV involvement in pulmonary sarcoidosis utilizing CMR. **(16,25)** We currently report on the prognostic value of RV LGE in addition to left ventricular (LV) LGE in patients suffering from pulmonary sarcoidosis.

8.2 Methods

Patient population

Between July 2001 and August 2010 we prospectively followed 84 consecutive patients with histologically proven pulmonary sarcoidosis. These patients had been referred for cardiac evaluation, either because of cardiac symptoms (palpitations, congestive heart failure, (pre)syncope, chest discomfort) or for routine cardiac assessment. **(Figure 1)** Patients were excluded in case of standard contraindications to DECMR. Approval for our project was obtained from the local Institutional Review Board.

CMR protocol

CMR studies were performed using a commercial 1.5 T MRI scanner with a cardiac-dedicated, phased-array coil. The CMR studies were ECG triggered by standard software. Studies consisted of multi-phase multi-slice steady-state-free precession (SSFP), and fat-saturated T2-weighted spin-echo (64 patients) breath-hold sequences of the short axis, vertical long axis and horizontal long axis views. The short-axis images covered the LV and RV from base to apex. The SSFP sequences (typical repetition time: 3.5 msec; echo-time 1.4 msec; flip-angle 55°, temporal resolution 50 msec, voxel size 1.6×1.6×10 mm, no gap) were performed to assess regional wall-motion abnormalities, ventricular volumes, masses and ejection fractions (LVEF, RVEF). T2-weighted studies were performed to assess for the presence of myocardial inflammation. Contrast-enhanced and T2-weighted images were obtained in diastole to minimize artifact due to cardiac motion. Ten minutes after the addi-

tional administration of 0.1mmol/kg gadolinium-diethylenetriaminepenta-acetic acid (Schering, Berlin, Germany), a two-dimensional segmented inversion recovery-gradient echo breath-hold sequence (short axis, vertical long axis, and horizontal long axis, voxel size $1.6 \times 1.6 \times 10$ mm, without gap), was used to assess for LGE. The inversion time (250 to 400 ms) was determined on an individual basis to obtain optimal nulling of the unenhanced myocardial signal.

CMR analysis

CMR studies were analyzed off-line by two experienced blinded observers who independently evaluated the study findings using commercially available software (CAAS MRV 3.4, Pie Medical Imaging, Maastricht, The Netherlands). Endocardial and epicardial contours were manually delineated in end-diastolic and end-systolic short axis slices to determine LV and RV end-diastolic volumes (LVEDV, RVEDV), end-systolic volume (LVESV, RVESV), LVEF, RVEF and LV and RV end-diastolic masses, which were indexed to body surface area. The presence and distribution of LGE and increased T2 signal, was determined by consensus, and LV LGE localized according to the 17-segment model. LGE was considered present only if confirmed on both short-axis and matching long-axis myocardial locations. LGE was quantified by a semiautomatic detection method using the signal intensity threshold of ≥ 2 SD above a remote reference region. The distribution of LGE was characterized as sub-endocardial, mid wall, sub-epicardial, patchy or confluent trans-mural. When more than one pattern was present, the distribution was characterized on the basis of the predominant pattern. There was excellent intra- and interobserver correlation for ventricular volumes, masses, and ejection fractions. Interobserver agreement when determining the presence/localization of LGE was good (κ 0.85, $p < 0.001$). The intra-class correlation coefficient for LV LGE was 0.989 [0.981-0.993] ($p=0.001$).

Clinical follow-up

Scheduling of follow up visits was 4-6 monthly and left at the discretion of the managing clinician. Resting 12-lead surface ECG's, and 24-72 hour ambulatory ECGs were performed, and evaluated for intermittent intra-ventricular or atrio-ventricular conduction disease, and/or ventricular arrhythmias. Sustained VT (sVT) was defined as VT with a rate >100 beats/min, lasting for at least 30 seconds. Implanted Cardioverter Defibrillators (ICD) or pacemakers (PM) were interrogated every 4 months and assessed for ventricular arrhythmias. At regular intervals and at the end of our study, outcome data were collected from the family physician and managing specialist.

Variables, definitions, adverse events, and composite end-points

The composite primary end-point consisted of newly developed AVB resulting in PM implantation, admission for CCF, sVT, appropriate ICD therapy for sVT or ventricular fibrillation (VF), or cardiac death. Appropriate ICD therapy was defined as ATP or shock for fast VT (R-R <320 ms) or VF. The composite secondary end-point included all-cause

death in addition to the primary end-point. Peak systolic RV pressures over 40 mm Hg were considered to represent pulmonary hypertension (PH). RV end-diastolic wall thickness over 5 mm was considered evidence of RV hypertrophy (RVH). RV dysfunction was defined as a right ventricular ejection fraction (RVEF) < 45% by CMR. (17)

Statistical Analysis: All statistical analyses were performed using statistical software (Version 21.0, SPSS; Chicago, IL). Continuous normally distributed data were expressed as mean $\pm$ SD, and between-group comparisons were made using the parametric *t* test for independent samples or Mann-Whitney test when appropriate. In non-normally distributed continuous data, the median and interquartile ranges were determined, and between-group comparisons were made with the Wilcoxon test. Categorical variables were assessed using the chi-square or Fischer Exact test when appropriate. Linear regression analysis was used to determine the relationship between LGE, LVEDV and LVEF. Univariate analyses of the risk for adverse outcome associated with selected variables were performed with the Cox proportional hazards model. A *p* value of < 0.05 was considered statistically significant. The hazard ratio (HR) for the prediction of events was calculated for each of the outcomes using a multivariable Cox regression model, two tailed values of *p* < 0.05 were considered significant. Composite event curves were determined according to the Kaplan-Meier method, and comparisons of cumulative event rates were performed using the log-rank test. Receiver-operating characteristic (ROC) curves were used to examine the performance characteristic of %LGE mass. Area under the curve (AUC), and 95% confidence of the ROC curve, was calculated to provide a measure of the accuracy of %LGE mass to predict combined adverse outcomes.

8.3 Results

Patient characteristics

Figure 1 and Table 2 demonstrate the baseline characteristics of the included 84 patients. Twenty-nine patients had CS according to the HRS criteria, 18 according to the JMHW criteria. (19) Twenty-five (30%) patients presented with cardiac symptoms (palpitations, (pre)syncope, chest discomfort, congestive heart failure) whilst the remaining 59 patients (70%) experienced of non-specific symptoms (fatigue) or were routinely screened for CS. According to the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities, an ICD or PM were implanted in respectively 14 (4 ICD/biventricular PM) and 2 patients after the baseline DECMR study. (18) Heart failure was managed according to current optimal practice.

CMR findings

The findings with DECMR are displayed in **Table 3**. Twelve patients (44%) had RV LGE, predominantly involving the right-sided interventricular septum, and/or ventricular insertion points. Two patients had isolated RV LGE. Patients with RV LGE had significantly

more %LV LGE than those without RV involvement (32% [23-41] versus 10% [2-18], $p=0.006$), and RV LGE correlated with the presence of PH ($p = 0.022$), RVH ($p = 0.050$) and impaired RV function ($p < 0.001$).

LGE involved 4.39% of LV mass, and predominantly involved the interventricular septum, and basal LV segments. LGE was equally distributed over the three myocardial layers, and was patchy (56%) or confluent trans-mural (44%). In 16 patients (59%) three myocardial layers were involved. In twelve percent of patients (7/59) who were routinely evaluated, asymptomatic myocardial scar was present, though significantly smaller when compared to the symptomatic group (8% [4-20] versus 28% [8-39], $p = 0.001$). LGE strongly correlated with the presence of cardiac symptoms, ECG abnormalities, VT, LVEDV and LVEF ($p < 0.001$). The trans-mural extent of LGE correlated with segmental wall motion abnormalities ($p < 0.001$). Linear regression analysis demonstrated a decrease in LVEF of 7.27% for every 10% increase in LGE (r^2 0.392, value $p < 0.001$, 95% CI, -5.25% - -9.30%). For every 10% increase in LGE the LVEDV increased 9.1 ml in volume (r^2 0.239, $p < 0.001$, 95% CI 5.27 ml - 12.92 ml). In patients with sVT at presentation the median LVEF was significantly poorer, and LV mass, LVEDV index, and %LV LGE significantly higher when compared to those without sVT at presentation (respectively 60% [53-67] versus 51% [34-68] ($p=0.001$), 55 ml [44-66], versus 73ml [50-95] ($p = 0.011$), 111 [80-142] versus 145 gram [95-195] ($p = 0.028$), and 14 (range 2-38) versus 33% [22-55] ($p = 0.016$)).

