SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 325-335

Cardiovascular magnetic resonance-guided diagnosis of cardiac affection in a Caucasian sarcoidosis population

Carmen Pizarro[1], Andreas Goebel[2*], Darius Dabir[2], Christoph Hammerstingl[1], Stefan Pabst[1], Christian Grohé[3], Rolf Fimmers[4], Birgit Stoffel-Wagner[5], Georg Nickenig[1], Hans Schild[2], Dirk Skowasch[1], Daniel Thomas[2]*

[1] Department of Internal Medicine II, Cardiology, Pneumology and Angiology, University Hospital Bonn, Bonn, Germany; [2] Department of Radiology, University Hospital Bonn, Bonn, Germany; [3] Department of Pneumology, Evangelische Lungenklinik Berlin, Berlin, Germany; [4] Institute for Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany; [5] Institute for Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Bonn, Germany

Abstract. *Background:* Clinically evidenced cardiac involvement in systemic sarcoidosis occurs in approximately 5% of patients, whereas post-mortem examinations identify cardiac sarcoidosis in over 60% of cases. *Objective:* Given the inconsistency of diagnostic approaches, we took aim at prospectively investigating the prevalence of cardiac sarcoidosis by cardiovascular magnetic resonance (CMR) in a primary Caucasian population and at correlating the results with standard clinical parameters. *Methods:* 188 patients with histologically proven sarcoidosis were included, provenient from the local pneumological department and a national sarcoidosis self-help association. All of them underwent CMR-imaging. Complementary 12-lead ECG, Holter monitoring, laboratory and pulmonary function testing were performed. *Results:* CMR-based diagnosis of cardiac sarcoidosis was made in 29 patients (15.4%), of whom 17 patients (9% of total cohort) exhibited increased relative gadolinium enhancement – reflecting acute inflammatory processes -, while 11 patients (5.9% of total cohort) showed late gadolinium enhancement as a marker for nonviable tissue damage. Both abnormalities were present in 1 patient (0.5%). Correlation analysis evinced significant association between CMR-diagnosed cardiac sarcoidosis and reduction in LVEF, increase in diastolic interventricular septal thickness, diastolic dysfunction as well as limited electrocardiographic abnormalities. Neither laboratory values nor pulmonary function parameters correlated with presence or activity of cardiac sarcoidosis. *Conclusions:* Among our predominantly Caucasian sarcoidosis study population, CMR-detected cardiac affection occurred in 15.4% and was missed by internationally valid standard clinical testing in all but one case. It reinforces CMR's diagnostic value as modality of choice to evaluate cardiac sarcoidosis. The estimation of its prognostic potential and its value in assessing the incidence of cardiac sarcoidosis however requires further longitudinal investigation. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 325-335)*

Key words: histologically proven sarcoidosis, cardiac sarcoidal involvement, caucasian population, cardiovascular magnetic resonance imaging

Introduction

Sarcoidosis is a heterogeneous, non-caseating granulomatous disease of unknown aetiology characterized by potential multisystemic affection (1). Its incidence varies depending on racial differences evidencing a 3.8-fold greater annual incidence of

Received: 14 December 2014
Accepted after revision: 9 April 2015
Correspondence: Daniel Thomas, M.D.,
Department of Radiology, University Hospital Bonn,
Sigmund-Freud-Str. 25, D-53105 Bonn, Germany.
Tel. +49-228-287-15237
Fax +49-228-287-19083
E-mail: Daniel.Thomas@ukb.uni-bonn.de

* Equally contributed

35.5/100,000 for African Americans compared with Caucasians (2). According to small observational trials, cardiac involvement occurs in 5% of patients with systemic sarcoidosis (3). However, autoptic studies exhibit cardiac affection in up to 64% of cases (4), insinuating a substantial underrecognition. After respiratory failure, sarcoidal heart involvement constitutes the second most common cause of death in sarcoidosis worldwide (5), and the leading cause of sarcoidal death in Japan (6). Its clinical presentation is determined by lesions' localization and predominantly comprises arrhythmias (7) and dilated cardiomyopathy up to heart failure (8). Nonetheless, sudden death can occur without prior cardiac events or symptoms, indicating the challenging necessity of establishing adequate evaluative modalities that allow for a timely diagnosis and effective monitoring of cardiac sarcoidosis.

In a cohort of 81 patients with extracardiac sarcoidosis, late gadolinium enhanced cardiac magnetic resonance (LGE-CMR) identified cardiac involvement in 26% that was associated with major cardiac adverse events (9). The study population comprised 73% African Americans who are known to exhibit a higher incidence of sarcoidosis than other ethnic groups.

The aim of this prospective study of a large-scaled sarcoidosis cohort was to determine the prevalence of cardiac sarcoidal affection in a primary Caucasian population by use of cardiovascular magnetic resonance imaging (CMR), to differentiate in dependence on the CMR-stated disease activity and with correlate the results to established non-invasive tests in order to assess their predictive value.

Methods

191 consecutive patients aged 18 to 70 with a history of histologically proven sarcoidosis were eligible for this prospectively conducted clinical cohort trial. Study population was composed of outpatients receiving treatment at the University Hospital's Department of Pneumology (Bonn, Germany) and patients recruited from a nationwide sarcoidosis self-help association. Exclusion criteria comprised presence of implanted metallic devices and foreign bodies, pregnancy and claustrophobia. To prevent occurrence of gadolinium-induced nephrogenic systemic fibrosis (10), we additionally excluded patients presenting with a glomerular filtration rate < 30 ml/min, acute kidney injury or receiving dialysis. Informed consent was obtained from each patient.

