Prognostic impact of baseline and follow-up CMR scans in acute myocarditis: evidence from a prospective multicentre Italian study (ITAMY trial)

By Dr. GD Aquaro & Dr. C Grigoratos

Cardiac magnetic resonance (CMR) is nowadays considered as the gold standard, non-invasive imaging technique for the diagnosis of acute myocarditis (AM) [1]. The main strength of CMR is its ability not only to detect non-ischemic myocardial damage associated with AM but also to assess its localization, extent, [2] and occasional pericardial involvement [3]. Moreover, CMR may offer a method for differential diagnosis with respect to other ischemic or non-ischemic causes of cardiac damage such as myocardial infarction with normal coronary arteries (MINOCA) [4]. For these reasons and in order to obtain a definite diagnosis, CMR is usually performed within the first 7-10 days after presentation of symptoms.

In the clinical setting, after a CMR diagnosis of AM has been established, a follow-up scan is considered appropriate in order to monitor the evolution of the myocardium and to document any resolution of signs of acute damage such as myocardial edema/hyperemia as well as to evaluate myocardial systolic function. Usually the follow-up scan is carried out approximately six months after symptom onset but up until recently there was only limited scientific evidence available regarding the real clinical significance of such repeat CMR exams.

Last year a number of AM studies provided additional evidence of the diagnostic and — more importantly — the prognostic importance of CMR. The presence of late gadolinium enhancement (LGE) was found to indicate poorer prognosis in a large series of patients with AM and preserved left ventricular ejection fraction (LVEF), especially when the LGE was located in the midwall layer of the interventricular septum [5]. LGE is universally accepted as a marker of definitive damage representing reparative fibrosis of irreversible myocardial damage [6]. However this dogma has for some time been questioned in the acute setting and specifically in the context of AM. By repeating CMR six months after the first diagnosis, Mahrholdt *et al.* [7] reported a complete disappearance of LGE in 26% of patients. This may suggest that LGE is not necessarily only a marker of myocardial fibrosis but rather could also be associated with acute inflammation, which after a few months may disappear completely in a number of patients.

In a recent publication from our group, we sought to examine the evolution of CMR signs of myocardial damage in detail and to investigate their clinical and prognostic significance in the acute setting of patients with AM and who had a follow-up CMR scan [8]. This study was the continuation of the ITAMY (ITAlian study in MYocarditis) multicenter investigation on the prognostic value of CMR in AM [5].

STUDY DESIGN

A total of 200 consecutive patients were enrolled from 2008 to 2014. The patients were all clinically suspected of having AM, i.e. were either symptomatic patients with pericarditic or pseudoischemic chest pain fulfilling one or more diagnostic criteria (new electrocardiogram modification, elevated troponin, wall motion abnormalities with preserved LVEF on echocardiography) or were asymptomatic patients with two or more of the diagnostic criteria. All patients had preserved LVEF.

A definite diagnosis of AM was made when two or more of the original CMR Lake Louise criteria (myocardial edema, hyperemia, and LGE) were present [9]. Endomyocardial biopsy was performed in cases where the CMR was inconclusive; the absence of obstructive coronary artery disease was verified by coronary artery angiography in all patients greater

The Authors
Giovanni Donato Aquaro MD & Crysanthos Grigoratos, MD
Fondazione Toscana G. Monasterio,
Via Giuseppe Moruzzi, 1
56124 Pisa, Italy