Follow up results

Figures 1A and 1B illustrate the base-line findings and outcomes. During a median FU of 56 months (1-90 months) 8 patients (30%) with LGE experienced an adverse event. All adverse cardiac events occurred in patients who had presented with cardiac symptoms. A 57 year-old female (NYHA class 3, non-dilated, scarred LV, LV LGE 32%, non-sustained VTs (nsVT) at rest) awaiting elective ICD implantation experienced SCD, one patient was admitted because of CCF, and six patients had appropriate ICD therapy/discharge for sVT/VF. The average annualized ICD therapy rate was 11.1%. Three layer confluent transmural LGE predicted arrhythmic events ($p=0.018$) and the composite primary endpoint ($p=0.003$). VT at inclusion or during FU did not correlate with any specific localization grouping of LGE, such as basal septal LGE. Two patients, one presenting with palpitations, the other with pre-syncopal symptoms, both without LGE (2/57, 4%) or T2 signal, suffered an adverse event, respectively sVT after 10 months, and PM implantation for 3rd degree AVB after 6 months. End-points occurred up to 80 months after baseline CMR. Three patients died of non-cardiac conditions, respectively sepsis, respiratory failure due to extensive pulmonary fibrosis and malignancy. None of the patients with non-specific symptoms, such as fatigue, who had been routinely evaluated for cardiac involvement and had LGE (7/59 (12%), LV LGE $5.9 \pm 3.8\%$) developed adverse cardiac events during follow up.

Predictors of events

Table 4 demonstrates the predictors of adverse events in our study. RV, LV and biventricular LGE were the strongest predictors for adverse events. Six of eight arrhythmic end-points occurred in patients with LVEF > 35%. Univariate Cox regression analysis found RV LGE 8.71 (95% CI 1.90-23.81), LV LGE (HR 9.22 (95% CI 1.96-43.45), and biventricular LGE (HR 12.09 (95% CI 3.43-42.68), to be the strongest predictors of the composite primary end-point. Multivariate Cox regression analysis, including CCF, LV LGE, biventricular LGE, any LGE, LGE with systolic ventricular dysfunction, LV dilation, and LV or RV systolic dysfunction, revealed biventricular LGE to be the best independent predictors of the composite primary and secondary end-points at follow up ($p < 0.001$, HR 10.2, 95% CI 2.92-35.71, respectively $p=0.001$, HR 6.80, 95% CI 2.19-21.28). None of the other parameters reached statistical significance. The Kaplan Meier event-free survival curves found RV LGE, LV LGE (log rank (Mantel Cox) $p = 0.001$) and biventricular LGE (log rank (Mantel Cox) $p \leq 0.001$) the strongest predictors for the composite primary end-point. RV LGE and biventricular LGE were the strongest predictors for the composite secondary end-point (log rank (Mantel Cox) $p \leq 0.001$). (**Figure 2**)

In the present patient population ROC curve analysis indicated that %LV LGE had the modest ability to predict the composite primary adverse outcome (AUC=0.77, 95% CI 0.58 to 0.95). A cut-off level of 7% LV LGE best predicted combined adverse cardiac outcomes, with a sensitivity of 70%, and a specificity of 85%. The test's positive and negative predictive values were 39% and 95% respectively. **Figures 3.1-4** demonstrate LGE in symptomatic patients with and without adverse events during FU.

One appropriate shock would be delivered for every 2.5 implanted ICDs in sarcoidosis patients, when based on the combination of cardiac symptoms, abnormal ECG and/or rhythm monitoring, and biventricular LGE or LGE >7% of LV mass.

8.4 Discussion

Our findings demonstrate that the extent and distribution of myocardial LGE in a cohort of predominantly middle-aged Caucasian women with chronic pulmonary sarcoidosis, correlates with ventricular volumes, systolic impairment, and most significantly predicts adverse (arrhythmic) outcome. Our study is the first to prospectively detail RV assessment, and include T2-weighted assessment in the majority of patients. (**Table 1**)

Recently systolic RV impairment, multi-focal RV LGE, and active RV granulomatous inflammation in CS were associated with LV LGE, sVT and death. (**2,7,11,12,21,22,24**) Our study is the first to demonstrate the direct relationship between RV LGE, RV volumes, RV systolic impairment, sVT, and death of all cause. In the absence of data on VT morphology it remains unclear whether the prognostic relevance of RV LGE is related to more extensive biventricular arrhythmogenic substrate or whether RV LGE itself is particularly arrhythmogenic. (**20,24**)

None of our patients with asymptomatic LGE suffered adverse cardiac events, while the majority of arrhythmic end-points (75%) occurred in patients with LVEF > 35%. Our

findings support the findings of several recent studies which evaluated the risk of SCD in CS patients and also recorded appropriate ICD therapy in a large proportion of patients with LVEF > 35%. **(4,7,12,19)**

The risk of VT and SCD in CS seems primarily related to amount and distribution of granulomas and scar, and not the systolic function. Arrhythmic substrate imaging with DECMR and/or PET determines the risk of arrhythmic events more accurately than LVEF. **(2,4,7,12,19,20,22,24)** The negative predictive value of LGE negative DECMR is excellent, with only one patient with LV LGE < 8% developing an arrhythmic event after 10 months of follow up. In the absence of prospective data, it seems prudent to follow asymptomatic sarcoidosis patients up with ECG and cardiac ultrasound, and evaluate suspected or confirmed CS with PET and/or DECMR. **(19)** Ongoing research will determine the optimal study follow-up interval. By reserving DECMR for sarcoidosis patients with cardiac symptoms, and/or abnormalities on basic assessment (resting ECG, ambulatory rhythm monitoring, and/or cardiac ultrasound), and implanting ICDs in patients with LGE $\geq 7\%$, costs could be contained and benefit optimized – in our study one appropriate shock was delivered for every 2.5 implanted devices. Our appropriate annual ICD therapy/ discharge rate of 11.1% compares to the 8.6-14.5% previously reported. **(19)** The value of routine programmed electrical stimulation (PES) as part of risk stratification in patients without palpitations or pre/syncopal events, with LGE and LVEF > 35% remains to be determined. **(19)**

Our study supports the recommendations of the 2014 HRS guidelines concerning the use of DECMR and device implantation. **(19)**

The prognostic studies summarized in **Table 1** generally report LGE in 25-30% of unselected patients cohorts, and uniformly confirm the relationship between the extent of LGE and adverse outcome. Our study confirmed the favorable prognosis of small, asymptomatic myocardial scars as previously reported. **(7,9,12,13,14)** The remarkable difference between our conclusions and those of Patel et al, who reported small asymptomatic scar in patients with mildly impaired systolic ventricular functions to be a strong risk factor for adverse events, could partly be explained by a difference in patient population and the distribution of LGE. **(4)** Patel's cohort mainly consisted of African American women with RV LGE in 67%, a potentially high risk scenario. Long-term outcomes in pts with CS have markedly improved due to modern heart failure management, including device therapy and arrhythmia ablation in selected patients. **(10,11,24,26,27)** Current annual mortality rates range from 0-4.2/100 pts compared to 7.5-12/100 pts as previously reported by Yazaki (2001) and Fleming (1987). **(19)** Our study is the first to include data on T2-weighted edema imaging. Active myocardial inflammation may increase arrhythmogenicity, but conflicting data exist concerning the efficacy of current immune-suppressive and anti-arrhythmic treatment in actually improving long-term outcomes in patients with active disease. **(11,12,19,20,24,26,27)** The presence of increased T2 signal in our cohort, managed with corticosteroids and methotrexate, did not correlate with adverse events during follow up. The accuracy for detecting active granulomatous sarcoidosis with T2-weighted Spin Echo sequences is however suboptimal, and we may well have underestimated inflammatory changes. **(3)** T2-mapping and FDG-PET have shown promise in diagnosing active disease

and guiding immune-suppressive management and have replaced spin echo assessment. (2,12,23,24)

8.5 Study limitations:

Our study is limited by relatively small number of, predominantly Caucasian, patients and few events. African-American and Japanese populations generally have higher rates of cardiac involvement with more extensive myocardial involvement, and possibly a more malignant course. (4,7,12,27) Intermittent ambulatory rhythm monitoring may have missed sVT. However the long-term outcome in our cohort still remained favorable. T1/T2 mapping would have increased the detection of interstitial fibrosis and inflammation and have potentially increased prognostic accuracy. (23,28)

8.6 Conclusions

LGE is the strongest, independent CMR predictor of future adverse cardiac events in sarcoidosis patients. RV involvement in addition to LV LGE increases risk of adverse cardiac outcomes and death of all causes. DECMR should ideally be performed in sarcoidosis patients with cardiac symptoms. Asymptomatic patients with LGE < 8% of LV mass and mildly impaired LVEF may not benefit from device therapy, and be monitored. Future prospective studies will help determine the timing of DECMR studies. Current medical management including device therapy has improved survival in this condition. (10,19,22,27)

8.7 Perspectives

Biventricular myocardial LGE is the strongest, independent CMR predictor of future adverse cardiac events in sarcoidosis patients. DECMR should ideally be performed in every sarcoidosis patient with cardiac symptoms and/or abnormal basic assessment. The presence of symptoms and extent of LGE, and not predominantly LVEF will guide the managing clinician in when to implant an ICD. Asymptomatic Caucasian patients with limited LGE < 8% of LV mass, and preserved LVEF, may not benefit from device therapy, and can be safely observed. Future research will focus on comprehensive diagnostic and prognostic strategies which will include serological markers of disease activity and heart failure, LGE characteristics, and pre- and post contrast T1/T2 mapping to evaluate interstitial fibrosis and extracellular matrix volume. Hybrid PET-CMR imaging may optimize detection and management of active inflammation. DECMR may help plan VT ablation and potentially increase success rates and outcomes.

