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Cardiovascular magnetic resonance in children with suspected myocarditis: current practice and applicability of adult protocols

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Abstract

Background: Cardiovascular magnetic resonance serves as a useful tool in diagnosing myocarditis. Current adult protocols are yet to be validated for children; thus, it remains unclear if the methods used can be applied with sufficient image quality in children. This study assesses the use of cardiovascular magnetic resonance in children with suspected myocarditis. *Methods:* Image data from clinical cardiovascular magnetic resonance studies performed in children enrolled in Mykke between June 2014 and April 2019 were collected and analysed. The quality of the data sets was evaluated using a four-point quality scale (4: excellent, 3: good, 2: moderate, 1: non-diagnostic). *Results:* A total of 102 patients from 9 centres were included with a median age (interquartile range) of 15.4(10.7-16.6) years, 137 cardiovascular magnetic resonance studies were analysed. Diagnostic image quality was found in 95%. Examination protocols were consistent with the original Lake Louise criteria in 58% and with the revised criteria in 35%. Older patients presented with better image quality, with the best picture quality in the oldest age group (13-18 years). Sedation showed a negative impact on image quality in late gadolinium enhancement and oedema sequences. No such correlation was seen in cardiac function assessment sequences. In contrast to initial scans, in follow-up examinations, the use of parametric mapping increased while late gadolinium enhancement and oedema sequences decreased. *Conclusion:* Cardiovascular magnetic resonance protocols for the assessment of adult myocarditis can be applied to children without significant constraints in image quality. Given the lack of specific recommendations for children, cardiovascular magnetic resonance protocols should follow recent recommendations for adult cardiovascular magnetic resonance.

Myocarditis is an important cause of morbidity and mortality in children and young adults, carrying a significant risk for the development of acute or chronic heart failure.[1–4] According to a recent study by Martins et al., only less than every third paediatric patient diagnosed with myocarditis recovers completely.[5] The variety and non-specificity of symptoms as well as its similarity to acute coronary syndrome may delay correct clinical and therapeutic decisions in patients with myocarditis. These symptoms include chest pain, dyspnoea, fatigue, and ventricular arrhythmia.[6] The clinical diagnosis can be supported by several diagnostic tools. However, due to their poor sensitivity and specificity in detecting a myocarditis, no single diagnostic tool is definitive in confirming or ruling out a diagnosis.[7] The gold standard is the endomyocardial biopsy, an invasive diagnostic tool with a considerable risk for complications. Its diagnostic validity may be impaired by sampling errors and high inter-observer variability in tissue interpretation.[8,9] Moreover, the typical distribution of changes in myocarditis is subepicardial and intramural – areas that are often inaccessible for endomyocardial biopsy.[5,10,11] Thus, the most promising non-invasive approach – cardiovascular magnetic resonance – has attracted more and more interest in recent years. In adults, cardiovascular magnetic resonance has been proven to be a useful tool for diagnosing myocarditis.[12] Furthermore, in children with myocarditis and newly diagnosed dilated cardiomyopathy MRI has shown a predictive value of cardiac recovery.[5,11,13] A first attempt at standardising cardiovascular MRI in adults with acute myocarditis was made in 2009 by the Lake Louise Criteria, where T1- and T2-based methods were combined for comprehensive tissue characterisation.[14] An updated version of these criteria based on more recent cardiovascular magnetic resonance acquisition techniques was published in 2018.[15] In children, the use of cardiovascular magnetic resonance for detecting myocarditis was first described in 1991.[16] The method has continued to gain popularity ever since. A more recent paediatric study conducted on a large cohort of patients with myocarditis over a period of time from 2006 to 2011 found an increase in usage of cardiovascular magnetic resonance by almost 23%.[17] The society for cardiovascular magnetic resonance recommendation for scanning patients with a COVID infection embraces inclusion of parametric mapping to imaging protocols in children and adults.[18] Nevertheless, in contrast to adults, the use of cardiovascular magnetic resonance for determining myocarditis in children has not been validated systematically, and standardised diagnostic guidelines and clinical protocols are still lacking. Besides the smaller total number of cases, additional diagnostic challenges in the paediatric group of patients include physiological aspects such as high heart rates, smaller anatomy, and limited compliance. As there are only a few contemporary paediatric studies, data regarding the use of cardiovascular magnetic resonance in children are still very limited. In particular, it remains unclear if the methods that are used in adult cardiovascular magnetic resonance can be applied with sufficient image quality in children, which is a prerequisite of their meaningful use for diagnostic purposes.[19–21].

