

Cardiac involvement in sarcoidosis

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Sarcoidosis is a systemic disease of unknown aetiology characterised by the formation of noncaseating epithelioid cell granulomas, which can occur in virtually any organ. Cardiac involvement is of critical importance, due to the poor prognosis if this organ manifestation is left undiagnosed and untreated. Early initiation of therapy seems to be associated with a good prognosis; therefore, the diagnosis of cardiac sarcoidosis should be made before irreversible damage has occurred. Nevertheless, the diagnosis of cardiac sarcoidosis still remains "an imperfect science, a hesitant art" [1].

Epidemiology

Cardiac sarcoidosis was first described by BERNSTEIN *et al.* [2] in an autopsy case. A period of 4 yrs later, SCHAUAMANN [3] demonstrated cardiac involvement in two further autopsy cases. In 1937, GENTZEN [4] reported about giant cell granulomas in two patients with endomyocardial fibrosis, which was the first publication of death due to cardiac sarcoidosis. Until 1980, literature reports were limited to mainly anecdotal descriptions of single or small numbers of patients. Clinically apparent cardiac involvement has since been noted in 2–10% of patients with proven sarcoidosis [1, 5–18]. Prior to the introduction of echocardiography, the distinction from cor pulmonale was probably imprecise. Since modern diagnostic tools, such as echocardiography, nuclear scan or magnetic resonance imaging (MRI), have become available, higher rates of patients with cardiac sarcoidosis have been reported. Nevertheless, the rate still remains influenced by the selection of the patients and the differences in the local health system [10, 12, 19–28].

The highest rates of cardiac involvement (from 20–78%) are found in necropsy series [6, 7, 22, 29–37]. In 1978, SILVERMAN *et al.* [30] analysed 84 consecutive autopsies in patients who died due to sarcoidosis at John Hopkins Hospital (Baltimore, MD, USA) between 1899 and 1977. They detected granulomas in the heart of 27% of the patients [30]. Similar frequencies of 20% and 19.5% were reported by LONGSCOPE and FREIMAN [32] and SHARMA *et al.* [6] in a series of 92 and 123 autopsied cases, respectively.

Apparently, there are differences in the presentation of the disease between patients from Europe and America and those from Japan. Japanese pathologists reported much higher rates of cardiac involvement, reaching as much as 50–78% [31–35, 38–40]. Whereas in the USA 13–50% of all sarcoidosis deaths have been attributed to cardiac involvement [33, 35], in Japan up to 85% of all deaths have been related to heart involvement [31, 40]. A retrospective clinical study from Haifa, Israel showed that only two out of 120 patients with sarcoidosis died due to cardiac involvement [20].

A questionnaire sent to 651 sarcoidosis-affected members of the German Sarcoidosis Patients Union (Deutsche Sarkoidose Vereinigung; see Appendix) revealed cardiac sarcoidosis in only 8% [11]. In this survey, the latency between the first symptoms, or first abnormal medical findings, and the ultimate diagnosis amounted for up to 7 yrs [11].

The involvement of the heart often remains subclinical, especially in patients with sudden cardiac death, as the changes in the heart are often just detected *post mortem* [1, 8, 22, 29–31, 33, 36, 37]. Cardiac sarcoidosis seems to be more frequent in younger patients and can also affect adolescents [19, 34–36].

The course of the cardiac and thoracic manifestations of sarcoidosis may not necessarily be concomitant. Cardiac sarcoidosis may occur at any point in time during the course of sarcoidosis, may occur in the absence of pulmonary or other organ involvement, or may be the initial presentation. In the follow-up of 52 patients with cardiac sarcoidosis from Bad Berka, the central sarcoidosis clinic of former Eastern Germany, in one-third of the cases the cardiac involvement became apparent only after the pulmonary changes had normalised [21]. Cardiac sarcoidosis should also be presumed in young individuals with unclear cardiac arrhythmias or dysfunction where it may be the first and only disease manifestation.

Cardiac sites of involvement

In principle, all cardiac structures can be involved (table 1) [29–54]. Most often the changes affect the conduction system and the myocardium [29] (figs 1 and 2). A valvular dysfunction mainly presents as mitral insufficiency and is usually the result of a granulomatous infiltration of the corresponding papillary muscle or a change in the ventricular architecture [46]. Direct involvement of the mitral valve is very rare, and of the other valves even more uncommon (<3%) [8, 13, 29].

Circumscribed myocardial involvement mostly presents as local hypertrophy or dyskinesia of the myocardium. In the further course, myocardial scarring and remodelling replaces the active granuloma, resulting in dilatation of the left ventricle, local hypokinesia or aneurysms (in 8–10%) [6, 7]. Diffuse involvement of the myocardium results in dilated cardiomyopathy, global hypokinesia, and left ventricular failure [6, 14, 41, 42, 45]. Cardiac sarcoidosis can also mimic right ventricular dysplasia [55, 56]. The myocardial lesions are occasionally associated with an active granulomatous arteritis of the coronary arteries [7].