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Disclosures

None.

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Table 1A: Retrospective DECMR studies evaluating the association between LGE and adverse outcomes in cardiac sarcoidosis.

Authors	Study	Study population	Follow up (months)	End points	Events	CMR findings	Predictive value for end-points	
							Positive (%)	Negative (%)
Shafie (2012) (5)	retrospective single-centre	37 pts, large percentage symptomatic CS, 68% female, Japanese	45	primary: nsVT/sVT secondary: CD/VT/CCF	8 11	LV LGE + for secondary end point LV LGE in 70%	31	100
Crawford (2014) (7)	retrospective multi-centre	51 pts, all CS, all LVEF > 35%, 84% female, 47% African-American, 45% Caucasian, 47% steroids, 31 ICD s	48	composite: death/VT/VF	15 3 CD 12 VT/VF	any LGE + multi-focal LGE + RV LGE + LV LGE in 63%, 14.5±12.1%, 13/32 also had RV LGE, these pts had more extensive LV LGE multi-focal LGE correlated with VT/VF	22 48 100	100 97 97
Ise (2014) (8)	retrospective single-centre	43 pts, all CS-LGE positive pts, 65% female, Japanese, all treated with steroids, 7 ICDs	39	composite: CD/VT/VF/CCF	23 6 CD 11 VT/VF	LV LGE ≥ 21.9% of LV mass steroid treatment improved LVEF in pts with small amounts of LGE	62	86
Nadel (2015) (10)	retrospective single-centre	106 pts, systemic sarcoidosis - 70% pulmonary, 32 CS - CMR defined by LGE, 40% female, 58% steroids, 19 ICDs	36.8	primary: SCD/VT/VF secondary: all cause mortality SCD/appr ICD shock SCD/VT/VF/AVB/CCF appr ICD shock	12 4 SCD 12 7 37	LGE + for primary end-point LGE + for secondary end-points	38 13 19	99 89 99
Ekström (2016) (11)	retrospective single-centre	59 pts, 50 CS pts, 48 with LV LGE, not reported on RV LGE, 64% female, Scandinavian, 35 ICDs	26	composite: CD/VT/VF/ heart transplantation	23 3 CD 5 VF 14 VT	LV LGE only independent predictor of composite cardiovascular end-point (HR 12.52) LV LGE > 22% LV LGE > 22% or VT/VF at presentation LV LGE extent and RVEF correlated with adverse outcome	75 74	76 92

Authors	Study	Study population	Follow up (months)	End points	Events	CMR findings	Predictive value for end-points	
							Positive (%)	Negative (%)
Murtagh (2016) (12)	retrospective single-centre	205 pts, extra-cardiac sarcoidosis, LVEF > 50% 69% female, 59% African- American, 60% steroids, 6 ICDS	36	composite: death/VT	12 8 ACD	LGE + LGE in 20% of pts for every 1% increase in LGE burden the hazard for an event increased 8%	32	99
Ogoston (2016) (13)	retrospective single-centre	56 pts, all CS as defined by presence of LGE, 67% female, 52% steroids	32	composite: death/appr ICD shock/ nsVT /sVT/ AVB/ CCF	16 1 CD 1 VT 10 CCF	LV LGE > 18 gram associated with 54 adverse outcome	54	96
Yasuda (2016) (14)	retrospective multi-centre	81pts, definite or suspected CS, 60.5% female, Japanese, 38.3% nsVT/sVT, 24.7% high degree AVB, 29.6% CCF, 52% steroids, 8 ICDS	22.1	composite: AVB/ CCF/ nsVT/sVT/ appr ICD therapy/ CD	30 3 CD 12 VT 7 CCF 4 PM	LV LGE in 94.9% of pts RV LGE in 57% of pts LV LGE 16.6±12.8% LGE ≥ 5.12 g/m ² sens 86%/spec 62% for VT/VF no events when LGE < 5.12 g/m ² and LV LGE ≤ 1 basal anteroseptal segment/RV LGE		

ACD – all cause death, AVB – high degree atrio-ventricular block, CCF – admission for congestive cardiac failure, CD – cardiac death, CS – cardiac sarcoidosis, HR – hazard ratio, ICD – implantable cardioverter defibrillator, LGE – late gadolinium enhancement, nsVT – non-sustained VT, LV – left ventricle, OR – odds ratio, RV – right ventricle, sVT – sustained VT, VF – ventricular fibrillation

Table 1B: Prospective DECMR studies evaluating the prognostic value of LGE in cardiac sarcoidosis.

Authors	Study	Study population	Follow up (months)	End points	Events	CMR findings	Predictive value for end-points	
							Positive (%)	Negative (%)
Cheong (2009) (3)	prospective single-centre	31pts, asymptomatic, 84% pulmonary, 71% female, 39% steroids	12		1 ACD	LV LGE in 26%, LV LGE 0.5-10%, 2/8 also RV LGE		
Patel (2009) (4)	prospective single-centre	81pts, few cardiac symptoms, 95% pulmonary, 62% female, 73% African-American, 65% steroids, 6 ICDs	21	composite: ACD/appr ICD shock/ PM implantation	8 5 CD 6 ACD 2 ICD	any LGE + LV LGE in 26%, median 6.1% [2.3-19%], 14/21 also RV/RV septal LGE, LGE + pts had 9 fold higher rate of adverse events	29	97
Greulich (2013) (6)	prospective multi-centre	155 pts, systemic sarcoidosis, suspected CS, 40% female, 72% steroids, 13 ICDs	31	composite primary: death/ aborted SCD/ appr ICD therapy composite secondary: primary end-point and/or nsVT and/or sVT	15 4 ACD 7 ICD therapy 15+20 6 sVT	any LGE + primary end point any LGE + secondary end point LGE in 25.5%, median 4.4% [2.9-8.8], mostly RV septal LGE	36 87	99 99
Nagai (2014) (9)	prospective single-centre	61pts, no cardiac symptoms, JMHV (2006) negative, LVEF $\geq$ 50%, stable sarcoidosis, 89% pulmonary, not on immunosuppressive agents, 66% female, Japanese	50	composite: death/symptomatic arrhythmia/ CCF	1 PM 3 ACD	LV LGE in 13% of pts 1 PM in LGE + group	0	94
Smedema (2016) (15)	prospective multi-centre	84 pts, pulmonary sarcoidosis, 64% female, 75% Caucasian, 15% Asian, 71% steroids, 14 ICDs	56	composite primary: AVB/appr ICD therapy/sVT/ CCF/CD	10 1 CD 6 ICD therapy	any LGE + LV LGE $\geq$ 7% LV LGE $\geq$ 22% RV LGE + biventricular LGE + any LGE + LV LGE in 32%, RV LGE in 14%	29 35 57 42 56 29	96 95 92 93 93 91

ACD – all cause death, AVB – high degree atrio-ventricular block, CCF – admission for congestive cardiac failure, CD – cardiac death, CS – cardiac sarcoidosis, HR – hazard ratio, ICD – implantable cardioverter defibrillator, LGE – late gadolinium enhancement, LV – left ventricle, nsVT – non-sustained VT, RV – right ventricle, sVT – sustained VT, VF – ventricular fibrillation.

Table 2: Patients baseline characteristics.

