Myocardial fibrosis in patients with a history of Kawasaki disease

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Objectives: Cardiac magnetic resonance (CMR) measurements of myocardial extracellular volume fraction (ECV) and late gadolinium enhancement (LGE) in patients with a history of Kawasaki disease (KD) were analyzed to determine whether fibrosis was increased compared to controls.

Methods: In this single center retrospective study, patients with KD who had a CMR with ECV measurement and LGE assessment were included. The ECV was calculated in the mid-left ventricle by measuring T1 values for blood pool and myocardium before and after gadolinium administration with a Look-Locker technique. CMR findings were compared to 20 control subjects.

Results: KD patients (n = 13) had a median age at CMR of 14.9 years (range, 7.5–36.0). Control subjects (n = 20) had a median age at CMR of 16 years (range, 11.0–36.0). Twelve KD patients had coronary aneurysms. The KD patients had a significantly lower indexed LV mass (p = 0.03) and LV mass/volume ratio (p = 0.01). ECV was not significantly different in KD patients and controls (0.26 (range, 0.20–0.30) vs. 0.25 (range, 0.18–0.28), p = 0.28). One KD patient (8%) had an increased (>0.28) ECV. LGE indicating focal fibrosis was found in 5 of 13 (38%) of KD patients. Patients with LGE tended to have a higher maximum coronary dimension z-score (p = 0.09).

Conclusions: In this study of KD patients, most of whom had aneurysms, ECV did not differ significantly from that in normal controls. Focal fibrosis based on LGE was common. Future larger studies should compare ECV in KD patients with and without aneurysms to define the risk of myocardial fibrosis after KD.

1. Introduction

Kawasaki disease (KD) is a systemic vasculitis of childhood and is the most common cause of acquired pediatric heart disease in the United States [1–3]. During the acute phase, many patients with KD have some degree of myocarditis, pericarditis, and endocarditis [1,4–7]. Although ventricular systolic dysfunction may be present initially, in the absence of coronary obstruction, it typically normalizes. Despite this, several studies have raised concern about the long-term health of the myocardium. Endomyocardial biopsies performed in KD patients several years after the acute phase have shown myocardial fibrosis in those with and without a history of coronary aneurysms [7–11]. In other conditions, fibrosis is associated with diastolic and systolic dysfunction, arrhythmia, and death. However, little is known about the prevalence and clinical consequences of myocardial fibrosis in KD.

Endomyocardial biopsy is the reference standard for assessment of fibrosis, but because it is invasive, expensive, and prone to sampling error, it is not well-suited for clinical and research purposes in KD patients. Cardiac magnetic resonance (CMR) is an alternative method for the assessment of fibrosis that has the advantage of being non-invasive. Two CMR techniques are used to detect myocardial fibrosis. The first is the late gadolinium enhancement (LGE) technique which detects focal fibrosis [12,13]. Focal fibrosis is a result of cell damage by necrosis and apoptosis that leads to scar formation in the myocardium [14]. The second CMR technique is based on myocardial T1 mapping and has been developed to quantify diffuse fibrosis by calculating the extracellular volume fraction (ECV) [15]. The ECV is the fraction of myocardium that is extracellular and is higher when there is more fibrosis. The ECV by CMR has been shown to correlate with myocardial collagen fraction by histopathology in adults with aortic stenosis, dilated cardiomyopathy, hypertrophic cardiomyopa-
thy, and amyloidosis, and in explanted hearts removed prior to transplantation for heart failure [16–21].

The purpose of our study was to utilize CMR techniques to determine the prevalence of both focal and diffuse fibrosis in patients with a history of KD and to assess whether fibrosis was associated with parameters of left ventricular (LV) systolic function, coronary artery dimension z-score, and arrhythmia.

