Characterization of Benign Myocarditis Using Quantitative Delayed-Enhancement Imaging Based on Molli T1 Mapping

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Abstract: Delayed contrast enhancement after injection of a gadolinium-chelate (Gd-chelate) is a reference imaging method to detect myocardial tissue changes. Its localization within the thickness of the myocardial wall allows differentiating various pathological processes such as myocardial infarction (MI), inflammatory myocarditis, and cardiomyopathies. The aim of the study was to characterize benign myocarditis using quantitative delayed-enhancement imaging and to investigate whether the measure of the extracellular volume fraction (ECV) can be used to discriminate between MI and myocarditis.

In 6 patients with acute benign myocarditis (32.2 ± 13.8 year-old, subepicardial late gadolinium enhancement [LGE]) and 18 patients with MI (52.3 ± 10.9 year-old, subendocardial/transmural LGE), myocardial T1 was determined using the Modified Look-Locker Imaging (MOLLI) sequence at 3 Tesla before and after Gd-chelate injection. T1 values were compared in LGE and normal regions of the myocardium. The myocardial T1 values were normalized to the T1 of blood, and the ECV was calculated from T1 values of myocardium and blood pre- and post-Gd injection.

Both inflammatory process and chronic fibrosis induce LGE (subepicardial in myocarditis and subendocardial in MI). The present study demonstrates that the determination of T1 and ECV is able to differentiate the 2 histological patterns.

Further investigation will indicate whether the severity of ECV changes might help refine the predictive risk of LGE in myocarditis.

Abbreviations: blood post = blood after gadolinium administration, blood pre = blood before gadolinium administration, ECV = extracellular volume fraction, Gd = Gadolinium, LGE = Late Gadolinium Enhancement, MI = myocardial infarction, MOLLI = Modified Look-Locker Imaging, MRI = Magnetic Resonance Imaging, myo post = myocardium after gadolinium administration, myo pre = myocardium before gadolinium administration, PSIR = Phase-Sensitive Inversion Recovery, TrueFISP = True Fast Imaging and Steady Precession.

OBJECTIVES

Cardiac nuclear magnetic resonance imaging (MRI) allows noninvasive characterization of myocardial tissue. Expansion of the interstitial space, or areas wherein cellular membrane permeability is abnormally high are visualized as hyper-intense signals on T1w images acquired at the pseudo steady-state phase after injection of a gadolinium chelate (Gd-chelate), and are commonly referred to “late gadolinium enhancement” (LGE). Fibrosis, inflammatory processes as well as membrane leakage are associated with disturbances of the distribution volume of Gd-chelates and LGE imaging is currently used as a reference method to investigate these structural changes. Location of enhanced areas within the thickness of the myocardial wall allows differentiating various pathological processes such as myocardial infarction (MI), inflammatory myocarditis, or cardiomyopathies. Typical LGE localization is subendocardial or transmural in MI, mid-wall in cardiomyopathies, and subepicardial in myocarditis.

The significance of LGE is not the same for the different pathologies. In chronic MI, Gd-chelates remain exclusively extracellular. The interstitial volume distribution in the fibrous scar of chronically infarcted zones is responsible for the LGE and speaking of increase in extracellular volume fraction (ECV) is well appropriate in this context. In myocarditis, the picture is very different. Endomyocardial biopsies show myocyte lesions, necrosis, infiltration of inflammatory cells, and interstitial edema. Gadolinium chelates not only diffuse in the interstitial inflammatory areas but also penetrate through the leaky sarcolemma in necrotic or dying cardiomyocytes. Areas of LGE are no longer just associated with an expansion of the extracellular volume.

The extent of these LGE areas has a strong prognostic value, which has given the technique a considerable clinical relevance. A recent improvement to this method has been the introduction of sequences that can measure the longitudinal relaxation time (T1) quantitatively in a clinical setting. When they are acquired before and after injection of gadolinium chelates, the ECV can be calculated.

The main objectives of the study were to characterize benign myocarditis using quantitative delayed-enhancement imaging and to investigate whether the measure of the ECV of Gd-chelates can be used as an additional variable to discriminate between MI and myocarditis.
PATIENTS AND METHODS

Patients
Patient clinical characteristics are summarized in Table 1. A myocarditis was clinically suspected in 6 consecutive patients on the basis of the following symptoms: chest pain after an acute episode of fever with inflammatory syndrome, ECG changes mimicking a pericarditis, elevation of cardiac enzyme levels (phosphocreatine kinase, troponin I). All patients underwent a coronary arteriography that was diagnosed as normal. Their cardiac MRI features were compared with those of 18 consecutive patients who were previously referred to the coronary care unit for an MI (chest pain, ST elevation on ECG, cardiac enzyme elevation). The coronary arteriography revealed a complete occlusion. A percutaneous angioplasty of the culprit lesion was immediately performed with restoration of the coronary flow. The delay between the onset of the MI and MRI examination was 26.0 ± 37.7 months (range 18–2356). For these patients, MRI was performed during routine clinical care in the intensive care unit.

