Cardiac magnetic resonance imaging in Churg-Strauss-syndrome. Impact of immunosuppressants on outcome assessed in a prospective study on 8 patients

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ABSTRACT

Objective. *To evaluate the effects of immunosuppressive therapy on cardiac abnormalities observed by cardiac magnetic resonance imaging (CMRI) in patients with Churg-Strauss syndrome (CSS).*

Methods. *We studied 8 patients with CSS and myocardial involvement on initial CMR images, who underwent follow-up CMRI after 6 months of immunosuppressive therapy.*

Results. *Among the 8 patients (mean age: 43 years; 4 women), 7 had clinical cardiac signs at CSS onset (cardiac insufficiency, 3; angina pectoris, 2; atrial fibrillation, 1; and pericarditis, 1); 4 of them had myocardial-delayed enhancement, 2 had perfusion defects and 1 had both CMRI anomalies. The patient without clinical manifestations of heart disease had myocardial delayed enhancement on CMRI. After 6 months of therapy, CMR images normalised for the patient without clinical cardiac signs at diagnosis, and 3 symptomatic patients, and abnormalities had regressed for 2 other symptomatic patients. Theses 5 initially symptomatic patients became asymptomatic after immunosupressive treatment. The last 2 patients with cardiac insufficiency at CSS diagnosis are still symptomatic with unchanged CMRI abnormalities.*

Conclusion. *CMRI is a sensitive, non-invasive method to detect cardiac lesions in patients whose conventional investigations indicated no cardiac disease and to assess the extent of cardiac involvement in symptomatic patients. CMRI can help evaluate the therapeutic effect of immunosuppressants in CSS.*

Introduction

Churg-Strauss syndrome (CSS) was first described in patients with asthma and a characteristic histological pattern of systemic necrotising vasculitis, tissue infiltration by eosinophils and extravascular granulomas (1). Cardiac involvement results from eosinophil infiltration into the myocardium, vasculitis of small vessels or both. Tissue abnormalities are observed in >50% of hearts examined at autopsy (1). When clinically symptomatic, CSS-related cardiomyopathy is associated with a poor outcome, and has been responsible for nearly half of deaths (2, 3), highlights the importance of early detection of myocardial involvement and treatment.

Cardiac magnetic resonance imaging (CMRI) yields substantial morphological and functional information in patients with a variety of disorders. Its ability to diagnose myocardial inflammation and detect myocardial perfusion defects, including microcirculatory disorders, has been described (4-6). This study examines the evolution of CMRI lesions in CSS patients, with or without cardiac manifestations, before and after immunosuppressive treatment.

Patients and methods

Patients

Eight consecutive patients, referred to the Department of Internal Medicine of Hôpital Cochin for management of CSS, as defined by the American College of Rheumatology criteria (7), systematically underwent CMRI. The local ethics committee (Comité de Protection des Personnes of Paris Cochin) approved the study. CMR images were obtained for all patients during an acute phase of their vasculitis, during the first weeks after CSS diagnosis (n=6) or during a relapse (n=1) or in a patient with steroid-resistant disease. Patients known to have previous clinically detected cardiac involvement, or

contraindications to CMRI were not considered for the study.
Five patients had a Five Factor Score (FFS) (8) ≥1 point. Patient 6 had pericarditis, patient 7 had atrial fibrillation and patient 5 was asymptomatic. Theses 3 patients despite their FSS=0 received steroids and immunossupressants because of the association of clinical symptoms and CMRI anomalies, and base on CMRI abnormalities alone for the latter.
Patients were treated with a combination of corticosteroids (initial dose, 1 mg/kg/day) and pulse cyclophosphamide (0.6 g/m^2) on days 1, 14 and 28, then every 3 weeks until remission was obtained (*i.e.* 6 pulses). The maintenance regimen comprised lower dose steroids to control asthma and azathioprine (2 mg/kg/day). In addition to steroids and cytotoxic agents, patients with cardiac insufficiency received angiotensin-converting enzyme inhibitors. Beta-blockers were precluded because of CSS-associated asthma.
Patients underwent CMRI during an active phase of their vasculitis and 6 months after, to evaluate imaging modifications and compare the findings with clinical outcome.

Methods
The following information was collected for all patients: sex, age, cardiovascular risk factors, clinical manifestations of CSS, history of cardiovascular manifestations, cardiovascular symptoms at the time of CMRI, and ECG and echocardiographic observations. Eosinophil count and C-reactive protein (CRP), brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), cardiac troponin I levels were determined. Left ventricular ejection fraction (LVEF) was considered decreased when <45%. Antineutophil cytoplasm antibodies (ANCA) were sought in sera from all patients by immunofluorescence and enzyme-linked immunosorbent assay (ELISA).

