Myocardial inflammation on cardiovascular magnetic resonance predicts left ventricular function recovery in children with recent dilated cardiomyopathy

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Aims
To analyse the predictive role of myocardial inflammation assessed by cardiac magnetic resonance (CMR) on the outcome of recently diagnosed dilated cardiomyopathy in children.

Methods and results
Over a period of 4 years, 66 children underwent CMR within 2 weeks after the diagnosis of dilated cardiomyopathy. CMR sequences sensitive for oedema, hyperaemia, and irreversible injury were applied: unenhanced cine steady-state free precession (SSFP), black-blood-prepared T1-weighted images, T2-weighted images, gadolinium-enhanced T1-weighted images (EGE), and late gadolinium-enhanced (LGE) images. Inflammatory cardiomyopathy defined as the presence of at least two CMR criteria was diagnosed in 31/66 children (CMR positive) while no criterion was present in the remaining 33 (CMR-negative). Only two patients had one positive criterion and were excluded from subsequent analysis. After a mean follow-up of 24 months, LV function recovery (LV ejection fraction > 55%) was more frequent in the CMR-positive group (24 vs. 11, P = 0.05). The presence of myocardial inflammation and elevated troponin levels at baseline were the two predictors of LV function recovery with an odds ratio of 3.76 (P = 0.02) and 2.76 (P = 0.03), respectively, in a logistic regression model. Persisting LGE was rare in patients of the CMR-positive group at control CMR (6/22) and was never observed in the CMR-negative group (0/16).

Conclusion
The presence of myocardial inflammation on CMR at time of diagnosis of a dilated cardiomyopathy in children is a strong predictor of LV recovery.

Keywords
myocarditis • cardiac magnetic resonance imaging • heart failure • children • inflammatory cardiomyopathy

Introduction
Inflammatory cardiomyopathy (WHO/ISFC) is defined as a myocarditis in association with cardiac dysfunction. An inflammatory process has been involved in the pathogenesis of dilated cardiomyopathy and may have different causes such as infectious, immune mediated, or toxic.1 In children, the incidence of newly diagnosed dilated cardiomyopathy has been estimated between 0.57 cases per 100 000 population per year for children 0–18 years of age and 0.73 cases per 100 000 population per year for children 0–10 years of age.2 The real incidence of inflammatory cardiomyopathy in children is underestimated since endomyocardial biopsy, the diagnostic gold standard, is infrequently used in clinical practice.3 In children with an identified cause of dilated cardiomyopathy, the incidence of myocarditis was 46%.4 Viral infection with invasion of the myocardium by inflammatory cells, with or without necrosis of myocytes, is the most commonly suggested cause. Inflammatory cardiomyopathy may completely recover but sometimes progresses insidiously to dilated cardiomyopathy.5–7 In a recent study, Alexander et al.8 showed that echocardiographic normalization of left ventricular function had occurred in 92% of children with histologically confirmed lymphocytic myocarditis while recovery was
observed only in 36% of those with non-specific histological findings. Confirming the diagnosis of inflammatory cardiomyopathy and myocarditis remains challenging in children, because the clinical presentation overlaps with that of other common pediatric infectious diseases. Its presentation is age dependent—prominent cardiac symptoms with heart failure in neonates and infants, non-specific flu-like illness in older children, and chest pain without left ventricular dysfunction in adolescents. This implies that the diagnosis of inflammatory cardiomyopathy requires a high level of suspicion early in the course of the disease and the use of appropriate investigations to confirm the diagnosis. Formerly, the diagnosis of inflammatory cardiomyopathy was made by endomyocardial biopsy and classified according to the Dallas criteria.9 The risk of endomyocardial biopsy in young children with severe left ventricular dilatation might be high. In addition, its value to establish prognosis is controversial because of its poor sensitivity, related to the patchy process of myocarditis. Some longitudinal studies found no difference in outcomes in pediatric patients with biopsy-proven myocarditis vs. those with clinically diagnosed myocarditis while others did.8–10 Cardiac magnetic resonance (CMR) imaging can serve as an interesting tool for non-invasive assessment of myocardial inflammation in children at time of diagnosis of dilated cardiomyopathy.11–15 It allows a more accurate detection of myocardial inflammation in the entire myocardium, evaluates global and regional ventricular functions, and could play a role in prognostication of outcomes.16 The International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis proposed precise diagnostic criteria for myocarditis, but these have only been scarcely used in children.17 Recently, Mavrogeni et al.18 used CMR and endomyocardial biopsy to evaluate myocarditis in a paediatric population, and showed that CMR was useful for the detection of myocarditis, especially in those with negative troponin and mild clinical presentation.