Corresponding Author
Dr. G D Aquaro,
E-mail: aquaro@ftgm.it

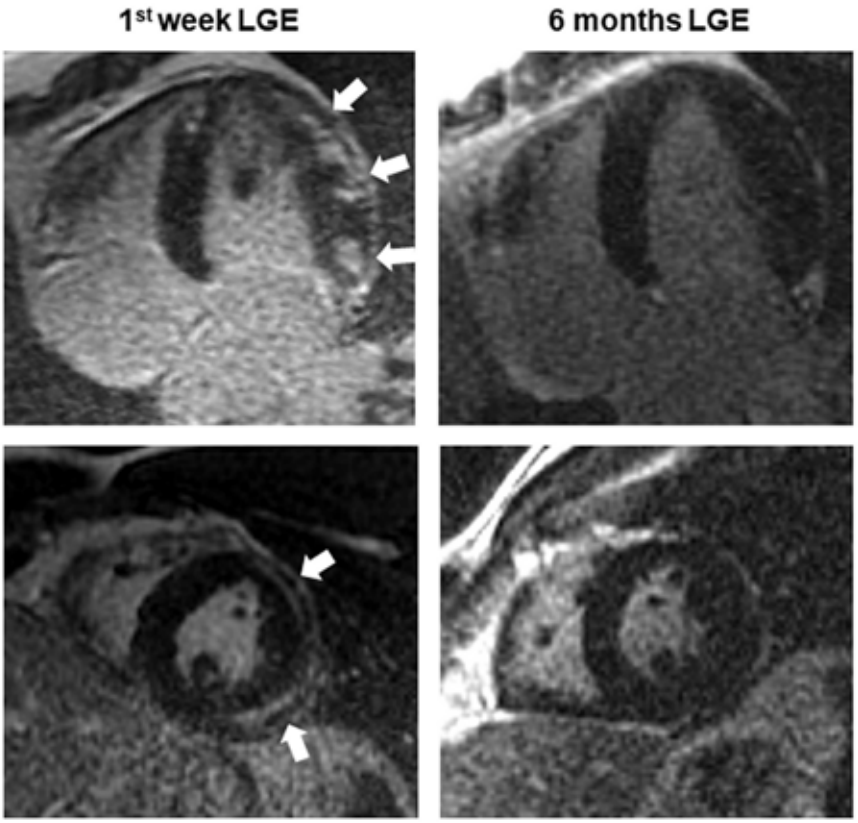

Figure 1. An example of a patient with acute myocarditis. Magnetic resonance was performed within the first week and 6 months after the onset of symptoms. Late gadolinium enhancement (LGE) was seen at the first MR examination but had disappeared completely after 6 months.

than 30 years of age. A follow-up CMR examination was performed six months (median 177 days) after the first exam.

The population we studied involved 187 patients (82 men, mean age 33 ± 13 years). Scans were interpreted by three CMR experts blinded to the clinical data. LV global and regional function on bSSFP images, myocardial edema on T2-weighted images, and LGE on post-contrast T1-weighted GRE images were assessed both in the baseline and follow-up CMR scans. Myocardial hyperemia was evaluated as previously reported [10] using post-contrast cine-SSFP images. Clinical follow-up of all enrolled patients was carried out for a median time of 7 years. During the follow-up, the occurrence of several major events was recorded. These were: cardiac death; resuscitated cardiac arrest; ventricular assist device implantation;, transplantation; and appropriate implantable cardioverter defibrillator (ICD) shock.

RESULTS

The main findings of our study were that at six months, myocardial edema had resolved in the majority of patients (84%), and complete healing with absence of edema and LGE, was seen in 11% of patients [Figure 1]. Moreover, LGE had disappeared completely in 10% of the patients, and the extent of LGE, as measured by the number of myocardial segments involved, decreased in almost half of the patients, remained unchanged in 30%, and increased in 14% of the patients. Surprisingly, patients with LGE but without edema had a poorer prognosis than those with LGE and persistent edema Likewise those patients with an increased extent of LGE at follow-up CMR had a poorer prognosis than those with an unchanged/decreased extent of LGE. Finally, midwall septal LGE and LGE without edema were independent predictors of cardiac events.

"…. in AM cases with evidence of edema, LGE should not be considered as a sign of irreversible myocardial damage…."

DISCUSSION

In interpreting these findings, we may speculate that LGE in AM is not necessarily due only to irreversible damage. A possible alternative explanation may be that LGE is caused by various conditions such as replacement fibrosis, edema, and protein overload (amyloidosis)that enlarge the interstitial space and consequently increase the volume in which gadolinium is distributed in the myocardium, thus causing a much slower wash-out rate [11]. The interstitial space could be increased not only by fibrosis but also by edema and inflammatory cell infiltration. Gadolinium contrast agents cannot enter into healthy and intact cells. However when macrophages phagocytize necrotic myocytes, then interstitial fluids containing gadolinium might in this way be incorporated into phagosomes.

Furthermore, inflammatory cells may obstruct lymphatic vessels, so slowing the wash-out of gadolinium from the interstitial space and participating in the creation of interstitial edema. For these and other reasons, it appears that, in AM cases with evidence of edema, LGE should not be considered as a sign of irreversible myocardial damage. This is emphasized by the finding that in some patients LGE actually disappears after six months.

The observation that in 14% of AM patients LGE increased, thus indicating a poorer survival rate, can be due to myocardial damage that had continued as the result of an autoimmune response or multiple relapse of myocarditis and can be associated with disease progression and worse outcome. Edema detected by CMR is only the "tip of the iceberg" in the inflammation process, and we postulate that in the chronic phase of AM, the autoimmune response might continue to induce myocardial injury albeit with slower progression and less aggressiveness than it does in the acute phase. In the chronic phase of AM, traditional CMR may not be sufficiently sensitive to