All patients with follow up	84 (100)
Female	54 (64)
Caucasian	63 (75)
Age, years	53.3±9.8
Diabetes Mellitus	3 (4)
Hypertension	7 (8)
Cardiac presentation	25 (30)
Syncope	4 (5)
Palpitations	9 (11)
Clinical congestive heart failure	8 (10)
Dyspnea NYHA class 0	50 (59)
NYHA class 1-2	29 (35)
NYHA class 3-4	5 (6)
Sustained Ventricular Tachycardia	10 (12)
Aborted Sudden Cardiac Death	1 (1)
Chest discomfort	3 (4)
Abnormal electrocardiogram	26 (31)
Pulmonary Arterial Hypertension	14 (17)
Medication at any time	
Steroids	60 (71)
Methotrexate	6 (7)
Loop diuretics	10 (12)
Spironolactone	10 (12)
Ace inhibitors/ATIIRB	11 (13)
Beta blockers	13 (16)
Amiodarone	15 (18)
CMR imaging parameters	
LVEF, %	60 [14-84]
Impaired LVEF ($\leq 50\%$)	16 (19)
Impaired LVEF with LGE	13 (15)
Impaired RVEF ($\leq 45\%$)	19 (18)
LVEDV, ml	112 [88-136]
LVEDV index, ml/m ²	58 [47-70]
LV dilation	8 (10)
LV mass, gr	116 [90-142]
LV mass index, gr/m ²	64 [44-84]
LVH	22 (26)
LV LGE present	27 (32)
LV LGE, gr	20 [8-45]
LV LGE, % of LV mass	15 [6-33]
RVEF, %	47 [40-54]
RVEDV, ml	140 [97-183]
RVEDV index, ml/m ²	78 [58-98]
RV dilation	13 (15)
RV mass, gr	43 [34-52]
RV mass index, gr/m ²	23 [18-28]
RVH	11 (11)
RV LGE present	12 (14)
T2 positive	10/69 (14)
Follow up, months	59.0±22.2 [3-108]

Cardiac events during follow up	10 (12)
Cardiac death	1 (1)
Admission for congestive heart failure	1 (1)
Appropriate ICD therapy	7 (8)
Atrio-ventricular block, Pacemaker implantation	1 (1)
Time to events, months	6 (1-80)

Values are n (%), median [IQR], or mean $\pm$ SD. CMR = cardiac magnetic resonance; EDV = end-diastolic volume; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RV = right ventricle; RVEF = right ventricular ejection fraction; RVH = right ventricular hypertrophy

Table 3: Characteristics of patients with and without LGE.

	LGE - n = 56	LGE + n = 28	p Value	OR (95% CI)
Female	19 (34)	11 (39)	0.638	
Caucasian	42 (75)	21 (75)	1	
Age, years	52.4±10.1	55.3±8.9	0.37	
Cardiac presentation	5 (9)	20 (71)	< 0.001	29.71 (8.44-104.60)
Syncope	1 (2)	3 (11)	0.096	7 (0.69-70.74)
Palpitations	2 (4)	7 (26)	0.004	9.60 (1.84-50.25)
Clinical congestive heart failure	2 (4)	6 (21)	0.012	7.86 (1.47-42.04)
Sustained Ventricular Tachycardia	3 (5)	7 (25)	0.011	6.30 (1.483-26.765)
Aborted Sudden Cardiac Death	0	1 (4)	0.321	
Chest discomfort	0	3 (11)	0.031	1.13 (0.99-0.129)
Dyspnea NYHA 0-2	55 (96)	26 (93)	0.96	
NYHA 3-4	2 (4)	1 (4)	1	
Diabetes Mellitus	3 (5)	0	0.548	
Hypertension	6 (11)	1 (4)	0.420	
Medication at any time				
Steroids	36 (63)	24 (86)	0.019	
Methotrexate	1 (2)	5 (18)	0.012	
Loop diuretics	2 (4)	8 (29)	0.001	
Spironolactone	2 (4)	8 (29)	0.001	
Ace inhibitors/ATIIIRB	1 (2)	10 (36)	< 0.001	
Beta blockers	2 (4)	11 (39)	< 0.001	
Amiodarone	2 (4)	12 (43)	< 0.001	
Pulmonary Arterial Hypertension	5 (9)	9 (32)	0.010	5.100 (1.508-17.243)
CMR imaging parameters				
LVEF %	64 [50-70]	55 [49-72]	< 0.001	
LVEDV ml	111 [91-131]	132 [92-172]	0.02	
LVEDV index ml/m ²	55 [48-62]	71[49-93]	0.007	
LV mass	114 [94-134]	122 [92-152]	0.599	
LV mass index gr/m ²	64 [44-84]	64 [43-85]	0.363	
LVH	26 (46)	15 (54)	0.410	
LV dilation	3 (5)	11 (39)	<0.001	11.216 (2.796-44.988)
LVEF ≤ 50%	3 (5)	13 (48)	<0.001	11.842 (2.342-59.879)
RVH	4 (7)	7 (25)	0.029	4.333 (1.147-16.366)
RV mass	39 [32-46]	42 [35-49]	0.753	
RV mass index gr/m ²	22 [16-28]	23 [20-26]	0.964	
RV ≤ 45%	6 (11)	13 (48)	0.011	7.222 (2.342-22.276)
RVEF %	48 [42-54]	46 [36-56]	0.288	
RVEDV ml	185 [143-227]	183 [140-226]	0.084	
RVEDV index ml/m ²	81 [61-101]	96 [69-123]	0.028	
T2 positive	1/45 (2)	9/24 (38)	<0.001	24.188 (2.834-206.451)
Follow up, months	52.4±22.1	61.7±21.5	0.62	
Events during follow up	2 (4)	8 (30)	0.001	
Time to event, months	8 (6-10)	4.5 (1-80)	0.701	

Values are n (%), median [IQR], or mean ±SD. * Values are for all patients with sarcoidosis (84). CI = confidence interval; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RV = right ventricle; RVEF = right ventricular ejection fraction; RVH = right ventricular hypertrophy.

Table 4: Univariate analysis for association with the primary composite end-point.

	No end-points n=74	Primary composite end-point n=10	p Value	OR (95% CI)
Female	48 (65)	6 (60)	0.76	0.81 (0.21-3.14)
Caucasian	56 (76)	7 (70%)	0.70	0.75 (0.175-3.21)
Age, years	53±10	55±7	0.66	
Cardiac presentation	15 (20)	10 (100)	<0.001	12.44 (3.037-50.994)
Syncope	2 (3)	2 (20)	0.02	9.00 (1.11-72.88)
Palpitations	4 (5)	5 (50)	<0.001	17.50 (3.54-86.46)
Clinical congestive heart failure	5 (7)	3 (30)	0.02	5.91 (1.16-30.15)
Sustained Ventricular Tachycardia	6 (8)	5 (50)	< 0.001	11.33 (2.54-50.51)
Aborted Sudden Cardiac Death	1 (1)	0	0.71	
Chest discomfort	3 (4)	0	0.52	
Dyspnea	72 (97)	9 (90)	0.24	
NYHA class 0-2				
NYHA class 3-4	2 (3)	1 (10)	0.24	4 (0.33-48.66)
Diabetes Mellitus	3 (4)	0	0.52	
Hypertension	7 (9)	0	0.31	
Medication at any time				
Steroids	51 (69)	9 (90)	0.17	
Methotrexate	5 (7)	1 (10)	0.71	
Loop diuretics	6 (8)	4 (40)	0.003	
Spironolactone	6 (8)	4 (40)	0.003	
Ace inhibitors/ATIIIRB	6 (8)	5 (50)	< 0.001	
Beta blockers	5 (7)	8 (80)	<0.001	
Amiodarone	7 (9)	8 (80)	<0.001	
ECG abnormalities at presentation	19 (26)	7 (70)	0.004	6.75 (1.59-28.78)
Pulmonary Hypertension	9 (12)	5 (50)	0.039	4.24 (1.133-15.833)
CMR imaging parameters				
LVEF %	55 [48-62]	50 [35-65]	0.01	
LVEDV ml	111 [88-134]	139 [107-171]	0.02	
LVEDV index ml/m ²	58 [38-78]	81 [64-98]	0.02	
LVEF < 50%	11 (15)	5 (50)	0.01	5.36 (1.33-21.68)
LVEF ≤ 35%	3 (4)	2 (20)	0.06	5.58 (0.81-38.60)
LV dilation	5 (7)	3 (30)	0.02	5.83 (1.44-29.72)
LVH	17 (23)	5 (50)	0.12	
LV mass	106 [84-128]	189 [151-227]	0.004	
LV LGE present	12 (4-74)	49 [32-66]	<0.001	11.58 (2.26-59.39)
LV LGE, % of LV	14 [3-36]	28 [20-36]	<0.001	
LV LGE with systolic impairment	8 (11)	5 (50)	0.001	8.25 (1.95-34.84)
RV LGE present	6 (8)	6 (60)	0.002	9.29 (2.350-36.696)
Biventricular LGE	5 (7)	5 (50)	0.004	10.47 (2.323-47.171)
RVH	7 (9)	4 (40)	0.062	4.10 (0.989-16.691)
RV mass	42 [33-51]	50 [38-62]	0.305	
RV mass index gr/m ²	22 [17-27]	25 [19-31]	0.1993	
RV dysfunction	14 (19)	5 (50)	0.042	3.82 (1.101-13.285)
RVEF %	47 [41-53]	47 [32-62]	0.793	
RVEDV	140 [98-182]	137 [93-187]	0.785	
RVEDV index ml/m ²	77 [57-97]	84 [61-107]	0.431	
T2 positive	7/52 (13)	3/7 (43)	0.13	3.18 (0.67-15.24)
Follow up, months	53±20	71±33	0.01	
Time to event, months		14.3 (1-80)		

Values are n (%), median [IQR], or mean ±SD. CI = confidence interval; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RV = right ventricle; RVEF = right ventricular ejection fraction; RVH = right ventricular hypertrophy.