Here, we prospectively used CMR to detect myocardial inflammation in a consecutive series of children with recently diagnosed dilated cardiomyopathy of unknown origin, and we sought to determine whether inflammation of the myocardium on CMR at time of diagnosis could predict the outcome.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of patients at baseline</th>
<th>Total</th>
<th>CMR positive</th>
<th>CMR negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>66</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Age [median, years (range)]</td>
<td>2.2 (1 day–16 years)</td>
<td>6.0 (1 day–16 years)</td>
<td>1.0 (1 day–15 years)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>33/33</td>
<td>17/16</td>
<td>16/17</td>
</tr>
<tr>
<td>Overt heart failure</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Fever</td>
<td>15</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>17</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>ECG anomalies</td>
<td>37</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Elevated troponin I, [μg/L (nl &lt; 0.05)]</td>
<td>35</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>LV ejection fraction % (median; range)</td>
<td>30; 10–49</td>
<td>25; 10–49</td>
<td>30; 15–48</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

### Methods

#### Patients

Over a period of 4 years, all children <18 years admitted to our Pediatric Cardiology Department were considered eligible for the study if they had developed for 3 months or less symptoms consistent with heart failure related to dilated cardiomyopathy of unknown origin. Dilated cardiomyopathy phenotype was defined as left ventricle (LV) end-diastolic diameter or volume was higher $+2z$-score for body surface area, and LV ejection fraction was lower 50%. A single investigator (D.B.) reviewed all cases at time of diagnosis.

All children had CMR within 2 weeks after inclusion. Exclusion criteria were ischaemic dilated cardiomyopathy such as anomalous origin of left coronary artery from the pulmonary artery, arrhythmogenic right ventricular dysplasia, any previous cardiac surgical procedures, association with a congenital heart defect, treatment with chemotherapeutic agents or pharmacological cardiotoxicity, endocrine disorders known to cause myocardial damage, chronic cardiac arrhythmias, immunologic diseases (maternal lupus or Sjögren syndrome), and any vasculitis. In addition, inborn errors of metabolism associated with LV dysfunction, known neuromuscular disorders when identified, and children with known familial history of dilated cardiomyopathy or in whom existence of a dilated cardiomyopathy in another family member could be identified were excluded.

A complete diagnostic evaluation was performed in all patients. Patients’ characteristics are given in Table 1. No patient had contraindications (allergy or renal failure) to gadolinium administration.

#### CMR imaging

CMR was performed using a 1.5 Tesla magnet (MR450 GE Medical systems, Milwaukee, WI, USA). Images were acquired with a 32-channel, phased-array cardiac coil and a vector electrocardiogram for R wave triggering using a standard CMR imaging protocol.

Cine-MR echo-gradient images were first used to locate the anatomic axes of the heart. All CMRs were performed in free breathing using sedation in children <25 kg.

