

ACQUIRED HEART DISEASE

Magnetic Resonance Angiography, Function and Viability Evaluation in Patients with Kawasaki Disease

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ABSTRACT

Objectives: We evaluated the ability of magnetic resonance imaging to perform a noninvasive assessment of coronary arteries, function and viability in one examination in a population with Kawasaki disease. **Background:** Magnetic resonance angiography (MRA) can identify coronary abnormalities in patients with Kawasaki disease (KD). Contrast enhanced cardiovascular magnetic resonance (ceCMR) is the current gold standard for scar detection. Steady-state, free precession (SSFP) cine is a reliable technique to evaluate myocardial function and wall motion. **Methods:** Twenty patients with KD aged 7–12 yrs, were examined. Coronary MRA was performed using a 1.5 T system with two ECG-triggered pulse sequences. ceCMR images were acquired 15 minutes after the IV injection of 0.1 mmol/kg Gd-DTPA using an inversion recovery sequence. SSFP cines were acquired using 6-mm short-axis slices from the atrioventricular ring to the apex. **Results:** Aneurysms of the coronary arteries were identified in 7 patients and coronary ectasia was present in the remaining 12 patients while 1 patient had both. Transmural anterior-apical scar was detected by ceCMR in two cases, while small inferior necrosis was identified in another 2 cases. Left ventricular function was deteriorated only in the two patients with antero-apical infarction. The presence of myocardial infarction was detected in the territory supplied by the involved coronary artery. **Conclusion:** In Kawasaki disease MRA, SSFP cine and ceCMR are able to perform noninvasive coronary artery evaluation, function and infarct detection in a single study.

INTRODUCTION

Kawasaki disease (KD) is an acute vasculitis of unknown etiology, usually occurring in children younger than 5 years of age. Infants and children may show myocarditis and/or pericarditis. Coronary artery aneurysms (CAA) develop in approximately

15–25% of untreated cases (1, 2) and can cause both short- and long-term morbidity and mortality (3). Approximately half of the children with coronary aneurysms during the acute phase of the disease have normal-appearing vessels examined by angiography 1–2 years later (4). CAAs may rupture, thrombose, or develop stenotic lesions. Serial evaluation of size and location of CAAs, ventricular function, ischemia and viability detection is necessary for further treatment. Transthoracic echocardiography is usually sufficient for this purpose in children, but it is deficient in adolescence (5).

Noninvasive coronary magnetic resonance angiography (MRA) has been successfully used in the diagnosis of anomalous origin of the coronaries (6), coronary artery disease (7), bypass graft evaluation (8) and Kawasaki disease (9, 10). Magnetic resonance imaging can also evaluate left ventricular function and wall motion defects. Although the incidence of pediatric disease is low (2–3%), the mortality rate due to myocardial infarction is 22% after the first infarction and 66 and 87% after the second

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and third infarctions, respectively (11). Contrast-enhanced cardiovascular magnetic resonance (ceCMR) is the gold standard for scar detection due to myocardial infarction, even in cases undetected by other techniques (12).

Our aim in this study was to assess the ability of CMR to evaluate coronary arteries, left ventricular function and incidence of myocardial infarction in one examination in patients with Kawasaki disease.

PATIENTS AND METHODS

Patients

Twenty patients (12 males), aged 7–12 years, were included in the study. All of the patients were referred for the evaluation of Kawasaki disease. They were asymptomatic (NYHA I), and the heart rate ranged 70–80 bpm. All of them underwent an X-ray coronary angiography within the last month prior to the MRI exam, and no thrombi were identified. A history of myocardial infarction was documented only in two patients, and they were treated with ACE-inhibitors. All patients were in antithrombotic treatment. Patients were ineligible for enrollment if they had a known contraindication for MRI. Patients' family gave informed consent, and the study was approved by the hospital's ethics committee.

Methods

MRI evaluation was performed using a 1.5 T Philips Intera CV MR scanner (Philips Medical Systems, Best, The Netherlands). A commercial, five-element, cardiac phased array receive coil was used for signal acquisition in all studies. All subjects were imaged supine with 4 electrodes on the anterior left hemithorax to obtain a vectorcardiogram (13), for electrocardiographically (ECG) gated acquisitions. Sedation was not used, and coronary MRA, function and viability studies were completed without complications. Total scan time did not exceed one hour.

