Persistence of Late Gadolinium Enhancement in Post-Acute Myocarditis Imaging

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Abstract

Background: Diagnosis of acute myocarditis (AM) is based on combining ECG and seromarkers, but endomyocardial biopsy (EMB) remains the gold standard. Cardiac Magnetic Resonance (CMR) has been established as a reference standard for the non-invasive diagnosis. CMR is useful for follow-up since it is able to non-invasively delineate the presence and extent of myocardial edema and myocardial left ventricle (LV) lesions, represented by late gadolinium enhancement (LGE). The follow-up depends on the individual scenario. The aim of this study is to correlate CMR findings with cardiac enzymes and inflammatory markers in patients with AM and to evaluate the utility of CMR follow-up, even after the resolution of the symptomatology.

Methods: Between 2008 to 2016 thirty-three consecutive patients with clinical and laboratory suspicion of AM referred for CMR within seven days from the beginning of the symptoms. The final analysis included 24 patients with AM CMR-confirmed. The follow-up was performed between 3 and 24 months from the diagnosis. CMR was performed using a standard protocol. Presence of edema and extent of myocardial LGE were examined. The comparison between the proportion of patients affected by edema at onset and that of patients affected at the various follow-up was conducted through the test of Mc Nemar. The effect of the predictors on the outcome was evaluated with a nonparametric two-sample Wald test.

Results: All patients showed edema and LGE at baseline CMR. The LV lateral wall resulted the most affected by edema (in particular the 12th segment), inferior and lateral wall of LV were the most involved by LGE. There was a highly significant effect (P<0.001) of the Troponin peak on the number of areas involved by LGE. At CMR follow-up, edema has resolved in all patients, LGE persisted in 23/24 patients.

Conclusions: There is a correlation between the levels of troponin and myocardial LGE extension in baseline CMR but not between clinical conditions of the patients and post-myocarditis imaging. The presence and the extent of LGE in CMR follow-up are not predictive of outcome in patients without severe hemodynamic compromise, but it can be considered rather an early sign of poor prognosis.

Keywords: Late gadolinium enhancement CMR; Myocarditis follow-up; Post-acute myocarditis imaging; Myocardial edema; Myocardial LGE

Introduction

Acute myocarditis (AM) is an inflammatory disease of the heart muscle most commonly caused by viruses [1]. Clinical presentation and outcome are variable, ranging from asymptomatic to fulminant myocarditis or sudden cardiac death [2].

The incidence of myocarditis, as ascertained by International Classification of Diseases, 9th Revision diagnoses, was 22 per 100,000 people [3]. The burden of myocarditis as a percentage of prevalent heart failure is 0.5% to 4.0% [4].

Diagnosis of this disease usually is based on combining ECG and sero-markers such as troponin that is useful to detect myocardial injury in patients with suspected AM. The accuracy of ECGs to detect myocardial ischemia is often low [5] and endomyocardial biopsy (EMB) remains the gold standard for diagnosis of AM. However, current guidelines recommend EMB in a limited number of clinical scenarios, particularly pseudo-infarction [6]. Cardiac Magnetic Resonance (CMR) has recently been established as a reference standard for the non-invasive diagnosis of myocarditis, since it allows a complete comprehension of both function and tissue characterization of the myocardium [1,7]. CMR is particularly useful for sequential follow-up since it is able to non-invasively delineate the presence and extent of myocardial edema and quantify myocardial left ventricle (LV) lesions [8], represented by the presence of late gadolinium enhancement (LGE) [9].

The best time to perform CMR imaging is usually 7 days after the onset of signs and symptoms, indeed, an earlier CMR study may be less sensitive due to the focal nature of the early stages of the disease [7,10]. In a patient with strong clinical evidence for myocarditis yet
negative criteria in the initial CMR study it may be necessary to repeat a scan already after one or two weeks to establish the diagnosis [11]. The follow-up depends on the individual scenario. A CMR at least 4 weeks after the onset of disease may be useful to differentiate uncomplicated involvement of the myocardium in a systemic viral illness from a complicated course with viral persistence or autoimmune/infectious disease [7]. A CMR at 3 months after the onset of disease may be useful to identify a complicated course. Persisting CMR markers for inflammation (LGE), translates the persistence of fibrosis and a higher risk of myocardial apoptosis [12].