Magnetic Resonance Imaging Protocol
Patients underwent cardiac MRI on a 3T clinical scanner (Magnetom Trio Tim; Siemens AG Healthcare Sector, Erlangen, Germany). After localization of the heart, cine imaging was performed using a standard TrueFISP sequence: 2-chamber view, 4-chamber view and 10 to 12 contiguous short-axis slices. The left ventricular volumes, ejection fraction, and ventricular mass were calculated using Segment® v1.8R0553, Medviso AB, Lund Sweden. T1 maps in short-axis orientation were acquired at 3 slices levels (basal, mid-ventricular, and apical) with a non-product Modified Look-Locker Imaging sequence (MOLLI) before gadolinium injection.9 This sequence consisted of 3 inversion blocks followed by 3, 3, and 5 image acquisitions synchronized to diastole but with variable inversion times. Acquisition blocks were separated by a 3-heartbeat recovery phase. The entire dataset was collected during 1 breath-hold at end-expiration. Main parameters were imaging recovery phase. The entire dataset was collected during 1 times. Acquisition blocks were separated by a 3-heartbeat.

T1 and ECV values are summarized in Table 2. Before gadolinium injection, T1 values and the ratio T1 of the myocardium/T1 of the blood (T1 myo/T1 blood) measured in normal areas of the myocardium and of blood were not significantly different between myocarditis and MI. However, T1 values of pathological regions were lower in myocarditis than in MI (T1 = 1179.2 ± 48.3 ms vs 1334.5 ± 123.7 ms, P = 0.001). Ten minutes after injection of Gad-DOTA, T1 values of normal myocardium and of blood were identical in the 2 groups, but T1 of pathological areas was higher in myocarditis than in MI patients (T1 = 446.8 ± 45.8 vs 360.5 ± 66.9 ms, P = 0.003), Figure 3A, and the ratio T1myoc/T1 blood = 1.35 ± 0.20 vs 1.02 ± 1.81, P = 0.008).

The calculated ECV was lower in LGE regions of myocarditis patients than in LGE areas of MI patients (34.5 ± 3.3% vs 53.8 ± 13.0%, P = 0.0001), Figure 3B. It was also noted that the normal myocardium ECV was slightly but significantly lower in myocarditis than in MI (22.8 ± 2.7% vs 26.2 ± 3.4%, P = 0.02).

Statistical Analysis
All values are reported as mean ± standard deviation. Unpaired Student t tests were used to compare continuous variables (expressed as mean ± SD). Chi-square tests were used to compare percentages. A P value <0.05 was considered as statistically significant. Analyses were performed with IBM® SPSS® statistics version 17.0.

RESULTS

Clinical Data
The demographic and clinical data are summarized in Table 1. Patients in the myocarditis group were younger than patients in the MI group (P = 0.001). Patients with myocarditis had normal coronary arteries; patients with MI had a 1-vessel disease (44.4 %), a 2-vessel disease (38.9 %), and a 3-vessel disease (16.7 %). A coronary angioplasty was performed in 83.3 % of patients of the MI group before MRI.

Cardiac Magnetic Resonance Findings
End-diastolic volume, left-ventricular mass, and ejection fraction were nearly normal in the 2 groups. In myocarditis, LGE was subepicardial in lateral, (n = 1), infero-lateral (n = 2), antero-lateral (n = 2) positions, or diffuse (n = 1). After MI, LGE was subendocardial in 12 patients and transmural in 6 patients. The localization was anterior (n = 1), antero-apical (n = 1), antero-lateral (n = 1), antero-septal (n = 1), antero-septo-apical (n = 9), lateral (n = 1), and inferior (n = 4). There was a good agreement between the location of the culprit lesion on the coronary tree and the localization of LGE areas. There was also an excellent agreement between LGE imaging and corresponding T1 maps in myocarditis (Fig. 1) and MI (Fig. 2).