Magnetic resonance angiography

The imaging protocol of MRA was accomplished without the use of nitrates and during free breathing. In order to compensate for respiratory motion artifacts, a prospective 2D real time navigator beam was properly placed on the patients' right hemidiaphragm for slice tracking and end-expiratory gating (14). The R wave of the ECG was used as a trigger for data acquisition, and all images were acquired in mid-diastole.

The MR luminography was performed using a 3D, segmented k-space, gradient-echo sequence (TE = 2.1 ms, TR = 7.5 ms, flip angle = 30°, 10 views per segment, reconstructed slice thickness = 1.5 mm, acquired in-plane spatial resolution = 0.7 mm × 1.0 mm) employing a T2-weighted preparation pre-pulse and a frequency selective fat-saturation pre-pulse (15). For the right coronary artery, a double oblique volume was imaged with use of the coordinates prescribed by a three-point planscan tool (16). For the left coronary artery system, a transverse volume

was scanned centered on the origin of the left main coronary artery.

Functional study

For each subject, localizing scans were obtained to define the long (2-chamber) axis of the left ventricle. A mid ventricular short axis view was then prescribed, and used to plan a 4-chamber view. The short axis orientation was then defined accurately, perpendicular to both the 2- and 4-chamber views. To cover the entire left ventricle, 12 contiguous (gap = 0 mm) short axis slices were acquired in each study. One slice was acquired per breath-hold (8 sec duration) in all instances. The imaging sequence was a 2D, multi-phase (16 cardiac phases were acquired per cardiac cycle resulting to a temporal resolution of 47 ms for a heart rate of 80 beats/min), steady-state free-precession (SSFP) sequence (TE = 1.5 ms, TR = 3.1 ms, flip angle = 70°, slice thickness = 8 mm, acquired in-plane spatial resolution = 1.8 mm × 2.0 mm) characterized by the application of balanced gradients in all directions.

Viability study

Intravenous gadolinium DTPA was administered at a dose of 0.1 mmol/kg. During the waiting time for the contrast agent to be cleared from the non-damaged myocardium, the cine scans for the functional study were performed. About 15 minutes post-injection, series of the viability study images were sequentially acquired in the vertical long and short axis planes (17, 18). The late enhancement imaging protocol used was a multiple 2D, segmented k-space, gradient-echo pulse sequence (TE = 3.5 ms, TR = 7.6 ms, flip angle = 20°, 30 views per segment, slice thickness = 8 mm, acquired in-plane spatial resolution = 1.3 mm × 1.8 mm) employing an 180°-inversion pre-pulse. Ten slices with a gap of 2 mm between them were derived in a single breath-hold (scan time of 29 ms for a heart rate of 80 beats/min). The shots were acquired in mid-diastole to reduce cardiac motion effects. The inversion delay time to null normal myocardium is patient and post-contrast time dependent. In this study, the inversion time was varied from 200 to 250 ms. Voxel size was of 1.3 × 1.8 × 8.0 mm³. Image selection for viability followed a previously published protocol (12). The selection of images for interpretation was based on the superiority of scar delineation.

Image analysis

For the coronary MRA studies, source images and multi-planar reformats (MPRs) along the path of the vessel of interest were evaluated on an image processing workstation (Easy Vision rel. 4.0, Philips Medical Systems) by two investigators blinded to each other. Epicardial coronary arteries were assessed for the presence of aneurysm, ectasia or stenosis. A coronary aneurysm was diagnosed if the internal lumen diameter was >4.0 mm. A coronary artery ectasia was defined as a distension of a part of a coronary vessel of up to one and a half times the diameter of an adjacent normal segment (23). Stenosis was defined as a

clinically significant lesion of >50% reduction in vessel diameter on MRA. Length and distance measurements were obtained from multiplanar reformatted images, while vessel diameter was measured as the full width half maximum of a signal intensity profile located perpendicular to the vessel lumen similarly to our previous work (9).

Cine images were analyzed qualitatively. For the qualitative analysis, patient images were randomized with images from eight normal volunteers and visually inspected by two observers blinded to the patient identity, clinical history, MRA and viability study results. Segmental wall thickness was scored by the consensus according to the following scheme: 0 = normal, 1 = mild-to-moderate hypokinesis, 2 = severe hypokinesis, 3 = akinesis and 4 = dyskinesis. Left ventricular endocardial borders were outlined on the end-systolic and end-diastolic short axis view images covering the entire LV. Papillary muscles were considered myocardium. Ejection fraction (EF) was calculated as follows: $EF = [(volume\ at\ end-diastole - volume\ at\ end-systole) / volume\ at\ end-diastole]$. Left ventricular volume enlargement was considered as the criterion for left ventricular dysfunction since it is related to an increased risk for LV remodeling and heart failure. Normal values of LV end-diastolic volume was 80–185 mL, LV end-systolic volume was 35–65 mL, and EF was 57–78%.

