Kawasaki disease: Studies on etiology, treatment and long-term follow-up

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Citation for published version (APA):
CARDIAC MAGNETIC RESONANCE IMAGING FOR NON-INVASIVE ASSESSMENT OF CARDIOVASCULAR DISEASE DURING THE FOLLOW-UP OF PATIENTS WITH KAWASAKI DISEASE

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ABSTRACT

Background:
Kawasaki disease (KD) is the most common cause of acquired coronary artery disease in childhood. In KD, the American Heart Association recommends echocardiography for routine coronary artery surveillance and nuclear perfusion scans and conventional coronary angiography in a selection of patients. Cardiac MRI (CMRI) may be a noninvasive and radiation-free alternative. We applied CMRI during the follow-up of patients with KD and assessed the performance of CMRI compared with echocardiography.

Methods and results:
Patients with KD aged ≥8 years were consecutively included. Sixty-three patients (median age, 14.6 years; 74.6% male sex) underwent a comprehensive CMRI protocol including adenosine stress testing to evaluate coronary artery anatomy, ischemia, and myocardial infarction. All patients underwent CMRI without significant complications. On CMRI, 23 coronary artery aneurysms (CAAs) were identified in 15 patients. CMRI detected thrombus formation in 6 CAAs in 4 patients, wall motion disturbances and ischemia in 4 patients, and delayed hyperenhancement indicating myocardial infarction in 5 patients. Wall motion and perfusion abnormalities were noted in territories supplied by affected coronary arteries. CMRI results were compared with recent echocardiography findings. In 6 patients of the 15 patients with CAAs upon CMRI, CAAs were not detected by echocardiography.

Conclusions:
A comprehensive CMRI protocol including adenosine-stress testing is feasible to identify coronary artery pathology, ischemia, and myocardial infarction in former patients with KD and compares favorably with echocardiography. CMRI may be used as a noninvasive and radiation-free imaging method for coronary artery surveillance during the long-term follow-up of patients with KD.
INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology that predominantly occurs in young children. KD is associated with the development of coronary artery aneurysms (CAAs) in 15% to 25% of untreated cases and in <10% of cases treated with high-dose intravenous immunoglobulins (IVIG). In approximately half of the patients CAAs resolve within 1 to 2 years. In the other patients, the aneurysms persist long-term and may lead to thrombosis and stenotic lesions that can cause myocardial ischemia and infarction. As a consequence, KD is the most important cause of acquired coronary artery disease in childhood. Serial coronary artery surveillance is necessary in patients with a history of KD.

In 2004, the American Heart Association (AHA) published guidelines for follow-up of patients with KD based on a consensus of experts. Patients are stratified into 5 risk levels according to their relative risk of myocardial ischemia and infarction. Serial echocardiography is recommended for patients without CAAs or with transient coronary artery dilatations normalizing within the first 6 to 8 weeks after the acute presentation of the disease (risk levels I-II). For patients with persistent CAAs, serial nuclear stress tests and conventional coronary angiography are recommended in addition to regular echocardiography (risk levels III-V).

The imaging modalities recommended in the AHA 2004 guidelines have some significant limitations. Echocardiography is the first choice for routine coronary artery surveillance and is used to screen patients with KD for the presence of coronary artery pathology. An important disadvantage of echocardiography is that only the proximal part of the coronary arteries can be visualized adequately, and CAAs, therefore, could be missed. In addition, echocardiography may be limited by operator dependency and becomes progressively more difficult if a child grows and body size increases. Nuclear perfusion scans are recommended to address ventricular function in relation to vascularization and ischemia with modest specificity, while resulting in high radiation exposure. Conventional coronary angiography is the gold standard for coronary artery evaluation and is able to detect CAAs, coronary artery stenosis, and thrombotic occlusion but results in risks associated with its invasive nature and the exposure to contrast and radiation. A well-known problem of conventional angiography is vascular damage at the puncture site, resulting in thrombosis and occlusion of the femoral artery, which may limit the repeated use of this imaging modality in patients with KD.

Cardiac magnetic resonance imaging (CMRI) has emerged as a noninvasive and radiation-free imaging modality with the ability to evaluate the coronary arteries, cardiac function, and myocardial perfusion. CMRI offers a detailed image of the coronary anatomy and may delineate proximal and more peripheral CAAs. CMRI also facilitates pharmacological stress testing to assess reversible ischemia and delayed contrast enhancement to visualize myocardial scar.