Figure 1A: Flow diagram of the baseline findings and adverse events during follow up included in the primary composite end-point up in 84 sarcoidosis patients.

HRS – Heart Rhythm Society 2014 criteria for the diagnosis of cardiac sarcoidosis **(19)**
JMHW – Japanese Ministry of Health and Welfare 2007 criteria for the diagnosis of cardiac Sarcoidosis **(1)**

Patient at risk

Months	0	20	40	60	80
No LGE	57	45	40	21	3
LV LGE	26	20	18	8	1

Figure 2A: Kaplan-Meier survival curve for LV LGE (composite primary end point).

Patients at risk

Months	0	20	40	60	80
No LGE	75	55	54	28	4
Bivent LGE	9	5	5	1	0

Figure 2B: Kaplan-Meier survival curve for biventricular LGE (composite primary end point).

Patients at risk

Months	0	20	40	60	80
No LGE	57	44	39	20	2
Any LGE	27	21	19	9	1

Figure 2C: Kaplan-Meier survival curve for any myocardial LGE (composite primary end point).

Patients at risk

Months	0	20	40	60	80
RV dysfunction -	66	45	25	26	4
RV dysfunction +	18	14	14	6	0

Figure 2D: Kaplan-Meier survival curve for RV dysfunction (composite primary end point).

Patients at risk

Months	0	20	40	60	80
No LGE	72	59	53	27	3
RV LGE	12	6	6	2	1

Figure 2E: Kaplan-Meier survival curve for RV LGE (composite primary end point).

Patients at risk					
Months	0	20	40	60	80
No LGE	72	59	53	30	3
RV LGE	12	6	6	2	1

Figure 2F: Kaplan-Meier survival curve for RV LGE (composite secondary end point).

Figure 3.1: DECMR of a middle-aged female patient who presented in CCF with frequent nsVT, left bundle branch block, LVEF 38% and extensive patchy LGE (38% LV mass), predominantly involving the right-sided interventricular septum, RV free wall, and LV mid- and sub-epicardial layers (arrows). A biventricular PM/ICD was implanted. During follow up of 62 months no adverse events occurred. (**A.** Inversion Recovery-Gradient Echo sequence, horizontal long axis view, **B.** Inversion Recovery-Gradient Echo sequence, short axis view, **C.** T2 weighted Spin Echo sequence – increased signal signifies inflammation of the RV free wall and LV apex)

Figure 3.2 DECMR in a patient with preserved systolic LV function, who presented with dyspnea and palpitations demonstrating predominantly apical LGE (arrows) (LV LGE 8%). Holter monitoring detected frequent episodes of nsVT. ¹¹¹ Indium-pentetreotide scintigraphy demonstrated active apical inflammation. An ICD was implanted and immune-suppressive and anti-arrhythmic therapy initiated. (**A.** Inversion Recovery-Gradient Echo sequence, horizontal long axis view, **B.** Inversion Recovery-Gradient Echo, vertical long axis view)

Figure 3.3 The implanted ICD detected episodes of sVT after 18 months. The top strip demonstrates unsuccessful ICD discharge for fast monomorphic VT, with eventual VF successfully reverted to a paced rhythm

Figure 3.4 DEC MR of a middle-aged male patient who presented with pre-syncope symptoms due to sustained VT originating from the RV. DEC MR demonstrated extensive patchy LV, in addition to LGE of the inferior RV segments and inferior RV insertion point (arrows). Anti-arrhythmic and immune suppressive treatment was started, and an ICD was implanted. PES on treatment was unable to illicit any monomorphic VT. During follow up of 79 months no adverse events occurred. (A. and B. Inversion Recovery-Gradient Echo sequence, short axis views

Chapter 9

General discussion

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology with symptomatic cardiac presentation in approximately five percent of patients. **(1)**

The clinical features of cardiac sarcoidosis (CS) include congestive heart failure, cor pulmonale, supraventricular- and ventricular arrhythmias, conduction disturbances, ventricular aneurysms, pericardial effusion and sudden death. **(2)**

The diagnosis of CS is made in the co-existence of non-caseating granulomas on myocardial biopsy or biopsies of any extra-cardiac tissue (with the exclusion of other causes for granulomatous inflammation such as mycobacterial or fungal infection), and cardiovascular abnormalities for which other possible causes have been excluded. **(2,3,4,5)** The prevalence of sarcoidosis in The Netherlands is estimated to be 20-30 per 100 000 population, while the prevalence of cardiac involvement was unknown until we published our findings in 2005. Postmortem studies in the United States suggested cardiac involvement in 20-30% percent of patients with sarcoidosis. **(6,7)** In Japan cardiac involvement is reported to be present in as many as 58% of sarcoidosis patients, and is responsible for as many as 85% of deaths from sarcoidosis. **(8,9)** As recent as in 2003 the illustrious OP Sharma (1936-2012), professor of medicine at the Keck School of Medicine (UCLA, Los Angeles), and life-long scholar of sarcoidosis, stated in an editorial entitled “Diagnosis of cardiac sarcoidosis. An imperfect science, a hesitant art” **(10)** “The diagnosis should be established early and accurately, and the treatment should be aggressive and effective. Both of these conditions have remained only partially realized. The search for a safe, reliable, and easily available diagnostic test for CS continues. ” In 1988 uncontrasted T1-weighted Cardiovascular magnetic resonance (CMR) was first used to demonstrate high-intensity mass lesions in the basal interventricular septum and apico-lateral left ventricular (LV) segment of a 30-year-old Caucasian man with syncopal episodes. **(11)** Since that first case-report in 1988 the number of publications on CMR in CS has accelerated from 1 manuscript per annum to over one per week. (PubMed, retrieved January 2019, total number of published manuscripts 534) Over the last 30 years CMR has continued to evolve. CMR is able to delineate and quantify the amount as well as the distribution of the pathological substrate, it being myocyte necrosis, infiltration, deposition or focal or diffuse interstitial replacement fibrosis. CMR provides superior image quality, without exposing patients to ionizing radiation, whilst generating direct information of the tissue characteristics of the myocardium. When we set out to study the promise of delayed contrast-enhanced CMR (DECMR) in the diagnosis, management and risk assessment of CS, only few case-reports had been published. Clinicians relied on electrocardiography, Doppler echocardiography, and ²⁰¹thallium SPECT, ⁶⁷gallium

SPECT, or technetium ^{99}Tc MIBI SPECT. DECMR, positron emission tomography (PET), and hybrid PET/CMR have overtaken these diagnostic tools.

Chapter 3 of this thesis reported on the aim to determine the prevalence of cardiac involvement in patients with pulmonary sarcoidosis (PS) in The Netherlands.

In 2005 we retrospectively evaluated the prevalence of cardiac involvement in 101 consecutive patients with pulmonary sarcoidosis (PS) who had been evaluated at the University Medical Centers of Rotterdam and Maastricht between 1998-2004. Our study was the largest published series to include CMR and first to systematically evaluate cardiac involvement in patients with sarcoidosis in The Netherlands. Standard assessment included 12-lead electrocardiography (ECG), ambulatory ECG, Doppler echocardiography, ^{201}Tl thallium SPECT, DECMR, coronary angiography to exclude coronary artery disease when indicated. CS was diagnosed according to a modified guideline of the Japanese Ministry of Health and Welfare (1993). Because of the limited diagnostic yield and invasive nature of the procedure with an associated risk of morbidity, we felt not justified to systematically subject patients who were screened for CS to endo-myocardial biopsy (EMB), and only performed biopsies in 9 patients. For the purpose of the present study the Japanese guideline was modified by excluding EMB as a diagnostic parameter. Sixteen of the 19 (84%) patients who presented with cardiac symptoms and 3 of the 82 (4%) who were screened for cardiac involvement were diagnosed with CS. DECMR diagnosed abnormalities suggestive of CS in 24 of 87 (28%) study patients. The prevalence of cardiac involvement in those screened for this condition based on the modified Guideline or DECMR were respectively 4% and 15%. The prognosis was good. The patients who presented with cardiac failure or ventricular arrhythmias due to CS had significant morbidity and a mortality rate of 25% during a mean follow up of 15 months. Nine (47%) patients had a pacemaker and/or ICD implanted. The prevalence of CS among Dutch patients with PS seems rather low. Nevertheless, looking at the grim prognosis of CS, physicians should consider regular screening of their PS patients for cardiac involvement. Relatively straight forward detection methods may be used for this purpose.