Contrast-enhanced images were scored by the consensus of the 2 observers on the basis of the transmural extent of hyper-enhanced tissue according to the following scheme: 1 = scar of 1% to 25% of LV wall thickness, 2 = scar of 26% to 50% of LV wall thickness, 3 = scar of 51% to 75% of LV wall thickness and 4 = scar of 76% to 100% LV wall thickness.

Statistical analysis

All measurements were expressed as mean $\pm$ standard deviation and/or range. Statistical significance of the differences between the examined methods was investigated with the paired Student's *t*-test. Comparison between XCA and MRA data was sought with Bland-Altman analysis. Statistical significance was considered for $p < 0.05$.

RESULTS

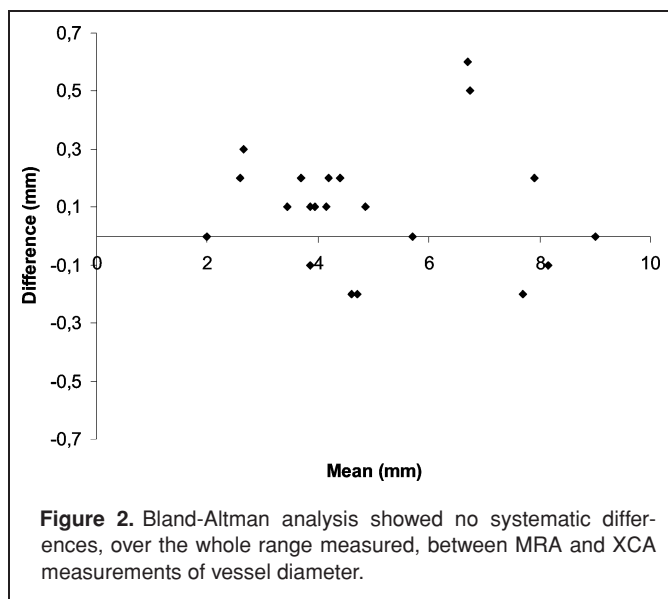
MRA measurements were obtained from all patients participating in this study. Total MR imaging time did not exceed one hour for any of the patients. Navigator efficiency was in the range of 35–55% (the lower navigator efficiency increases the scan time, without any influence on image quality). Example of a coronary magnetic resonance angiography in a patient with LAD aneurysm and anterior-apical myocardial infarction is shown in Figure 1.

The average length of continuously visualized left main (LM) with left anterior descending (LAD) coronary artery, left circumflex artery (LCx) and right coronary artery (RCA) by MRA was 4.8 ± 0.8 , 3.2 ± 1.0 and 8.9 ± 1.2 cm, respectively. The distance of the lesions from the coronary ostia with MRA was 3.2 ± 0.5 mm for LAD and 4.58 ± 1.19 mm for RCA. No lesion was found in LCx.



Figure 1. (Top) Coronal magnetic resonance angiography with LAD aneurysm (arrow). (Bottom) Contrast-enhanced CMR, indicative of antero-apical myocardial infarction in the same patient (area between arrows).

In 7 patients aneurysms of the coronary arteries were identified, while coronary ectasia alone was present in the remaining 12 patients. One patient presented both lesions. The non-affected parts of LAD had a diameter of 2.56 ± 0.26 and of RCA 2.43 ± 0.29 mm, respectively. Aneurysm diameter was 5.56 ± 2.54 (range: 2–9) mm by MRA vs. 5.40 ± 2.59 (range: 2–9) mm by XCA and aneurysm length was 8.54 ± 4.40 (range: 4.10–16) mm by MRA vs. 8.45 ± 4.55 (range: 4–16.20) mm by XCA. Ectasia diameter was 4.11 ± 0.42 (range: 3.50–4.90) mm by MRA vs. 4.06 ± 0.46 (range: 3.40–4.80) mm by XCA. There was no difference between MRA and XCA measurements (p :NS). A Bland-Altman analysis for the two methods showed no systematic differences over the whole range of vessel diameter values encountered in this study (Fig. 2). Stenotic lesions were not identified in any patient. Slow flow or thrombi were also not detected in any patient by both techniques.