CMR parameters of the LV were obtained by acquiring short-axis view, four-chamber view, and two-chamber view as steady-state free precession (FIESTA) images [200–380 mm field of view, 6–8-mm slice thickness, no gap, one excitation (three in free breathing), 22 views/segment.
for heart rate $< 75$ bpm, 14 if $> 75$ bpm, excitation time/repetition time 1.5–4.5 ms, flip angle 55° before injection, 65° after contrast injection, and matrix 224 $\times$ 192. Black-blood-prepared T2-weighted (T2-STIR) and T1-weighted images were acquired along the four-chamber view, two-chamber view, and the short-axis planes of the left ventricle (200–380 mm field of view, 6–8 mm slice thickness, no gap, one excitation, excitation time/repetition time 75–85/1200 ms for T2-weighted images, 35/700 ms for T1-weighted images, and matrix 224 $\times$ 192). These were followed by contrast-enhanced images (intravenous administration of a bolus of gadolinium chelate, Dotarem, Guerbet, 0.2 mmol/kg body weight). Enhanced cine-SSFP (flip angle 65°) and black-blood-prepared double inversion recovery fast spin-echo images with T1 weighting were acquired along the four-chamber view, two-chamber view, and short-axis planes of the left ventricle. Delayed enhancement images were acquired with an inversion recovery gradient echo pulse sequence, 10 min after injection of contrast media, in the short axis covering the entire left ventricle from the mitral valve plane to the ventricular apex. The following parameters were used: 200–380 mm field of view, 8 mm slice thickness, no gap between each slice, repetition time 4.6 ms, echo time 1.3 ms, flip angle 20°, acquisition matrix 224 $\times$ 192, and inversion time optimized to nullify normal myocardium (range 240–300 ms).

All images were analysed with a dedicated workstation (ADW 4.5, GE Medical system).

Left ventricular volume and ejection fraction were measured from short-axis images. Criteria that we used to diagnose myocardial inflammation were as follows:¹⁷,¹⁸ (i) evidence of regional or global myocardial oedema with T2 hyperintensity (T2 ratio $> 2$, where T2 ratio = Signal intensity myocardium/Signal intensity skeletal muscle); (ii) evidence of myocardial hyperaemia and capillary leak with early gadolinium enhancement on cine-SSFP and/or T1-weighted images (acquired early after contrast injection) compared with the skeletal muscle (EGE); or (iii) evidence of myocardial necrosis and fibrosis (visual assessment) with non-ischaemic regional distribution at LGE imaging.

The evaluation of EGE was done on both sequences on cine-SSFP (visual assessment) soon after contrast injection and T1-weighted images, but the quality of T1-weighted images, performed in free breathing in the majority of patients, was not sufficient for a quantitative evaluation. We therefore considered the visual assessment on cine-SSFP as the only criterion for EGE assessment.

Myocardial inflammation was diagnosed when at least two criteria were present.

CMR images were reviewed for image quality for each sequence. We classified each CMR sequence as ‘excellent’, ‘good’, or ‘with significant artefact’. Both ‘excellent’ and ‘good’ image qualities were considered sufficient to identify the criterion for inflammation.

Outcomes and follow-up
After CMR, patients were classified into two groups: CMR positive for patients with at least two criteria for myocardial inflammation; CMR negative for patients with dilated cardiomyopathy phenotype without evidence of myocardial inflammation on CMR (Figure 1). All patients had regular follow-up based on clinical status with clinical examination and non-invasive tests, including ECG and echocardiography. Study outcomes were death, heart transplantation, and echocardiographic LV function. Echocardiographic LV function’s evolution was classified from the most recent echocardiogram data available into two categories. First, ecocardiographic left ventricular recovery was defined if LV end-diastolic dimensions were $\leq +2$ of z-score and LV ejection fraction $\geq 55$%; second, echocardiographic persisting dilated cardiomyopathy phenotype was defined if LV dimensions remained $\geq +2$ of z-score with LV ejection fraction $\leq 50$%. In addition, we considered that full recovery was obtained when the patient could be weaned of chronic heart failure treatment.

Statistical analysis
All the results were expressed as mean $\pm$ SD, except when stated otherwise. Analysis of continuous variables was performed by use of an unpaired $t$-test. A value of $P < 0.05$ was accepted as significant. Categorical variables were analysed by a two-tailed Fisher’s exact test. Logistic regression was performed in R 3.0.2 by fitting a generalized linear model. Kaplan–Meier estimation of recovery of left ventricular function was performed in R 3.0.2.