The aim of this study was to apply within a single procedure a comprehensive CMRI protocol including adenosine stress testing to assess coronary artery pathology, reversible ischemia
and myocardial infarction during the follow-up of patients with KD, and secondly, to assess to what extent CMRI identifies coronary artery lesions missed by echocardiography. We hypothesized that CMRI is suitable for coronary artery surveillance in patients with KD and, hence, can serve as a noninvasive and radiation-free imaging alternative for the imaging modalities recommended in the current AHA guidelines.

METHODS

Patients
This study was conducted between September 2007 and October 2010 at the Emma Children’s Hospital (Amsterdam, The Netherlands). Patients were included if they were aged ≥8 years and had a history of KD. The age threshold was raised to avoid the use of anesthetics. Patients were prospectively included in consecutive order of outpatient consultation. Patients were ineligible for the study if they had a known contraindication for CMRI apart from young age. Medical records were reviewed to collect clinical characteristics of the patients with KD. Based on echocardiography data, patients were divided into the following 3 groups before CMRI performance: group 1, patients without CAAs; group 2, patients with transient CAAs (ie, patients with coronary artery lesions during the acute phase that normalized during follow-up); and group 3, patients with persistent CAAs (III). The study was approved by the ethics committee of our hospital, and written informed consent was obtained from all subjects and/or their families.

Echocardiography
Transthoracic echocardiography was performed during routine follow-up of the patients with KD using a GE Vivid 7 ultrasound imaging system. The 2D examinations were performed by an experienced examiner. The evaluations included display of the main trunk of the coronary arteries and, if possible, display of the more distal segments. Furthermore, left ventricular function, wall motion abnormalities, and the function of the cardiac valves were investigated. For this study, echocardiographic images were centrally reread and evaluated by an experienced pediatric cardiologist (I.K.).

The time window between echocardiographic and CMRI examination was <6 months. We aimed to perform CMRI after echocardiographic evaluation. In some cases, the order was reversed for practical reasons. In all cases, the pediatric cardiologist and radiologist were blinded for each other’s results.

CMRI
The CMRI protocol was performed on a 1.5 Tesla whole-body MRI scanner equipped with cardiac software (Avanto; Siemens; Erlangen, Germany). The complete imaging protocol included magnetic resonance coronary angiography (MRA), first-pass perfusion, and late
gadolinium enhancement studies. The examination was completed within 60 minutes and without the use of any form of sedation. The MRA imaging study was performed during free breathing and without the use of contrast. To compensate for respiratory motion artifacts, a navigator beam was placed on the patients' right hemidiaphragm for end-expiratory gating. An ECG-gated 3D steady-state free precession (SSFP) sequence with T2 and fat-saturation prepulses was used to visualize the coronary arteries in a whole-heart approach. Breath-hold, ECG-gated, 2D SSFP sequences were applied to detect wall motion abnormalities in 2-chamber, 3-chamber, 4-chamber, and short-axis views. Turbo fast low-angle shot (FLASH) sequences were used to evaluate myocardial first-pass perfusion in 3 to 5 short-axis slices during intravenous contrast medium infusion (gadolinium at a dose of 0.1 mmol/kg body weight). This sequence was performed after administration of 1 mg/kg adenosine in 6 minutes to detect ischemia after adenosine stress. It was repeated without adenosine to detect (reversible) ischemia at rest. After 5 to 15 minutes, inversion recovery Turbo-FLASH was performed in 2-chamber, 3-chamber, 4-chamber, and short-axis views to detect myocardial scar by delayed hyperenhancement.