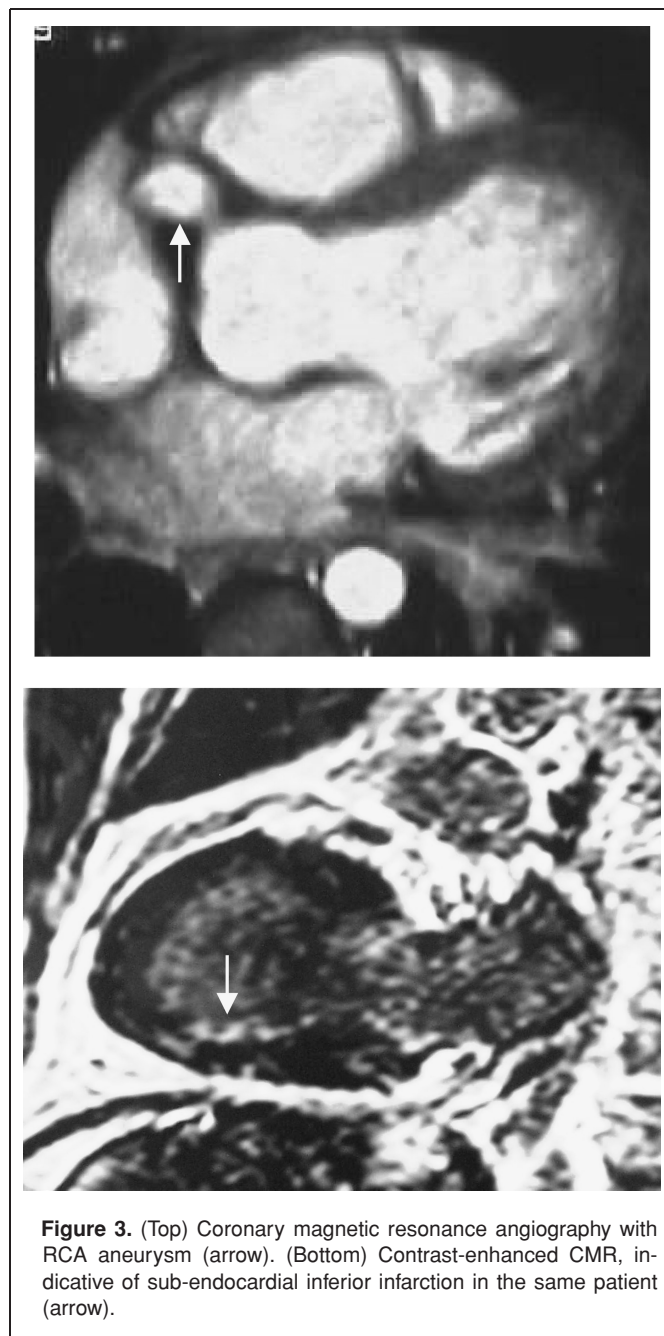


The average end-diastolic, end-systolic volume and ejection fraction (EF) were 170.5 ± 19.9 mL, 56.7 ± 21.5 mL and $67.1 \pm 8.9\%$, respectively. Left ventricular functional capacity (as indicated by ejection fraction evaluation) was within normal values in 18 out of 20 patients. In the 2 patients with history of myocardial infarction EF was 40 and 45% respectively and anterior-apical akinesia (score 3) was identified in both of them. A transmural anterior-apical scar was documented in the same area using ceCMR (score 4). Mild inferior hypokinesia (score 1) and a small, subendocardial inferior infarction were detected by ceCMR (score 1) in other two patients, without a clinical history of myocardial infarction. Example of a patient with RCA aneurysm and subendocardial infarction is shown in Fig. 3. A synopsis of the results derived from coronary angiography, cine SSFP and delayed enhancement imaging is presented in Table 1.

DISCUSSION

This study evaluated the ability of MRI to identify coronary artery aneurysm, ectasia or stenosis, left ventricular function and the incidence of myocardial infarction in a pediatric population with Kawasaki disease. MRA, compared to x-ray coronary angiography, accurately detected all lesions in the imaged part of coronary vessels. In two patients with a history of myocardial infarction during the acute phase, ceCMR documented the presence of transmural anteroapical scar. CeCMR also identified the presence of a small subendocardial inferior infarction, unnoticed by the clinical history, in two more cases. In the functional study anterior-apical akinesia was found in the areas with transmural antero-apical infarction and inferior hypokinesia in the area of inferior myocardial infarction. Ejection fraction was reduced only in the two patients with the transmural scar.