Prior to the CMR study, standardized questionnaire-based clinical evaluation on any time occurrence of cardiac symptomatology, cardiac comorbidities and sarcoidal findings was performed. In case of CMR-based diagnosis of cardiac sarcoidosis, locally treated patients were re-examined by CMR at a six-month interval and their medication was adjusted at local physician discretion. Participants recruited through the sarcoidosis association received no local CMR-follow up.

Electrocardiogram and transthoracic echocardiography

All patients treated at the local pneumological department systematically underwent 12-lead electrocardiogram (ECG), Holter monitoring and transthoracic echocardiography as part of their routine medical care. Electro- and echocardiographic features of self-help association-recruited patients were assessed by collection from their medical reports.

In line with the Japanese Ministry of Health and Welfare Guidelines (JMHWG) on sarcoidosis, revised in 2009 (11), which in turn form the basis of the recently published German consensus paper on diagnostics and therapy of cardiac sarcoidosis (12), pathological electro- and echocardiographic findings were pre-defined as depicted in Table 1.

Laboratory testing

Immediately prior to CMR conduction, blood sampling was performed and encompassed biomarkers that have previously been reported to correlate with sarcoidosis activity or cardiac injury: a complete blood-cell count, serum angiotensin converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), C-reactive protein (CRP), cardiac troponin I (cTnI) and plasma N-terminal pro-BNP (NT-proBNP) were assessed.

Pulmonary function tests

Testing comprised spirometry, bodyplethysmography and determination of diffusion capacity

Table 1. Tested electro- and echocardiographic criteria, as defined by the current JMHWG and German consensus paper

12-lead electrocardiography	Ambulatory ECG monitoring	Transthoracic echocardiography
• Advanced atrioventricular block	• Supraventricular arrhythmia	• LVEF<50%
• Abnormal Q wave	• Ventricular arrhythmia	• Diastolic dysfunction
• Axis deviation	• Ventricular tachycardia	• Regional abnormal wall motion
• Right/Left bundle branch block	• >1000 VES/24hours	• Ventricular aneurysm
• QRS fragmentation		• Wall thickening

Abbreviations: VES = ventricular extrasystoles; LVEF = left ventricular ejection fraction

for carbon monoxide. Parameters were assessed in absolute terms and in percentages of the predicted values, in conformity with the European Respiratory Society guidelines (13).

Cardiovascular magnetic resonance imaging

All cardiovascular CMR studies were acquired on a clinical 1.5T scanner (1.5T Intera, Philips Healthcare, Best, The Netherlands), equipped with a cardiac phased-array coil. The imaging protocol followed recommendations on standardized cardiovascular magnetic resonance imaging (14). After acquisition of scout images for determining the standard cardiac views, cine CMR was carried out. For visualization of myocardial oedema, fat-suppressed T2-weighted black-blood turbo spin echo sequences were acquired in the short axis orientation. Dynamic T1 imaging was performed for assessment of early relative contrast enhancement as previously described (15). Delayed enhancement imaging covering the standard cardiac axes was performed 12-15 minutes after gadolinium injection (0.1 mmol/kg gadolinium-DTPA). Total examination time was 45 to 60 minutes. Assignment of late enhancing lesion localization was performed in accordance with the American Heart Association's standardized myocardial segmentation and nomenclature (16). Two experienced radiologists, blinded to all clinical data, independently evaluated CMR images. In case of discordant results, the studies were reassessed to reach consensus.

Statistical analysis

Descriptive statistics are presented as absolute numbers and percentages or means (±SD), when appropriate. CMR-diagnosed cardiac sarcoidosis was correlated to clinical data, serological, electrocardiographic, echocardiographic and pulmonary parameters by use of Pearson's χ^2 test – in case of categorical variables –, or unpaired t-test, when continuous parameters were compared. A p-value < 0.05, resulting of 2-tailed tests, was considered threshold for statistical significance. Statistical analyses were performed using SPSS Statistics 22 software (IBM, Armonk, NY, USA).

Results

From June 2011 till September 2013, 191 patients with histologically proven sarcoidosis, meeting the inclusion criteria, were identified for possible participation in the study. Of these, one patient was excluded due to obesity-driven technical CMR conduction difficulties. A further two excluded patients were kidney transplanted and run risk of developing gadolinium-induced nephrogenic systemic fibrosis, albeit GFR values were within the normal range.

Demographic characteristics and clinical data of the enrolled 188 patients are summarised in Table 2. Data comparison based upon the different patient proveniences (local pneumological department and nationwide self-help association) is outlined in Table 3, revealing no intercohortal differences in distribution of characteristics with the sole exception of a predominance of female patients in the association-recruited cohort (66.7% versus 48.3%, p=0.01).