2. Methods

2.1. Patients

We identified KD patients who had had a CMR examination with LGE and ECV measurement at Boston Children’s Hospital using a retrospective database review. A search also identified control subjects of similar age in whom LGE and ECV had been assessed and had normal CMR studies. Demographic, clinical, and procedural data were abstracted from the electronic medical record. For the KD patients, the maximum coronary artery dimension z-score at any time was identified by review of the echocardiography reports. The study protocol was approved by our hospital’s institutional review board.

2.2. CMR

CMR examinations were performed on a 1.5 T scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands). T1 measurements for ECV calculation were obtained using a previously described Look-Locker technique with bolus contrast administration [22]. This approach was selected because its accuracy and reproducibility have been established [23]. Moreover, compared with a modified Look-Locker inversion recovery approach [24], it has more complete sampling of the T1 recovery curve and is potentially less affected by heart rate [25]. The latter point was important because a wide range of heart rates was expected due to the broad age range in the study. An electrocardiogram-gated breath-hold Look-Locker sequence with a segmented gradient echo cine acquisition was performed at a single mid-ventricular short-axis slice, once prior to and 3 times following contrast administration. Gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) was used for contrast with a dose of 0.2 mmol/kg for patients < 20 kg and 0.15 mmol/kg for patients ≥ 20 kg. Signal intensity versus time curves were generated for 6 equal segments of the LV myocardium, and the blood pool using commercially available software (QMASS MR, Medis Medical Imaging Systems, Leiden, the Netherlands). From these curves, the T1 values were calculated by fitting to an analytical expression for the inversion recovery signal intensity. The myocardial R1 (R1 = 1/T1) was plotted against the blood pool R1. The slope of this relationship defines the partition coefficient for gadolinium (λ) [26]. The myocardial ECV was then computed using the following equation: 

$$ECV = \frac{1}{\lambda} - \frac{1}{1-hematocrit expressed as a fraction}$$

Six segmental ECV values were averaged to obtain an overall ECV value. The ECV measurement excluded regions of the myocardium with LGE to distinguish between diffuse and focal fibrosis.

LGE imaging was performed 15 min after contrast administration using a standard 2-dimensional breath-hold phase-sensitive inversion recovery sequence with the inversion time selected to null the myocardial signal. Images were acquired in multiple long- and short-axis ventricular planes to encompass the entire myocardium. The images were systematically reviewed, and the number of enhancing LV segments (17-segment model) and the pattern (transmural, mid-wall, subendocardial, subepicardial) were recorded. LV end-diastolic volume, end-systolic volume, ejection fraction, and mass were measured from a stack of cine steady-state free precession short-axis images in a standard fashion [28].

2.3. Statistics

Data are reported as medians and ranges for continuous variables, and counts and percentages for categorical variables. The Mann-Whitney test was used to compare ECV in KD versus control patients, and to explore the association of LGE with demographic parameters, CMR parameters, and the maximum coronary artery dimension z-score. The Fisher exact test was used to compare LGE in KD versus control patients. A linear mixed model was used to test for a significant difference between the ECV segments. Spearman rho correlation coefficients were used to assess associations between demographic parameters, CMR parameters, maximum coronary artery dimension z-score, and ECV measurements. Intraobserver agreement was assessed by calculating the mean difference and the intraclass correlation coefficient. All statistical tests were two-sided. Results were considered significant if the p-value was < 0.05. Analyses were performed using SPSS version 19.0.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patients and controls

Thirteen KD patients were included in the study, and their demographic and history information are shown in Table 1 and Table 2. Their median age at the time of CMR was 14.9 years (range, 7.5–36.0), 8 (62%) were males, and 12 of the 13 had a history of coronary artery aneurysms. The median age at KD diagnosis of 3 years (0.3–11.1), and median time interval from diagnosis to CMR of 10.8 years (0.3–34.3). Two patients had a history of chest pain and a clinical diagnosis of a prior myocardial infarction. Both of these patients also had a history of coronary aneurysms. Two other patients had a history of coronary bypass surgery. Twenty normal controls were included in the study. Their median age at the time of CMR was 16.0 years (11.0–36.0) and 13 (65%) were males. The indications for normal control CMRs included abnormal electrocardiogram (n = 5), possible arrhythmogenic right ventricular dysplasia (n = 9), family history of sudden death (n = 4), possible vascular ring (n = 1), and chest pain (n = 1). Their CMR studies and subsequent evaluations determined that they had no cardiac disease.