Kawasaki disease is the most common cause of acquired heart disease in children. The intravenous gamma globulin reduces the incidence of coronary lesions; however, coronary abnormalities



may still develop as the result of treatment failure or late diagnosis. The presence of stenosis and the dimensions of aneurysm play an important role in the development of myocardial ischemia. Moreover, slow blood flow (19) and aneurysm size (20) may be a causative factor for thrombosis. Serial evaluation of aneurysm dimensions is essential to guide patients' treatment.

In early childhood transthoracic echocardiography is adequate to visualize the coronaries. As children grow, follow-up is hampered by the need of serial coronary angiography, which is an invasive procedure. MRA has been successfully used as an alternative noninvasive technique for aneurysm evaluation in Kawasaki disease (10, 21).

Table 1. MRA, XCA, function and viability results in patients with kawasaki disease

Case	Lesion	MRA (mm)	XCA (mm)	EDV (mL)	ESV (mL)	EF (%)	Wall motion (score)	Ce-CMR (score)
1	RCAan	14 × 7.6	14.4 × 7.8	140	45	68		
	LADec	3.8	3.9					
2	RCAan	8.5 × 5.7	8.6 × 5.7	150	50	67		
	LADan	13.3 × 8.1	13.5 × 8.2					
3	LADan	16 × 9	16.2 × 9	215	115	40	AA-AK (3)	AA- Scar (4)
4	RCAan	7 × 4	6.8 × 3.9	150	52	65		
	LADan	10 × 7	9.7 × 6.5					
5	LADan	12 × 7	11.5 × 6.4	220	120	45	AA-AK (3)	AA- Scar (4)
6	LADec	4.6	4.8	170	58	66		
7	RCAec	3.8	3.9	180	60	67		
8	RCAec	4.5	4.7	160	42	74		
9	LADec	4.3	4.1	170	48	72		
10	RCAec	3.5	3.4	172	51	70		
11	RCAan	4.3 × 8	4.2 × 7.8	180	45	75	Inferior HK (1)	ISE- Scar (1)
12	LADec	3.5	3.4	182	55	70		
13	RCAec	4.9	4.8	175	45	74		
	LADec	4.3	4.1					
14	RCAan (prox.)	4.3 × 2.8	4.1 × 2.5	160	50	69		
	RCAan (distal)	4.1 × 2.7	4.0 × 2.5					
15	RCAan (prox.)	4.6 × 2.8	4.3 × 2.5	170	55	68		
	RCAan (distal)	4.4 × 2.0	4.1 × 2.0					
16	LADec	4.0	3.9	160	42	74		
17	RCAec	3.8	3.6	170	55	68	Inferior HK (1)	ISE- Scar (1)
18	LADec	4.2	4.1	156	45	71		
19	LADec	4.5	4.3	180	60	67		
20	RCAec	3.9	3.8	150	42	72		

Ec = Ectasia, An = Aneurysm, EDV = End-diastolic Volume, ESV = End-Systolic Volume, EF = Ejection Fraction, AA = Anteroapical, ISE = Inferior Sub-Endocardial, AK = Akinesis, HK = Hypokinesis.

In this study MRA was feasible in all patients examined and was safely accomplished without any complication. Dimension measurements were feasible in all acquired images. The agreement between MRA and X-ray coronary angiography for the measurement of ectasia and aneurysm dimensions and for clinically significant coronary stenosis observed in this study has been previously reported (9, 10, 21, 22). In the patient population studied, x-ray angiography and the MR imaging methods used did not detect any thrombi or stenotic lesions. This fact did not allow an integrated evaluation of all aspects of the disease.

Cardiovascular MRI is a fast evolving field. The addition of ceCMR gives the opportunity for accurate infarct detection in these patients without the use of radiation. Evaluation of myocardial viability by MRI has some potential advantages. Studies in adults have demonstrated that the superior spatial resolution of MRI over nuclear techniques allows detection of smaller defects and differentiation of subendocardial from transmural infarction (12), and this is translated into a clinical benefit. The superior spatial resolution of MRI may be particularly important for pediatric patients, given the smaller size of cardiac chambers. Additionally, MRI is a nonradiating, easily repeatable technique. The ceCMR imaging protocol is simple, easily applicable, and takes only 15 minutes to be accomplished. However, poor cooperation of pediatric patients to breath-hold techniques may sometimes result in sub-optimal viability images. The current limitations

of MRI in pediatric patients include the lack of validation of ceCMR against a gold standard technique and limited temporal resolution in patients with fast heart rates.