Analysis of CMR images
CMR images were obtained with a 1.5-T imager Avanto 76×32 SQ Siemens Medical Solutions, Erlangen, Germany), using a dedicated cardiac, ECG-triggered, phased-array coil. After gradient-echo localisers, functional examinations (Cine-MRI) were performed using a breath-held, short-axis segmented steady-state free precession (SSFP) sequence, with coverage of the entire left ventricle and a single slice per breath-hold. Gadolinium-DOTA-enhanced acquisitions were obtained with a LV short-axis-gradient echo pulse sequence for 50 cardiac cycles during the first-pass of gadolinium-DOTA (perfusion scanning with 5 images per cycle, intravenous bolus of 0.1 mmol/kg, at 5 ml/s) followed by an LV short-axis inversion recovery gradient echo sequence, 10 min after a second 0.1 mmol/kg bolus of gadolinium-DOTA for delayed enhancement imaging. Additional 4-chamber or 2-chamber views were imaged as needed. Endocardial borders were outlined on end-diastolic and end-systolic short-axis cine images with dedicated software (Argus). Volumes and LVEF were derived by summation of endocardial contours.
The processed and enhanced hard copy images were analysed side-by-side by 2 radiologists and 1 cardiologist with expertise in contrast-enhanced CMRI, blinded to all information, including date of examination and patient's name. The myocardium was examined using the17-segment model (9). The extent of delayed-enhanced tissue within each segment was scored with a 5- point scale (10), with a score of 0 indicating no hyperenhancement, 1 meaning hyperenhancement of 1 to 25% of the tissue, 2 hyperenhancement of 26 to 50% of the tissue, 3 hyperenhancement of 51 to 75% of the tissue, and 4 hyperenhancement of 76 to 100% of the tissue. The findings were interpreted as abnormal when the readers independently described the same abnormal presence, distribution, and localisation of delayed enhancement. A segmental perfusion defect was considered to be present when the signal intensity was attenuated in a myocardial region on the first-pass perfusion CMRI images >10 s after contrast-medium injection, compared with the enhancement of the normal myocardium. Differences in interpretation among the experts were resolved by consensus.

Statistical analysis
All statistical analyses were performed using StatView software (Abacus Concept, Berkeley, CA). Among the patients with CMRII abnormalities, symptomatic patients were compared to asymptomatic patients. The number of involved segments, the mean myocardial delayed-enhancement score, and patients' LVEF were analysed in each group using a non-parametric test (Mann-Whitney U-test or Fisher's exact test, when appropriate). A mean $p<0.05$ was considered to be statistically significant.

Results

Baseline observations
The characteristics of the 8 patients (mean age: 43 years, 4 women) included in this study are summarised in Tables I and II. Seven of them had clinical manifestations of cardiac involvement: cardiac insufficiency (patients 1, 2 and 4) angina pectoris (patients 3 and 8), atrial fibrillation (patient 7), and pericarditis (patient 6). Five of them had ECG abnormalities. Patients 1, 2 and 4 with cardiac insufficiency had elevated cardiac troponin and BNP/NT-proBNP levels, and echographic LV dysfunction. Patients 7 and 8 also had high cardiac troponin, (associated with atrial fibrillation or angina pectoris respectively) without elevated BNP/NT-proBNP and with normal echocardiography. Only patient 4 was ANCA-positive.
CMR images showed myocardial delayed enhancement (with intramyocardial or subepicardial distribution) in patients 1, 4, 6 and 8, perfusion defects in patients 3 and 7, and patient 2 had both anomalies. LVEF was decreased in patients 1, 2 and 4 (39%, 15%, and 20% respectively).
Asymptomatic patient 5 had a normal echocardiogram and ECG, and normal levels of cardiac biological markers. CMRI revealed myocardial-delayed enhancement with an intramyocardial distribution.

Patients' characteristics after 6 months of immunosuppressive therapy
All patients were in CSS remission, 6 months after starting treatment. Among the 3 patients with cardiac insufficiency,

Table I. Demographic, clinical and laboratory characteristics of 8 patients with Churg-Strauss syndrome who underwent early cardiac magnetic resonance imaging.

