Predictive value of CMR criteria for LV functional improvement in patients with acute myocarditis

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Aim
We assessed the value of cardiovascular magnetic resonance (CMR) criteria (‘Lake Louise Criteria’) for predicting left ventricular (LV) functional improvement in patients with acute myocarditis.

Methods and results
We studied 37 patients who referred for acute myocarditis during clinically acute myocarditis and after a 12-month follow-up. CMR sequences sensitive for oedema, hyperaemia, and irreversible injury were applied. Global and regional oedema were defined using published quantitative signal intensity (SI) cut-off values (area with an SI of >2 SD above visually normal myocardium). LV function was analysed using six long-axis views, with an increase of at least 5% of left ventricular ejection fraction considered as improvement. Out of a total of 37 patients, 29 met the CMR Lake Louise criteria (LL+) and eight did not (LL−). Baseline and 12-month ejection fraction (EF) were significantly lower in LL+ (53.2 ± 8 vs. 62.2 ± 5, P = 0.007 and 58.9 ± 4 vs. 62.9 ± 5, P = 0.045, respectively). At follow-up, EF increased in LL+ but remained unchanged within normal limits in LL− groups (delta EF: 5.7 ± 9.8 vs. 0.7 ± 2.0). The presence of global or regional myocardial oedema was strongly associated with an increase of EF ≥ 5%. In a multivariate analysis, the presence of global and/or regional oedema on admission was the only independent predictor of an increase of EF (P = 0.046).

Conclusion
In patients with clinically suspected acute myocarditis, the presence of positive CMR criteria is associated with LV function recovery. Myocardial oedema as defined by CMR was the strongest parameter, indicating that the observed increase of EF may be due to the recovery of reversibly injured (oedematous) myocardium.

Keywords
Cardiovascular magnetic resonance • Criteria • Prognostic • Acute myocarditis

Introduction
Over the last decade, cardiovascular magnetic resonance (CMR) has become a key non-invasive diagnostic tool for assessing myocarditis.1,2 In addition to the accuracy for assessing functional and morphological ventricular anatomy, structure, and function, CMR allows for assessing the activity of inflammatory changes using markers for myocardial oedema, hyperaemia, capillary leak, and irreversible injury applying a combination of non-contrast (T2-weighted imaging) and gadolinium-enhanced [early and late gadolinium enhancement (LGE)] techniques.3,4 After early reports on T2-weighted CMR imaging in children with myocarditis,5 gadolinium-enhanced magnetic resonance imaging was introduced as a marker for myocardial inflammation6 and later LGE was utilized to detect irreversible myocardial injury in patients with myocarditis.7,8 Based on these approaches, a group of CMR and myocarditis experts proposed a set of diagnostic CMR criteria for myocarditis called ‘Lake Louise Criteria’, considered indicative of myocarditis in the presence of at least two of the following three findings:

(i) Global or regional myocardial oedema as defined by a myocardial signal intensity (SI) ratio as normalized to skeletal muscle of at least two (global oedema) and/or a myocardial region with at least two standard deviations (SDs) above remote normal tissue (regional oedema) in T2-weighted images,

(ii) Hyperaemia/capillary leakage as defined by an increased early gadolinium uptake [early Gd enhancement/early gadolinium enhancement (EGE) ratio of at least 4.0] on T1-weighted early Gd enhancement images, and

(iii) Irreversible myocardial injury in a non-ischaemic regional distribution pattern (areas with an SI of at least 2 SD above remote myocardium) in late Gd enhancement images.

If two or more of these criteria were obtained, myocardial inflammation can be predicted or ruled out with a diagnostic accuracy of 78%.9

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Consequently, CMR is increasingly accepted as the standard diagnostic test for myocarditis. However, the predictive value of these criteria on functional outcome is not known. The purpose of this study was to assess the Lake Louise (LL) Criteria for their predictive value with respect to left ventricular (LV) functional improvement in patients with acute myocarditis.