Involvement of the conducting system or the septum results in bradycardic arrhythmias or conduction disturbances, such as variable degrees of atrioventricular (AV) block or bundle branch block [7, 8, 29]. Clinically, completely healed scars still

Table 1. – Manifestations of cardiac sarcoidosis

Clinical manifestation	Histology
Asymptomatic granulomas	Incidental granulomas in the myocardium
Conduction defects (e.g. bundle branch block)	Granulomatous or fibrotic involvement of the conduction system
Atrial arrhythmias	Ventricular dysfunction, pulmonary arterial hypertension, myocardium or nerve involvement
Mitral insufficiency	Papillary muscle dysfunction
Ventricular aneurysms	Myocardial fibrosis
Ventricular tachyarrhythmias	Granulomas or scars in the myocardium
Congestive heart failure	Remodelling of the heart by inflammatory or fibrotic processes.
Pericardial effusions or fibrosis	Inflammation, fibrosis and/or fluid in the pericardium

Adapted from [18].

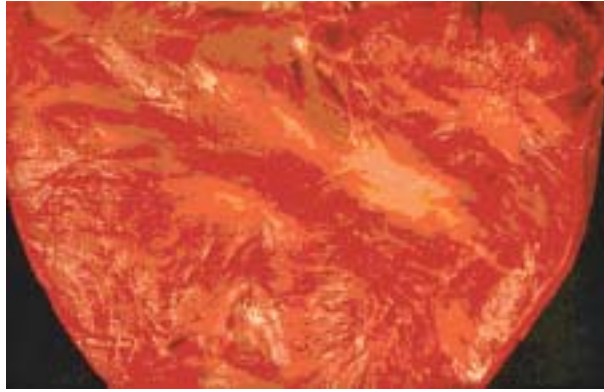


Fig. 1. – Macroscopic view of a left ventricle with cardiac sarcoidosis.

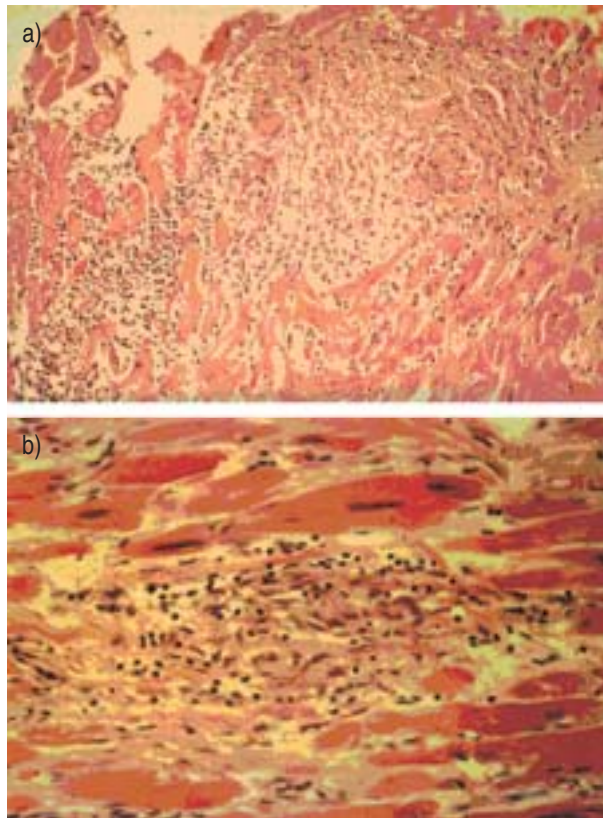


Fig. 2. – Microscopic view of myocardial granulomas in sarcoidosis. a) low power; b) high power view.

represent an arrhythmogenic substrate that can promote arrhythmias by micro-re-entry. Granulomas are most often found in the septum and the free wall of the left ventricle, and rarely seen in the myocardium of the atrium or right ventricle due to the minor amount of muscle [29]. Therefore, supraventricular arrhythmias most likely result from

atrial dilatation, secondary to ventricular dysfunction, than from granulomatous infiltration of the atrial myocardium [8, 29].

Infiltration of the pericardium may lead to pericardial effusions and fibrosis [29, 53–54]. Constrictive pericarditis has also been described [44]. Pericardial effusions can be detected by echocardiography in 10–21% of patients with pulmonary or systemic sarcoidosis, even in the absence of cardiac symptoms [54, 57].

Diagnostic approach

Many diagnostic tests can be performed in the assessment of patients suspected of suffering from cardiac sarcoidosis. They all have their own advantages and disadvantages. The present authors propose a stepwise diagnostic approach, starting with easy and widely accessible tests and ending with the more expensive and invasive procedures (table 2).

ECG

NUMAO *et al.* [47] observed pathological findings in the 12-lead ECG in 22% of 963 Japanese patients with sarcoidosis, but also in 17% of a control group of healthy persons with the same distribution of age and sex. CHAPELON-ABRIC *et al.* [58] found ECG abnormalities in 22% of 41 patients with cardiac sarcoidosis compared with 77% who had abnormal echocardiographies. The study by FLEMING *et al.* [7] of 300 patients with cardiac sarcoidosis in England revealed ventricular arrhythmias in 45%, conduction disturbances in 38%, supraventricular arrhythmias in 28%, and sudden cardiac death in 16%.