Study population offered a slight predominance of women (55.3%, n=104) and exhibited a mean age of 52±13 years, with Caucasian origin representing 97.3% (n=183) of the entire population

Table 2. Patient demographic and clinical characteristics

All patients, n	188
Age, years	52 ± 13
Female gender, n (%)	104 (55.3%)
Race, n (%)	
Caucasian	183 (97.3%)
African	3 (1.7%)
Asian	1 (0.5%)
Hispanics	1 (0.5%)
Affected organs, n (%)	
Lung	122 (64.9%)
Lymph node	118 (62.8%)
Skin	52 (27.7%)
Eye	25 (13.3%)
Liver	19 (10.1%)
Peripheral/central nervous system	15 (8.0%)
Musculoskeletal system	10 (5.3%)
Radiographic stage in case of lung affection, n (%)	
I	34 (27.9%)
II	50 (41%)
III	31 (25.4%)
IV	7 (5.7%)
Löfgren syndrome, n (%)	10 (5.3%)
NYHA functional class, n (%)	
No limitations	42 (22.3%)
I	55 (29.3%)
II	69 (36.7%)
III	22 (11.7%)
IV	0 (0%)
Cardiac symptoms*	
Chest pain, n (%)	48 (25.5%)
Dizziness, n (%)	51 (27.1%)
Syncopal episode, n (%)	8 (4.3%)
Fatigue, n (%)	68 (36.2%)
Dyspnoea, n (%)	73 (38.8%)
Medical treatment at CMR conduction, n (%)	76 (40.4%)
Equivalent prednisone dose at CMR conduction, mg	6.6 ± 12.1
Pulmonary function parameters	
FEV1, l	2.98 ± 0.97
FEV1, % predicted	91.18 ± 18.90
IVC, l	3.53 ± 1.17
IVC, % predicted	86.58 ± 18.15
DLCO, mmol/min/kPa	6.49 ± 2.30
DLCO, % predicted	67.24 ± 18.49
DLCO/VA, mmol/min/kPa/l	1.40 ± 0.33
DLCO/VA, %0 predicted	90.83 ± 21.33

Data are presented as mean ± SD or total number and percentage (in parentheses).
*Cardiac symptoms refer to any time occurrence, not to presence at CMR conduction.
Abbreviations: NYHA = New York Heart Association; FEV1 = forced expiratory volume in 1 second; IVC = inspiratory vital capacity DLCO = diffusion capacity for carbon monoxide; VA = alveolar volume

Table 3. Characteristics according to patient's provenance

	Patients recruited by local pneumological department (n=116)	Patients recruited by self-help association (n=72)	p-value
Age, years	51 ± 13	53 ± 13	0.39
Female gender, n (%)	56 (48.3%)	48 (66.7%)	0.01
Race, n (%)			
Caucasian	111 (95.7%)	72 (100%)	0.07
African	3 (2.5%)	0 (0%)	
Asian	1 (0.9%)	0 (0%)	
Hispanics	1 (0.9%)	0 (0%)	
Affected organs, n (%)			
Lung	69 (59.5%)	53 (73.6%)	0.07
Lymph node	67 (57.8%)	51 (70.8%)	0.16
Skin	27 (23.3%)	25 (34.7%)	0.06
Eye	12 (10.3%)	13 (18.1%)	0.06
Liver	13 (11.2%)	6 (8.3%)	0.10
Peripheral/central nervous system	8 (6.9%)	7 (9.7%)	0.12
Musculoskeletal	5 (4.3%)	5 (6.9%)	0.43
Löfgren syndrome, n (%)	7 (6.0%)	3 (4.2%)	0.16
Cardiac symptoms			
Chest pain, n (%)	27 (23.3%)	21 (29.2%)	0.61
Dizziness, n (%)	27 (23.3%)	24 (33.3%)	0.27
Syncopal episode, n (%)	4 (3.4%)	4 (5.6%)	0.49
Fatigue, n (%)	35 (30.2%)	33 (45.8%)	0.60
Dyspnoea, n (%)	41 (35.3%)	32 (44.4%)	0.09
Medical treatment at CMR conduction, n (%)	47 (40.5%)	29 (40.3%)	0.86
Equivalent prednisone dose at CMR conduction, mg	7.60 ± 13.05	5.13 ± 10.48	0.21

Data are presented as mean ± SD or total number and percentage (in parentheses).

provenance. Mean duration since diagnosis of sarcoidosis averaged 114 months (median 73 months). Pulmonary sarcoidal involvement was present in 64.9%; main extrapulmonary manifestation is depicted in Table 2.

The percentage of patients in whom a cardiac involvement had already been diagnosed prior to CMR conduction, solely accounted for 0.5% (n=1). Löfgren syndrome was present in 5.3% of patients, none of whom exhibited cardiac sarcoidal manifestation.

CMR identified cardiac sarcoidosis (CS) based on the presence of early relative gadolinium enhancement, regional oedema or late gadolinium enhancement in 15.4% of the whole study population (Figure 1). Correlation analyses evinced no differences in CS prevalence in terms of ethnicity (p=0.93). Pearson's χ^2 test revealed a significant dependence of CS occurrence on concomitant lymph node affection (p=0.013), whereas there was no association between CS and other sarcoidal organ involvement.