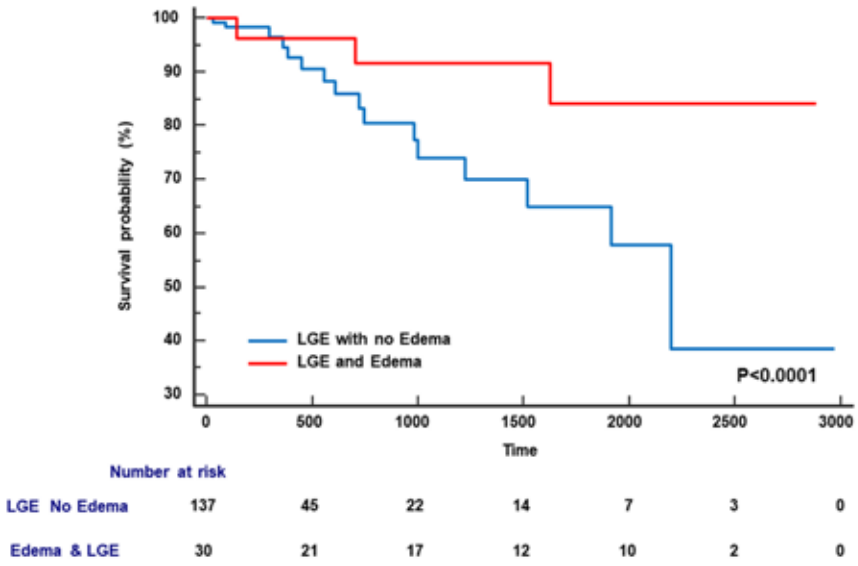

Figure 2: Kaplan Meier survival curves of patients with edema and late gadolinium enhancement, LGE, (as determined from six-months CMR examinations) compared to patients who only had LGE. It can be seen that patients with LGE and no edema had poorer prognosis. The presence of edema is associated with active inflammation and greater likelihood of recovery, whereas LGE alone may be considered as indicating definitive fibrosis. Figure modified from Aquaro *et al*, [8].

detect edema using the conventional T2-STIR technique. However, novel sequences such as T2 mapping could improve myocardial edema detection, increasing the sensitivity of CMR in both the subacute and chronic phases [12].

One last finding of our study that was somewhat surprising, was that patients with LGE and no edema had in fact a poorer prognosis than those with persistent edema [Figure 2]. The explanation of this observation is not immediately obvious. The only possible mechanism that can be postulated is that in patients with LGE and edema a potential healing process is still feasible, whereas in those without edema, LGE represents a definitive, irreversible fibrosis. From a prognostic point of view, the best independent predictors of cardiac events in our study population was thus found to be the presence of LGE without edema and a midwall septal pattern of LGE.

CONCLUSION

In conclusion we may say that in patients with AM and preserved LVEF, LGE should not be interpreted as necessarily indicating definitive fibrosis when edema is also observed, since the LGE disappears during follow-up in a considerable number of patients. CMR should be performed in all patients where there is a clinical suspicion of AM and, when positive, CMR should be repeated at six months after symptom onset in order to assess the evolution of the signs of myocarditis. The presence of isolated LGE without edema six months after symptom onset is associated with a poorer prognosis, particularly when it involves the midwall layer of the interventricular septum. LGE without edema is to be considered as evidence of irreversible damage due to reparative fibrosis, whereas the persistence of edema, found in approximately one-third of patients, is a marker of ongoing inflammation and could be associated with a residual chance of complete recovery.

"…. the persistence of edema, found in approximately one-third of patients, is a marker of ongoing inflammation and could be associated with a residual chance of complete recovery…."

FUTURE PROSPECTS

In the future, studies should address and confirm our findings by the use of novel CMR sequences, mainly parametric imaging, in order to characterize the evolution and prognostic value of native T1 and T2 extracellular volume mapping in patients with acute myocarditis.

REFERENCES

1. Grigoratos C, Di Bella G, Aquaro GD. Diagnostic and prognostic role of cardiac magnetic resonance in acute myocarditis. Heart Fail Rev. 2019;24:81–90.
2. Aquaro GD *et al*. Role of right ventricular involvement in acute myocarditis, assessed by cardiac magnetic resonance. Int J Cardiol. 2018;271:359–365.
3. Di Bella G *et al*. Clinical Value and Prognostic Impact of Pericardial Involvement in Acute Myocarditis. Circ Cardiovasc Imaging. 2019;12: e008504.
4. Dastidar AG *et al*. Prognostic Role of CMR and Conventional Risk Factors in Myocardial Infarction With Nonobstructed Coronary Arteries. JACC Cardiovasc Imaging. 2019; 12: 1973–1982.
5. Aquaro GD *et al*. & Cardiac Magnetic Resonance Working Group of the Italian Society of Cardiology. Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function: ITAMY Study. J Am Coll Cardiol. 2017; 70: 1977–1987.
6. Gulati A *et al*. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA. 2013; 309: 896–908.
7. Mahrholdt H *et al*. Presentation, Patterns of Myocardial Damage, and Clinical Course of Viral Myocarditis. Circulation [Internet]. 2006 [cited 2020 Jun 9];114:1581–1590. Available from: *https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.105.606509*
8. Aquaro GD *et al*. Prognostic Value of Repeating Cardiac Magnetic Resonance in Patients With Acute Myocarditis. Journal of the American College of Cardiology [Internet]. 2019 [cited 2020 Jun 9];74:2439–2448. Available from: *https://linkinghub.elsevier.com/retrieve/pii/S0735109719377368*
9. Friedrich MG *et al*. & International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009; 53: 1475–1487.
10. Perfetti M *et al*. A fast and effective method to assess myocardial hyperemia in acute myocarditis by magnetic resonance. Int J Cardiovasc Imaging. 2014; 30: 629–637.
11. Kim RJ *et al*. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000; 343: 1445–1453.
12. von Knobelsdorff-Brenkenhoff F *et al*. Detection and Monitoring of Acute Myocarditis Applying Quantitative Cardiovascular Magnetic Resonance. Circ Cardiovasc Imaging. 2017;10(2):e005242