The aim of this study was to assess the German use of cardiovascular magnetic resonance in a cohort of children with suspected myocarditis. We specifically investigated imaging protocols and image quality. Our study includes the review of selected acquisition parameters used in parametric mapping.

Materials and methods

Patient selection and data collection

This study is a subanalysis from Mykke – a prospective multicenter registry for children and adolescents with suspected myocarditis (ClinicalTrials.gov Identifier: NCT02590341) collecting data on clinical courses, diagnostics, and therapy.[22] Ethical approval was first obtained at the initiating centre (German Heart Center Berlin, Germany) from the ethics committee of Charité – Universitätsmedizin Berlin and subsequently confirmed by the local authorities of all collaborating centres (ID EA2/074/13). Within the MYKKE registry, patient data are entered in an online database, hosted by the Competence Network for Congenital Heart Defects, Germany. Image data from clinical cardiovascular magnetic resonance studies performed in children enrolled in Mykke between June 2014 and April 2019 were collected on a central image server at the coordinating centre and analysed for this study. The inclusion criteria were as follows: age <18 years old and clinically suspected myocarditis. All patients or their legal guardians provided written informed consent. The indication for cardiovascular magnetic resonance was set by the referring physician. Demographic data and basic functional and volumetric cardiovascular magnetic resonance analysis were extracted from the registry database. Patients were divided into 3 groups according to their age at the time of cardiovascular magnetic resonance (0-1, 2-12, 13-18 years).[22]

Cardiovascular magnetic resonance image analysis

Data analysis and interpretation were performed at the coordinating centre by two independent clinicians (2 and 5 years of experience in cardiac imaging, respectively). In case of discrepancies, a joined reading was performed and a consensus was agreed upon. Visual (qualitative) analysis was done for balanced steady state free precession cine images, T2-weighted, short tau triple inversion recovery and turbo-spin-echo imaging, late gadolinium enhancement, phase-sensitive inversion recovery as well as for T1 and T2 mapping. The quality of each data set was evaluated using a four-point quality scale, similar to a previous study of Monti et al.[23]: a score of 4 indicated excellent image quality with artefacts not affecting the heart, 3 – good image quality with minor involvement of the heart, 2 – moderate image quality with severe artefacts and a score of 1 – non-diagnostic. In scans with image quality >"1," the image quality would be sufficient to enable using the scan in the diagnostic process. The use of T1-weighted turbo-spin-echo, early gadolinium enhancement imaging, and magnetic resonance angiography was examined without the application of quality scale. The MRI image analysis was carried out using Horos medical image viewer (Nimble Co. LLC d/b/a Purview, Annapolis, MD USA).

Statistical analysis

Categorical variables are summarised by frequencies and percentages. For continuous measures, data are presented as median values and interquartile ranges. Pearson's chi-square test and Fisher`s exact test were used to compare dichotomous variables. For comparison of independent groups, Mann–Whitney U and Kruskal–Wallis tests were applied. A probability value of <0.05 was considered statistically significant. Data were analysed with IBM Corp. SPSS Version 24.0 (Armonk, NY, USA).

Results

Demographics

A total of 102 patients from 9 centres with a clinically suspected myocarditis were included in the study between June 2014 and April 2019. The youngest age group (0-1 years) consisted of 10 patients, the middle age group (2-12 years) of 31 patients and the oldest age group (13-18 years) of 96 patients. The median age was 15.4 (interquartile range 10.7-16.6) years with a body surface area of 1.7 (1.2-1.9) m^2, and 71% were male. The time from admission to cardiovascular magnetic resonance was 8.0 (4.0-20.3) days. A follow-up cardiovascular magnetic resonance was available in 35 patients. Patient characteristics and basic MRI findings are listed in Table 1.

cardiovascular magnetic resonance sequences

Cardiovascular magnetic resonance was performed in 96% using a 1.5 T system (Siemens Healthcare, Erlangen, Germany; Philips, Best, The Netherlands; Genesis Signa, General Electric Medical Systems, Milwaukee, WI, USA). A 3 T system (Siemens Healthcare, Erlangen, Germany) was used in 4% of the examinations. Four per cent of the scans were done under general anaesthesia, 8% under deep

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Table 1. Demographics and basic CMR findings