The introduction of the ICD might improve outcome in CS. During a mean follow up of 15 months (3-54 months), the ICD delivered appropriate therapy in only 1 of 6 patients.

Chapters 3, 4, 5, 6 and 7 reported on the aim of this thesis to determine the distribution and extent of myocardial sarcoidosis with DECMR. Our findings correlated with those at postmortem reported by Silverman and Roberts. **(6,7)**

DECMR demonstrated patchy 3 layer left ventricular (LV), mid-myocardial and epicardial enhancement in predominantly the basal interventricular septum (IVS), lateral LV, and the anterolateral papillary muscles in approximately 30% of PS patients. Resulting eccentric mitral regurgitation was significant in few patients. In several patients confluent, (near) transmural late gadolinium enhancement (LGE) was present, generally with local loss of wall thickness, signifying replacement fibrosis. **Chapter 7** described the first prospective CMR study to specifically report on the prevalence, and distribution of RV involvement due to CS in 87 PS patients. LGE was demonstrated in 30 patients (34%). Right ventricular LGE was present in 16% of patients diagnosed with pulmonary sarcoidosis, and in 48% of patients with LV enhancement. The pattern of RV LGE consisted predominantly in free

wall enhancement (8 pts), ventricular insertion point enhancement (10 pts) and right-sided IVS enhancement (11 pts). The presence of RV LGE correlated with pulmonary arterial hypertension, RV systolic dysfunction, hypertrophy and dilation.

In **Chapter 4** we determined that DECMR was of additional diagnostic value to standard assessment with electrocardiography, Doppler-echocardiography, ^{201}Tl scintigraphy and DECMR in 55 PS patients who underwent evaluation for cardiac involvement between 2002-2004. DECMR provided accurate estimation of the extent of cardiac involvement and revealed signs of early infiltration not detected by standard assessment. Standard evaluation diagnosed CS in 13 while DECMR diagnosed myocardial scarring (2.5 ± 1.9 segments) in an additional 6 patients. The extent of LGE correlated with disease duration, ventricular dimensions and function, severity of mitral regurgitation and the presence of ventricular tachycardias. Patients in whom cardiac involvement was only diagnosed with DECMR had significantly less myocardial scarring and functional impairment compared to patients diagnosed with standard assessment. Our study was the first to evaluate the value of comprehensive CMR assessment in addition to resting and ambulatory ECGs, Doppler-echocardiography and ^{201}Tl scintigraphy. We found DECMR to be highly sensitive in detecting abnormalities that suggest cardiac involvement in patients with histologically confirmed PS. Our findings demonstrate a strong correlation between electrocardiographic and echocardiographic abnormalities and the amount of LV LGE with DECMR. The distribution of LGE correlated well with the localization of inflammation and fibrosis reported in postmortem studies of patients with CS. **(6,7)** Limited, non-transmural or patchy myocardial scar tissue, frequently found at postmortem evaluation of CS patients, may remain undetected by electrocardiography, ultrasound or scintigraphy, but be detected by DECMR due to its high spatial resolution and inversion-recovery gradient echo sequences that increase signal intensity differences by almost 500%. **(12,13)** The additional value of CMR to standard assessment was demonstrated in 6 patients (11%) in whom LV involvement was only diagnosed by DECMR. Since disease in this group was of shorter duration in comparison to the group diagnosed with standard assessment, and myocardial involvement limited, the findings in these patients may well reflect early involvement.

In **Chapter 5** we determined the diagnostic accuracy of DECMR for cardiac involvement in patients with PS compared to the, in 2005, gold-standard diagnostic Japanese Guidelines (1993). We demonstrated DECMR to be a valuable diagnostic tool to determine cardiac involvement in patients with sarcoidosis. We performed an analysis of the 12-lead ECGs, 24-hours ambulatory ECGs, echocardiograms, thallium scintigrams and DECMR studies in 58 biopsy proven PS patients assessed for CS. The diagnosis of CS was made in 12 of 58 (21%) patients. The sensitivity and specificity of CMR were 100%, and 78%, the PPV and NPV 55% respectively 100%, with an overall accuracy of 83%. The low PPV of 55% reflects the ability of CMR to detect small myocardial lesions which had not resulted in conduction delay, repolarization abnormalities, or regional changes in wall thickness or function, and hence were not detected by ECG, echocardiography or SPECT. Long-term FU as discussed in **Chapter 8** will determine the significance of these small asymptomatic contrast-enhancing LV lesions.

In **Chapter 6** we reviewed the value of DECMR in differentiating patients with CS from those with coronary artery disease (CAD) and recent myocardial infarcts. LGE by CMR is the most accurate non-invasive method to evaluate myocardial necrosis or focal replacement fibrosis caused by acute myocardial infarction, chronic myocardial infarction or NICM. **(14)** The distribution of LGE was valuable in differentiating between ischemic and non-ischemic myocardial scarring. **(15-18)** Since a significant number of patients with CS present with symptoms of heart failure or chest pain, similar in nature to those in patients with CAD, we aimed to determine whether CMR, and specifically the pattern of LGE, would allow us to distinguish the CS patients from patients with CAD and recent myocardial infarcts. Our study was the first to systematically compare the distribution of LGE in CS with the findings in patients with coronary artery disease. DECMR was helpful in the non-invasive differentiation between patients with CS and patients with CAD and previous myocardial infarcts. However, in approximately a third of patients with coronary artery disease, subepicardial or patchy, three layer LGE was found, a pattern that was suggestive of a non-ischemic etiology such as CS. Additional angiographic information was needed to correctly classify 11 patients with CAD and 3 with CS. Two experienced blinded observers classified patients by assessing the distribution of LGE. LV LGE was present in 29/30 CS (mean 3.8 segments, range 0 – 12), all infarct (mean 4.3 segments, range 0 – 9), and none of the patients in the control group. The amount of LV LGE did not differ significantly between CS and infarct patients ($19 \pm 11\%$ and $19 \pm 12\%$, $P = 0.8$). The CS group exhibited a predominantly patchy, 3 layer LGE ($P = 0.01$), whereas confluent transmural LGE ($P = 0.04$) with a vascular distribution ($P < 0.001$) was prevalent in the infarct group. Significantly more RV LGE ($P = 0.01$) and dilation ($P = 0.02$) were found in the CS group. The two observers classified patients correctly as CS in 72% and 83% of cases, as ischemic in nature in 77% and 80% of cases, and as normal in 90% and 100% respectively.

In **Chapter 7** we describe the prevalence and distribution of RV LGE in patients diagnosed with PS. This was the first prospective DECMR study to specifically evaluate the prevalence, and distribution of RV involvement in CS. Left ventricular involvement demonstrated by DECMR has been extensively reported. Until recently limited attention has been given to the prevalence, relevance and prognostic value of RV involvement in CS. CMR is the preferred imaging tool to evaluate the healthy and diseased RV. **(19-23)** We evaluated 87 patients diagnosed with PS with DECMR for RV involvement. Pulmonary artery pressures were non-invasively evaluated with Doppler echocardiography. Approximately 30% of an unselected patient population with PS had LV involvement, half of which had RV involvement. More extensive LV enhancement correlated with RV involvement. Right ventricular enhancement may result from direct infiltration and resulting scar, or pulmonary hypertension. Previous studies associated impaired systolic RV function and RV enhancement with ventricular tachy-arrhythmias. We demonstrated RV enhancement with DECMR to be mostly multi-focal, involve the septum and correlate with increased right ventricular volumes, hypertrophy and impaired systolic function. Pulmonary arterial hypertension correlated with the presence of RV LGE. The direct relationship between RV enhancement, its size and systolic function, as previously demonstrated in LV sarcoidosis, has not been reported before. Since RV sarcoidosis occurs in patients with more extensive LV disease, the reported prognostic relevance of RV disease may at least partly reflect the

