JACC: CARDIOVASCULAR IMAGING VOL. 7, NO. 3, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2013.10.011

# CMR Sensitivity Varies With Clinical Presentation and Extent of Cell Necrosis in Biopsy-Proven Acute Myocarditis

Marco Francone, MD, PhD,* Cristina Chimenti, MD, PhD,†‡ Nicola Galea, MD,* Fernanda Scopelliti, PhD,§ Romina Verardo, PhD,§ Roberto Galea, MD,‖ Iacopo Carbone, MD,* Carlo Catalano, MD,* Francesco Fedele, MD,† Andrea Frustaci, MD†§
*Rome, Italy*

**OBJECTIVES** The aim of this study was to determine whether clinical presentation and type of cell death in acute myocarditis might contribute to cardiac magnetic resonance (CMR) sensitivity.

**BACKGROUND** Growing evidence indicates CMR is the reference noninvasive tool for the diagnosis of acute myocarditis. However, factors affecting CMR sensitivity are still unclear.

**METHODS** We retrospectively evaluated 57 consecutive patients with a diagnosis of acute myocarditis made on the basis of clinical history (≤3 months) and endomyocardial biopsy evidence of lymphocytic infiltrates (≥14 infiltrating leukocytes/mm$^2$ at immunohistochemistry) in association with damage of the adjacent myocytes and absence or minimal evidence of myocardial fibrosis. CMR acquisition protocol included T2-weighted (edema), early (hyperemia), and late (fibrosis/necrosis) gadolinium enhancement sequences. Presence of ≥2 CMR criteria denoted myocarditis. Type of cell death was evaluated by using in situ ligation with hairpin probes.

**RESULTS** Three clinical myocarditis patterns were recognized: infarct-like (pattern 1, n = 21), cardiomyopathic (pattern 2, n = 21), and arrhythmic (pattern 3, n = 15). Tissue edema was observed in 81% of pattern 1, 28% of pattern 2, and 27% of pattern 3. Early enhancement was evident in 71% of pattern 1, 67% of pattern 2, and 40% of pattern 3. Late gadolinium enhancement was documented in 71% of pattern 1, 57% of pattern 2, and 47% of pattern 3. CMR sensitivity was significantly higher in pattern 1 (80%) compared with pattern 2 (57%) and pattern 3 (40%) ($p < 0.05$). Cell necrosis was the prevalent mechanism of death in pattern 1 compared with pattern 2 ($p < 0.001$) and pattern 3 ($p < 0.05$), whereas apoptosis prevailed in pattern 2 ($p < 0.001$ vs. pattern 1 and $p < 0.05$ vs. pattern 3).

**CONCLUSIONS** In acute myocarditis, CMR sensitivity is high for infarct-like, low for cardiomyopathic, and very low for arrhythmic clinical presentation; it correlates with the extent of cell necrosis–promoting expansion of interstitial space. (J Am Coll Cardiol Img 2014;7:254–63) © 2014 by the American College of Cardiology Foundation

From the *Department of Radiology, Oncology and Pathology, La Sapienza University, Rome, Italy; †Department of Cardiovascular, Respiratory, Nefrologic, Anestesiologic and Geriatric Sciences, La Sapienza University, Rome, Italy; ‡IRCCS San Raffaele La Pisana, Rome, Italy; §IRCCS L. Spallanzani, Rome, Italy; and the ‖Fondazione IRCSS Ospedale Maggiore Policlinico Università degli Studi di Milano, Rome, Italy. The study was supported by the Italian Ministry of Health (grants RF-2009-1511346, RBFR081CCS, and MRAR08Y012). All authors have reported that they have no relationships relevant to the contents of this paper to disclose. The first 2 authors contributed equally to this study.

Manuscript received September 3, 2013; revised manuscript received October 8, 2013, accepted October 10, 2013.

Clinical diagnosis of acute myocarditis is often challenging due to the wide spectrum of its presentations, ranging from a subclinical disease characterized by flu-like symptoms to an "infarct-like" syndrome with acute chest pain or to sudden death related to the new onset of arrhythmias and complete heart block (1). The true incidence of this condition is therefore unknown and certainly underestimated in the community. The diagnosis is usually presumptive, and serologic test results and conventional imaging tools such as echocardiography or selective coronary angiography fail to provide a definite diagnosis in most of the cases (1). For these reasons, endomyocardial biopsy (EMB), with use of the Dallas criteria, immunohistochemistry, and polymerase chain reaction for viral genomes, is still regarded as the diagnostic gold standard technique providing additional insight about possible underlying etiologies and pathogenic mechanisms (2).