**Methods**

**Study population**

We prospectively studied patients referred to our centre for acute myocarditis with (i) recent onset symptoms as defined by at least one of the following: dyspnoea, chest discomfort, and fatigue; (ii) evidence for myocardial injury defined by: newly abnormal electrocardiogram (ECG) (ST changes, conduction defects) or elevated troponin levels in the absence of renal failure or new unexplained LV dysfunction; and (iii) absence of relevant coronary artery disease as defined by a coronary angiogram without stenosis of 50% or more (except for patients with low probability for coronary artery disease as defined by an age of < 35 years and absence of risk factors).

Exclusion criteria were (i) known pre-existing cardiovascular disease that could explain symptoms (e.g. valvulopathy, congenital heart disease, etc.), (ii) evidence of chronic myocarditis, or (iii) known contraindications to CMR. The local ethics committee approved the study, and all patients gave informed written consent.

**CMR imaging protocol**

CMR was performed using a 1.5T scanner (Magnetom Avanto™, Siemens Healthcare, Erlangen, Germany) 2.8 ± 1.6 days after the onset of symptoms. LV function was assessed using standard ECG-gated cine SSFP sequences in six long-axis views. For oedema imaging, a T2-weighted sequence (short-time of inversion triple inversion recovery) using a body coil was applied in three short-axis slices across basal, mid, and apical segments. For inflammatory markers reflecting hyperaemia and capillary leak, we used a T1-weighted turbo spin echo sequence before and during the first 3 min after intravenous (i.v.) contrast administration of 0.1 mmol Gd-DTPA per kg body weight. Ten to fifteen minutes after i.v. contrast administration, LGE images were acquired in short-axis slices covering the entire LV using a phase-sensitive inversion recovery gradient (slice thickness 10 mm, no gap; TE 3.32 ms, flip angle 25°, matrix 156 × 256; FOV 340–400 mm).

**CMR analysis**

All images were analysed by an observer blinded to all non-imaging data. For all analyses, certified CMR image evaluation software was used (cmr42, Circle Cardiovascular Imaging, Inc., Calgary, AB, Canada).

**LV parameters**

Endocardial and epicardial borders of the LV myocardium were manually traced, and end-diastolic, end-systolic volumes indexed (ESVI) to body surface area, ejection fraction (EF) were calculated. The change (delta) of these parameters was defined as value\_follow-up - value\_baseline.

**Oedema**

Global oedema was defined by a myocardial SI ratio LV myocardium over skeletal muscle in the same slice of at least 2.0. To ensure that slow-flowing blood is not included in the assessment, endocardial and epicardial borders were drawn carefully.

Regional oedema was identified semi-automatically using a computer-aided SI analysis with colour-coded display of relative SI, normalized to skeletal muscles. Regional oedema was defined as an area or a region with at least 10 conjoint pixels with an SI ratio of at least 2.0 (Figure 1).

**Increased EGE**

Myocardial early Gd enhancement was defined by %SI increase post- vs. pre-contrast and the EGE ratio was calculated by dividing the myocardial enhancement to skeletal muscle enhancement, using a cut-off of at least 45% for the myocardial enhancement and/or an EGE ratio of at least 4.0.

**Late gadolinium enhancement**

LGE images were visually assessed for the presence and location of the LGE using complete short-axis coverage. In patients with visual LGE, quantification of injury was performed by tracing endocardial and epicardial contours, excluding trabecles and papillary muscles. The Otsu-Auto-Threshold method, an automatic method for an optimal threshold, was used for quantifying LGE. This method automatically

![Figure 1: Assessment of regional myocardial oedema. (A) T2-weighted imaging in a patient with acute myocarditis and focal area of high SI within the lateral wall (arrow). (B) Computer-aided SI analysis with colour-coded display of relative SI, normalized to skeletal muscle. Blue indicates an SI ratio of the myocardium to skeletal muscle of two or more, indicating oedema, green indicates normal SI.](image-url)
Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total of patients (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>43 ± 16</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>29/8</td>
</tr>
<tr>
<td>ECG (ST-changes)</td>
<td>21 (57%)</td>
</tr>
<tr>
<td>Troponin T</td>
<td>0.5 ± 0.7 µg/L</td>
</tr>
<tr>
<td>Duration between symptoms and first CMR (days)</td>
<td>2.8 ± 1.6</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; CMR, cardiovascular magnetic resonance.