extent of left ventricular arrhythmogenic substrate. Right ventricular enhancement in sarcoidosis may be caused by direct granulomatous infiltration, but also be related to pulmonary hypertension. Right ventricular dilation, systolic impairment, and inflammation, as demonstrated with positron emission tomography (PET), in sarcoidosis have been associated with adverse outcome, particularly ventricular tachy-arrhythmias. **(23-30)** In **Chapter 8** we investigated whether RV LGE carries similar prognostic relevance in the first prospective study of this kind. We determined that RV LGE predicts adverse events in addition to LV LGE during long-term follow up. Our study is the first to demonstrate the direct relationship between RV LGE, RV volumes, RV systolic impairment, sVT, and death of all cause. RV and LV LGE were demonstrated in respectively 12 (14%) and 27 (32%) of 84 consecutive biopsy proven PS patients. RV LGE, LV or biventricular LGE yielded Cox hazard ratios of 8.71 (95% CI 1.90-23.81), 9.22 (95% CI 1.96-43.45), and 12.09 (95% CI 3.43-42.68) for the composite primary end-point of adverse cardiac outcomes. In a multi-variate model the predictive value of biventricular LGE for the composite primary and secondary end-points was strongest. Kaplan Meier event-free survival curves were most significant for RV LGE and biventricular LGE. Biventricular LGE at presentation is the strongest, independent predictor of adverse outcome during long-term follow up. Asymptomatic myocardial scar < 8% of LV mass carried a favorable long-term outcome. Right ventricular LGE indeed predicted ventricular tachy-arrhythmias and all cause death during follow up. In the absence of data on VT morphology it remains unclear whether the prognostic relevance of RV LGE is related to more extensive biventricular arrhythmogenic substrate or whether RV LGE itself is particularly arrhythmogenic. None of our patients with asymptomatic LGE suffered adverse cardiac events, while the majority of arrhythmic end-points (75%) occurred in patients with LVEF > 35%. Our findings are supported by the results of recent studies which evaluated the risk of SCD in CS patients, and also recorded appropriate ICD therapy in a large proportion of patients with LVEF > 35%. **(3,20,23,25)** The risk of VT and SCD in CS seems predominantly related to amount and distribution of granulomatous infiltration and scar, and not primarily the systolic function. Arrhythmic substrate imaging with DECMR and/or PET determines the risk of arrhythmic events more accurately than LVEF. **(3,20,23,25,20,28,30,31)** The negative predictive value of LGE negative DECMR is excellent, with only one patient with LV LGE < 8% developing an arrhythmic event after 10 months of follow up. In the absence of prospective data, it seems prudent to follow asymptomatic sarcoidosis patients up with ECG and cardiac ultrasound, and evaluate suspected or confirmed CS with PET and/or DECMR. **(3)** Our studies support the recommendations of the 2014 HRS guidelines concerning the use of DECMR and device implantation. **(3)**

Until recently the prognosis of CS was considered dismal. Flemming et al reported 44% of 250 CS patients surviving 5 years. **(32)** Roberts et al estimated survival after the development of cardiac symptoms to be 2 years. **(6)** Long-term outcomes in patients with CS have remarkably improved due to accurate diagnostic imaging with CMR and PET, modern medical heart failure management, including device therapy, arrhythmia ablation and transplantation in selected patients. **(33-38)** Current annual mortality rates range from 0-4.2/100 pts compared to 7.5-12/100 pts as previously reported by Yazaki (2001) and Fleming (1986). **(39,40)** Five-year survival rates have improved from 44% to current 5 and 10-

year survival rates of over 90%. **(32-40)** Our studies are limited by the relatively small number of predominantly Caucasian, patients and few events. African-American and Japanese populations generally have higher rates of cardiac involvement with more extensive myocardial involvement, and possibly a more malignant course. **(2,8,9)** LGE is the strongest, independent CMR predictor of future adverse cardiac events in sarcoidosis patients. RV involvement in addition to LV LGE increases risk of adverse cardiac outcomes and death of all causes. DECMR should ideally be performed in sarcoidosis patients with cardiac symptoms. Asymptomatic patients with LGE < 8% of LV mass and mildly impaired LVEF may not benefit from device therapy, and be monitored. When we first evaluated the diagnostic accuracy of DECMR the only published Guidelines had not included this modality yet. **(41)** Since 2007 DECMR has gradually been included in the Diagnostic and Management Guidelines of 5 professional Societies, and the prominence of DECMR has increased from being a minor to becoming a major criterium for the diagnosis of CS with additional prognostic relevance. **(3,42-47)** Recent editorials have captured the current status of CMR in the management of (suspected) CS. “CMR has high diagnostic accuracy and prognostic value for the evaluation of individuals with suspected CS.” **(48)** “... novel CMR mapping techniques can detect subclinical myocardial changes in sarcoidosis, adding value to the diagnosis of patients otherwise being classified as having normal cardiac findings.” **(49)** The limits of CMR have not been reached. Ultra-high field CMR and compressed-sensing techniques will continue to shorten scan times, improve image resolution and quality, which will allow for detailed assessment of the atria and RV. **(50,51,52,53)** Prospective studies will help determine the value of native T1 mapping, and the assessment of the extra cellular myocardial volume (ECV) by the use of native and post-contrast T1 maps. Hybrid PET-CMR imaging with T2 mapping have optimized detection and management of active inflammation. Mapping multiple relaxation times simultaneously will similarly save time and remove confounders introduced by the interaction of relaxation times. Three-dimensional mapping allows for more complete characterization of disease distribution, so-called CMR fingerprinting of the myocardium, which implies the generation of structural, mechanical, functional as well as biochemical information. **(50,54,55)** DECMR will help plan arrhythmia ablation and potentially increase success rates and outcomes. Recent advances have made real-time CMR guided EMB in patients with suspected isolated CS and CMR-guided ablations of (supra)ventricular arrhythmias a reality. **(56,57,58)**

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Chapter 10

Summary

When we set out to formally evaluate the value of contrast-enhanced cardiovascular magnetic resonance (CMR) for the diagnosis and management of cardiac sarcoidosis (CS) little was known of the prevalence of cardiac sarcoidosis in The Netherlands.

In **Chapter 2** we reviewed contrast-enhanced CMR in the diagnosis and management of CS. The aim of this review was to provide relevant clinical and pathophysiological background on CS, whilst introducing cardiovascular magnetic resonance imaging (CMR) as a technology, and detailing its past, current and future role in the management of CS. **Chapter 3** details the prevalence of cardiac involvement in patients with pulmonary sarcoidosis (PS) assessed at two University Medical Centres in The Netherlands. We reviewed the findings in 101 consecutive patients who either presented to us with symptoms of cardiac involvement, or were screened for CS during 1998 -2004. Sixteen of the 19 (84%) patients who presented with cardiac symptoms and 3 of the 82 (4%) who were screened for cardiac involvement were diagnosed with CS (adapted Japanese 1993 criteria). Once PS patients developed CS, their prognosis became grim, with 4 deaths (20%), and 9 cardiac device implants (47%). The CS patients who presented with cardiac failure or ventricular arrhythmias had significant morbidity and a mortality rate of 25% during a mean follow up of 15 months. In contrast, PS patients diagnosed with asymptomatic, small, focal scar fared well. Our study was the first to systematically evaluate cardiac involvement in patients with sarcoidosis in The Netherlands, and at that stage the largest published to employ CMR. **Chapter 4** reported the additional value of gadolinium-enhanced CMR to standard assessment with electrocardiography, Doppler-echocardiography, and ²⁰¹thallium scintigraphy for cardiac involvement in 55 patients with PS.

Of the 55 patients evaluated, standard evaluation diagnosed cardiac involvement in 13 while CMR diagnosed myocardial scarring in an additional 6 (11%) patients. The extent of delayed enhancement correlated with disease duration, ventricular dimensions and function, severity of mitral regurgitation and the presence of ventricular tachycardias. Patients in whom cardiac involvement was only diagnosed with CMR had less focal myocardial scarring and functional impairment compared to patients diagnosed with standard assessment. CMR provided an accurate estimation of the extent of cardiac involvement, and may have reveal signs of early infiltration that were not detected by standard assessment. The extent of LGE related to severity of cardiac involvement and may therefore have prognostic implications

Chapter 5 evaluated the accuracy of gadolinium-enhanced CMR in the diagnosis of cardiac sarcoidosis.