Demographics (n = 102)	
Age (years)	15.4 (10.7-16.6)
Gender (male)	72 (70.6)
Body Surface Area (m^2)	1.7 (1.2-1.9)
Weight (kg)	60.0 (36.3-75.0)
Time from presentation to CMR (days)	8.0 (4.0-20.3)
CMR findings (n = 137)	
Magnetic field strength	
1.5 T	131 (95.6)
3 T	6 (4.4)
Hardware manufacturer	
Siemens	95 (69.3)
Philips	40 (29.2)
GE	2 (1.5)
LVEF (%)	58.0 (49.9-64.0)
Indexed LVEDV (ml/m^2)	86.0 (74.0-100.5)
Required anaesthesia for CMR	
Deep sedation	11 (8.0)
General anaesthesia	6 (4.4)
No sedation	120 (87.6)

Values are n (%) or median (interquartile range). CMR: cardiovascular magnetic resonance, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume.

conscious sedation with use of free-breathing sequences, and 88% without any sedation. Table 2 presents an overview of the performed sequences at initial and follow-up examinations. The initial protocol included sequences assessing cardiac function, combined with late gadolinium enhancement applied in 99%, and oedema imaging in 82%. Late gadolinium enhancement standard 2 D, standard 3 D and phase-sensitive inversion recovery sequences were used. In addition, mDixon and FLASH sequences were used – however, their image quality was not evaluated using the 4-point scale. In the baseline as well as the follow-up MRI, the use of the 3 D sequences was more frequent. The image quality of the scans using 3 D sequences was better than the ones using 2 D sequences (in the 3 D technique 35.3 % of the scans presented an excellent image quality, whereas in the 2 D technique 31.5 % of the scans displayed an excellent image quality. T1 mapping (pre- and/or post-contrast) was performed in 74% of the examinations and T2 mapping in 28%. Sixty per cent of scans included early gadolinium enhancement. In the follow-up examinations we observed an increase in the use of parametric mapping – T1 native by 13% ($p = 0.22$), post-contrast by 8% ($p = 0.44$) and T2 by 17% ($p = 0.09$). Nevertheless, there was a decrease in the use of T2-weighted imaging (by 5%, $p = 0.61$), early gadolinium enhancement (by 11%, $p = 0.32$) and late gadolinium enhancement (by 2%, $p = 0.44$). In 58% (80/137) of the data sets, the applied examination protocol was consistent with the original Lake Louise Criteria. Thirty-five per cent (48/137) of the data sets used an examination protocol that was compatible with the revised version of the Lake Louise Criteria. Respectively, according to the original Lake Louise Criteria, 42% of the scans were incomplete. According to the revised Lake Louise Criteria, 65% of the scans were incomplete.

Table 2. CMR sequences performed at initial and follow-up CMR

Sequence	Initial CMR *n* = 102	Follow-up CMR *n* = 35
Cine sequences		
2CH	100 (98.0)	33 (94.3)
4CH	101 (99.0)	34 (97.1)
3CH	86 (84.3)	32 (91.4)
SAX	102 (100.0)	34 (97.1)
Trans	47 (46.1)	12 (34.3)
bSSFP (+)	102 (100.0)	34 (97.1)
Oedema sequences		
STIR SAX	84 (82.4)	27 (77.1)
STIR 2CH	12 (11.8)	4 (11.4)
STIR 4CH	25 (24.5)	4 (11.4)
STIR 3CH	10 (9.8)	3 (8.6)
Late enhancement		
Look-Locker	97 (95.1)	32 (91.4)
Standard 2D	80 (78.4)	27 (80.0)
Standard 3D	89 (87.3)	30 (85.7)
PSIR	80 (78.4)	24 (68.6)
Early enhancement	64 (62.7)	18 (51.4)
T1 mapping native		
MOLLI 3-3-5	23 (22.5)	7 (20.0)
MOLLI 5-3	13 (12.7)	9 (25.7)
shMOLLI	0 (0.0)	1 (2.9)
T1 mapping post-contrast	53 (52.0)	21 (60.0)
T2 mapping		
GraSE	13 (12.7)	9 (25.7)
Gradient Echo	16 (15.7)	7 (20.0)
Magnetic resonance angiography	7 (6.9)	3 (8.6)

Values are given in n and %. CMR: Cardiovascular Magnetic Resonance, 2CH: 2 Chamber view, 4CH: 4 Chamber view, 3CH: 3 Chamber view, SAX: Short Axis view, bSSFP: Balanced Steady State Free Precession, STIR: Short Tau Inversion Recovery, PSIR: Phase-Sensitive Inversion Recovery, MOLLI: Modified Look-Locker inversion recovery, SASHA: Saturation recovery single-shot acquisition, ECV: Extracellular volume, GraSE: Gradient and Spin-Echo.