3.2. LV volume, ejection fraction, and mass

The CMR parameters of KD patients and controls are shown in Table 3. There was no significant difference between KD patients and controls for LV ejection fraction or indexed end-diastolic volume. The KD patients, however, had a significantly lower indexed LV mass (p = 0.03) and LV mass/volume ratio (p = 0.01).

Table 1

| Patient characteristics (n = 13) |
|---------------------------------|
| Age at CMR, years               | 14.9 (7.5–36.0) |
| Males                           | 8 (62%)         |
| Age at KD diagnosis, years      | 3.1 (0.3–11.1)  |
| Interval between KD diagnosis and CMR, years | 10.8 (0.3–34.0) |
| History of coronary artery aneurysms, n | 12 (92%) |
| Maximum coronary artery dimension z-score | 21.4 (–0.9–67.5) |
| History of coronary artery bypass surgery | 2 (15%) |
| History of ventricular arrhythmia | 1 (7.7%) |

Values are median (range) or n [%]. CMR, cardiac magnetic resonance; KD, Kawasaki disease.
3.3. Extracellular volume fraction

The ECV values for KD patients and controls are shown in Table 3 and Fig. 1. The reported ECV excludes regions of the myocardium with LGE. There was no significant difference in ECV between KD patients (median 0.26 (0.20–0.30)) and controls (median 0.25 (0.18–0.28) (p = 0.28). Among the KD patients, there was no significant difference in ECV among the 6 myocardial segments (p = 0.46). Using an LV ECV of 0.28 as the upper limit of normal based on prior studies in our unit[22,29], 1 KD patient (8%) had an increased ECV (0.30). ECV was not significantly associated with age at KD diagnosis, time since diagnosis, maximum coronary artery dimension z-score, indexed LV mass, LV mass/volume ratio, indexed LV end-diastolic volume, or LV ejection fraction.

Intraobserver agreement for ECV calculation was assessed in 5 randomly selected KD patients and 5 randomly selected controls. The mean intraobserver difference was 0.012 ± 0.010, and the intraclass correlation coefficient was 0.92 (95% CI: 0.68 to 0.98).

3.4. Late gadolinium enhancement

LGE was present in 5 of the 13 KD patients (38%). Among these, 4 patients had LGE that was either subendocardial (n = 2) or transmural (n = 2) in a coronary distribution consistent with a myocardial infarction (Figs. 2 and 3). One KD patient had punctate LGE involving the mid anterior and anteroseptal wall. The remaining patient had subendocardial LGE involving the mid-anterior and anterior segments. The KD patient with a punctate LGE pattern did not have a clinical history of myocardial infarction and had undergone coronary artery bypass surgery. The presence of LGE was not associated with the age at KD diagnosis, time since diagnosis, indexed LV mass, LV mass/volume ratio, indexed LV end-diastolic volume, or LV ejection fraction. Patients with LGE tended to have larger maximum coronary artery dimension z-scores than those without LGE (p = 0.09). LGE was not found in any of the controls.

4. Discussion

4.1. Previous studies

Myocarditis in the acute phase of Kawasaki disease has been documented in autopsy series [7,30], biopsy results [11,31,32], and demonstrated on cardiac magnetic resonance imaging [7,30,31,32].