In 2005 the diagnosis of CS was made according to the guidelines of the Japanese Ministry of Health and Welfare (1993). CMR had not been incorporated in the guidelines, and the diagnostic accuracy of CMR for the diagnosis of CS had not yet been evaluated. We performed an analysis of the 12-lead ECGs, 24-hours ambulatory

ECGs, echocardiograms, thallium scintigrams and gadolinium-enhanced CMR studies in 58 biopsy proven PS patients assessed for CS. The diagnostic accuracy of CMR for CS was determined with modified Japanese guidelines as gold standard. Twelve of the 58 patients were diagnosed with CS (21%). The sensitivity and specificity of CMR were 100%, and 78%, the PPV and NPV 55% respectively 100%, with an overall accuracy of 83%. The combination of ECG and CMR had a sensitivity and specificity of 100% and 96%, and PPV and NPV of respectively 86%, and 100%, with an overall accuracy of 97%.

Late gadolinium enhancement (LGE) accurately delineates myocardial necrosis or focal fibrosis. The pattern of LGE in ischemic and non-ischemic myocardial disease is different, and might be helpful in distinguishing CS from ischemic disease. The pattern of LGE in CS has been reported to be patchy, multi-segmental, not related to coronary artery territories, while predominantly involving the mid myocardial and subepicardial layers. In **Chapter 6** we reviewed the value of delayed contrast-enhanced CMR (DECMR) in differentiating patients with CS from those with coronary artery disease and recent myocardial infarctions. The DECMR studies of 30 patients with CS were compared to those performed in 30 consecutive infarct patients, who had been managed with primary coronary interventions, and 10 healthy controls. Two experienced blinded observers classified patients by assessing the distribution of LGE. Gadolinium CMR was helpful in differentiating patients with CS from patients with ischemic heart disease and previous myocardial infarctions. In a subgroup of ischemic patients the pattern of LGE was atypical, and suggestive of non-ischemic etiology. Cardiac involvement in sarcoidosis is reported in up to 30% of patients. Left ventricular involvement demonstrated by DECMR has been well validated. We sought to determine the prevalence and distribution of RV LGE in patients diagnosed with PS. In **Chapter 7** Right ventricular involvement in CS demonstrated with CMR. We prospectively evaluated 87 patients diagnosed with PS with contrast-enhanced cardiac magnetic resonance for RV involvement. Right ventricular enhancement was present in 16% of patients diagnosed with PS, and in 48% of patients with LV enhancement. The presence of RV enhancement correlated with pulmonary arterial hypertension, RV systolic dysfunction, hypertrophy and dilation. More extensive LV enhancement correlated with RV involvement. Right ventricular enhancement may result from direct infiltration and resulting scar, or pulmonary hypertension. Previous studies associated impaired systolic RV function and RV enhancement with ventricular tachy-arrhythmias. We demonstrate RV enhancement with cardiac magnetic resonance to be mostly multi-focal, involve the septum and correlate with increased RV volumes, hypertrophy and impaired systolic function. Finally in **Chapter 8** we present the long-term follow up of 84 consecutive biopsy proven pulmonary sarcoidosis patients after baseline DECMR. Biventricular LGE at presentation was the strongest, independent predictor of adverse outcome during long-term follow up. Small asymptomatic LV myocardial scar of < 8% of LV mass carried a favorable long-term outcome. RV delayed enhancement correlates with systolic RV dysfunction and predicts ventricular tachy-arrhythmias as well as all cause death during follow up. This is the first pro-

spective study to detail the prognostic relevance of right ventricular involvement in pulmonary sarcoidosis, and reports on improved long-term outcomes when cardiac sarcoidosis is managed according to current guidelines.

Chapter 11

Valorisation

Cardiac sarcoidosis (CS) is a relatively rare but potentially devastating condition, which predominantly affects productive, middle-aged individuals. The results of the studies summarized in this thesis have helped improve the diagnosis and management of this condition. Knowledge valorization stands for the translation of academic wisdom to societal benefit. This can potentially be achieved by a broad range of products and activities. Our work made use of commercially available (imaging) technology, hardware and (post-processing) software. Its aim was to demonstrate the exciting benefits of available imaging technology, Delayed-Enhanced Cardiovascular Magnetic Resonance (DECMR), and improve patient outcomes i.e. to prevent sudden cardiac death and promote quality of life. The practical application of our work was translated into the current Guidelines. **(1-7)** Findings with DECMR have been included as a major criterium in international, diagnostic and management, guidelines for CS. DECMR has been demonstrated to be a valuable diagnostic tool in sarcoidosis patients with cardiovascular symptoms and, as second line imaging technology, in patients with electrocardiographic or Doppler-echocardiographic abnormalities. Ongoing long-term prospective studies, which make use of the latest advances in CMR, may increase the success of targeted arrhythmia ablation, and result in more cost-effective implantation of cardioverter defibrillators.

The words of professor OP Sharma uttered in 1994 still ring true. “Myocardial sarcoidosis is difficult to diagnose, follows a treacherous course that may lead to death, and responds poorly and randomly to treatment.” “To deal successfully with the menace of myocardial sarcoidosis , one must first learn to think of the entity”. “Once the presence of the wolf is suspected, further diagnostic studies should be aggressively pursued to establish the extent and severity of the illness.” **(8)**

Knowledge about this condition, its insidious, non-specific nature, which mimics a number of alternative systemic conditions, needs to be actively promoted amongst all medical disciplines. The threshold for cardiac referral and evaluation should be low and any delays in the diagnostic process avoided. All available platforms, analogue (brochures, lectures, workshops) and digital (websites, podcast, ebook), should be recruited, targeting healthcare workers, professional societies, medical insurers, and the greater public.

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Chapter 12

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Solo Deo Gloria!

Chapter 13

Curriculum Vitae

Jan-Peter Smedema was born on May 1st 1964 in Sneek, The Netherlands. He attended high school in Den Helder, and studied Medicine at the Free University in Amsterdam. After finishing his compulsory basic military training he enjoyed working in the Respiratory Unit, Department of Medicine, at the Central Military Hospital in Utrecht (1989-1990). His first clinical work experience as civilian was in Cardio-Thoracic Surgery (Prof L Eysman, 1990-1991) and the Amsterdam Department of Interventional Cardiology (Dr F Kiemeneij, 1991-1992) at the Onze Lieve Vrouwe Gasthuis. The doors of opportunity and clinical exposure beckoned in South Africa. Starting in the Cardiac Unit at Ga-Rankuwa Hospital, Medical University of South Africa, Pretoria (Prof P Magobo) and Baragwanath Hospital, Johannesburg (Prof P Sareli, 1992). In 1993 he transferred to Tygerberg Hospital, the training hospital of Stellenbosch University, where he finished his training as a specialist physician (FCP (SA), MMed (Int Med), 1998), and enrolled in the cardiology training program (Prof AF Doubell). Whilst working in the Cardiac Unit, he encountered his first patient with cardiac sarcoidosis (CS), an encounter which ignited a life-long fascination with this condition. He visited professor AC van Rossum (VUMC, Amsterdam), immersed himself in Cardiovascular Magnetic Resonance (CMR) and started a local CMR program in Cape Town. After marrying his sweetheart CMR radiographer (who taught him more than just the basics of CMR), he took up professor D Pennell's invitation of a CMR fellowship at the Royal Brompton (2000). Subsequently he finished his clinical training as a cardiologist at the Thorax Centre, Erasmus University Rotterdam (Prof ML Simoons, 2002), where he met dr Robert-Jan van Geuns. They combined efforts and studied CS with delayed enhanced CMR (DECMR) in Rotterdam. Their collaboration continued after Jan-Peter was appointed as consultant cardiologist at Maastricht University Medical Centre (2002). Under the tutelage of professors AP Gorgels and HJGM Crijns his preliminary work studying of the value of DECMR in the management of CS, expanded formally into a PhD project. In 2005 he was invited to return to Cape Town to provide cardiovascular imaging services, and be trained in interventional cardiology (dr A Saaiman). He was appointed honorary consultant at the Department of Medicine, Groote Schuur Hospital, University of Cape Town, and studied cardiomyopathy and tuberculous heart disease with DECMR (professors BM Mayosi and G Ainslie, 2005-2006). Since 2005 he has practiced as an interventional cardiologist with Netcare in Cape Town. Jan-Peter developed an interest in stroke medicine, joined a local stroke team, and obtained the MSc (Stroke Medicine), through the European Stroke Organization/Danube University, Austria (2015). He is currently enrolled in the Sports Science/Exercise Medicine program at the Sport Science Institute of South

Africa (MPhil, UCT), and hopes to qualify as a sports physician in 2020. Jan-Peter continues to reside in Cape Town, South Africa, and enjoys life with his wife Elmarie, and two children, Joshua (19) and Maja (15). In his spare time he runs, hikes, and attempts to improve his golfing skills under the tutelage of his son.

Awards: Best oral presentation, South African Heart Association meeting 2010.

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