Image quality

Table 3 lists the findings on image quality for the different sequences. Image quality ranged from excellent to non-diagnostic. Exemplary gradings of all the sequences analysed are illustrated in Figure 5. A diagnostic image quality was found in 95% of the analysed data sets. Ninety-eight per cent of Cine scans had diagnostic image quality, among them 34% with an excellent image quality. Twenty-seven per cent (30/111) of oedema sequences were graded as excellent and 9% as not non-diagnostic. The T2-weighted scans performed under conscious sedation were respiratory-gated, the late gadolinium enhancement scans were not. The late gadolinium enhancement sequences were performed in the SENSE technique in order to improve the resolution and the signal-to-noise ratio. Among the late gadolinium enhancement sequences, the best overall picture quality

Table 3. Sequence quality information

Sequence	Performed	Non-diagnostic 1	Moderate Quality 2	Good Quality 3	Excellent Quality 4
Cine sequences					
2CH	133 (97.1)	4 (3.0)	20 (15.0)	68 (51.2)	41 (30.8)
4CH	135 (98.5)	2 (1.5)	25 (18.5)	54 (40.0)	54 (40.0)
3CH	118 (86.1)	5 (4.2)	15 (12.7)	50 (42.4)	48 (40.7)
SAX	136 (99.3)	1 (0.7)	27 (19.9)	71 (52.2)	37 (27.2)
Trans	59 (43.1)	7 (11.9)	5 (8.5)	30 (50.8)	17 (28.8)
Edema sequences					
STIR SAX	111 (81.0)	10 (9.0)	31 (27.9)	40 (36.0)	30 (27.0)
STIR 2CH	16 (11.7)	4 (25.0)	4 (25.0)	6 (37.5)	2 (12.5)
STIR 4CH	29 (21.2)	10 (34.5)	12 (41.4)	4 (13.8)	3 (10.3)
STIR 3CH	13 (9.5)	3 (23.1)	2 (15.4)	5 (38.5)	1 (7.7)
Gradient Echo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
T1 mapping					
Native	54 (39.4)	1 (1.2)	5 (9.3)	23 (42.6)	25 (46.3)
Post-contrast	74 (54.0)	0 (0.0)	1 (1.4)	45 (60.8)	28 (37.8)
T2 mapping	43 (31.4)	2 (4.7)	12 (27.9)	18 (41.9)	11 (25.9)
Late enhancement					
Standard 2D	108 (78.8)	10 (9.3)	15 (13.9)	49 (45.4)	34 (31.5)
Standard 3D	119 (86.9)	8 (6.7)	24 (20.2)	45 (37.8)	42 (35.3)
PSIR	104 (75.9)	6 (5.8)	20 (19.2)	36 (34.6)	42 (40.4)

Values are given in n and %. 2CH: 2 Chamber view, 4CH: 4 Chamber view, 3CH: 3 Chamber view, SAX: Short Axis view, STIR: Short Tau Inversion Recovery, PSIR: Phase-Sensitive Inversion Recovery.

was seen in phase-sensitive inversion recovery images with 40% excellent and only 6% non-diagnostic data sets. For 32% of the standard 2D data sets and 35% of the standard 3D data sets, late gadolinium enhancement image quality was graded as being excellent. The best overall image quality was noted for T1 mapping, where 46.3% of native and 37.8% of post-contrast examinations were graded as excellent. Diagnostic image quality was found in all performed post-contrast T1 maps and in 98% of native studies (Fig 1). There were no statistically significant differences in T1 mapping image quality between MOLLI 3-3-5 and MOLLI 5-3 (native: $p = 0.15$, post-contrast: $p = 0.33$) or between GE and GraSE techniques in T2 mapping ($p = 0.33$). The best picture quality in Cine sequences was seen in the oldest age group (13-18 years; 2 chamber view: $p = 0.00$, 4 chamber view: $p = 0.047$, 3 chamber view: $p = 0.17$, short-axis planes: $p = 0.02$; Fig 2). Exemplary findings are illustrated in Figure 3. In Cine imaging and T2 mapping, the image quality was not significantly different when comparing scans acquired with and without use of sedation (2 chamber view: $p = 0.06$, 4 chamber view: $p = 0.79$, 3 chamber view: $p = 0.19$, short-axis planes: $p = 0.31$, T2 mapping: $p = 0.28$). In other tissue characterisation sequences, the use of deep sedation influenced the image quality negatively (T1 mapping before the application of the contrast agent: $p = 0.03$, post-contrast: $p = 0.01$, late gadolinium enhancement 2D: $p = 0.01$, 3D: $p = 0.00$, phase-sensitive inversion recovery: $p = 0.03$; Fig 4).