Table 2

Patient characteristics.

| Patient | Age (yrs) | Gender | Coronary aneurysm | Mean ECV | LGE | Wall motional abnormalities | EF (%) | Serum biomarkers |
|---------|-----------|--------|-------------------|----------|-----|-----------------------------|--------|-----------------|
| 1       | 36        | F      | Y                 | 0.28     | None| None                        | 58     | None            |
| 2       | 23        | M      | N                 | 0.22     | None| None                        | 46     | None            |
| 3       | 14        | M      | Y                 | 0.22     | Subendocardial and midwall in the LV mid anterolateral and inferolateral wall segments | None | None            | 57     | Troponin T 0.03 ng/mL |
| 4       | 7         | M      | Y                 | 0.27     | None| None                        | 58     | None            |
| 5       | 7         | F      | Y                 | 0.26     | None| None                        | 61     | None            |
| 6       | 11        | M      | Y                 | 0.24     | None| None                        | 61     | None            |
| 7       | 22        | F      | Y                 | 0.21     | Transmural in the LV mid inferior and inferolateral segments | None | None            | 55     | None            |
| 8       | 15        | M      | Y                 | 0.27     | Transmural in the LV mid-anteroseptal and anterior segments | None | None            | 46     | None            |
| 9       | 11        | M      | Y                 | 0.30     | Subendocardial in the LV mid-anteroseptal and anterior segments | None | None            | 60     | C-reactive protein 0.16 mg/dL |
| 10      | 10        | M      | Y                 | 0.23     | Transmural in the LV apical septal and apical cap segments | None | None            | 59     | None            |
| 11      | 17        | F      | Y                 | 0.26     | Punctate midwall in the LV mid anterior and anteroseptal segments | Hypokinesis of the LV mid anterior and anteroseptal segments | 60     | None            |
| 12      | 25        | F      | Y                 | 0.26     | N   | None                        | 57     | None            |
| 13      | 30        | M      | Y                 | 0.20     | N   | None                        | 59     | None            |

Table 3

CMR parameters.

|                      | KD (n = 13) | Controls (n = 20) | p      |
|----------------------|-------------|-------------------|--------|
| LV ejection fraction, % | 58 (46–61)  | 60 (55–74)        | 0.18   |
| LV end-diastolic volume, ml/m² | 90 (70–135)  | 87 (67–137)       | 0.73   |
| LV mass/BSA, g/m²    | 41 (32–79)  | 54 (34–86)        | 0.03   |
| LV mass/volume, g/ml | 0.53 (0.31–0.77) | 0.64 (0.46–0.87) | 0.01   |
| ECV                  | 0.26 (0.20–0.30) | 0.25 (0.18–0.28) | 0.28   |
| LGE                  | 5 (38%)     | 0 (0%)            | 0.005  |

Values are median (range) or n (%). BSA, body surface area; CMR, cardiac magnetic resonance; ECV, extracellular volume fraction; KD, Kawasaki disease; LGE, late gadolinium enhancement; LV, left ventricular.
imaging studies [33,34], and biomarker abnormalities [35,36], and is the most common cause of demise in the earliest days of illness [7]. This has generated concern about the long-term effects of KD on the myocardium. Indeed, histologic studies have demonstrated the presence of diffuse interstitial and focal fibrosis in KD patients both with and without coronary aneurysms or stenosis [7–11,30–32,37]. In the largest study of right ventricular biopsies, 201 patients with KD had myocardial abnormalities, including myocarditis, fibrosis and cellular disarrangement, detected at all times after disease without relation to presence of coronary aneurysms [32]. Biomarker studies have also suggested abnormal matrix remodeling in KD patients both with and without persistent coronary abnormalities, although alterations in extracellular matrix biomarkers were greater in those with persistent coronary abnormalities [38].

Whereas sequelae of coronary artery aneurysms, including myocardial infarction and ischemic myopathy, are the predominant cause of long-term morbidity and mortality in KD, myocarditis in the acute phase of the disease producing diffuse myocardial fibrosis could also impact late myocardial function [39]. Using cardiac MRI, we investigated whether children with KD had myocardial fibrosis. We found that ECV, a measure of diffuse fibrosis, was elevated in 1 of 13 patients and that LGE, an indicator of focal fibrosis, was present in 5 out of 13 patients. ECV was not significantly different between KD patients and controls in this small cohort. LGE tended to be present in KD patients with a higher maximum coronary artery dimension z-score and ECV was not significantly associated with the maximum coronary artery dimension z-score. KD patients had significantly lower LV mass and mass/volume ratio compared with normal controls.