Results

Patient characteristics
During the study period, 71 children admitted to our institution met inclusion criteria. Five patients with fulminant myocarditis were admitted to our intensive care unit for cardiac mechanical assistance or in critical condition with cardiogenic shock. CMR could not be performed at the early phase of the disease, and they were excluded from the study. Diagnosis of lymphocytic myocarditis in these five patients was confirmed by autopsy or surgical biopsy performed during ECMO or ventricular assist device implantation. Finally, 66 patients (median age 2.2 years, range 1 day–16 years) were included in the study. None had arrhythmias at time of CMR. The median delay between the diagnosis of LV dysfunction and CMR was 8 days.

Characteristics of patients at presentation are given in Table 1.
CMR at baseline
In 33/66 children, CMR identified at least one criterion for inflammation of the myocardium. Figures 1–3 illustrate the three criteria used for diagnosing myocardial inflammation. Table 2 and Table 3 show the distribution of CMR signs in children with myocardial inflammation. Two had only an increase in global myocardial signal intensity on T2-weighted images, but EGE and LGE could not be performed for technical reasons. Both were considered to have myocardial inflammation as they had additional supportive evidence for this diagnosis, one of them being assisted with ECMO after CMR. However, as they did not fulfill the criteria for positive CMR, they were excluded from statistical analysis.

LGE was done in 31/33. In 14/31, the LGE was present in more than two left ventricular segments, and limited to two or one cardiac segment in 17/31 cases. LGE was usually seen in the subepicardial part of the myocardial wall. Contrast enhancement had a transmural patchy distribution in 9/31 cases, with intramyocardial foci in 2/31 cases. One patient had evidence of right ventricular myocardial inflammation. In eight cases, pericardial effusion was present, and in five cases, late gadolinium enhancement was also detected in the pericardium.

In the remaining 33 patients, CMR did not show myocardial inflammatory changes or myocardial fibrosis/scar at time of diagnosis. One of these 33 patients was clinically highly suspect to have inflammatory cardiomyopathy, and while CMR was normal, she underwent endomyocardial biopsy that showed histological evidence of inflammatory infiltrates within the myocardium associated with myocyte necrosis. No other endomyocardial biopsy was performed in this series. In addition, three newborns in this group had clinical and biological diagnosis of enterovirus infection associated with left ventricular severe dysfunction. They were highly suspect to have enterovirus-related inflammatory cardiomyopathy, but CMR did not evidence any inflammation in the myocardium. The remaining 29 children with no signs of inflammation on CMR were finally diagnosed with dilated cardiomyopathy of unknown origin.

CMR images were reviewed for image quality in all patients. CMR sequences were considered excellent or good to identify the criteria in 62/66 for myocardial oedema with T2 hyperintensity, in 59/66 for visual assessment on EGE sequences, and in 61/66 for LGE sequences.

Initial management
Mechanical circulatory support by ECMO (median duration 13 days, range 2–17 days) was required in four patients of the CMR-positive group. No patient in the CMR-negative group needed mechanical support. Patients with severe heart failure received either intravenous inotropic support when necessary or intravenous diuretics. Immune globulin therapy, steroids, or immunosuppressive treatment was given on a case-by-case decision basis. After the acute phase of the disease, patients received ACE inhibitors in combination with beta-blockers. Oral diuretic therapy with furosemide or spironolactone was pursued after discharge only in children with evidence of congestive heart failure. Anticoagulation with warfarin was given to children with LV ejection fraction ≤30% at hospital discharge.

Outcomes and follow-up
Three patients died (two in the CMR-positive group who had 3/3 criteria present at baseline and one in the CMR-negative group) (Figure 4). One child in the CMR-negative group underwent heart transplantation. Five children were lost to follow-up. The two patients with a single positive CMR criterion were excluded of follow-up analysis. Survival after a mean of 24 months of (range 6–55 months) follow-up was 95%.