See page 264

Establishing a correct diagnosis of the disease may be crucial for a tailored therapeutic strategy (immunosuppressive, immunomodulatory, and/or antiviral) to reduce risk of progression to chronic active disease and dilated cardiomyopathy (3). However, widespread utilization of the EMB is limited in clinical practice by its invasiveness and by the possible associated inherent procedural risks; its use in acute myocarditis has been indicated when functional impairment, malignant arrhythmias, or failure of supportive treatment occur (4).

In this clinical setting, cardiac magnetic resonance (CMR) has become the reference noninvasive diagnostic tool allowing identification of the various hallmarks of myocardial inflammation represented by edema, fibrosis, and hyperemia and combining its unique tissue characterization capabilities with assessment of biventricular regional and global function (5–8).

Clinical experience, however, has shown that CMR signal abnormalities are variably observed in acute myocarditis, and sensitivity of the examination may be influenced by the pattern and extent of myocardial involvement, which actually reflects clinical presentation of disease. In the present article, we report CMR sensitivity in 57 patients with biopsy-proven acute myocarditis and its relationship with type of clinical presentation and mechanism of cell death.

## METHODS

**Patient population.** We retrospectively reviewed our clinical database of 118 patients admitted to our institution during a 3-year period (from March 2008 to April 2011) with a clinical suspicion of acute myocarditis (clinical history ≤3 months) who underwent both CMR and EMB. Fifty-seven patients (48%) had a histological diagnosis of acute myocarditis based on histology and immunohistochemistry and represented our patient population. In particular, the histologic diagnosis of acute myocarditis included evidence of lymphocytic infiltrates in association with damage of the adjacent myocytes, according to the Dallas criteria (9) implemented by the immunohistochemical definition of inflammatory cells (≥14 infiltrating leukocytes/mm$^2$, preferably T lymphocytes or activated T cells) (10) and the absence or minimal evidence of myocardial fibrosis, suggesting an acute process.

Patients were excluded from the analysis if there was evidence of significant coronary artery disease or valvular abnormalities, systemic diseases, and a clinical history ≥3 months. The local ethics committee provided approval for this investigation, and the patients gave their written informed consent.

**CMR acquisition protocol.** CMR imaging was performed with a 1.5-T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) using a body and phased array coil. The body coil was adopted for measurements of the relative signal intensities of the myocardium and skeletal muscle because of its more homogeneous signal.

Cine steady-state free precession (cine-SSFP) CMR images were acquired during breath-holds in the short-axis, 2-chamber, and 4-chamber planes; on short-axis images, the left ventricle was completely encompassed from the base to the apex, acquiring a total of 10 to 12 images. Cine-SSFP images were obtained using the following parameters: repetition time 51.3, echo time 1.21, a flip angle of 45°, an 8-mm slice thickness, a matrix of 256 × 256, a field of view ranging from 340 to 400 mm, and a voxel size of 2.0 × 1.3 × 8.0 mm.

For T2-weighted short-tau inversion recovery (T2w-STIR) imaging, a breath-hold black-blood, segmented turbo spin echo technique was adopted, using a triple inversion recovery preparation module (repetition time, 2 R-to-R intervals; echo time 75 ms; flip angle 180°; inversion time 170 ms; slice thickness 8 mm; no interslice gap; field of view 340 to 400 mm; matrix 256 × 256; and voxel size 2.3 × 1.3 × 8 mm). Technical details of this sequence have been described elsewhere (11).

**ABBREVIATIONS AND ACRONYMS**

**Cine-SSFP** = cine steady-state free precession

**CMR** = cardiac magnetic resonance

**ECG** = electrocardiogram

**EER** = early enhancement ratio

**EMB** = endomyocardial biopsy

**Gd-BOPTA** = gadobenate dimeglumine

**LGE** = late gadolinium enhancement

**LV** = left ventricular

**T2w-STIR** = T2-weighted short-tau inversion recovery