Distribution analysis of most late enhancing lesions identified mid to basal inferoseptal ventricular areas to be predilectively affected (Figure 2), a result that is in line with prior reports (9,17). Differentiation as a function of disease activity resulted in a distribution of 9% (n=17) offering acute, inflammatory changes, 5.9% (n=11) having myocardial scar and 0.5% (n=1) presenting both acute and chronic phase cardiac abnormalities. CMR- follow up study was carried out in 12 out of 29 patients (41.4%). In four patients, medical immunosuppressive treatment was meanwhile escalated (steroidal dosage increase, addition of azathioprine), resulting in a regredience of early relative gadolinium enhancement in all four patients. None of the eight remaining patients without medication adjustment developed aggravation of CMR-stated cardiac affection: 7 patients presented consistent findings,

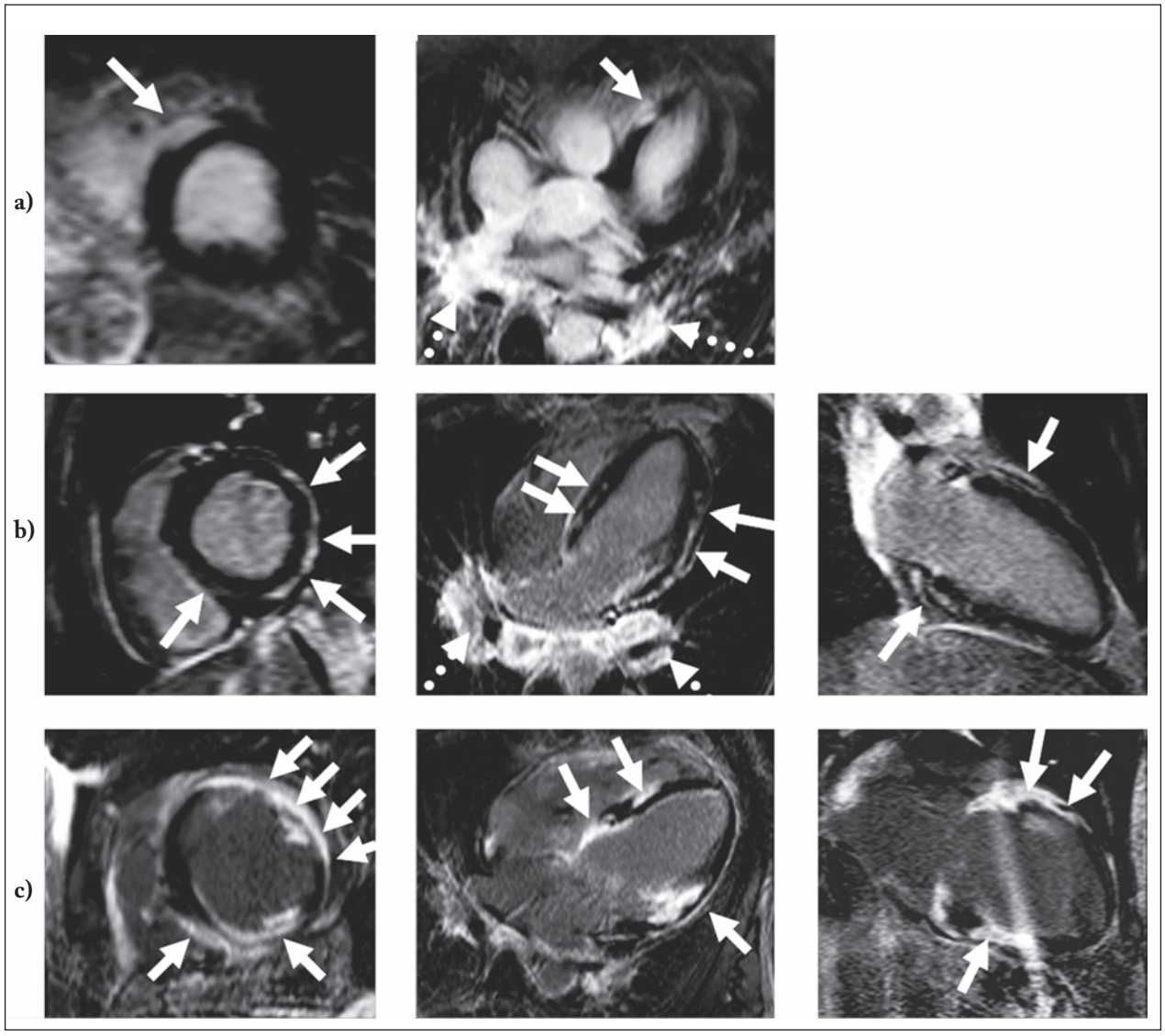

Fig. 1. Typical examples of cardiac involvement detected by CMR. Panel **a** through **c** are showing various extends of cardiac involvement in the short-, horizontal-, and vertical-long axis (from left to right). In case **a**, mild subepicardial and midmyocardial involvement is seen at the midventricular level. Case **b** reveals extensive subepicardial as well as midmyocardial involvement. Note, there is substantial enlargement of the LV-cavity as a consequence of diffuse involvement in case **c**. Arrows with full line pointing at LGE, arrows with dotted line point at enlarged lymph nodes.

while 1 patient showed spontaneous remission of early relative contrast enhancement.

CMR-assessed global cardiac function parameters and volumes are given in Table 4 and revealed significant correlation of CS-status with mean left ventricular ejection fraction (LVEF) and diastolic interventricular septal thickness (IVSD) (p=0.03 and p=0.03, respectively; Table 4).