The CMR diagnosis of AM is based upon Lake Louise Criteria: increased signal in T2 weighted sequences; early enhancement after Gadolinium injection in T1 weighted sequences; the presence of LGE with "non-ischemic" pattern (subepicardial localization) in T1 weighted IR sequences [11]. The presence of LGE and edema at CMR have 91% specificity, with demonstrated good predictive value compared to histology [2,7]. LGE in acute myocarditis (present in 44%-88% of the cases) usually is localized in inferolateral segments and less frequently in anteroseptal segments. However, LGE and edema may be distributed in a multi-focal or diffuse way [7,10]. LGE extension correlates with an increased rate of major cardiac events at follow-up [8,13].

The aim of this study is to correlate CMR findings with cardiac enzymes and inflammatory markers (in particular the peak values of troponin I, Creatinine phospho-kinase (CPK) and C-reactive protein (PCR) at onset) in patients with AM and to evaluate the utility to monitor these patients with CMR follow-up, even after the resolution of the symptomatology.

Materials and Methods

Study population

Between 2008 to 2016 we retrospectively analyzed thirty-three consecutive patients that were referred for CMR with "highly suspected clinical acute or fulminant myocarditis" as the primary clinical question, based on their clinical symptoms, ECG features and levels of cardiac enzymes. All patients with acute chest pain syndromes, with symptom onset <2 weeks before CMR or patients with onset presentation of ventricular arrhythmias, syncopal spells or abnormal ECG and AM CMR-confirmed were included. Patients with diagnosis of coronary artery disease or other myocardial diseases have been excluded.

Thirty-one patients (94%) had AM CMR-confirmed but some of them were lost to follow up, therefore the final analysis included 24 patients.

First CMR was performed within a week from the beginning of the clinical symptoms. While the follow-up was performed between 3 months and 24 months from the diagnosis, with the same CMR protocol, after the disappearance of the symptoms and when the values of the enzymes and inflammatory indices had returned to the normal range.

The studied population was divided into 4 groups according to the time of follow up: I group with-follow up at 3 months (3 patients; 12%), II group at 6 months (10 patients; 42%), III group at 12 months (5 patients; 21%) IV group and at 24 months (8 patients; 33%).

This study was approved by our institutional review board and all patients signed a consent form before CMR scan.

Cardiac magnetic resonance imaging protocol

All CMR scans were performed using a clinical 1.5-T Optima MR450w GEM release software DV25 GE Healthcare, Waukesha, WI, USA). VCG-gated breath-hold cine images sequences were acquired using steady-state free precession sequences in contiguous multiple short-axis views from the mitral valve to the LV apex (7 mm slice thickness, 3 mm gap) and three standard long-axis views (two, three and four chamber view). Spatial resolution was 0.7 mm × 0.7 mm, effective echo time TE=1.8 ms, effective repetition time TR=4 and flip angle 50°.

The presence of myocardial edema was evaluated with the dark-blood T2-weighted short tau inversion recovery (STIR) sequence (T2w-STIR; spatial resolution 0.7 mm × 0.7 mm, slice thickness 8 mm, effective echo time TE=82 ms, effective repetition time TR=2 RR intervals during breath-hold, flip angle 155°, TI=160 ms) on short axis.

Late gadolinium enhancement was performed at least 10 minutes after bolus intravenous administration of gadolinium-gadoteric acid (DOTA) (0.15 mmol/kg Dotarem, Guerbet, France) using inversion recovery gradient echo sequences (echo time TE=3.3, repetition time TR=7, flip angle, 20°; slice thickness 8 mm; gap 2 mm; spatial resolution, 0.7 mm × 0.7 mm) at the same location of cine views (two, three, four chambers and short axis), with inversion times adjusted to null normal myocardium.

Image analysis

Presence of edema (assessed from STIR-T2w images) and extent of myocardial LGE were examined in consensus by two expert readers: one cardiologist and one radiologist (qualitative assessment). The distinction in 17 myocardial segments according to the studies of Cerqueira et al. was used to localize edema and LGE in the left ventricular wall [14]. Left ventricular (LV) end-diastolic volumes (EDV), LV-end-systolic volumes (ESV), right ventricular (RV)-EDV, RV-ESV and LV-ejection fraction (EF), RV-EF were quantified from short-axis cine images by standard methods measured offline using ReportCARD 4.0 (GE Healthcare, Waukesha, WI, USA).