**CMR imaging analysis**

CMRI studies were analyzed by the 2 radiologists involved in the study. The radiologists were blinded for the echocardiography results and the clinical patient characteristics. CMRI images were evaluated for the presence of aneurysms of the main epicardial coronary arteries. The right coronary artery (RCA), left main coronary artery (LMCA), left descending coronary artery (LAD), and left circumflex artery (LCX) were assessed. An abnormal coronary artery was defined according to criteria established by the Japanese Ministry of Health in 1984 (ie, a lumen diameter >3 mm in children aged <5 years, >4 mm in those aged >5 years, or 1.5 times the size of an adjacent segment or an irregular lumen19. CAAs with a lumen diameter >8 mm were classified as giant1. The coronary arteries also were evaluated for the presence of thrombi and stenotic lesions. Thrombi were diagnosed as a low-signal mass against the wall of the aneurysmatic coronary artery, with a filling defect in the aneurysm in both the coronary sequences and the sequences with delayed enhancement. A stenotic lesion was defined as clinically significant if the reduction in vessel diameter was >50%. Myocardial wall motion was qualitatively analyzed and classified as normal or abnormal, which includes hypokinetic, dyskinetic, or akinetic wall motions. A 17-segment model was used for analysis20. Segmental myocardial first-pass perfusion after adenosine stress was evaluated qualitatively and assessed as normal or as revealing a perfusion defect. In patients with first-pass perfusion defects after adenosine stress, myocardial perfusion at rest was also assessed. Delayed contrast-enhanced images were evaluated visually for areas of delayed hyperenhancement indicating scar due to myocardial infarction21. Delayed hyperenhance-
mment was categorized as subendocardial (≤ 50% wall thickness) or transmural (>50% of wall thickness).

Statistics
Data, including clinical characteristics and CMRI findings, were summarized using SPSS for Windows version 16.0 statistical software. Data are expressed as numbers with percentages, as mean ± SD, or as median with interquartile ranges (IQR) where appropriate. Bland-Altman analysis was applied to assess agreement between CMRI and echocardiography measurements of maximal proximal coronary artery diameter in patients without CAAs and the maximal CAA diameter in affected KD patients.

RESULTS
Patient characteristics
Sixty-three patients with KD (median age, 14.6 years; IQR, 12.5-18.6; 74.6% male) were consecutively enrolled during follow-up as outpatients. Patient characteristics are described in Table 1. Three patients had retrospectively received a diagnosis of KD after presentation with an acute myocardial infarction at a young age. Group I (normal coronary arteries) comprised 41 patients; group II (transient aneurysms), 12 patients, and group III (persistent aneurysms), 10 patients. The median interval between echocardiography and CMRI was 1.3 months (IQR, 0.62-2.63 months).

Table 1. Clinical characteristics of the study patients (n=63)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at CMRI examination in years, median (IQR)</td>
<td>14.6 (12.5 - 18.6)</td>
</tr>
<tr>
<td>Sex: male</td>
<td>47 (74.6)</td>
</tr>
<tr>
<td>Age at KD onset in years, median (IQR)</td>
<td>3.6 (1.7 – 8.0)</td>
</tr>
<tr>
<td>Interval acute KD – CMRI in years, median (IQR)</td>
<td>10.2 (6.3 – 13.8)</td>
</tr>
<tr>
<td>Diagnosis: complete KD *</td>
<td>53 (85.5)</td>
</tr>
<tr>
<td>Treatment:</td>
<td></td>
</tr>
<tr>
<td>Treatment with IVIG</td>
<td>54 (85.7)</td>
</tr>
<tr>
<td>Treatment with aspirin</td>
<td>58 (92.1)</td>
</tr>
<tr>
<td>Treatment with steroids</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Coronary artery status **</td>
<td></td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>41 (65.1)</td>
</tr>
<tr>
<td>Transient CAA</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Persistent CAA</td>
<td>10 (15.9)</td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise indicated.
* According to the clinical criteria for diagnosis of KD1
** Coronary artery status before CMRI performance
Abbreviations: CAA=coronary artery aneurysm; IVIG=intravenous immunoglobulins; IQR=interquartile range
All CMRI examinations were performed without significant medical complications. In 2 patients, first-pass perfusion studies were not completed because of adenosine-related side effects (nausea, headache, and palpitations).

Upon CMRI, normal coronary arteries were observed in 46 (73.0%) patients. The mean vessel diameter in these non-affected patients was 3.3±0.5 mm for the left and 2.8±0.4 mm for the right proximal coronary arteries. In 15 (23.8%) patients, 23 CAAs were identified, and the aneurysms were classified as giant in 5 patients. CMRI results of the 15 patients with CAAs are presented in Table 2. CMRI detected CAA-associated thrombus formation in 6 CAAs in 4 patients. In 2 patients, the coronary arteries could not be evaluated because of insufficient CMRI quality due to breathing artifacts.