Electro- and echocardiographic data were available for 146 (77.7%) and 132 patients (70.2%), respectively. 12-lead ECG changes that were identified to correlate with the presence of cardiac sarcoidosis, comprised third-degree atrioventricular block (p=0.02), pathological Q-waves (p=0.02), incomplete left bundle branch block (p=0.02) and QRS fragmentation (p=0.02). Holter monitoring

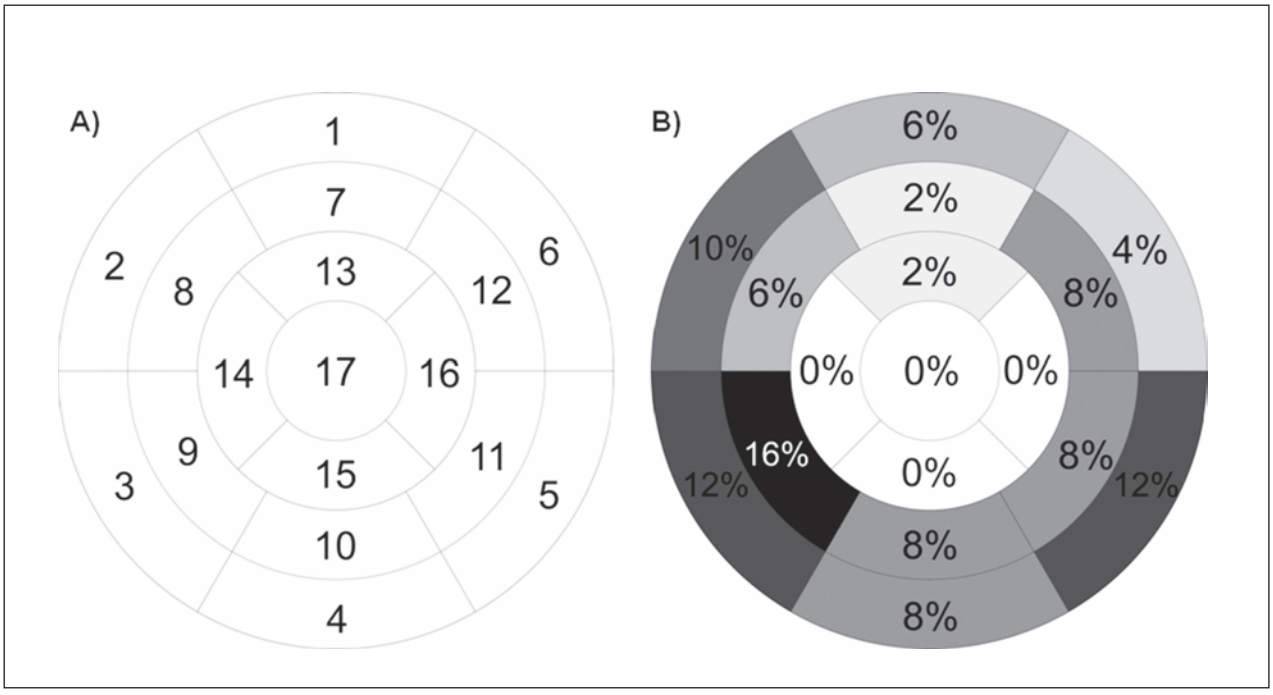

Fig. 2. a Illustration of late enhancing myocardial segments according to bull's eye plots of ventricular segmentation (16) and **b** percentage distribution in the 188 studied patients

evidenced a burden of > 1000 ventricular extrasystoles/24h to be significantly associated with CS (p=0.002).

In terms of echocardiographic assessment, diastolic dysfunction ≥ I° and reduction of LVEF <50% were found to be the only echocardiographic abnormalities that correlated with cardiac sarcoidosis (p=0.04 and p=0.02, respectively).

By laboratory analysis, none of the tested parameters showed significant distributive differences between the CS-positive and the CS- negative cohorts (Table 4). Likewise, pulmonary function parameters exhibited no association with CS and were similar in both groups.

Discussion

The present study prospectively analysed the frequency of CMR-detected cardiac sarcoidal involvement in a large, almost exclusive Caucasian study population with histologically proven sarcoidosis. Prevalence of CMR-based cardiac affection was identified to account for 15.4%. The predictive value of parameters assessed by standard clinical testing and specified by the current guidelines emerged to be moderate.

Despite lacking gold standard, CMR-guided diagnosis of cardiac sarcoidosis by assessment of late gadolinium enhancement (LGE) constitutes the favoured diagnostic approach. Patel et al. compared LGE-CMR to the then valid consensus criteria and identified LGE-stated cardiac sarcoidosis in 26% of sarcoidal patients (9). Comparison with our data emphasizes a substantially higher CS prevalence in Patel's cohort. This discrepancy may be due to Patel´s predominantly African American study population of 73% which in turn is known to experience a higher sarcoidosis occurrence that can possibly be extrapolated to cardiac affection. In a Dutch study cohort (18), Smedema et al. complemented the 1993 modified Japanese Ministry of Health and Welfare Guidelines (JMHWG) (19) with LGE-CMR for diagnosis of CS and determined a LGE-CMR-based CS prevalence of 32.8%. This discrepancy from our finding can primarily be traced back to