The prevalence of ECG changes seems to be related to the severity of the disease. SILVERMAN *et al.* [30] compared clinical data with autopsy findings. Only 15% of the patients without cardiac involvement at autopsy had ECG abnormalities. This proportion increased to 42% in patients with mild cardiac involvement (visible only on microscopy), and to 75% in patients with severe involvement (gross evidence of granulomas or infiltration). A comparison between Swedish and Japanese patients did not show significant differences in the frequency and type of ECG changes [51]. Taken from these series, ~20–40% of patients with sarcoidosis have detectable ECG

Table 2. – Diagnostic approach in the evaluation of cardiac sarcoidosis

Step 1	ECG Routine procedure in each patient with sarcoidosis In case of no abnormality and no complaints stop
Step 2	Holter monitor and echocardiography In case of ≥ 1 abnormalities, perform ≥ 1 of the following dependent on the availability in the clinical setting
Step 3	MRI: useful in detecting granulomas and/or fibrosis Thallium or other nuclear scans: useful in assessing ischaemia, necrosis or granulomas MIBG scan: useful in detecting autonomic dysfunction PET scan: useful in detecting granulomas Coronary angiography: useful in excluding coronary artery disease
Step 4	Endomyocardial biopsy In the case of no other histological confirmation of sarcoidosis and of no clinical picture compatible with sarcoidosis. If there is already biopsy confirmation of sarcoidosis in any other tissue of the body, there is no indication for a biopsy of the heart

MRI: magnetic resonance imaging; MIBG: I-123 meta-iodobenzylguanidine; PET: positron emission tomography.

abnormalities. More sophisticated ECG measurements, such as late potentials or heart rate variability, are nonspecific and do not play a role in the diagnostic or prognostic assessment.

Exercise ECG and exercise testing (spiroergometry) seem to be more sensitive than the resting ECG, and are more helpful in discriminating a myocardial ischaemia or to differentiate between cardiovascular and pulmonary limitations [6, 48–51]. A reduced increase of the heart rate with exercise has been reported [52]. Often exercise performance and peak oxygen uptake are much better than expected from the ejection fraction (EF) of the left ventricle. This is already explained by the fact that the myocardium is not damaged diffusely and there is still healthy muscle around the granulomas in all parts of the ventricular wall. The present authors perform an exercise test in all patients with severely reduced left ventricular function. The result enables us to recommend the amount of physical activity to the patients and estimate the necessity of listing for heart transplantation. Furthermore, exercise testing allows a reliable measurement of the therapeutic effects (table 3).

24-h Holter monitoring is important for the diagnosis and for risk estimation. In a prospective study of 38 patients with sarcoidosis referred to a cardiology clinic, 67% of the 12 patients with confirmed cardiac involvement had >100 extra ventricular beats·day⁻¹ versus only 8% of the 26 patients without cardiac sarcoidosis and only 5% of a control group of 58 healthy individuals [49]. The Holter ECG plays a crucial role in defining the indications for an antibradycardic pacemaker, as well as the implantation of an internal defibrillator. Any abnormality on Holter monitoring or ECG should be further evaluated by echocardiography and/or other studies.

Echocardiography

Echocardiography is a useful noninvasive method to demonstrate morphological as well as functional changes of the heart (figs 3 and 4). Due to low costs and high availability, it is particularly well suited for follow-up examinations. The sensitivity can further be improved by performing a stress-echocardiography, tissue Döppler technique or using pulmonary capillaries passing contrast fluid [59]. Echocardiography has been reported to show pathological findings in 14–77% of the patients with sarcoidosis, and also in patients with a normal ECG [24, 26, 27, 53–59]. Many of the older studies on this topic have been published in the 1980s, when the available ultrasound equipment was far

Table 3. – Results of exercise testing and echocardiography in a 45-yr-old female with proven cardiac sarcoidosis, normal lung function tests and no other disease[#]

	Before treatment	After 9 months of treatment with 10–40 mg prednisolone and biventricular pacemaker
Ejection fraction %	20	45
Diameter LV mm	77	54
Diameter RV mm	32	27
VO ₂ peak mL·kg ⁻¹ ·min ⁻¹	980	1170
VO ₂ peak·kg ⁻¹	16.1	19.5
Maximum load W	88	100
Maximum HR 1·min ⁻¹	145	105
RQ	1.3	1.4
T _L CO	75	80

LV: left ventricle; RV: right ventricle; VO₂: maximal oxygen uptake; HR: heart rate; RQ: respiratory quotient; T_LCO: transfer factor of the lung for carbon monoxide. [#]: VO₂ in the first test was much better than expected from echocardiography; the improvement in the second test only minor compared with the marked improvement of the ejection fraction, partly explained by an abnormally low increase of the HR under exercise.

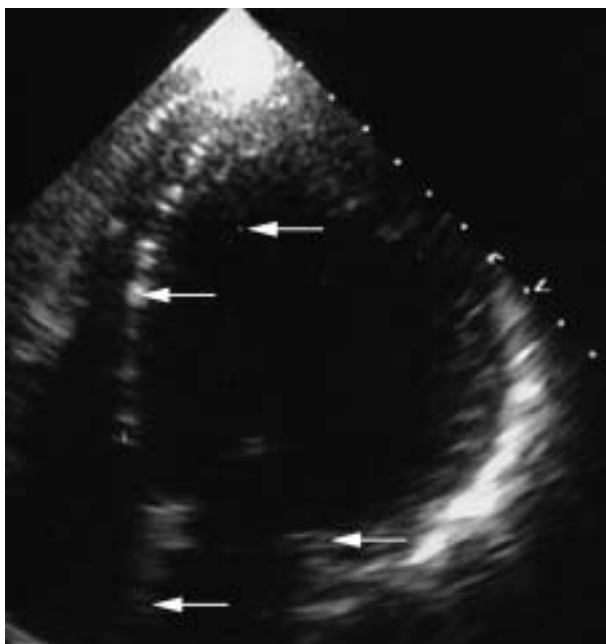


Fig. 3. – Echocardiography in proven cardiac sarcoidosis. Dilated left ventricle. The septum is thinned and shows echo-dense dots like pearls on a string, interpreted as local scarring. Arrows point to, from top to bottom, the left ventricle, septum, mitral valve and left atrium, respectively.