Normal first-pass perfusion studies after adenosine stress were observed in 53 (84.1%) patients. In 4 patients (6.3%), first-pass perfusion defects were detected in 13 myocardial segments after adenosine stress. In 11 of the 13 segments (84.6%), wall motion abnormalities were noted. All patients with first-pass perfusion defects had severe coronary artery pathology, and the defects were detected in territories of affected coronary arteries (Table 2). In 1 of these 4 patients, the ischemia was reversible at rest. First-pass perfusion studies after adenosine stress could not be evaluated in 5 patients (7.9%). In the 2 patients with adenosine-related side effects, first-pass perfusion studies were not completed, and in 3 patients, technical problems occurred because of inadequate bolus-timing. CMRI documented CAAs in 1 of the patients with unsuccessful first-pass perfusion studies after adenosine stress. This patient had normal first-pass perfusion studies at rest (Table 2, #13).

Segmental late gadolinium enhancement was normal in 58 patients. Delayed hyperenhancement was noted in 16 segments of 5 patients and was transmural in 9 segments and subendocardial in 7 segments (Table 2). In 4 of these 5 patients with delayed hyperenhancement, wall motion abnormalities were detected in the same myocardial areas. In the remaining patient, the hyperenhancement was subendocardial and did not result in wall motion abnormalities. In 2 patients, the myocardial infarction went unnoticed in

Figure 1.

Examples of CMRI images of KD patients showing a normal right coronary artery (A), a giant aneurysm of the right coronary artery with thrombosis (B), and a basal inferoseptal-inferior myocardial infarction (C).
**Table 2. CMRI results of 15 patients with coronary artery aneurysms**

<table>
<thead>
<tr>
<th>#</th>
<th>Age (Yrs)</th>
<th>Sex</th>
<th>Group **</th>
<th>MRA: location and diameter of CAA</th>
<th>First-pass perfusion adenosine / rest</th>
<th>Location first-pass perfusion defect</th>
<th>Delayed hyper-enhancement</th>
<th>Wall motion abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>10.6</td>
<td>M</td>
<td>I</td>
<td>LCA bifurcation (5.1 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>2*</td>
<td>20.0</td>
<td>M</td>
<td>I</td>
<td>LMCA (5.8 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>3*</td>
<td>9.4</td>
<td>M</td>
<td>II</td>
<td>Prox. RCA (5.1 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>4*</td>
<td>13.2</td>
<td>M</td>
<td>II</td>
<td>Prox. LAD (4.8 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>5*</td>
<td>18.3</td>
<td>M</td>
<td>II</td>
<td>Prox. LCA (5.8 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>6§</td>
<td>15.2</td>
<td>M</td>
<td>II</td>
<td>Prox. LAD (4.9 mm), RCA irregular lumen</td>
<td>Yes / Yes</td>
<td>Mid antero septal</td>
<td>Mid/basal inferior (subendocardial)</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>11.8</td>
<td>M</td>
<td>III</td>
<td>LCA bifurcation (6.7 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>15.3</td>
<td>M</td>
<td>III</td>
<td>LMCA (5.8 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>15.4</td>
<td>M</td>
<td>III</td>
<td>LAD (7.3 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>16.2</td>
<td>M</td>
<td>III</td>
<td>RCA (8.1 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>18.5</td>
<td>M</td>
<td>III</td>
<td>LAD (7.5 mm)</td>
<td>Normal / -</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>12§</td>
<td>22.6</td>
<td>M</td>
<td>III</td>
<td>LAD (15.0 mm + thrombus), RCA (22.1 mm + thrombus, 176 mm + thrombus)</td>
<td>Yes / Normal</td>
<td>Mid/apical inferior</td>
<td>Mid and apical inferior (subendocardial)</td>
<td>Hypokinesis</td>
</tr>
<tr>
<td>13‡</td>
<td>23.8</td>
<td>M</td>
<td>III</td>
<td>Prox. LAD (6.8 mm), LCX (9.1 mm), Prox. RCA (12 mm + thrombus)</td>
<td>Failed / Normal</td>
<td>-</td>
<td>Basal/mid inferior (transmural)</td>
<td>Akinesis</td>
</tr>
<tr>
<td>14‡</td>
<td>32.5</td>
<td>M</td>
<td>III</td>
<td>LAD (14.2 mm + 11.5 mm), RCA (39.8 mm + slow flow / thrombus)</td>
<td>Yes / Yes</td>
<td>Basal/mid inferior</td>
<td>Basal/mid inferior (transmural)</td>
<td>Akinesis</td>
</tr>
<tr>
<td>15‡</td>
<td>43.8</td>
<td>F</td>
<td>III</td>
<td>Prox. LAD (26.2 + thrombus), Mid LAD (10.0 mm), Distal LAD (7.5 mm)</td>
<td>Yes / Yes</td>
<td>Apex</td>
<td>Apex (transmural)</td>
<td>Akinesis</td>
</tr>
</tbody>
</table>