Table 4. Data comparison of patients with and without CS

	CMR-based diagnosis of cardiac sarcoidosis (n=29)	CMR-based exclusion of cardiac sarcoidosis (n=159)	p-value
Age, years	49 ± 12	52 ± 13	0.36
Female gender, n (%)	12 (41.4%)	92 (57.9%)	0.10
Race, n (%)			
Caucasian	29 (100%)	154 (96.9%)	0.93
African	0 (0%)	3 (1.9%)	
Asian	0 (0%)	0 (0%)	
Hispanics	0 (0%)	0 (0%)	
Löfgren syndrome, n (%)	0 (0%)	10 (6.3%)	0.21
Cardiac symptoms			
Chest pain, n (%)	10 (34.5%)	38 (23.9%)	0.09
Dizziness, n (%)	7 (24.1%)	44 (27.7%)	0.99
Syncopal episode, n (%)	2 (6.9%)	6 (3.8%)	0.06
Fatigue, n (%)	7 (24.1%)	61 (38.4%)	0.31
Dyspnoea, n (%)	9 (31.0%)	64 (40.3%)	0.85
Pulmonary function parameters			
FEV1, l	3.02 ± 0.92	2.97 ± 0.99	0.86
FEV1, % predicted	90.48 ± 17.49	91.32 ± 19.25	0.86
IVC, l	3.72 ± 1.06	3.50 ± 1.19	0.46
IVC, % predicted	88.59 ± 15.07	86.18 ± 18.75	0.60
DLCO, mmol/min/kPa	6.95 ± 2.70	6.39 ± 2.22	0.34
DLCO, % predicted	70.16 ± 19.84	66.66 ± 18.27	0.45
DLCO/VA, mmol/min/kPa/l	1.37 ± 0.30	1.41 ± 0.34	0.63
DLCO/VA, % predicted	90.17 ± 20.01	90.96 ± 21.68	0.88
CMR imaging variables			
LVEF, %	63.8 ± 9.9	67.1 ± 6.9	0.03
IVSD, mm	10.5 ± 1.5	9.7 ± 1.7	0.03
LVEDV, ml	117.4 ± 46.0	113.7 ± 25.4	0.05
ECG pathologies			
Abnormal Q-wave	3 (10.3%)	3 (1.9%)	0.02
Advanced atrioventricular block	1 (3.4%)	0 (0%)	0.02
Axis deviation	2 (6.9%)	7 (4.4%)	0.56
QRS fragmentation	1 (3.4%)	0 (0%)	0.02
Incomplete RBBB	3 (10.3%)	0 (0%)	0.46
Complete RBBB	3 (10.3%)	0 (0%)	0.46
Incomplete LBBB	1 (3.4%)	0 (0%)	0.02
Complete LBBB	0 (0%)	0 (0%)	
Holter monitoring pathologies			
Supraventricular arrhythmia	3 (10.3%)	8 (5.0%)	0.26
>1000 VES/24 hours	4 (13.8%)	3 (1.9%)	0.002
Ventricular tachycardia	0 (0%)	2 (1.3%)	0.54
Echocardiographic pathologies			
LVEF<50%	1 (3.4%)	0 (0%)	0.02
Diastolic dysfunction ≥ I°	9 (31.0%)	24 (15.1%)	0.04
Regional abnormal wall motion	1 (3.4%)	2 (1.3%)	0.39
Ventricular aneurysm	0 (0%)	0 (0%)	
Wall thickening	0 (0%)	2 (1.3%)	0.54

(continued)

Table 4. Data comparison of patients with and without CS

	CMR-based diagnosis of cardiac sarcoidosis (n=29)	CMR-based exclusion of cardiac sarcoidosis (n=159)	p-value
Laboratory parameters			
Leucocytes, G/l	7.26 ± 2.52	6.67 ± 2.59	0.28
CRP, mg/l	6.66 ± 15.36	3.96 ± 5.87	0.12
ACE, U/l	41.82 ± 35.85	41.31 ± 27.25	0.93
sIL-2R, U/ml	835.59 ± 457.38	823.73 ± 1402.72	0.97
cTnI, ng/ml	0.02 ± 0.02	0.02 ± 0.02	0.96
NT-proBNP, pg/ml	82.27 ± 135.76	128.64 ± 278.41	0.41

Data are presented as mean ± SD or total number and percentage (in parentheses).
Abbreviations: FEV1 = forced expiratory volume in 1 second; IVC = inspiratory vital capacity;
DLCO = diffusion capacity for carbon monoxide; VA = alveolar volume; LVEF = left ventricular ejection fraction
IVSD = interventricular septum dimension; LVEDV = left ventricular end diastolic volume; RBBB = right bundle branch block
LBBB = left bundle branch block; VES = ventricular extrasystoles; CRP = C-reactive protein; ACE = angiotensin converting enzyme
sIL-2R = soluble Interleukin-2 receptor; cTnI = cardiac troponin I; NT-proBNP = N-terminal pro-BNP

Smedema´s inclusion of a substantial portion of patients presenting cardiac symptomatology at CMR conduction that in turn augmented the probability of diagnosing CS. Moreover, our study population comprised a >3-fold larger number of patients, indicating a minor susceptibility to statistical outliers.