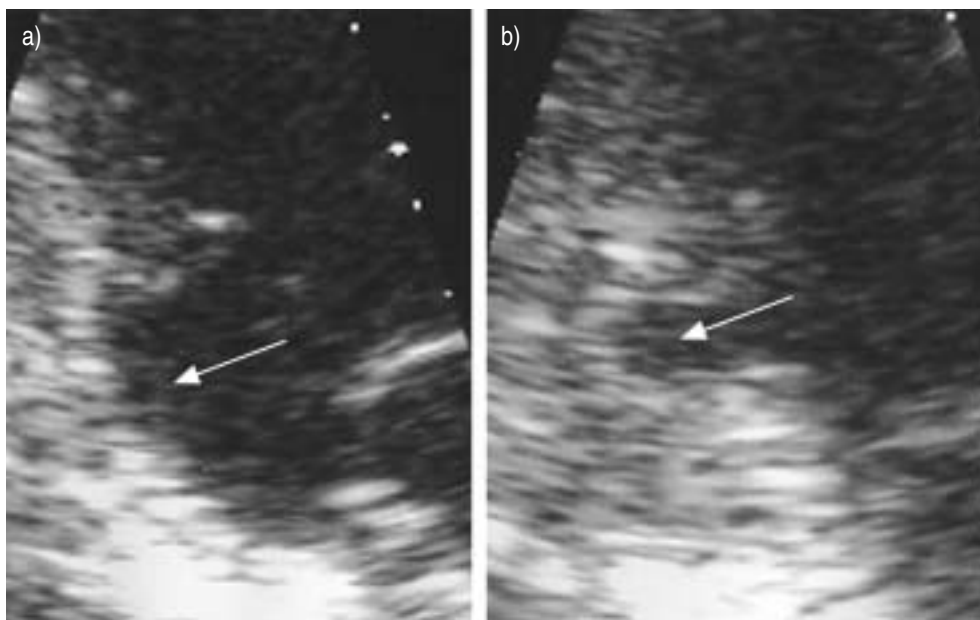


Fig. 4. – Echocardiography of the posterior wall of the left ventricle, showing a very circumscribed akinesia of ~1 cm. In a) diastole, the arrow points to the bulged wall of the left ventricle, postero-basal, and in b) systole, the arrow points to circumscribed akinesia at the upper end of the bulged area, stimulating an aneurysm of 1 cm diameter.

less sophisticated and of less optimal resolution than today. In the opinion of the current authors, echocardiography should be one of the basic examinations in the evaluation and follow-up of patients with sarcoidosis.

YAZAKI *et al.* [60] compared 15 patients with cardiac sarcoidosis and 30 patients with idiopathic dilated cardiomyopathy (DCM). A total of 73% of the patients with sarcoidosis had circumscribed thinning or thickening of the wall of the left ventricle, usually of the septum. An involvement of the septum was always accompanied by an AV conduction disturbance or block. In the patients with DCM, just 17% showed a circumscribed widening of the wall, but never a regional hypertrophy. Many other diseases, such as valve dysfunction, cor pulmonale, hypertrophic cardiomyopathy or amyloidosis can usually be well differentiated by ultrasound scan due to typical or pathognomonic features. In patients with proven cardiac sarcoidosis, a diastolic dysfunction is reported for approximately half of all patients in studies with echocardiography, as well as with MRI of the heart [61].

Radionuclide imaging

Myocardial imaging with ^{201}Tl has been most frequently used and investigated in patients with suspected sarcoidosis. This radionuclide is absorbed by the living heart muscle cell. Areas with scars, necrosis, ischaemia or inflammation accumulate less ^{201}Tl and appear as cold spots. In cardiac sarcoidosis, the segmental defects detected at rest are reversible or decrease in size on delayed scans or with exercise, dipyridamole or adenosine. This phenomenon, called "reverse distribution", differs from ischaemic changes in coronary artery disease, in which defects at rest worsen or fail to improve with exercise, dipyridamole or adenosine. However, patchy thallium perfusion defects are nonspecific for sarcoidosis even in the presence of normal coronary arteries. Unfortunately, they also occur in other causes of myocardial infiltration, inflammation or cardiomyopathy. In addition, just a minor portion of all patients with sarcoidosis develop relevant cardiac involvement and the method is associated with a high radiation burden. Pathological results have been found in 13–75% of all examined patients depending on the size and composition of the study group [6, 24, 25, 28, 61–74].

The ^{67}Ga scan seems to have a lower sensitivity than the ^{201}Tl scintigraphy [68, 73–81]. Patients with a positive result in the ^{67}Ga scan nearly always demonstrate pathological changes in the ^{201}Tl scan. It was hoped that an improvement in the diagnostic approach or the estimation of the further course of the disease would occur when both tools were combined, but this was not proven until now [73, 74, 76–78]. The myocardial infiltration in sarcoidosis can also be detected with $^{99\text{m}}\text{Tc}$ -pyrophosphate scans, but no comparative studies with ^{201}Tl have been done [81]. The $^{99\text{m}}\text{Tc}$ -sesta-methoxy-isobutyl-isonitrile ($^{99\text{m}}\text{Tc}$ -mibi) single-photon emission computed tomography scan seems to be superior to ^{201}Tl scanning, but only a limited number of studies are available [71, 82–83].