Patient	Age (yrs)	Sex	History of Clinical Symptoms	Cardiac Symptoms	Abnormalities		cTnI* (ng/ml)	BNP/NT-proBNP* (ng/ml / pg/ml)	CRP* (mg/l)	Eosinophils (/mm³)	ANCA
					ECG	Echocardiographic					
1	53	F	Sinusitis, asthma, mononeuritis multiplex	Cardiac insufficiency	QS V1–V3	Global hypokinesia	0.05	234/ND	<5	4,910	Negative
2	51	F	Sinusitis, asthma, mononeuritis multiplex, pulmonary infiltrates	Cardiac insufficiency	QS V1–V3	Severe global hypokinesia	7.81	ND/3525	71	4,620	Negative
3	36	F	Sinusitis, asthma, mononeuritis multiplex, pulmonary infiltrates	Angina pectoris	Inverted T wave V3–V6	None	< 0.04	ND/158	3	1,800	Negative
4	54	M	Sinusitis, asthma, mononeuritis multiplex, pulmonary infiltrates	Cardiac insufficiency	ST Depression V5, V6	Severe global hypokinesia	10	ND/1363	136	13,000	Negative
5	43	M	Sinusitis, asthma, mononeuritis multiplex	None	Normal	None	< 0.04	ND/62	65	3,000	Negative
6	35	F	Asthma, purpura, pulmonary infiltrates	Pericarditis	Normal	None	< 0.04	ND/104	8	2,420	Positive
7	39	M	Sinusitis, asthma, mononeuritis multiplex, pulmonary infiltrates, purpura, hepatitis	Initial atrial fibrillation	Normal	None	1.98	ND/66	5.3	1,210	Negative
8	38	F	Sinusitis, asthma, mononeuritis multiplex	Angina pectoris	Inverted T wave, D2, D3, aVF, V1–V3	None	0. 61	ND/229	< 1	6,440	Negative

F: female; M: male; ECG: electrocardiographic; cTnI: cardiac troponin I; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; CRP: C-reactive protein; ANCA: antineutrophil cytoplasmic antibodies; ND: not done.
*Normal values: cTnI: <0.04 ng/ml; BNP: <60 ng/l; NT-proBNP: <300 pg/ml; CRP: <2.5 mg/l.

Table II. Cardiac magnetic resonance imaging (CMRI) observations and left ventricular ejection fraction (LVEF) before (baseline) and after 6 months of immunosuppressive therapy for 8 patients with Churg-Strauss syndrome.

Patient	Baseline				At 6 months			
	CMRI Findings	DE Score	Segments Affected (17-segment model)	LVEF (%)	CMRI Findings	Segments Affected (17-segment model)	DE Score	LVEF (%)
1	DE	12	1, 2, 8, 7	39	Unchanged	1,2,8,7	12	39
2	DE Perfusion defects	8 –	1, 8, 9, 10 & 11 4, 10, 11, 12, 14, 15 & 16	15	Marked attenuation Marked attenuation	1, 9 & 10 4, 10, 11, 12 & 15	4 –	30
3	Perfusion defects	–	3,4,5,11	51	Marked attenuation	4,11	–	59
4	DE	14	1, 3, 7, 9, 11 & 13	20	Unchanged	1, 3, 7, 9, 11 & 13	14	20
5	DE	3	2, 3 & 8	70	Normalisation	–	0	67
6	DE	1	17	66	Normalisation	–	0	54
7	Perfusion defects	–	10 & 4	47	Normalisation	–	–	50
8	DE	4	9	55	Normalisation	–	0	52

DE: delayed enhancement.

patients 1 and 4 remained symptomatic. None of the others had cardiac manifestations. NT-proBNP or BNP levels had declined in all patients but remained above the normal range in patients 1, 2 and 4 who had cardiac insufficiency before treatment. Cardiac troponine I levels and eosinophil counts normalised for all patients. The 6-month CMR images had normalised for patient 5 who had been clinically asymptomatic at diagnosis. Five patients symptomatic at baseline (patient 2, cardiac insufficiency; patients 3 and 8, angina pectoris; patient 7, atrial fibrillation; patient 6, pericarditis) became asymptomatic; CMR images normalised for patients 6, 7 and 8, and patients 2, and 3 had partial regressions of their initial abnormalities. CMR images remained unchanged with persistent delayed enhancement for patients 1 and 4 who had persistent cardiac insufficiency. LVEF increased (+15%) in 1/3 patients with initial cardiac insufficiency and initial LVEF <45%. LVEF was unchanged in the 2 others.