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DISCUSSION

Classically, cardiac MRI distinguishes MI and myocarditis on the basis of the topographical distribution of LGE: the former generating subendocardial to transmural LGE, and the latter being associated essentially with sub-epicardial LGE. In this study, we showed that quantitative T1 mapping after gadolinium injection reveals another important difference: the distribution volume fraction of Gd-chelates was found to be significantly lower in myocarditis patients than in patients with chronic MI.\textsuperscript{13,14}

The visual search for LGE has become a routine practice in cardiac MRI and has been described in many conditions: chronic MI, primary cardiomyopathies (dilated and hypertrophic), acute myocarditis, inflammatory cardiomyopathies (Churg and Strauss syndrome), aortic stenosis, hypertension, congenital heart disease, and infiltrative cardiomyopathies.

TABLE 1. Clinical Characteristics

| Characteristic               | Myocarditis (N = 6) | Myocardial Infarction (N = 18) | P    |
|-----------------------------|---------------------|--------------------------------|------|
| Age (years)                 | 32.2 ± 13.8         | 52.3 ± 10.9                    | 0.001|
| Gender                      | Male/Female         | 6/0                            | 17/1 | 0.54 |
| NYHA functional class       | 1.00                | 1.22                           | 0.16 |
| Documented CAD              | 1 vessel            | 0 (0%)                         | 8 (44.8 %) | 0.06 |
|                             | 2 vessels           | 2 (11.2 %)                     | 7 (38.9 %) | 0.33 |
|                             | 3 vessels           | 4 (21.1 %)                     | 3 (16.7 %) | 0.38 |
| Culprit lesion              | Left anterior descending artery | 0 (0%) | 12 (66.7 %) |
|                             | Circumflex artery   | 0 (0%)                         | 2 (11.2 %) | 0.33 |
|                             | Right coronary artery | 0 (0%) | 4 (21.1 %) | 0.07 |
|                             | Previous percutaneous angioplasty | 0 (0%) | 15 (83.3 %) | 0.07 |
| CPK                         | 472 ± 28            | 2323 ± 3076                    | 0.06 |
| Troponin I                  | 8.6 ± 13            | 98 ± 161                       | 0.33 |
| Indexed LV EDV (mL/m²)      | 93.7 ± 11.9         | 82.8 ± 37.8                    | 0.07 |
| LV ejection fraction (%)    | 70.0 ± 9.5          | 64.6 ± 8.2                     | 0.82 |
| Indexed LV mass (g/m²)      | 66.7 ± 10           | 82.7 ± 35.4                    | 0.38 |

CAD = coronary artery disease, CPK = phosphocreatine kinase, EDV = end-diastolic volume, ESV = end-systolic volume, LV = left ventricle.

FIGURE 1. Diastolic image of lateral subepicardial LGE (arrows) and corresponding T1 maps before and after gadolinium in myocarditis. IR-TFL = inversion recovery turbo FLASH; PSIR = phase-sensitive inversion recovery.

FIGURE 2. Diastolic image of inferior subendocardial LGE (arrows) and corresponding T1 maps before and after gadolinium in myocardial infarction. IR-TFL = inversion recovery turbo FLASH; PSIR = phase-sensitive inversion recovery.
amyloidosis, sarcoidosis, Fabry’s disease, glycogen storage disease.

Only a few studies have quantitatively evaluated the LGE using T1 mapping. The calculated ECV in the fibrous scar of MI areas was found at 53.8 ± 13.0% (n = 18) in our study, 68.5 ± 8.6% (n = 33) in the study by Kellman et al,15 and 51 ± 8% (n = 36) in the study by Ugander et al.11 On the contrary, the volume fraction of Gd-DOTA distribution was measured at 34.5 ± 3.3% (n = 6) in the LGE areas of myocarditis group of our study and at 39% to 56% (n = 7) in study by Kellman et al.15 Between both studies, there were some differences in the absolute values reported, but T1 increases after Gd-DOTA were significantly lower in myocarditis patients than in the MI group.

LGE is clinically important, as its strong prognostic value has been established in various diseases. In acute MI, Larose et al16 demonstrated that the event-free survival at 6 months was higher when the LGE volume was <23% than >23% (P = 0.0001). In nonischemic dilated cardiomyopathy (Assomull et al),17 midwall fibrosis was present in 35% of patients and was associated with a higher rate of mortality and hospitalization (P = 0.01). In hypertrophic cardiomyopathy, the absence of myocardial fibrosis is an independent predictor of event-free survival. In patients with severe aortic valve disease, Azevedo et al18 demonstrated that the amount of myocardial fibrosis was an independent predictor of mortality after aortic valve replacement.