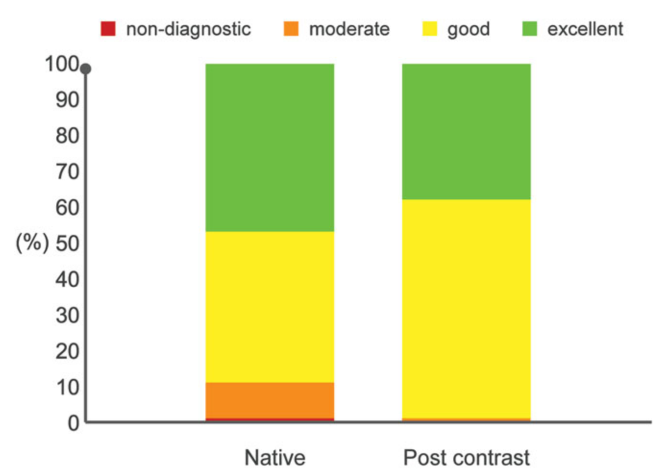

Figure 1. T1 mapping – image quality.

Discussion

This study presents a view on the German use of cardiovascular magnetic resonance in children with suspected myocarditis, including an overview of cardiovascular magnetic resonance techniques, protocols, and of the resulting image quality in these patients. Our study showed good image quality in 95% of the

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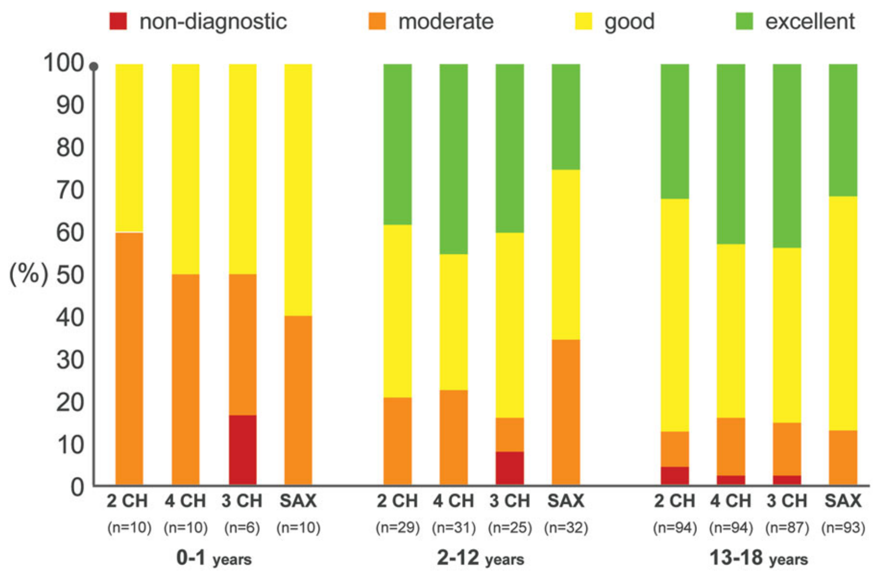

Figure 2. Picture quality in relation to patient age in CINE imaging. 2CH: 2 chamber view, 4CH: 4 chamber view, 3CH: 3 chamber view, SAX: short axis view.