*These 6 patients showed discrepancies between echocardiography and CMRI for the identification of CAA (Figure 2)

**Before CMRI performance KD patients were divided in three groups based on their coronary artery status: normal coronary arteries (I), transient coronary abnormalities (II), and persistent coronary abnormalities (III).

†These three patients presented with an acute myocardial infarction and had been treated with successful thrombectomy (#13), a CABG procedure (#15), and one is planned for surgery (#14). In all cases the diagnosis of KD was made retrospectively.

§ Patients were referred for a CABG procedure after the CMRI examinations.
the medical history examination. Both patients were referred for a coronary artery bypass
graft (CABG) procedure after confirmation of the severe lesions by conventional coronary
angiography. In none of the patients without coronary artery pathology were wall motion
abnormalities or perfusion defects detected. Examples of CMRI studies of a normal coronary
artery, a giant CAA with thrombosis, and delayed hyperenhancement are shown in Figure 1.

Comparison of CMRI and echocardiography for CAA identification

CMRI results were compared with the echocardiography findings (Figure 2A). In all patients
without CAs upon CMRI, recent echocardiography also showed normal coronary arteries.
Bland-Altman analysis for CMRI and echocardiography showed no systematic differences in
the maximal diameter of the proximal coronary arteries in these unaffected patients (Figure
3A).

In 6 of the 15 patients with CAs upon CMRI, the lesions were missed by recent echocardi-
ography because of the peripheral localization of the CAs or poor echocardiographic
windows. CMRI and echocardiography images of these 6 patients are presented in Figure
2B. In 2 patients, the coronary artery lesions had remained unrecognized upon all previous
echocardiographic evaluations (group I). The 4 remaining patients with CAs missed by
recent echocardiography had shown transient dilatations in the past on echocardiography
(group II).

In the other 9 patients with CAs on CMRI, coronary artery pathology was also identified
upon echocardiography (group III). Of the 16 CAs documented in these 9 patients on
CMRI, 4 were invisible with echocardiography. Bland-Altman analysis of maximal diameter of
the 12 visible aneurysms revealed good agreement between CMRI and echocardiography
measurements, although the wider aneurysms tended to show larger differences, which
can be related to wall-associated thrombus in these CAs (Figure 3B).

Figure 3.

Bland-Altman analysis of the agreement between CMRI and echocardiography measurements for the
maximal proximal coronary artery diameter in unaffected patients (A) and the maximal coronary artery
aneurysm diameter (B). The difference in diameter between CMRI and echocardiography is plotted versus
the mean diameter ([(CMRI + echocardiography)/2]. The mean difference (solid line) and ± 2SD (dashed lines)
are shown.
A: a flow diagram containing the comparison of echocardiography and CMRI findings for the identification of coronary artery aneurysms (CAA) in the three groups of KD patients.

B: images are shown of the 6 patients with discrepancies between echocardiography and CMRI: patient I: LCA bifurcation aneurysm (5.1 mm); patient II: LMCA aneurysm (5.8 mm); patient III: LAD aneurysm (4.9 mm); patient IV: RCA aneurysm (5.1 mm); patient V: proximal LCA aneurysm (5.8 mm); patient VI: LAD aneurysm (4.8 mm).
Implementation of the current guidelines

Considering the current AHA guidelines, we determined how many of the imaging studies in addition to routine echocardiography should at least have been performed compared with reality (Table 3). The number of nuclear perfusion scans and conventional coronary angiographies was considerably lower than recommended according to the guidelines.