Overall, 55 children survived without heart transplantation and could be regularly followed in our Institution. Thirty-three out of
55 (60%) normalized their LV function (LVEF > 55%) and dimensions on echocardiography, and this occurred more frequently in patients of CMR-positive group compared with the CMR-negative group [22/27 (81%) vs. 11/28 (39%), \( P < 0.05 \), Figure 4]. Age at diagnosis, gender, and baseline CMR LV ejection fraction did not predict complete LV recovery. The presence of myocardial inflammation and elevated troponin levels at baseline were the two predictors of LV function recovery with an odds ratio of 3.76 (\( P = 0.02 \)) and 2.76 (\( P = 0.03 \)), respectively, in a logistic regression model including the presence or absence of myocardial inflammation, baseline CMR LV ejection fraction, elevated troponin level, fever at diagnosis, gender, and age. Oral heart failure treatment was progressively stopped in children who normalized their LV function and who were stable for at least 6 months after normalization of LV function. None of them had recurrent LV dysfunction after weaning of heart failure drugs. Twenty-two out of 55 (40%) had persisting LV dysfunction (LVEF < 50%) with or without improvement of LV ejection fraction on echocardiography at last follow-up: 5 in the CMR-positive group vs. 17 in the CMR-negative group (\( P < 0.05 \)). In this group, median LV ejection fraction was 41% (range 20–54).

### Discussion

Here, we show that the presence of CMR-positive criteria for myocardial inflammation in children with recently diagnosed dilated cardiomyopathy is the strongest predictor of LV function recovery. Identifying myocardial inflammation has therefore immediate
consequence on treatment strategy but has also prognostic implications. The predictive value of CMR criteria for LV functional improvement has been recently shown in adult patients with acute myocarditis. Recent advances in the diagnosis of inflammatory cardiomyopathy have centred on the development of CMR to identify more precisely myocardial inflammation. It is of note that clinical presentation of children with and without myocardial inflammation on CMR was different in our series (Table 1). Suspicion of inflammatory cardiomyopathy could have been made using the commonly used integrated synopsis of clinical symptoms mostly chest pain, with elevated troponin I, ECG anomalies particularly ST-T segment changes, T-wave inversion, atrioventricular block, arrhythmia, and echocardiographic findings in almost half of the patients. As endomyocardial biopsy if infrequently used in children in this condition, CMR imaging appeared a useful adjunct to clinical assessment in diagnosing inflammatory cardiomyopathy.

The first description of T2-weighted findings in children was done > 20 years ago, but reported series on CMR characteristics in children with suspected inflammatory cardiomyopathy are lacking. CMR has been used to identify myocardial inflammation during the convalescence of Kawasaki disease and may be helpful for therapeutic decision making in this indication. Here, we show that CMR imaging is feasible in children with suspicion of inflammatory cardiomyopathy or dilated cardiomyopathy of unknown origin with very limited technical failures. The prevalence of myocardial inflammation diagnosed by CMR was 50% in our series. The overall prevalence of myocardial cardiomyopathy was even higher as five patients with histologically proven inflammatory cardiomyopathy who were on ECMO did not have CMR, and one patient with strong suspicion of viral myocarditis and no inflammation on CMR had lymphocytic myocarditis on endomyocardial biopsy. We did not propose to estimate the sensitivity and specificity of CMR as we cannot prove that patients without myocardial inflammation or LGE on CMR did not have inflammatory cardiomyopathy. It is also of note that CMR sensitivity to detect myocardial inflammation is low in new borns with dilated cardiomyopathy as three neonates with clinical and biological evidence for enterovirus neonatal myocarditis had no evidence of myocardial inflammation but fully recovered. Lack of sensitivity of CMR to detect myocardial inflammation might also explain why some children with apparently idiopathic dilated cardiomyopathy fully recovered their LV function. Over the same study period, we also performed CMR in 11 children with high clinical and biological suspicion of myocarditis and normal LV function. They were excluded from our study that aimed to predict LV recovery in children with LV dysfunction. Using the same CMR criteria, CMR was positive for at least 2/3 criteria in all of them. None had LV dysfunction during follow-up.