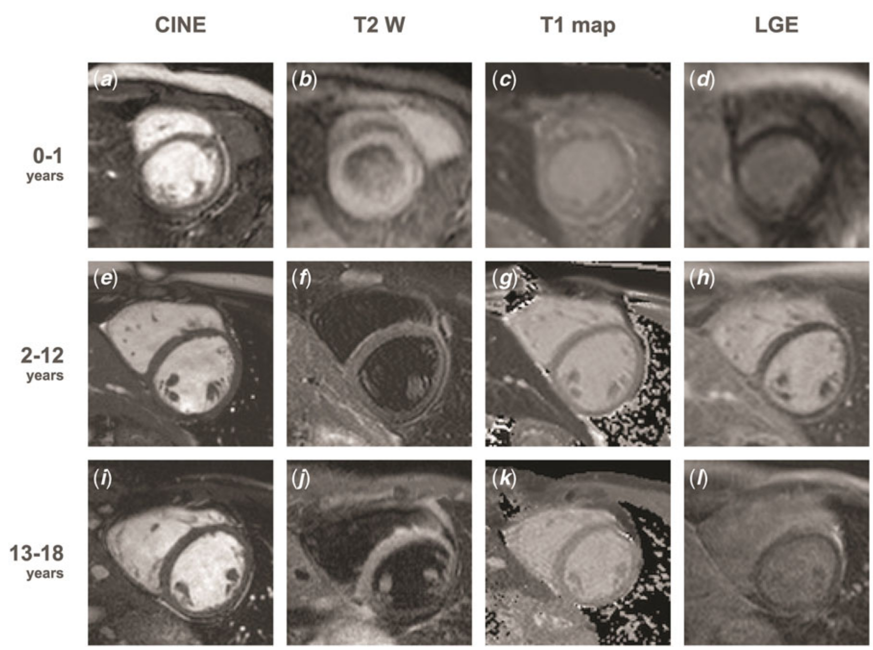

Figure 3. Mid-ventricular short axis slices demonstrating: CINE imaging, oedema imaging, native T1 mapping, and late gadolinium enhancement imaging for every age group, respectively (0-1 years: a, b, c, d; 2-12 years: e, f, g, h; 13-18 years: i, j, k, l).

children, comparable to data acquired in a study describing children undergoing pulmonary valve replacement (92% diagnostic-quality images).[24] Furthermore, the image quality demonstrated a strong dependence on age: older patients showed better image quality, possibly due to better compliance and physiological differences such as lower heart rate and larger size of anatomical structures. The use of sedation in smaller children seems to be an important factor as it influences the scan quality in tissue characterisation sequences negatively.

The original Lake Louise criteria, combining T2 ratio, early and late gadolinium enhancement, still remain an essential tool for diagnosing acute myocardial inflammation in many centres. In our cohort, over half of the scans used a study protocol that was consistent with the original criteria, whereas a previous paediatric study on myocarditis found that the original Lake Louise Criteria were employed in only 28% of scans.[25] The fact that the original criteria were used at such a high rate despite the lack of validation or standardisation studies in children underlines the lack of alternative approaches, which has been compensated for by the publication of the revised Lake Louise criteria in 2018.[15] The revised criteria combine conventional cardiovascular magnetic resonance and mapping techniques as markers for inflammatory myocardial injury. The new proposed cardiovascular magnetic resonance protocol consists of a "2 of 2" diagnostic target combination, including at least one positive T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted imaging) and at least one positive T1-based criterion (prolonged myocardial T1 time, increased extracellular volume, or presence of late gadolinium enhancement). Another essential modification is the absence of early gadolinium enhancement, as recent data suggested that excluding early gadolinium enhancement from the original study protocol would not substantially hamper diagnostic accuracy.[15,26]

In adults, cardiovascular magnetic resonance mapping techniques have demonstrated their superiority over classical tissue

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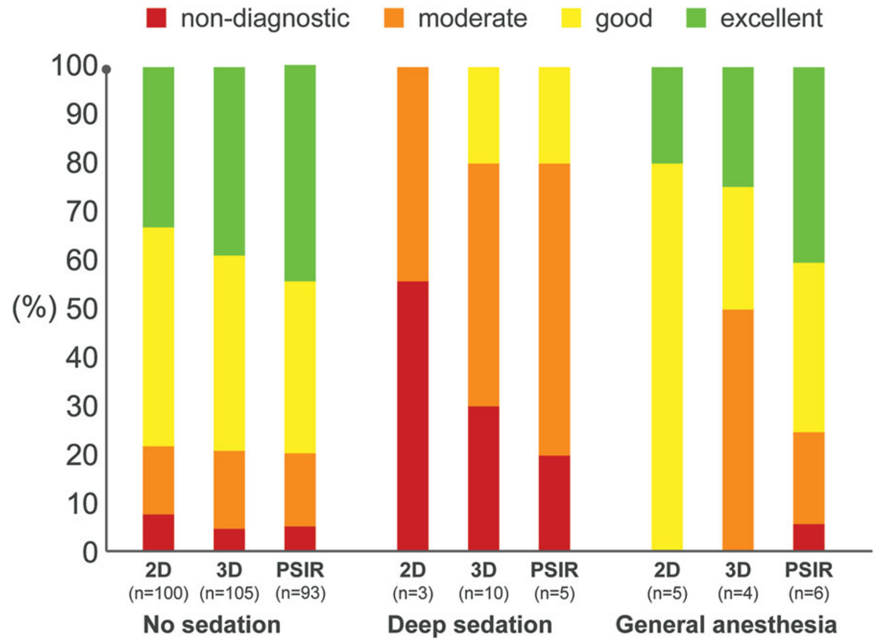