**Table 3.** Number of SPECT and conventional coronary angiography (CAG) as recommended by the current AHA guidelines and performed in our cohort of 63 KD patients prior to CMRI examination

<table>
<thead>
<tr>
<th>AHA risk level</th>
<th>Number of patients</th>
<th>No. of examinations (at least) by current guidelines</th>
<th>Current practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SPECT</td>
<td>CAG</td>
</tr>
<tr>
<td>I-II</td>
<td>No or transient coronary artery dilatations</td>
<td>53</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>Solitary CAA of 3 - 6 mm in one or more coronary arteries</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>CAA ≥ 6 mm, or multiple CAAs in one coronary artery</td>
<td>4</td>
<td>7 (15)**</td>
</tr>
<tr>
<td>V</td>
<td>Coronary artery obstruction ‡</td>
<td>4</td>
<td>7 (14)**</td>
</tr>
</tbody>
</table>

* The numbers of examinations are calculated from the date that the guidelines were published in 2004.

** Considering biannual SPECT to be sufficiently informative; annual SPECT (as recommended in the current guidelines in level IV-V patients) would increase the number as indicated between brackets.

‡ Three out of these 4 patients presented with an acute myocardial infarction. Numbers of examinations are calculated from the date of presentation.

**DISCUSSION**

The results of this study demonstrate that CMRI is feasible in former patients with KD to assess the presence of CAAs, wall motion disturbances, ischemia, and myocardial infarction. The comprehensive CMRI protocol including adenosine stress testing can be performed without anesthetics in patients aged ³8 years. We identified CAAs on CMRI that were not detected by recent echocardiography in almost 10% of the patients, including 2 patients without prior coronary artery lesions upon serial echocardiography. CMRI identified perfusion defects and delayed hyperenhancement in 5 patients with persistent CAAs. In patients without coronary artery pathology, no wall motion or perfusion abnormalities were noted.

**Current AHA guidelines**

Echocardiography, conventional coronary angiography and nuclear perfusion scans are the imaging modalities recommended in the current guidelines for follow-up of patients with KD. These AHA 2004 guidelines are based on a consensus of experts until long-term studies facilitate a more evidence-based practice. According to the guidelines, we rely on
serial echocardiography in patients without CAAs or with transient dilatations (levels I-II). However, the experts have recognized the limitations of echocardiography and mention that CMRI may therefore be of value in selected patients with KD. Results of the present CMRI study confirm that a considerable number of CAAs remain unrecognized by echocardiography only because of peripheral localization or poor echocardiographic windows. For patients with persistent coronary artery lesions (levels III-V), the AHA guidelines recommend serial stress tests and conventional coronary angiography to evaluate the coronary anatomy and to assess the existence and functional consequences of CAAs. Nuclear stress tests are proposed annually or once every 2 years, depending on the diameter and number of CAAs. Conventional coronary angiography is reserved for patients with large (≥ 6 mm) or multiple CAAs, in cases of symptoms indicating myocardial ischemia, and for patients with an abnormal stress-test. If these guidelines are implemented, level III to V patients need repeated diagnostic examinations, leading to a great number of invasive procedures and a high radiation burden. It is important to reduce the exposure to ionizing radiation to a minimum because of the carcinogenic effects. Especially in children, the radiation burden has to be reduced because children are more sensitive to the carcinogenic effects than adults and have a longer life expectancy, resulting in a larger time window for expressing damage due to the radiation.

In this cohort of patients with KD, referred from all over the country, implementation of the AHA 2004 guidelines was evaluated. Considering the results, implementation had not become routine in level III to V patients. Invasiveness, radiation burden, and the complication rate of nuclear perfusion scans and conventional coronary angiography are assumed to be the main reasons for lack of adherence.