Only one prior study has examined LGE and ECV by CMR in KD patients. Muthusami et al. evaluated 19 KD patients and found that among LGE negative segments, ECV was significantly higher in “near LGE positive” than in “remote from LGE positive” segments and also higher in segments with severe coronary artery disease (p = 0.04) [40]. Unlike our study, this report did not perform a comparison between ECV in KD patients versus control subjects. In our study, ECV was measured only at the mid-ventricle and thus did not have the full anatomic coverage needed to address variation with proximity to regions of LGE. Both studies suggest that myocardial abnormalities are found in territory supplied by diseased coronary arteries. There are also 4 previous KD publications using the CMR LGE technique without ECV measurement [41–44]. Similar to our study, they all report patients with LGE in a myocardial...
dial infarction pattern, some of whom had no known history of an earlier MI.

4.2. Clinical implications

LGE, representing regions of focal myocardial fibrosis, was found in 5 (38%) of patients in this study, and was unexpected in 3 of the 5 patients as they had no clinical history of myocardial infarction or coronary artery revascularization. LGE has important clinical implications since it has been found to be associated with an increased likelihood of mortality, sudden cardiac death and arrhythmias in multiple conditions in adults, including ischemic and nonischemic cardiomyopathies and aortic stenosis [45–49]. KD patients had a significantly lower LV mass and mass/volume ratio than control subjects in this study. This has not been reported in KD patients previously, although it has been described in adult patients with a history of myocardial infarction [50,51]. Regional wall thinning in adult patients with a history of myocardial infarction is believed to be secondary to chronic myocardial ischemia [50]. The etiology of lower LV mass and mass/volume ratio in our cohort of KD patients may also be secondary to chronic myocardial ischemia.

An overall elevated ECV in regions without LGE was identified in 1 patient in this small cohort comprised primarily of patients with coronary artery aneurysms. The clinical implications of diffuse myocardial fibrosis and an elevated ECV are important in KD patients. Previous histology studies indicate that KD patients both with and without coronary aneurysms develop myocardial fibrosis [7–11,37]. Those with coronary aneurysms develop ischemic fibrosis secondary to coronary artery obstruction and those without have been presumed to develop diffuse fibrosis secondary to myocarditis associated with the acute KD illness. Patients with diffuse fibrosis may be at risk for the development of cardiomyopathy over time. An elevated ECV is associated with increased mortality independent of the presence of LGE in conditions such as heart failure, myocardial infarction, amyloidosis, and adults with repaired tetralogy of Fallot [52–63]. An elevated ECV has also been associated with adverse clinical outcomes in adults with aortic stenosis including decreased exercise performance and increased mortality following aortic valve replacement surgery [18,19]. Thus, an elevated ECV may identify KD patients who are also at higher risk for adverse clinical outcomes, and thus need more frequent follow-up assessments.

4.3. Limitations

The limitations of this study include that it was a single center, retrospective, cross-sectional study with a small sample size, limiting our range of patients and our ability to do a more comprehensive multivariable analysis. Our study also had a CMR referral bias for patients with coronary aneurysms (12 of 13 subjects). ECV measurements were derived from a single mid-ventricular slice. Although this is the same approach that was used to validate the technique with myocardial collagen fraction, regional variation in ECV across the entire left ventricle was not assessed.

5. Conclusions

In this small study of patients with a history of KD, an elevated ECV representing diffuse fibrosis was present in 1 in 3 (8%). LGE representing focal fibrosis was found in 5 in 13 (38%) of KD patients. Patients with LGE tended to have larger coronary artery dimension z-scores. Future larger studies evaluating ECV and LGE in patients with and without coronary aneurysms may help to further define the long-term adverse effects of KD on the myocardium.

Declaration of Competing Interest

There are no conflicts of interest.

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