derives a threshold and calculates the area with an abnormal SI from the SI histogram without user input.11

Statistical analysis

All statistical analysis was performed using SPSS 19 for Mac. Data are presented as mean (SD). The normal distribution of data was assessed with a single sample Kolmogorov–Smirnov test. Independent samples and non-parametric t-tests were used to evaluate differences between groups. Sensitivity and specificity for increasing in EF were calculated. Multivariate linear backward analysis was used to identify independent predictors of LV function improvement. A P-value of < 0.05 was considered indicating statistical significance.

Results

Patients characteristics

A total of 37 patients were included in the study. Table 1 summarizes the characteristics of the overall population. The majority of patients were male with a positive troponin (24/37 patients, 65% had a troponin ≥ 0.07 mcg/L) and/or ST changes on ECG. Sixteen patients (43%) underwent a coronary angiogram, of which none showed significant coronary artery disease.

LL criteria: baseline and 12-month follow-up

The prevalence of each of the CMR criteria for myocarditis at baseline and at 1 year is shown in Figure 2.

A total of 29 patients fulfilled CMR diagnostic criteria for myocarditis and 8 did not. Twenty patients fulfilled all three LL criteria.

Global or regional oedema was present in 26 patients on admission; 8 patients had global oedema, 18 had regional oedema, and 2 patients had both. The prevalence of global oedema was similar in women (25%) and in men (24%).

At 1 year, only four patients had regional oedema, no patient had global oedema. EGE was positive in 28 patients on admission and in 8 patients at 1 year. All of these patients had abnormal EGE initially.

LGE was present in 25 patients on admission and in 16 patients at 1 year; 9 patients had a complete resolution of LGE. Three of eight female patients exhibited LGE lesions. All patients had a non-ischaeamic LGE pattern including midwall, sub-epicardial, or transmural but never limited to the sub-endocardium. The amount of LGE decreased significantly from the acute to the healed phase (11.7 ± 6.9 vs. 8.2 ± 3.5 g, respectively, P < 0.001).

Myocarditis at follow-up: a total of eight patients had the diagnosis of myocarditis at follow-up. Two patients had simultaneous regional oedema and EGE at 1 year. One patient had simultaneous regional oedema and LGE at 1 year. Five patients had simultaneous EGE and LGE at 1 year.

Change in LV parameters

Table 2 summarizes the changes in LV parameters according to the presence or absence of LL criteria. Patients with two or more positive criteria exhibited a significantly lower EF at baseline and at 1 year, significantly higher ESVI at baseline than those with no LL criteria. At follow-up, EF significantly increased in patients with positive LL criteria but not in patients without LL criteria. There was an increase of left ventricular ejection fraction (LVEF) of 6.6 ± 9.9% in patients with regional and/or global oedema at baseline vs. 0.2 ± 1.8% in patients without oedema. An increase (ΔEF 6.1 ± 9.8%) was also observed in patients with an increased EGE ratio at baseline, but not in patients without increased EGE ratio (ΔEF 0.5 ± 1.8%). Furthermore, there was an increase in patients without LGE, albeit

Table 2  CMR LV parameters at baseline and at 1 year according to the presence or absence of LL criteria