CMR images at 6 months and their analysis

Compared patients 5, 6 and 8 whose CMR images normalised, those with persistent (patient 1 and 4) or only partial regression (patient 2) of CMR myocardial delayed enhancement after treatment had more involved myocardial segments (mean: 5 versus 1.6, respectively p=0.07), a higher myocardial score (mean: 11.3 versus 2.6, respectively; p=NS) and lower LVEF (mean: 24% versus 59%, respectively p=NS)

Patients 1 and 4 with persistent myocardial delayed enhancement remained symptomatic after treatment, whereas the patients 5, 6 and 8, whose myocardial delayed enhancement normalised had become asymptomatic at 6 months.

Among patients 2, 3 and 7, who had perfusion defects on their initial CMR images, none were symptomatic after immunosuppressive therapy. CMR images normalised in patient 7 and the abnormalities had regressed partially in the 2 others.

Discussion

We described 8 CSS patients in who, in addition to conventional investigations, underwent systematic CMRI before treatment and after 6 months of immunosuppressive therapy. This systematic approach identified the presence and/or the extent of cardiac involvement in patients with clinical cardiac symptoms or not. CMRI can detect early manifestations of myocardial involvement, before onset of clinical, ECG or echocardiogram abnormalities.

For patients with cardiac insufficiency, CMR images visualised the extent of cardiac involvement, revealing more abnormal myocardial segments and higher myocardial scores than for the other patients. CMRI abnormalities were also found in 1 asymptomatic which prompted us to prescribe cyclophosphamide in addition to steroids, thus modifying to our previous therapeutic approach which had been to treat patients only when they presented clinical or biological symptoms of CSS severity (*i.e.* FFS ≥1).

CMRI might help to evaluate the effect of immunosuppressive treatment, in CSS patients. After 6 months of treatment, asymptomatic patient 5 and symptomatic patients 6-8 with moderate extension of CMRI lesions (≤3 myocardial segments) at initial evaluation, had completely regressed for CMRI abnormalities, whereas symptomatic patients 1-4 with more extensive involvement of their initial CMRI lesions (≥4 involved myocardial segments), had only partial regressions or persistent lesions. These observation suggest that immunosuppressrants were effective and achieved full cardiac recovery in clinically asymptomatic patient 5 who had CMR proven myocardial lesions, and in symptomatic patients with moderately extensive of CMRI lesions. Even when patients were symptomatic, CMR images showed that attenuation could also be obtained, however, for the more severely affected patients CMR images improved but remained abnormal despite clinical symptom abatement. When cardiac symptoms (cardiac insufficiency) persisted after

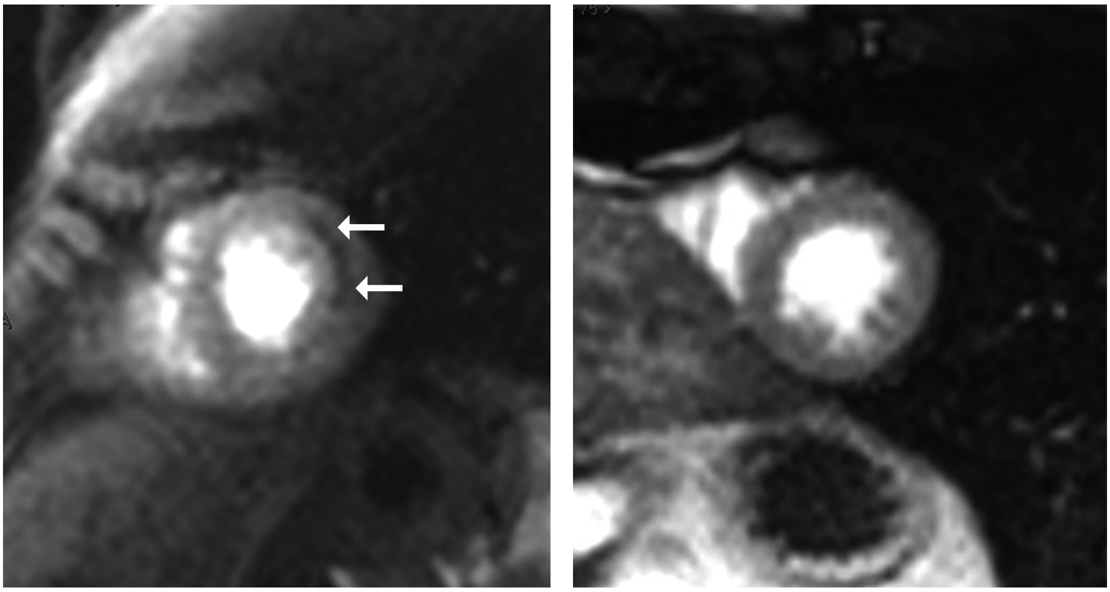

Fig. 1A. Gadolinium first-pass perfusion CMRI in short axis view. (**A**) Before treatment: perfusion defect of the anterolateral wall. (**B**) After treatment: regression of the perfusion defect.