**Cardiac MRI**

CMRI is a noninvasive and radiation-free imaging method that overcomes many of the aforementioned disadvantages. Previous studies have shown complete agreement between CMRI and conventional coronary angiography for identification of CAA, coronary occlusions, and coronary stenosis in patients with KD. A high accuracy of CMRI for measurement of the diameter and length of coronary aneurysms also has been reported previously. Suzuki et al also applied CMRI and echocardiography in a relatively large cohort of patients. Sixty-nine aneurysms were observed in 106 patients on echocardiography, and an additional 28 aneurysms were observed by CMRI. The present study confirms that CAAs remain unrecognized by echocardiography in a considerable number of patients. The study of Suzuki et al was limited to MRA studies only. In the present study, we combined coronary artery visualization with wall motion analysis, adenosine stress testing, and late-enhancement imaging. To the best of our knowledge, our study is the first to evaluate a comprehensive CMRI protocol including adenosine stress testing in a relatively large cohort of only patients with KD.
Studies comparing first-pass perfusion CMRI and single-photon emission computed tomography (SPECT) imaging have indicated that CMRI is more sensitive for the identification of flow-limiting stenosis. CMRI late-enhancement imaging is the reference tool for the assessment of areas of myocardial infarction. The high spatial resolution of CMRI facilitates identification of small subendocardial areas of infarction. In the present study, 2 patients with a small infarction were identified, unnoticed by the medical history examination. Both patients underwent a CABG procedure.

**Other imaging modalities**

Echocardiography is readily and widely available, takes little operator time, and is relatively less expensive compared with CMRI; therefore, it will remain the mainstay for routine follow-up of patients with KD. As is also suggested in a recent review by Mavrogeni et al, we believe that CMRI will not substitute echocardiography in the future but may be performed as second step after echocardiography during the follow-up of patients with KD. Bland-Altman analysis showed good agreement between echocardiography and CMRI for maximal coronary artery diameter and maximal CAA diameter. There tended to be a larger difference in measurements in cases of wider CAAs. This may be explained by thrombus formation and irregularities in these aneurysms, limiting echocardiographic evaluation.

CT angiography is another noninvasive imaging method that could be of value in patients with KD because of its excellent sensitivity for the detection of coronary aneurysms, stenosis, and calcifications. The radiation burden of CT angiography is again an important drawback, although the radiation dose has already been reduced greatly with recent improvements. Further developments may result in CT angiography being another reasonable alternative for detailed coronary artery evaluation, although perfusion and late-enhancement studies are not possible with CT angiography.

**Recommendations**

Based on the results of the present study, CMRI may be a reliable imaging method for coronary artery surveillance during the follow-up of patients with KD. CMRI may identify CAAs missed by echocardiography and may be a valuable alternative for patients with persistent CAAs, combining anatomic and functional evaluation into 1 examination without the use of radiation or any invasive procedure. In patients with a history of KD, we therefore recommend CMRI performance during follow-up as a second step after echocardiography. The exact place and applicability of CMRI in the guidelines for follow-up of patients with KD has to be assessed in future studies. The CMRI protocol could be restricted to MRA studies for patients without known coronary artery pathology because we did not identify first-pass perfusion defect or delayed hyperenhancement in patients without coronary artery lesions. When coronary artery lesions are unexpectedly identified upon MRA, perfusion and
late gadolinium enhancement also may be performed. This has to be validated in future research as well.

**Limitations**

There are limitations to the present study. First, a comparison of CMRI with conventional coronary angiography as the gold standard is lacking because of ethical judgment. However, previous studies have already reported excellent agreement between coronary angiography and CMRI for coronary artery evaluation\textsuperscript{11-14, 22-24}. Secondly, although we included patients in consecutive order of outpatient consultation, the study population contains a high percentage of patients with CAAs compared with the literature of cardiovascular sequelae in KD (<10% CAA). This is explained by referral bias (ie, the more severe cases are being referred to a tertiary hospital). Moreover, patients with coronary artery pathology visit the outpatient department more frequently following acute KD phase, which also explains male predominance – another risk factor of coronary artery aneurysms in KD\textsuperscript{1}. Finally, we only included patients aged ≥8 years during follow-up of the disease to avoid the use of anesthetics. For use of CMRI during the acute phase or in the follow-up of younger patients, general anesthesia will be necessary to obtain diagnostic image quality.

**CONCLUSION**

A comprehensive CMRI protocol for coronary artery surveillance is feasible during the follow-up of KD patients from the age of 8 years onwards, and compares favorably with simultaneous echocardiography. CMRI is able to detect the presence of CAAs, wall motion abnormalities, reversible ischemia and myocardial infarction without the use of radiation or invasive procedures. We recommend future studies to incorporate CMRI in the guidelines for follow-up of patients with KD.

**ACKNOWLEDGEMENTS**

We are grateful to research nurses and secretarial support.
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