<table>
<thead>
<tr>
<th></th>
<th>LL+</th>
<th>LL−</th>
<th>Overall</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 29)</td>
<td>(n = 8)</td>
<td>(n = 37)</td>
<td></td>
</tr>
<tr>
<td>Baseline EF</td>
<td>53.2 ± 8</td>
<td>62.2 ± 5</td>
<td>55.1 ± 8</td>
<td>0.007</td>
</tr>
<tr>
<td>1 year EF</td>
<td>58.9 ± 4</td>
<td>62.9 ± 5</td>
<td>59.7 ± 5</td>
<td>0.045</td>
</tr>
<tr>
<td>Delta EF</td>
<td>5.7 ± 9.8</td>
<td>0.7 ± 2</td>
<td>4.6 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline ESVI</td>
<td>41.7 ± 11</td>
<td>31.1 ± 8</td>
<td>39.4 ± 12</td>
<td>0.024</td>
</tr>
<tr>
<td>1-year ESVI</td>
<td>34.7 ± 7</td>
<td>30.2 ± 7</td>
<td>33.7 ± 7</td>
<td>0.135</td>
</tr>
<tr>
<td>Delta ESVI</td>
<td>−7.8 ± 11</td>
<td>−0.8 ± 4</td>
<td>−5.7 ± 10</td>
<td>0.373</td>
</tr>
<tr>
<td>Baseline EDVI</td>
<td>88.6 ± 14</td>
<td>81.9 ± 19</td>
<td>87.2 ± 15</td>
<td>0.291</td>
</tr>
<tr>
<td>1-year EDVI</td>
<td>84.2 ± 13</td>
<td>81.3 ± 13</td>
<td>83.5 ± 13</td>
<td>0.563</td>
</tr>
<tr>
<td>Delta EDVI</td>
<td>−4.5 ± 8</td>
<td>−0.9 ± 9</td>
<td>−3.7 ± 8</td>
<td>0.110</td>
</tr>
</tbody>
</table>

LL, Lake Louise; EF, ejection fraction; ESVI, end-systolic volume indexed; EDVI, end-diastolic volume indexed.
variable ($\Delta$EF 5.1 ± 10%). Finally, there was a significant increase of EF in patients with myocarditis at 12 months ($\Delta$EF 10.6 ± 16%) as opposed to patients without myocarditis at baseline ($\Delta$EF 0.7 ± 2%).

To better understand the association between LL criteria and changes in LVEF, we divided the population into two groups according to the increase of EF ($\Delta$EF ≥ 5%) and the absence of increase ($\Delta$EF < 5%; Figure 3). LL criteria, especially the presence of global and/or regional oedema was strongly associated with an increase of EF ($P = 0.009$). The presence of an increased EGE ratio shows a strong, yet not significant trend to predict LV function recovery ($P = 0.051$). There was no relationship between the presence of LGE and the increase of EF over the course of myocarditis.

The presence of oedema had a sensitivity and specificity of 100 and 42%, respectively, for predicting an increase in EF.

**Predictors of an increase of systolic function**

Multiple linear regression analysis was used to identify independent predictors of an increase in LVEF from baseline. The strongest independent predictor was the presence of global and/or regional oedema (Table 3). We also conducted a linear regression analysis for prediction of changes in LVESVI. The presence of oedema was also the only independent predictor of changes in LVESVI (non-standardized coefficient $-10.5; P = 0.007$).

**Discussion**

In our study, the presence of CMR criteria for active myocarditis (LL criteria) was associated with lower EF and a higher end-systolic volume at baseline and a lower EF after 12 months. Oedema was the only independent predictor for improvement in systolic function and a decrease of end-systolic volume. Prognostic CMR data in myocarditis are still scarce. Recently, Grün et al. 17 analysed a large population of biopsy-proven viral myocarditis patients who underwent CMR within the 5 days of initial presentation. They found that presence of LGE was the best independent predictor of all-cause mortality and cardiac mortality. In a sub-group of 77 patients with CMR follow-up, LGE did not predict recovery. These results, however, cannot be compared with ours because in their study, the CMR diagnosis of myocarditis was based on biopsy and one CMR criterion only (LGE). In a recent study on 62 patients with acute onset cardiomyopathy, McLellan et al. 13 showed that global EGE predicts recovery of LV function whereas the presence of myocardial oedema or LGE alone was not predictors. However, in this retrospective study, only global oedema was assessed by STIR sequence and not regional oedema; moreover, only a few patients had myocardial oedema (T2 SI ratio 2.0 ± 0.1). In a small population, Wagner et al. 14 observed that EGE which is still increased 4 weeks after disease onset was associated with a lower EF and more symptoms after 30 months. Another study by Mavrogeni et al. 15 found that both EGE and LGE may predict heart failure.