Statistical analysis

Qualitative and quantitative variables were expressed as number and percentages and as mean value ± standard deviation (SD).

The comparison between the proportion of areas affected by edema or involved in LGE at onset and at follow-up was conducted through an exact binomial test on two-tailed proportions.

The comparison between the proportion of patients affected by edema at onset and that of patients affected at the various follow-up was conducted through an exact test for the paired proportions (binomial) of Mc Nemar.

To identify predictors of the number of areas of the edema site and the number of areas involved was applied a model for count outcome, the Poisson regression with robust variance estimators ("sandwich"). The effect of the predictors on the outcome was evaluated with a nonparametric two-sample Wald test on the coefficients. The models used include among the predictors age, Troponin peak and ejection fraction. To check that there are no bias in the estimation of standard errors, as control, was also applied a negative binomial regression model, and the results of the respective analyzes were compared, resulting as overlapping. In all analyzes the p-values lower than α=0.05
were considered significant. Data analysis was performed using the Stata software version 13.0.

Results

Study population

All of the patients included into the study were young men of a mean age of 33.2 years ± 11 years with a normal Body Surface Area (BSA) (Table 1). All of the patients presented fever and prodromal symptoms during the last week before hospital admission. Twenty-two (92%) of patients had a chest pain, one patient had dyspnea and only 2 patients (8%) had fulminant presentation and syncope. Patients with fulminant presentation had been supported by Intra-Aortic Balloon Pump (IABP) and one by Extra Corporeal Membrane Oxygenation (ECMO) for 7 days. Most of study patients (71%), at the hospital admission, showed an ST-elevation "myocardial-infarction-like" ECG or (21%) an abnormal but aspecific ECG and only 2 patients (8%) presented normal ECG.

With the exception of patients with fulminant myocarditis, none of the patients had major alterations to the echocardiographic exam indeed the mean EF calculated by echocardiography was 53% ± 15%. Fourteen patients (58%) underwent coronary angiography to rule out ischemic diseases, while the other patients were excluded for their young age and the absence of cardiovascular risk factors.

The myocardial biopsy was done in 3 patients: 2 because of recurrent myocarditis and one considering the critical clinical conditions. All biopsy confirmed inflammatory reaction but not the specific pathogen of myocarditis (Table 1).

Baseline CMR findings

The mean baseline LV-EF in the 24 patients was 62% ± 7%. Left ventricular (LV) end-diastolic volumes (EDV), LV-end-systolic volumes (ESV), right ventricular (RV)-EDV, RV-ESV and LV-ejection fraction (EF) were in the normal ranges for age. All patients showed edema and LGE.

LGE involved the subepicardial/intramural layer inferior and lateral wall in 18 patients (75%), the anterior and anteroseptal wall in 8 patients (33%), and other segments in 1 patients (4%) [15].

The areas most affected by LGE was 5 and 11-12 and three peaks corresponding to the involvement of areas 5-6, 11-12 and 15-16 have been identified. Almost all patients had edema in at least one of these areas. Statistical analysis of myocardial involvement by edema reveals a significant trend to affect these regions by more than 50% (P<0.001). The tendency remains statistically significant even if we evaluate only 11-12 (P=0.004) or 15-16 (P=0.019) areas but is not significant for the 5-6 areas alone (P=0.648) (Figure 1).

Edema involved the subepicardial layer of inferior and lateral wall in 17 patients (71%), the anterior and anteroseptal wall in 8 patients (33%), and other segments in 4 patients (17%).

The areas most affected by edema were 12 and 16 (respectively 62.5% and 58.3%) (Figure 2).

Hypo/akinesia of the ventricular wall was observed in seven patients (29%). Four patients in II group (40%), one patients in III group (25%) and three patients in IV group (38%).