Iodine-123 meta-iodobenzylguanidine, an analogue of norepinephrine, is a tracer for the functioning of sympathetic neurons. This allows visualisation of the sympathetic innervation of the heart and a quantitative assessment of pre-synaptic sympathetic nerve terminal disturbances. An imbalance of the sympathetic tone is considered to increase the propensity to develop ventricular arrhythmias in various cardiac diseases and conditions, and also in sarcoidosis [84].

In summary, in the absence of cardiac symptoms radionuclide imaging should not be used as routine screening for cardiac involvement in patients with sarcoidosis, and should not be repeated very frequently in the follow-up in patients with a positive test result due to the high radiation burden and the availability of less harmful tests. However, in the

presence of normal coronary arteries, the perfusion defects on ^{201}Tl imaging in patients with known systemic sarcoidosis strongly suggest cardiac involvement.

Magnetic resonance imaging

Gated cardiac MRI imaging, as a noninvasive method of investigation, is very promising and is being more frequently used in cardiac sarcoidosis. Apart from case reports dating back to 1988 [79], there are increasing numbers of small studies becoming available [61, 70, 72, 85–89]. SHIMADA *et al.* [70] demonstrated localised enhancements on gadolinium-enhanced cardiac MRI in eight out of 16 patients with suspected cardiac sarcoidosis, indicative of interstitial oedema, inflammation or scarring; ^{201}Tl scanning was abnormal in seven patients, and the ECG in only two patients. Under corticosteroid therapy, these changes improved or vanished in a follow-up examination after 1 month.

The pictures of MRI are accurate in their detail and are able to demonstrate structural and functional abnormalities, which can usually be well differentiated from ischaemic lesions by the different shape and distribution of the abnormal area. Due to this advantage and the lack of radioactivity, the method is well suited for follow-up investigations in patients with positive findings, but limited by availability and costs [72, 85, 86]. In a small series by the present authors, characteristic, unambiguous abnormalities in untreated patients with newly diagnosed cardiac sarcoidosis were found (figs 5–7). In contrast, all the patients with proven cardiac sarcoidosis and long-term steroid therapy only presented nonspecific changes, such as enlargement of the ventricle or hypokinesia, but not the typical regional changes in the myocardium itself.

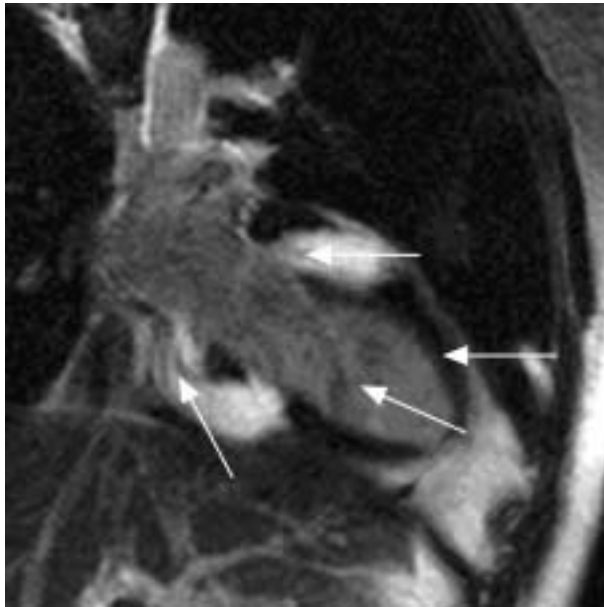


Fig. 5. – Cardiac magnetic resonance imaging scan of a patient with histologically-proven cardiac sarcoidosis. Involved areas are seen in white, which corresponds to enrichment of contrast (gadolinium) in acutely involved myocardium near the basis of the papillary muscles of the left ventricle. Normal myocardium and coronary arteries present in dark stain (two-chamber view of the left ventricle, long axis, 1.5 Tesla, T1-weighting, fast-spin echo, contrast gadolinium, inversion recovery sequence). Arrows point to, going clock wise, contrast-enriched myocardium (white), normal myocardium (dark), filling (blood) of the left ventricle (grey) and the coronary arteries, respectively.

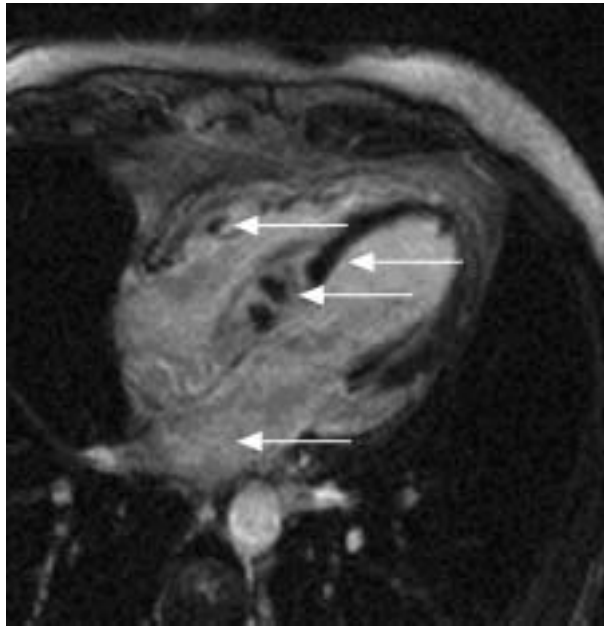


Fig. 6. – Cardiac magnetic resonance imaging scan of a patient presenting with atrioventricular block 2nd to 3rd degree: typical thickening and contrast enrichment of the basal septum in the four-chamber view. Arrows point to, from top to bottom, the right ventricle, left ventricle, thickened basal septum with inhomogeneous contrast enrichment due to sarcoidosis, and left atrium, respectively.

