



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 $\geq 5\%$. 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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Table 1 Patient characteristics

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

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-ischaemic 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).

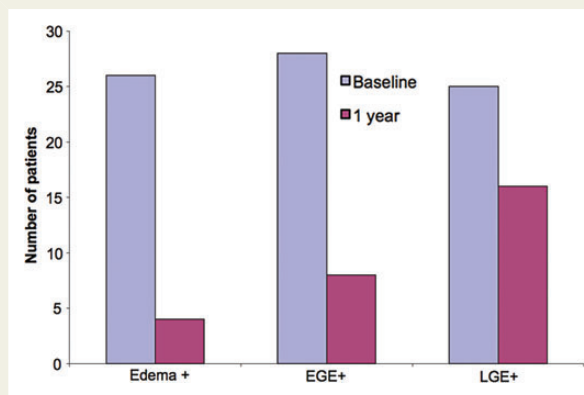


Figure 2: Number of patients with positive CMR criteria for myocarditis at baseline and at 1 year after clinically acute myocarditis.

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

	LL+ (n = 29)	LL- (n = 8)	Overall (n = 37)	<i>P</i> -value
Baseline EF	53.2 ± 8	62.2 ± 5	55.1 ± 8	0.007
1 year EF	58.9 ± 4	62.9 ± 5	59.7 ± 5	0.045
Delta EF	5.7 ± 9.8	0.7 ± 2	4.6 ± 9	0.001
Baseline ESVI	41.7 ± 11	31.1 ± 8	39.4 ± 12	0.024
1-year ESVI	34.7 ± 7	30.2 ± 7	33.7 ± 7	0.135
Delta ESVI	-7.8 ± 11	-0.8 ± 4	-5.7 ± 10	0.373
Baseline EDVI	88.6 ± 14	81.9 ± 19	87.2 ± 15	0.291
1-year EDVI	84.2 ± 13	81 ± 13	83.5 ± 13	0.563
Delta EDVI	-4.5 ± 8	-0.9 ± 9	-3.7 ± 8	0.110

LL, Lake Louise; EF, ejection fraction; ESVI, end-systolic volume indexed; EDVI, end-diastolic volume indexed.

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

variable ($\Delta EF 5.1 \pm 10\%$). Finally, there was a significant increase of EF in patients with myocarditis at 12 months ($\Delta EF 10.6 \pm 16\%$) as opposed to patients without myocarditis at baseline ($\Delta EF 0.7 \pm 2\%$).

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 ($\Delta EF \geq 5\%$) 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.¹² 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 irreversible¹⁶ and is typically present for $\sim 2-3$ 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

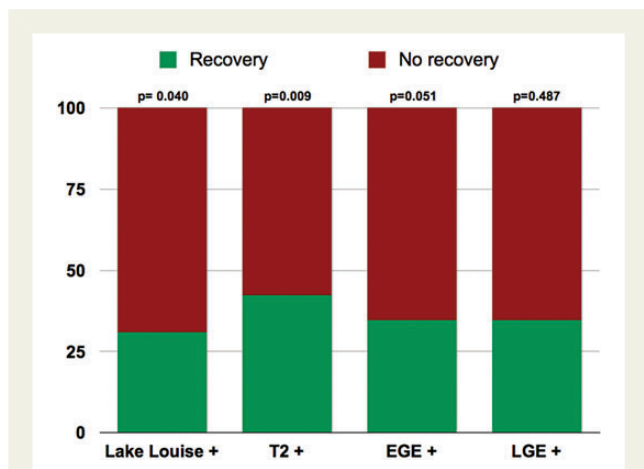


Figure 3: Proportion of patients with or without recovery, related to the presence of each of the three CMR criteria (LL criteria) and 'two of three' at first presentation. Patients with CMR evidence for myocardial oedema were more likely to encounter an improvement of the EF. LL+, presence of LL criteria; EGE+, presence of early gadolinium enhancement; LGE+, presence of late gadolinium enhancement.

Table 3 Multivariate analysis for predictors of increase in EF

	Full model			Reduced model		
	Non-standardized coefficient	Standard error	P-value	Non-standardized coefficient	Standard error	P-value
Constant	-0.02	0.165	0.906			
Oedema+	0.448	0.215	0.046	0.440	0.162	0.10
EGE+	0.284	0.255	0.270			
LGE+	-0.231	0.248	0.125			

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.*¹⁷ 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^{18–20} 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.*⁴ 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.²¹

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 fulfil 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.

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