Ten patients (42%) showed EF at lower limits and one patient (4%) showed EF reduced. No significance correlation was found among the potential clinical predictors of the site of edema (Table 2). While there was a highly significant effect (P<0.001) of the Troponin peak on the number of areas involved by LGE (Table 3).

| Number of the patients (24) | Mean |
|----------------------------|------|
| Age                        | 33.2 ± 11 (range 15-50) |
| BSA (kg/m2)                | 2.6 ± 0.9 |
| Caucasian ethnicity        | 22 (92%) |
| Men                        | 24 (100%) |

Clinical presentation

| Dyspnea                  | 1 (4%) |
| Chest pain               | 22 (92%) |
| Syncope                  | 2 (8%) |
| Fulminant presentation   | 2 (8%) |
| Recent fever             | 24 (100%) |
| Prodromal symptoms       | 24 (100%) |
| Sore throat              | 8 (33%) |
| Gastrointestinal disorders| 7 (29%) |
| Associated autoimmune disorders| 1 (4%) |

ECG at admission

| Normal                  | 2 (8%) |
| ST segment elevation    | 17 (71%) |
| Abnormal ST-T segment   | 5 (21%) |
| AV block or BBS         | 0 |

Laboratory findings

| Peak troponin I         | 26.3 ± 12 (N.V. <0.1 mg/L) |
| PCR                     | 7.47 ± 6 (N.V. <0.5 mg/100mL) |
| LVEF by Echo at admission | 53% ± 15% (10% – 65%) |
| Biopsy                  | 3 (13%) |
| IABP                    | 2 (%) |
| ECMO                    | 1 (4%) |
| Coronarography          | 14 (58%) |

Table 1: Study population.
The majority of patients at follow-up showed LGE but none of them presented edema. The test used to demonstrate the null hypothesis that the proportion of edema at follow-up did not differ from baseline was highly significant at 6 months ($P=0.002$) and 24 months ($P=0.008$). "Expected" and imputable to the extremely small number of observations available in the sample for those periods ($n=3$ and $n=5$ respectively).

### Clinical follow-up

All patients were alive at the time of follow-up. The general characteristics of the patients of the different groups did not differ substantially, nor significant clinical differences emerged during the follow-up between the components of the various groups. In most of patients (83%) the signs and symptoms at the diagnosis were no longer present, none of the patients made pharmacological therapies to improve cardiac function (Table 4).

### Discussion

It is common practice to use clinical findings, cardiac enzymes, and inflammatory markers to monitor treatment response and clinical course in myocarditis, but this strategy may not be sufficient to risk-stratify patients with myocarditis and CMR may add value to other methods commonly used for diagnosis.
CMR is used as a reference standard in the diagnosis and follow-up of AM since it allows to study cardiac function and quantify myocardial damage non-invasively. The follow-up, whose duration varies for each patient, then allows the tissue characteristic during the evolution of the disease [1,7,8]. The CMR studies the presence and extent of myocardial edema and late gadolinium enhancement, sign of myocardial lesion [9].

The presence of intramyocardial edema and LGE are MR diagnostic criteria of myocarditis and are typically localized in inferolateral segments, less frequently in anteroapical segments [7]. In our study the LV lateral wall resulted the most affected by edema (the 12th segment), furthermore inferior and lateral wall of LV were the most involved of LGE, according to previous studies [16,17] (Figure 3).

Table 4: Clinical follow-up.

| Patients        | I Group (FU months) | II Group (FU months) | III Group (FU months) | IV Group (FU months) |
|-----------------|---------------------|----------------------|-----------------------|----------------------|
| Alive           | 100%                | 100%                 | 100%                  | 100%                 |
| Fulminant       | 33%                 | 10%                  | 0%                    | 0%                   |

Figure 3 (A and B): Black blood STIR T2 sequence in the short ventriculat axis: LV lateral wall affected by edema. T1 sequence with Gd foro studying LGE: inferior and lateral wall involved of LGE.

In all the patient's edema disappeared at the follow-up; indeed, edema is a sign of acute myocarditis and it is known that the acute phase of myocarditis takes only a few days [3,18]. Patients with fulminant myocarditis were associated with significant reduction of EF, sign of myocardial damage and higher troponin I level.

At CMR follow-up LGE persisted in 23/24 patients and involved the inferior and lateral wall in 19 patients (79%), the anterior and anteroapical walls in 8 patients (33%) and other segments in 3 patients (13%). The qualitative evaluation showed that LGE extension decreased compared with baseline CMR, according to several studies that have described the decrease of late enhancement areas at the follow-up [18-20]. This might explain why as healing progresses, the edema is resolved, the scar contracts, the myocardium remolds and, therefore, the extension of the late enhancement area decreases. In some cases, microscars persist but are below the MR spatial resolution and this could explain the visual disappearance of the late enhancement regions occur. On other occasions, the enhancement areas may persist without changes [18-20].