In contrast to the above mentioned studies that almost exclusively analysed LGE in CMR, we incorporated T2-weighted imaging as well as early relative gadolinium enhancement. Whereas LGE assesses predominantly nonviable- fibrotic or necrotic-tissue and is indicative of poor prognosis (20), T2 imaging and early relative gadolinium enhancement detect acute inflammatory injury resulting in myocardial oedema or hyperperfusion. Schulz-Menger et al. previously reported correlation of early relative contrast enhancement in patients with suspected cardiac sarcoidal involvement that normalized after steroid treatment (15). In a population of 16 patients presenting systemic sarcoidosis, Shimada et al. identified early enhancing lesions that were likewise regredient after glucocorticoid therapy (21). Both studies imply the value of early local and global contrast enhancement in viable myocardium that may mainly occurs in early CS stages. In equal manner to the above depicted courses, we objectified early relative enhancement regression under steroid treatment which permits application of early gadolinium imaging for guidance of medical therapeutic management. Quantitative T1 mapping has now emerged as a robust clinical tool for myocardial tissue characterization and may be superior to assessment of relative early gadolinium enhancement (22). However, its value for sarcoidosis evaluation needs yet to be established.

Over a ten-year period, Greulich and colleagues enrolled and examined 155 patients with clinically suspected cardiac sarcoidosis by CMR-guided LGE-assessment and ascribed prognostic relevance to the presence of LGE (20). Contrary to Greulich´s study cohort, we presupposed biopsy-proven sarcoidosis for study inclusion, while Greulich accepted a clinical criteria-based diagnosis of sarcoidosis. Moreover, we consciously included all sarcoidal patients irrespectively of any cardiac symptomatology or previously detected cardiac affection in order to prevent preselection and provide insights into actual CS prevalence in the general sarcoidal population, even in patients lacking cardiac symptoms. A further difference to the above mentioned study constitutes our complemental assessment of early relative contrast enhancement that enabled us to evaluate myocardial changes and their medical influenceability in the early phases of CS.

Clinical manifestation of CS covers the entire range of silent course up to sudden cardiac death. Given its frequently prognosis-limiting nature, the necessity for a precise diagnostic methodology to define CS presence and guide CS therapy arises. Principally based on the JMHWG, revised in 2009 and serving as a global CS diagnostic standard (11), the German Respiratory and Cardiac Societies recently published a consensus paper that provides diagnostic and therapeutic algorithms for CS (12). In previously diagnosed extracardiac sarcoidosis, it suggests a stepwise approach with the initial evaluation includ-

ing 12-lead ECG, 24-h ECG and transthoracic echocardiography. In case of predefined abnormalities by initial evaluation, additional non-invasive imaging via CMR or 18F-Fluorodeoxyglucose (FDG)-PET is recommended, with pathological findings allowing for the final diagnosis of CS. We identified a ventricular extrasystolic (VES) load > 1000 VES/24h, third-degree atrioventricular block, Q-waves, incomplete left bundle branch block and QRS fragmentation to significantly correlate with CMR-proven CS, the first three and first four electrocardiographic findings satisfying the JMHWG and German consensus criteria, respectively, and underlining their diagnostic value. Subgroup analysis on the basis of CMR-stated pathology acuteness evinced occurrence of electrocardiographic pathologies in acute as well as chronic CS stages. This is in line with Crouser et al. (23) who described ECG abnormalities to be significantly associated with both myocardial T2 mapping as well as pathological LGE-CMR.

The sole echocardiographic abnormalities that exhibited significant correlation with CMR findings were presence of diastolic dysfunction graded ≥ I and reduction of left ventricular ejection fraction (LVEF) <50%; the latter is integrated in the CS baseline assessment of the JMHWG and the German guidelining statement. Nonetheless, neither interventricular basal septum thinning, nor wall motion abnormalities, nor valvular dysfunction - all of which represent further established JMHWG criteria - were linked to CMR-stated CS. Vice versa, recognition of cardiac involvement by application of German consensus paper that envisages a stepwise approach and CMR- or FDG-PET-conduction under the premise that prior ECG- and TTE-assessment ascertains at least one pathological finding, would have solely permitted identification of 48.3% (14 out of 29 patients) of the present CMR-diagnosed cardiac sarcoidosis cases. Comparably, appliance of revised JMHWG in our cohort would have enabled us to only diagnose one affected patient owing to endomyocardial biopsy. In case of lack or incongruity of cardiac histology, the JMHWG-based CS diagnostic pathway would have failed to detect 28 out of 29 presently diagnosticated CS cases, admittedly with the restriction that we did not perform radionuclide myocardial imaging. In due consideration of the above mentioned crucial CS-underrecognition, necessity of up valuing CMR in the CS diagnostic approach becomes evident.

The value of laboratory blood tests in CS has been indeterminate. Date and colleagues described plasma brain natriuretic peptide (BNP) to be significantly elevated in patients with CS, compared to a pulmonary sarcoidosis cohort, and ascribed diagnostic utility to this biomarker (24). However, these authors based their diagnosis of CS solely on the 1993 published JMHWG (19) which in turn have been demonstrated to be significantly less sensitive for CS-detection than CMR (9) and might therefore have contributed to a bias in their patient group assignment in an already small numbered total cohort of 21 participants.