Due to intra-cellular and interstitial oedema, tissue T2 relaxation time is increased and results in high SI areas on T2-weighted images. It sensitively indicates myocardial injury before it becomes irreversible 16 and is typically present for ~2–3 weeks. In our study, regional oedema was more frequent than global oedema. At follow-up, there was a resolution of myocardial oedema in the majority of patients (70% of patients had oedema initially vs. 10% at 1 year). Zagrosek et al. 17 provided CMR follow-up data on 36 patients 18 ± 10 months after myocarditis. In accordance to our study, they showed that global oedema (they did not report the presence or absence of regional oedema) and EGE were elevated in most of

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**Table 3** Multivariate analysis for predictors of increase in EF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-standardized coefficient</th>
<th>Standard error</th>
<th>P-value</th>
<th>Non-standardized coefficient</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>Reduced model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>−0.02</td>
<td>0.165</td>
<td>0.906</td>
<td>0.137</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Oedema+</td>
<td>0.448</td>
<td>0.215</td>
<td>0.046</td>
<td>0.440</td>
<td>0.162</td>
<td>0.10</td>
</tr>
<tr>
<td>EGE+</td>
<td>0.284</td>
<td>0.255</td>
<td>0.270</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGE+</td>
<td>−0.231</td>
<td>0.248</td>
<td>0.125</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EGE+, presence of early gadolinium enhancement; LGE+, presence of late gadolinium enhancement.
the patients (86 and 80%, respectively, at admission); both decreased during the follow-up. We also observed that the extent of high-intensity areas in LGE images decreased over time. We, however, found a smaller amount of LGE and observed complete resolution of LGE in a larger proportion of patients. The difference between these observations can be explained by less severe disease and by shrinkage of small scars below the detectability threshold. It is well known that necrotic tissue is replaced by fibrosis and accompanied by a contraction of the evolving scar. Furthermore, Zagrosek et al. reported that the T2 SI ratio in the acute phase correlated significantly with the change in end-diastolic volume. In our study, we showed that oedema (defined by regional or global high SI) at admission correlated significantly with the increase of EF and is an independent predictor of changes in EF and in indexed ESV. These findings underscore the notion that high SI on T2-weighted CMR images is an accurate marker for oedema, indicating the acuity of myocardial injury and that the observed increase in EF at follow-up in the group with positive LL criteria is due to recovery of reversibly injured, oedematous and thus dysfunctional myocardium.

In contrary, persisting increased SI on T2-weighted images at follow-up could be persisting oedema. This has been suggested by Gutberlet et al., who found that in suspected chronic myocarditis, persistent oedema, and/or EGE at follow-up identified persistent myocardial inflammation. In fact, in their series of 83 patients with clinically suspected chronic myocarditis, the T2 SI ratio had the highest sensitivity for detecting chronic inflammation.

Although T2-weighted CMR technology has improved, the STIR sequence has several limitations including high signal from stagnant blood, low signal-to-noise ratio, and high sensitivity to myocardial motion. An alternative approach is quantitative T2 mapping for detecting global and diffuse changes in the myocardium. Another novel quantitative technique is T1 mapping that allows direct tissue characterization and has been shown recently to have excellent diagnostic performance in patients with acute myocarditis.

Our study is limited by its sample size. We may, therefore, have missed additional relationships between LL criteria and functional outcome. Another limitation is the absence of histological validation of the diagnosis of myocarditis. We were not able to provide immunohistological validation of inflammation because our patients did not fulfill clinical indications for endomyocardial biopsy and it would not have been ethical to expose patients to this risk. Therefore, our results are valid in a population of patients with a clinical suspicion of acute myocarditis without histological validation.

Conclusions

In patients with clinically suspected acute myocarditis, the presence of CMR criteria for inflammation (‘Lake Louise Criteria’) is associated with LV function recovery. Among these criteria, the presence of regional or global myocardial oedema was the strongest predictor, indicating that the observed improvement of systolic function likely reflects recovery of reversibly injured myocardium.

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Conflict of interest: M.G.F. is board member, advisor and shareholder of Circle Cardiovascular Imaging Inc.

References