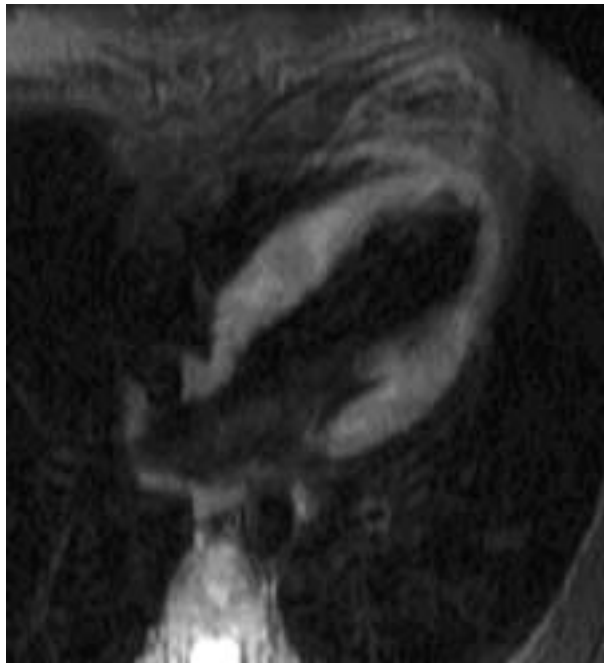


Fig. 7. – Cardiac magnetic resonance imaging scan: diffuse involvement of the heart in histologically-proven cardiac sarcoidosis. The focal and nodular differences in the contrast enrichment and the local thickening of the myocardium are well visible (same view as in figure 2, but different T1/T2-weighting)

These unpublished data are in agreement with a recent publication by SKOLD *et al.* [61]. They studied 18 consecutive patients with sarcoidosis. They observed regional myocardial contrast enhancement on MRI in only two patients despite abnormalities on ECG and/or echocardiography in the majority of patients [61]. MRI imaging is not possible in patients with implanted pacemakers [70, 71, 79, 85–92]. Cardiac MRI still needs further investigation in myocardial sarcoidosis before it can be considered as the diagnostic test of choice.

Positron-emission tomography

To date, there are only case reports and a few small studies available [93–96]. YAMAGISHI *et al.* [93] examined 17 patients with cardiac sarcoidosis by (13)N-NH(3)/(18)F-fluoro-2-deox-d-glucose (FDG) positron-emission tomography (PET) and identified a myocardial (13)N-NH(3)-defect in 13 patients and an increased (18)F-FDG uptake in 14 patients. Only six of these patients had a positive ^{201}Tl scan and only three patients a positive ^{67}Ga scan in the heart [93]. ISHIMARU *et al.* [94] found in 10 out of 32 patients with sarcoidosis, but in none of a control group of 30 subjects, a focal pattern in the myocardium. None of the patients exhibited abnormal findings on ^{67}Ga scan and only four on $^{99\text{m}}\text{Tc}$ -Mibi scan [94]. Thus, PET imaging seems promising, being more sensitive than ^{201}Tl and ^{67}Ga scanning, but it is expensive and further studies are needed to clarify its role in the management of cardiac sarcoidosis in the future.

Invasive examinations

Cardiac catheterisation with coronary angiography is done in the majority of patients with suspected cardiac sarcoidosis in order to exclude coronary artery disease.

Endomyocardial biopsies, introduced in 1962, are nearly always taken from the right ventricle, whereas sarcoid granulomas are more commonly located in the parts of the heart with larger muscle masses, predominantly in the left ventricle. The smaller and more circumscribed the lesions are, the lower the likelihood to hit them in the biopsy. Thus, the degree of sampling error is high, and as expected, the reported success rate of endomyocardial biopsy is generally <25% [38, 39, 47, 97–100]. Therefore, the present authors do not recommend the routine use of biopsy to confirm myocardial involvement if the diagnosis of cardiac sarcoidosis can be substantiated by other techniques.

Clinical criteria for diagnosis

In the experience of the current authors, the criteria of the Japanese Ministry of Health and Welfare from 1993 [70] to diagnose cardiac sarcoidosis are useful and reliable (table 4). These criteria distinguish between histologically-proven and clinically-based diagnosis of cardiac sarcoidosis. In the clinically-based diagnosis, the cardiac involvement by sarcoidosis must be proven histologically at an extracardiac site. In addition, characteristic ECG abnormalities (*i.e.* bundle branch block, AV-dissociation or complex ventricular arrhythmias) as well as structural or functional abnormalities of the myocardium must be present. Excluded are patients in whom these changes are already explained by other diseases, such as myocardial infarction or cor pulmonale.