In our study, none of the tested laboratory parameters revealed significant correlation with CMR-based CS, not even if only cases with acute inflammed tissue damage were examined. Established laboratory values for extracardiac sarcoidal inflammatory processes (sIL-2R) and granulomatous burden (ACE) lacked association with CS diagnosis or severity, a finding that to our knowledge is first described in the present study. Laboratory testing is conclusively non-diagnostic in CS and thereby consistent with the current diagnostic standards.

There are several limitations to be considered. Our study population was composed of two different patient provenances comprising outpatients treated by the local pneumological department and patients linked to the nationwide sarcoidosis self-help association. However, except for gender distribution, data comparison did not reveal statistically significant intercohortal differences in demographic characteristics. In respect of availability of ECG and TTE we have to recognize that only the locally treated patient group exhibited complete database, whereas the percentage of association-recruited patients presenting 12-lead ECG, ambulatory ECG monitoring and TTE was 41.7%, 12.5% and 22.2%, respectively.

Despite the large study population size, the number of CMR-detected CS encompassing both early and late disease stages was small, limiting an extrapolation of the observed correlation of electro- and echocardiographic abnormalities to the different disease stages. Although present CS-rate distribution did not exhibit significant interethnic differences, it is primarily ascribable to the limited number of Non-Caucasian participants that in turn is

due to pour study concept of investigating CS in a mainly Caucasian cohort.

Conclusively, with a prevalence of 15.4%, CMR-detected cardiac sarcoidal involvement in a primary Caucasian sarcoidosis patients exceeds the observationally reported cardiac affection three times over. However, cardiac involvement as detected by clinical standard testing as well as magnetic resonance imaging appears to be less frequent in the presently examined Caucasian sarcoidosis population than in previously studied Japanese or African American cohorts.

With the intend to evaluate the prognostic potential of CMR results, additional longitudinal follow-up of this study cohort for evaluating the occurrence of arrhythmic events or progressive heart failure would help to definitely determine the significance of CMR in CS and would permit a timely initiation of medical or device therapeutic approaches.

Acknowledgements

The authors would like to acknowledge the invaluable assistance of Bernd and Hildegard Stachetzki who chair "Sarkoidose-Netzwerk e.V.", a German sarcoidosis self-help association, and enabled us to conduct this large numbered trial.

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-65.
2. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 1997; 145: 234-41.
3. Johns CJ, Michele TM. The clinical management of sarcoidosis. A 50-year experience at the Johns Hopkins Hospital. Medicine (Baltimore) 1999; 78: 65-111.
4. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 1978; 58: 1204-11.
5. Gideon NM, Mannino DM. Sarcoidosis mortality in the United States 1979-1991: an analysis of multiple-cause mortality data. Am J Med 1996; 100: 423-7.
6. Baughman RP1, Winget DB, Bowen EH, Lower EE. Predicting respiratory failure in sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 1997; 14: 154-8.
7. Banba K, Kusano KF, Nakamura K, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. Heart Rhythm 2007; 4: 1292-9.
8. Yazaki Y, Isobe M, Hiroe M et al; Central Japan Heart Study Group. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol 2001; 88: 1006-10.
9. Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. Circulation 2009; 120: 1969-77.
10. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol 2006; 17: 2359-62.
11. Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. J Cardiovasc Electrophysiol 2009; 20: 578-83.
12. Costabel U, Skowasch D, Pabst S, et al. Cardiac sarcoidosis: diagnostic and therapeutic algorithms. Pneumologie 2014; 68: 124-32.
13. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC, Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16: 41-52.
14. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E; Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 2008; 10: 35.
15. Schulz-Menger J, Wassmuth R, Abdel-Aty H, et al. Patterns of myocardial inflammation and scarring in sarcoidosis as assessed by cardiovascular magnetic resonance. Heart 2006; 92: 399-400.
16. Cerqueira MD, Weissman NJ, Dilsizian V, et al; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segementation and nomenclature for tomographic imaging of the heart. Circulation 2002; 105: 539-42.
17. Vignaux O. Cardiac sarcoidosis: spectrum of MRI features. AJR 2005; 184: 249-54.
18. Smedema JP, Snoep G, van Kroonenburgh MP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol 2005; 45: 1683-90.
19. Hiraga H, Yuwai K, Hiroe M. Guideline for the Diagnosis of Cardiac Sarcoidosis: Study Report on Diffuse Pulmonary Diseases (in Japanese). Jpn Ministry Health Welfare 1993; 23-4.
20. Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. JACC Cardiovasc Imaging 2013; 6: 501-511.
21. Shimada T, Shimada K, Sakane T, et al. Diagnosis of cardiac sarcoidosis and evaluation of the effects of steroid therapy by gadolinium-DTPA-enhanced magnetic resonance imaging. Am J Med 2001; 110: 520-7.
22. Ferreira VM, Piechnik SK, Robson MD, Neubauer S, Karamitsos TD. Myocardial Tissue Characterization by Magnetic Resonance Imaging: Novel Application of T1 and T2 Mapping. J Thorac Imaging 2014; 29: 147-54.
23. Crouser ED, Ono C, Tran T, He X, Raman SV. Improved detection of cardiac sarcoidosis using magnetic resonance with myocardial T2 mapping. Am J Respir Crit Care Med 2014; 189: 109-12.
24. Date T, Shinozaki T, Yamakawa M, et al. Elevated plasma brain natriuretic peptide level in cardiac sarcoidosis patients with preserved ejection fraction. Cardiology 2007; 107: 277-80.