In our study, all the patients who had an initial heart failure, at CMR presented persistent LGE without remarkable changes. In these cases, the pharmacological treatment of patients with AM and strict clinical follow-up is necessary. Moreover, knowing the level of myocardial fibrosis is useful because it may contribute to the development of diastolic dysfunction [18].

Indeed, results reported by Grün et al., found that the presence of LGE was an independent predictor of long-term all-cause mortality and cardiac mortality [21].

The cardiac enzymes are usually normalized in patients at the end of hospital admission, but their clinical risk is based on the LGE during follow-up. Barone-Rochette et al. reported a relationship between LGE extent at 3 months and adverse cardiovascular outcomes, including death of any cause, heart transplant, or recurrence of myocarditis within a year [22]. Whether persistence or increase of LGE at 3-month follow-up reflects active or persistent inflammation or rather scar remains unclear [7].

The data of Berg [23] show that cardiac enzymes and inflammatory markers do not sufficiently predict LGE findings in myocarditis and that CMR may represent with LGE an additional diagnostic tool for improved risk stratification at 3-month follow-up even if serum markers have normalized. Berg's data support findings of other groups describing LGE as risk marker for adverse cardiovascular events in myocarditis.

Although their study population is small, the data are relevant because of 2 major findings. In most of cases, in whom cardiac and inflammatory markers normalized, LGE improved similarly. However, in a considerable percentage of those patients, persistence of LGE was detected albeit to a lesser degree. In some, there was even worsening LGE despite of normalization of laboratory parameters.

From clinical point of view cardiac enzymes, especially troponin I level is important for the diagnosis of acute myocarditis, but the presence of troponin release is not prognostically relevant in the myopericardial inflammatory syndromes and thus should not be used for a prolonged follow-up or additional investigation [24].

Our results do not fully agree with this point of view, our study shows a correlation of the level of cardiac troponin and the number of segments with LGE in patients with acute myocarditis at onset. The more compromised patients had increased myocardial damage detected by cardiac enzyme as well as by CMR. However, this correlation does not occur at follow-up because although LGE persists, troponin is within the normal range.

Wagner et al., reported the relationship of CMR findings to long-term outcome in 16 patients with acute myocarditis who were followed for 30 ± 4 months and studied by serial CMR and he concluded that the contrast-enhanced CMR may be a useful, non-invasive tool for long-term follow-up of patients with acute myocarditis. Furthermore Wagner et al. observed also that relatively early MRI findings may predict longer-term outcomes [25].

Based on the follow-up of this study, until 24 months, there was no strong correlation between the persistence of LGE and the occurrence of adverse cardiovascular events, except in patients with heart failure in whom the LGE remained stable, however, the persistence of LGE at follow-up can be considered an early sign of unfavorable prognosis and therefore an alarm to continue a long-term follow-up.

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Study Limitations

The first limitation of this study is the lack of correlation with the EBM, that represents the gold standard in the diagnosis of AM but is a retrospective study and in our institution the EBM is performed only in three patients because of their critical clinical conditions. The follow-up time has not been standardized because it was based on clinical needs and performed for each patient after the disappearance of the symptoms and when the values of the enzymes and inflammatory indices had returned to the normal range.

We cannot perform quantitative evaluation of LGE because presently we do not have dedicated software. Quantitative analysis of LGE% changes could provide additional information regarding the healing process and the degree of residual inflammation or fibrosis in the first months after AM [2].

Lastly, we studied a limited population therefore further studies will be needed to confirm our results.

Conclusion

This study confirmed that the regions most affected by edema and LGE, in baseline CMR of patients with AM, are characteristically later and inferior walls of LV. This study showed that there is a correlation between the levels of troponin at the onset and myocardial LGE extension in baseline CMR, but not at follow-up. Previous studies state that CMR reveals cardiac signal intensity changes in patients with acute myocarditis; however, the natural history of these changes and their relationship to individual outcomes are unknown [25]. In our study, patients with LGE at follow-up 24 months after the onset of the disease did not experience any adverse cardiovascular events, nor very different clinical conditions from the patient that already showed LGE disappearance at the 6-month follow-up, this shows that the presence and extent of LGE in the CMR follow-up are not predictive of outcome in patients with previous AM.

Further studies, hopefully prospective, could be useful to understand if, in asymptomatic patients, the persistence of LGE at follow-up can be considered rather an early sign of poor prognosis.

Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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