Table 4. – Guidelines for diagnosing cardiac sarcoidosis[#]

Histological diagnosis group	Cardiac sarcoidosis is confirmed when histological analysis of operative or endomyocardial biopsy specimens demonstrates epithelioid granuloma without caseating granuloma
Clinical diagnosis group	In patients with a histological diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is suspected when item a) and ≥ 1 of items b–e) are present: - Complete right bundle branch block, left axis deviation, AV block, ventricular tachycardia, premature ventricular contraction[†] or abnormal Q or ST-T change on the ECG - Abnormal wall motion, regional wall thinning or dilatation of the left ventricle on the echocardiography - Perfusion defect by ²⁰¹Tl-myocardial scintigraphy or abnormal accumulation by ⁶⁷Ga-citrate or ^{99m}Tc-PYP myocardial scintigraphy - Abnormal intracardiac pressure, low cardiac output, abnormal wall motion or depressed ejection fraction of the left ventricle on cardiac catheter examination - Interstitial fibrosis or cellular infiltration over moderate grade in myocardial biopsy even if the findings are nonspecific

Taken from [70]. AV: atrioventricular; Tl: thallium; Ga: gallium; PYP: pyrophosphate. [#]: Japanese Ministry of Health and Welfare, 1993; [†]: over grade 2 in Lown's classification of premature ventricular tachycardia.

Management and prognosis

The specific treatment of cardiac sarcoidosis is similar to the treatment of other organ involvement. Standard therapy is the administration of systemic corticosteroids (CS) [6–8, 14, 58, 70, 97, 98, 101–108]. Recommendations are based on case reports and retrospective studies. Prospective or randomised trials for cardiac sarcoidosis have not been performed. Whereas good short-term responses have been reported, data concerning long-term efficacy or criteria for dosage, duration, or potential cessation of CS therapy are scarce. Cardiac-specific treatment of cardiac dysfunction or arrhythmias is guided by theoretical and empirical considerations based on the experience with other cardiomyopathies in which treatment has been validated in large multi-centre trials. Treatment of cardiac sarcoidosis is difficult and requires careful monitoring of efficacy and safety of therapeutic agents [18].

Antiarrhythmic therapy

The indication to implant an antibradycardic pacemaker is easy to decide. Today biventricular pacemakers are available to improve the systolic function and diastolic filling. This is achieved by resynchronising the contraction of the left ventricle and prolonging the diastolic filling time when wide QRS complexes lead to an asynchrony and asynergy of the work of the left ventricle. Biventricular pacing seems to be associated with a higher survival rate over time in other cardiomyopathies with wide QRS complexes [109, 110].

Many questions remain to be answered regarding antitachycardic systems, such as the automatic implantable cardioverter defibrillator (AICD), or combined systems. In patients with sustained or recurrent ventricular tachyarrhythmia's, in combination with a syncope or a resuscitation event, who are at high risk for sudden death, the AICD is surely mandatory. In view of the high rate of sudden deaths in cardiac sarcoidosis, not only a secondary but preferably a primary protection would be desirable. However, the question of prophylactic AICD implantation is difficult to decide. The prognostic importance of complex ventricular tachyarrhythmias can only be assessed in combination with other factors, such as the left ventricular function. This function can remarkably improve with CS therapy, but a myocardial scar, as residual of sarcoid granulomas or inflammation, still represents an arrhythmogenic substrate. In contrast, the implantation of an AICD is very expensive, demands the change of the aggregate every few years and can be frightening to

the patients in case of accidental shocks. Therefore, the decision to implant an AICD, with the right timing, is at present bound to the individual case [102, 109–118]. Nevertheless, many authors believe that the current data are sufficient to justify the prophylactic implantation of an AICD in patients at risk. Along these lines, WINTER *et al.* [101] investigated seven patients with cardiac sarcoidosis who all had documented sustained ventricular tachyarrhythmia. Despite antiarrhythmic and CS medication, two patients died due to sudden cardiac death, and four patients had recurrent ventricular tachyarrhythmias. All four patients who received an AICD experienced at least one adequate shock, which obviously saved them from sudden death [101].

Antiarrhythmic drug therapy is empirical. Amiodarone is the preferred drug, but appears to be less effective than in other cardiomyopathies. Often bradycardic and tachycardic arrhythmias can be found simultaneously, restricting the use of antiarrhythmic drugs in the absence of a pacemaker. The value of invasive electrophysiological examinations for a differentiated antiarrhythmic therapy or for estimating the probability of cardiac events seems to be very limited [111–117].

Corticosteroids

A study by YAZAKI *et al.* [42] strongly supports the early and long-term administration of corticosteroids in order to improve the grim prognosis of cardiac sarcoidosis. YAZAKI *et al.* [42] retrospectively reviewed the course of the disease in 95 patients who were diagnosed with cardiac sarcoidosis from 1984–1996. Overall survival rates were 85% at 1 yr, 72% at 3 yrs, 60% at 5 yrs, and 44% at 10 yrs. During a mean follow-up of 68 months, 29 patients (30%) died of congestive heart failure and 11 (12%) experienced sudden death. A multivariate analysis identified the New York Heart Association (NYHA) functional class (hazard ratio=7.7 per NYHA class increase; $p=0.0008$), the left ventricle end-diastolic diameter (hazard ratio=2.6 per 10 mm increase; $p=0.02$) and sustained ventricular tachycardia (hazard ratio=7.2; $p=0.03$) as independent predictors of mortality. Prognosis was excellent in those patients who were treated with CS early, before systolic dysfunction developed. The 5-yr survival rate was 75% for all steroid-treated patients. In those with a left ventricular EF of $\geq 50\%$ before treatment, the 10-yr survival rate was 89%, compared with only 27% in those with an EF of $<50\%$. There was no difference in survival curves between patients with high initial dose (≥ 40 mg) and low initial dose (<30 mg) of prednisone. A total of 20 out of the 95 patients had autopsy-proven cardiac sarcoidosis and had never been treated, and they had a poor 5-yr survival rate of only 10%. In summary, this study shows that starting CS before the occurrence of severe systolic dysfunction results in an excellent clinical outcome, and that a high initial dose of prednisone may not be essential for cardiac sarcoidosis.