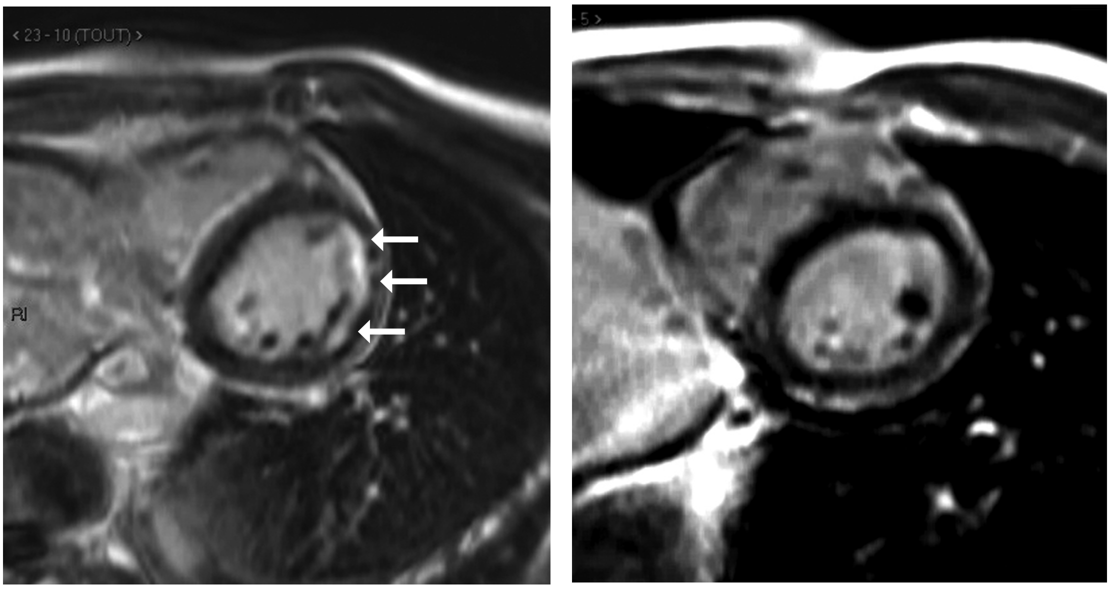

Fig. B. Gadolinium-enhanced inversion recovery gradient-echo acquisitions in short axis-view. (**A**) Before treatment: intramyocardial-delayed enhancement of the anterolateral wall. (**B**) After treatment: full regression of delayed enhancement.

immunosuppressive treatment so did CMRI abnormalities.

Occurrence, extension and outcome after treatment of myocardial-delayed enhancement on CMR images in CSS patients might have prognostic value. Further investigations are needed to decide whether the presence of isolated CMRI anomalies should lead to therapy intensification with immunosuppressants in cardiac clinically asymptomatic patients.

In animal models and in humans (11, 12), it has been shown that myocardial-delayed enhancement was associated with histologically proven fibrosis and active myocarditis. None of our 8 patients had a history of cardiac disease and CMRI was performed during an active phase of CSS. Myocardial delayed enhancement seen on the initial CMR images might reflect myocardial necrosis and/or inflammation. Persistent or partial regression of myocardial-delayed enhancement in some patients might indicate the evolution of active myocardial lesions towards fibrosis or persistence of chronic myocardial inflammation.

The ability of CMRI to diagnose myocardial inflammation and perfusion defects was previously reported by others (6, 11). Baccouche *et al*. (13) reported that myocardial lesions, detected by CMRI and histological examination, in a CSS patient with chest pain resolved under steroids and immunosuppressive therapy, as did their clinical symptoms. Smedema *et al*. (6) described a CSS patient with CMRI perfusion defects attributed to myocardial ischemia due to small-vessel vasculitis.

In conclusion, CMRI is a sensitive, non-invasive method to detect cardiac lesions in patients without evidence of cardiac disease on conventional investigations and to evaluate the extent of cardiac lesions in symptomatic patients. CMRI assessment of cardiac involvement could be helpful to decide whether immunosuppressants are indicated in addition to corticosteroids. The preliminary results presented here need to be confirmed in further prospective studies.

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