Figure 4. Image quality in relation to sedation in late gadolinium enhancement. 2D: late gadolinium enhancement standard 2D, 3D: late gadolinium enhancement standard 3D, PSIR: phase-sensitive inversion recovery.

characterisation techniques in several trials. In a study conducted by Ferreira et al., native T1 mapping showed higher diagnostic yield compared with T2-weighted and late gadolinium enhancement imaging.[27] In the MyoRacer Trial, T2 mapping had the highest sensitivity (73%) in patients with chronic symptoms.[28] The latter technique has also proven itself useful in ruling out active inflammation and differentiating between an acute and chronic process.[29] The gradually increasing importance of novel mapping techniques, which subsequently has led to the aforementioned revision of the Lake Louise criteria, is also reflected in our study: we found growing usage of parametric mapping in the follow-up examinations compared to the initial examinations. Parametric mapping has numerous advantages such as direct quantification of signal changes, higher signal-to-noise ratio and shorter breath holds with fewer breathing motion artefacts. Combined with the resilience to arrhythmias, parametric mapping results in more robust image quality and subsequently better diagnostic performance, as seen in our study where the majority of native and post-contrast T1 mapping sequences resulted in excellent or good picture quality.[30] Also Cornicelli et al. showed in a relatively small cohort of children with myocarditis a superior performance of parametric mapping techniques as compared to the original Lake Louise approach.[31] Similar to adult applications, care has to be taken that values of myocardial T1 and T2 are compared to reference values that were generated with the same technical setup as the patient data. Moreover, reference ranges should be matched for the age group of the patients. Nevertheless, in spite of the growing use of the parametric mapping illustrated in our study, according to the revised Lake Louise Criteria, 65% of the scans included in our analysis were incomplete. This further stresses out the urgent need for standardisation of study protocols by parallel publication of recommendations for scanning children and adults, as it was done in an society for cardiovascular magnetic resonance guideline for patients with COVID-19.[18] Aside from highlighting the excellent performance of modern parametric mapping techniques in children, our study has important implications regarding the utility of deep sedation versus general anaesthesia during cardiovascular magnetic resonance in children. In the past, several studies on this subject have produced contradictory results. One study stated that cardiovascular magnetic resonance scans performed under deep sedation had substantially more motion artefacts.[32] As opposed to this, Fogel et al. published that cardiovascular magnetic resonance scans performed under conscious sedation presented with similar image quality and diagnostic yield compared to general anaesthesia.[33] Our study showed that in small children, necessitating the use of sedation for performing cardiovascular magnetic resonance, ventricular function assessment and parametric mapping in T2 technique do not significantly benefit from the use of general anaesthesia instead of deep sedation, whereas classical tissue characterisation techniques, requiring longer breath holds, resulted in better image quality under general anaesthesia. Therefore, in the future, the growing use of myocardial mapping techniques might contribute to reducing the need for general anaesthesia in small children and protecting the youngest patients from the risk of severe complications related to this procedure.[34,35]

Our findings show that currently used adult cardiovascular MRI protocols for myocarditis can be applied to children without significant limitations in image quality. The excellent technical performance of parametric myocardial mapping techniques found in this paediatric cohort allows using protocols that assess the revised Lake Louise criteria. In the absence of specific recommendations for children, such protocols should be employed for paediatric myocarditis in order to increase standardisation and comparability of results.