KATO *et al.* [106] reported similar results in 20 patients, all with AV block and normal cardiac function initially. During a mean follow-up period of 79 months, the seven patients receiving CS experienced no decline in the EF and none of them died. AV-block regression was seen in four of these seven patients receiving CS. The 13 untreated patients developed a decline in the mean EF from $60.5 \pm 6.4\%$ to $37.6 \pm 17.3\%$, and two (15%) of them died. Ventricular tachycardia occurred in 62% of the untreated, but in only 14% of the treated patients.

SHIMADA *et al.* [70] studied eight patients with cardiac sarcoidosis and abnormalities on contrast-enhanced MRI. After one month of higher doses of prednisolone ($30\text{--}40 \text{ mg}\cdot\text{day}^{-1}$), the localised high-intensity signals markedly diminished in all eight patients. VIGNEAUX *et al.* [72] followed 12 patients with cardiac sarcoidosis by MRI. All six patients receiving higher doses of CS were scored as cleared or improved at the 12

months follow-up MRI. One patient on low dose prednisone of 10 mg·day⁻¹ was stable, the five patients not receiving any CS therapy were scored as stable or worsening [72].

CHIU *et al.* [105] studied 43 patients with cardiac sarcoidosis by echocardiography before and after CS therapy. In patients with initial left ventricular EF >55%, long-term steroid treatment (mean follow-up time at 88 months) showed preventive effects on left ventricular remodelling and left ventricular function. Patients with left ventricular EF between 30% and 54% showed significant reductions in left ventricular volume and improvements in left ventricular EF. However, in patients with left ventricular EF <30%, neither left ventricular volume reductions nor left ventricular EF improvements were observed. This study underlines previous observations [42] that CS therapy may not be as effective in the late stage of cardiac sarcoidosis with severe left ventricular dysfunction.

Recently, CHAPELON-ABRIC *et al.* [58] reported promising long-term follow-up data. They observed an improvement in 87% of 41 patients with cardiac sarcoidosis after an average follow-up of 58 months, and 54% were regarded as cured. Two patients worsened, but they received very late or no treatment. There was no case of sudden death in this series. These patients were treated early with CS (n=39), and another immunosuppressant was added (n=13) in case there was an insufficient response to CS. Treatment was stopped in 13 patients who were apparently cured, after a mean duration of CS of 34 months (range 9–109 months). Relapses occurred in three out of these 13 patients during a 36-month follow-up (range 4–92 months), affecting the heart in two cases.

In summary, despite the lack of large prospective and randomised studies there is no doubt about the effectiveness of CS therapy. Questions still remain about the right dose and the duration of therapy. According to the experience of the present authors and the above mentioned studies, a relapse/death can occur after reducing the dose to <10 mg prednisone, despite prior stable course of the disease. The present authors advise that CS administration should be long-term (≥2 yrs), if not lifelong.

Other immunosuppressants

There are many case reports and small, uncontrolled studies on additional therapeutic agents administered in sarcoidosis including methotrexate, azathioprine, hydroxychloroquine, chloroquine, cyclophosphamide, cyclosporine A, thalidomide, pentoxifylline, infliximab (anti-tumour necrosis factor), but experience with cardiac sarcoidosis is limited [18, 103, 119–139]. Nevertheless, the current authors believe that there is a place for combining CS with either azathioprine, hydroxychloroquine or methotrexate to achieve a CS-sparing effect and reduce CS toxicity in patients with cardiac sarcoidosis who may need lifelong therapy.

Heart transplantation

Heart transplantation should be considered in patients with severe heart failure refractory to medical therapy [8, 101, 107]. Recurrence of sarcoidosis in the transplanted heart is possible and may respond to intensified CS therapy [140–142]. The right moment for listing a patient for heart transplantation is still an individual decision of the responsible doctor/health centre. Alongside the current functional status, the course and complications of the disease have to be considered. However, medical treatment should always be attempted before listing a patient for transplantation. In some patients with severe heart failure and previously undiagnosed sarcoidosis, transplantation can be avoided by treating the disease successfully with CS.

Summary

Clinically evident cardiac sarcoidosis is noted in 2–10% of patients, although occult involvement is much higher. The involvement of the heart is an important prognostic factor in sarcoidosis. Early treatment, predominantly with corticosteroids, prevents irreversible damage of the heart and seems to be associated with good prognosis.

Technical progress has led to improvements and new diagnostic techniques that allow a better assessment of the structure and function of the heart. However, for early diagnosis there is still no single diagnostic tool with acceptable reliability. A histological confirmation is rarely obtained, and the diagnosis is, therefore, a challenge and dependent on clinical rules. The most decisive approach is to suspect the disease and to introduce, in good time, further investigations according to the clinical presentation, *e.g.* cardiac arrhythmias in young patients.

Specific therapy is long term, often lifelong, and is based on corticosteroids with or without immunosuppressants. The symptomatic treatment of cardiac arrhythmias and dysfunction corresponds to experience with dilated cardiomyopathy.

The indication and timing of implantable defibrillators and transplantation still raises many questions.

Keywords: Cardiac involvement, diagnosis, heart, sarcoidosis, treatment.

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