Survival and ventricular remodelling in myocarditis and idiopathic dilated cardiomyopathy in childhood have been extensively studied in large national registries. These studies clearly showed that children with recently diagnosed left ventricular dysfunction have a better prognosis if they are diagnosed with lymphocytic myocarditis than with idiopathic dilated cardiomyopathy. Considering the better outcome of inflammatory cardiomyopathy compared with dilated cardiomyopathy of unknown origin, it seems reasonable to attempt to differentiate these diseases at initial diagnosis. In our study, echocardiographic normalization of LV function occurred in 83% of children of the CMR-positive group compared with 39% of children in the CMR-negative group. This proportion is close to that of the Australian registry that compared children with histologically proven myocarditis vs. those without myocardial inflammation on biopsy. This may be again related to the lack of sensitivity of CMR to detect myocardial inflammation. It might also be due to the fact that some children may present at time of overt heart failure but the LV dysfunction might have started months before. In control, CMRs that were performed in patients of the CMR-positive group, myocardial fibrotic sequelae were rare and remained very limited in size. In addition, control CMR performed in the CMR-negative group did not show any evidence for fibrotic lesions. Again if inflammation of the myocardium is not long lasting, CMR can be negative and this might explain why some children with apparently idiopathic dilated cardiomyopathy fully recovered their LV function. Finally, CMR results might have influenced the therapeutic strategies particularly for the most recent patients, but the role of immunosuppressive therapies on outcome cannot be addressed in this non-comparative series.

It is of note that LGE was present in all patients with myocardial inflammation but two in whom gadolinium injection was not done. This percentage of LGE is higher than in the adult population in which it varies from 61 to 95%. The distribution of LGE was mostly subepicardial, with transmural involvement in only 10% of cases and no case of only subendocardial involvement, consistent with data previously reported in adults. It has been reported that risk factors for poor outcome were transmural myocardial involvement, left ventricular dilatation, and LV ejection fraction < 30%. We were not able to show a correlation between extent of myocardial damage on CMR and outcome in our short series.

Limitations of the study

In this study, we cannot address CMR sensitivity and specificity by comparing diagnosis performances of endomyocardial biopsy and CMR to confirm inflammatory cardiomyopathy in children with new-onset LV dysfunction. EGE analysis has to be considered with caution in our series as we had to limit our analysis to visual assessment. In our series, four patients with LGE had no EGE on cine-SSFP after contrast. All patients with EGE had LGE. As these two sequences have potentially the same mechanism, they both should be positive in the acute phase of myocardial inflammation, reflecting early presence of contrast medium and its late persistence. Lack of sensitivity of EGE as well as more frequent significant artefacts for this sequence might explain this discrepancy. We could not obtain control CMR at a standard delay after baseline CMR in all children as indication for control CMR was driven by the clinical evolution and had to be accepted by the parents who usually had a hard time at the disease’s onset. Control CMR should probably be repeated after a few years’ follow-up in all these patients to analyse ventricular remodelling and fibrotic scars more precisely. We cannot address the issue of the effect of any specific treatment on outcomes as therapy was decided on a case-to-case basis. Finally, inflammatory cardiomyopathy is mostly regarded as a viral disease in children, but other causes have been described, and CMR does not distinguish between viral, autoimmune, or other rare causes of myocardial inflammation.
Conflict of interest

Cardiologie du Foetus à l'Adulte –ARCFA.

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Funding

Conclusion

CMR is certainly the best modern and safer modality to confirm myo-
cardial inflammation in children but it must be interpreted in the
context of the entire clinical picture as CMR suffers of technical lim-
itations. In children with symptoms of heart failure and clinically sus-
pected new onset dilated cardiomyopathy, the presence of positive
CMR criteria for myocardial inflammation predicts LV function re-
covery, indicating an important role of CMR as a very useful diagnostic
tool in this population.

Funding

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Correlation

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