There might be a selection bias related to cardiovascular magnetic resonance, with less severely ill patients having higher chances of undergoing cardiovascular magnetic resonance and patients with more severe illness not being sent for cardiovascular magnetic resonance. Therefore, our results might not represent the entire population of children with suspected myocarditis. In this study, we did not address the diagnostic power of cardiovascular magnetic resonance by examining its sensitivity and specificity. Furthermore, similarly to another paediatric study, the decision about performing a follow-up cardiovascular magnetic resonance was taken by the referral cardiologist according to local policies

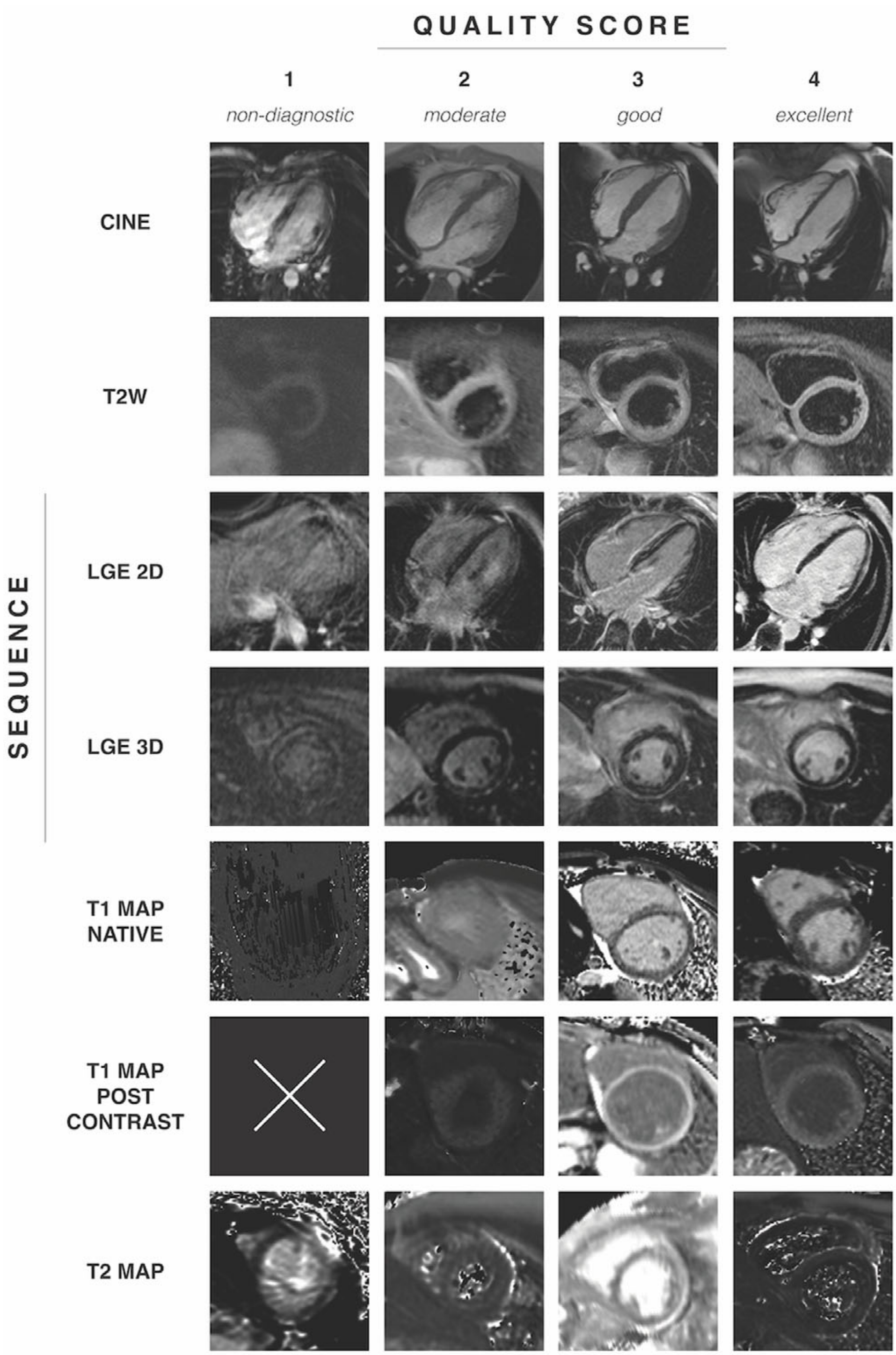

Figure 5. Exemplary quality gradings of all the sequences analysed. T2W: T2-weighted imaging, LGE 2D: late gadolinium enhancement standard 2 D, LGE 3D: late gadolinium enhancement standard 3D.

and a repeated written consent of a legal guardian was needed.[11] As a result, only 34% of our patients received a follow-up cardiovascular magnetic resonance. This might have led to the heterogeneity of the data acquired at follow-up cardiovascular magnetic resonance.

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