These studies were based on the presence or absence of LGE and its extent in the myocardium. Myocardium T1 quantification by T1 mapping sequences is a recent technique and its prognostic significance has not yet been evaluated for myocarditis. It will be important to determine whether quantitative T1 mapping will refine the prognostic value of LGE and the outcome prediction of either recovery or development of dilated cardiomyopathy.

Myocardial lesions might either be focal (“macroscopic”) with areas of LGE or diffuse (“microscopic”) with normal-

### TABLE 2. T1 and EVF Values, Before and After Gadolinium, in Myocarditis and Myocardial Infarction

| Characteristic | Myocarditis (N = 6) | Myocardial Infarction (N = 18) | P |
|----------------|---------------------|-------------------------------|---|
| T1 normal regions before Gd (ms) | 1155.3 ± 63.9 | 1212.3 ± 98.6 | 0.26 |
| T1 LGE regions before Gd (ms) | 1179.2 ± 48.3 | 334.5 ± 123.7 | 0.0001 |
| T1 blood before Gd (ms) | 1756.5 ± 26.7 | 1775.1 ± 72.2 | 0.36 |
| T1 normal regions after Gd (ms) | 556.0 ± 50.3 | 540.6 ± 12.3 | 0.56 |
| T1 LGE regions after Gd (ms) | 446.8 ± 45.8 | 360.5 ± 66.9 | 0.003 |
| T1 blood after Gd (ms) | 346.5 ± 62.4 | 357.2 ± 70.0 | 0.73 |
| T1 normal regions/T1 blood before Gd | 0.65 ± 0.03 | 0.68 ± 0.06 | 0.33 |
| T1 LGE regions/T1 blood before Gd | 0.67 ± 0.02 | 0.75 ± 0.06 | 0.009 |
| T1 normal regions/T1 blood after Gd | 1.47 ± 0.28 | 1.56 ± 0.08 | 0.45 |
| T1 LGE regions/T1 blood after Gd | 1.35 ± 0.20 | 1.02 ± 1.81 | 0.008 |
| ECV normal myocardium (%) | 22.8 ± 2.7 | 26.2 ± 3.4 | 0.02 |
| ECV LGE regions (%) | 34.5 ± 3.3 | 53.8 ± 13.0 | 0.0001 |

ECV = extracellular volume fraction, Gd = Gadolinium, LGE = late gadolinium enhancement.

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**FIGURE 3.** (A) T1 LGE area/T1 blood values after Gd-DOTA for myocarditis (n = 6) and myocardial infarction (n = 18). Box and whisker plots show median, 25, and 75 percentiles and range. T1 of myocardium with LGE was significantly higher in myocarditis than in myocardial infarction (P = 0.008). (B) ECV values (%) for myocarditis (n = 6) and myocardial infarction (n = 18). ECV of myocardium with LGE was significantly lower in myocarditis than in myocardial infarction (P = 0.0001).
appearing myocardium: only quantitative T1 mapping may allow to detect changes in the distribution volume of Gd-chelates. In the present study, myocardial T1 was only measured in patients with focal LGE (myocarditis, MI). Further studies must explore the ECV of patients with normal-appearing myocardium, without focal LGE\(^1\) and determine whether the measure of Gd-chelate distribution volume fraction may help predict long-term survival in benign and severe myocarditis in larger series.

ECV of normal-appearing left-ventricular segments appeared slightly but significantly higher in the MI group than in the myocarditis group (26.2 ± 3.4% vs 22.8 ± 2.7%, \(P<0.02\)). In his study about remodeling after MI, W. Chan et al\(^1\) demonstrated that post-Gd T1 values in remote myocardium were shorter than controls, suggesting an interstitial tissue expansion in noninfarcted areas.

The limitation of the MOLLI sequence is the inconsistent R-R period during breath-holds. A new method\(^2\) has recently been developed incorporating a nonrigid motion correction (MOCO) before applying the pixel-wise fit. T1 measurements are also affected by various factors including \(B_0\) and \(B_2\) fields inhomogeneity, as well as the patient renal clearance.\(^2\) In the present study, the time between diagnosis of myocarditis and MI imaging could be responsible for the differences in calculated ECV: range: 18 days (acute MI) to 2356 days (chronic) in MI, 2 to 6 days in myocarditis.

In conclusion, this study demonstrated that quantitative T1 mapping and calculation of Gd-chelate distribution volume fraction were able to differentiate 2 mechanisms of myocardial diseases responsible for LGE: inflammatory process in myocarditis and fibrous scar in chronic MI.

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