CeCMR has already been successfully used for viability evaluation in patients with Kawasaki disease (24). This is a first effort in pediatric patients with Kawasaki disease to perform simultaneously coronary MRA, function and ceCMR evaluation in a single study. The detection of four patients with myocardial infarction in our population of twenty patients is higher compared to other studies in Kawasaki disease (11). This may be attributed to a referral bias, with the more severe cases being referred to a tertiary center for evaluation.

Left ventricular function assessment using SSFP is a reliable technique for serial patient evaluation. In combination with MRA and ceCMR, SSFP gives an integrated image of patient functional status and facilitates clinical decisions. The presence of only two patients with reduced ejection fraction (40% and 45%) proves that only a small percentage of patients with Kawasaki disease present severe ventricular deterioration. Since this minority is in high risk, a detailed serial evaluation using CMR can be of great value.

Consequently, MRA and simultaneously cine and ceCMR appear promising for the non-invasive evaluation of these patients. A full protocol of MRI examination, including stress application, is expected to offer a more comprehensive approach for serial follow-up in Kawasaki disease.

ABBREVIATIONS

XCA	X-ray Coronary Angiography
MRA	Magnetic Resonance Angiography
CeCMR	Contrast Enhanced Cardiovascular Magnetic Resonance
SSFP	Steady-State Free Precession
KD	Kawasaki Disease
CAA	Coronary Artery Aneurysm

REFERENCES

- Kato H, Ichinose E, Yoshioka F, et al. Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study. *Am J Cardiol* 1982;49:1758–66.
- Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation* 1996;94:1379–85.
- Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease. *Circulation* 1994;89:916–22.
- Akagi T, Rose V, Benson LN, et al. Outcome of coronary artery aneurysms after Kawasaki disease. *J Pediatr* 1992;121:689–94.
- Geva T, Kreutzer J. Diagnostic pathways for evaluation of congenital heart disease. In: Crawford, MH, DiMarco JP, eds. *Cardiology* London: Mosby International; 2001. pp. 7–41.
- Post JC, van Rossum AC, Bronzwaer JG, et al. Magnetic resonance angiography of anomalous coronary arteries: a new gold standard for delineating the proximal course? *Circulation* 1995;92:3163–71.
- Kim WY, Danias PG, Stuber M, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med* 2001;345:1863–9.
- Molinari G, Sardanelli F, Zandrino F, et al. Value of navigator echo magnetic resonance angiography in detecting occlusion/patency of arterial and venous, single and sequential coronary bypass grafts. *Int J Card Imaging* 2000;16:149–60.
- Mavrogeni S, Papadopoulos G, Douskou M, et al. Magnetic resonance angiography is equivalent to x-ray coronary angiography for the evaluation of the coronary arteries in Kawasaki disease. *J Am Coll Cardiol* 2004;43:649–52.
- Greil G, Stuber M, Botnar R, et al. Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki disease. *Circulation* 2002;105:908–11.
- Kitamura S. The role of coronary bypass operation on children with Kawasaki disease. *Coron Artery Dis* 2002;13:437–47.
- Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445–53.
- Fischer SE, Wickline SA, Lorenz CH. Novel real-time R-wave detection algorithm based on the vectorcardiogram for accurate gated magnetic resonance acquisitions. *Magn Reson Med* 1999;42:361–70.
- Stuber M, Botnar RM, Danias PG, et al. Submillimeter three-dimensional coronary MR angiography with real-time navigator correction: comparison of navigator locations. *Radiology* 1999;212:579–87.
- Botnar RM, Stuber M, Danias PG, et al. Improved coronary artery definition with T2-weighted, free breathing three-dimensional coronary MRA. *Circulation* 1999;99:3139–48.
- Stuber M, Botnar RM, Danias PG, et al. Double-oblique free-breathing high resolution three-dimensional coronary magnetic resonance angiography. *J Am Coll Cardiol* 1999;34:524–31.
- Wu E, Judd RM, Vargas JD, et al. Visualisation of the presence, location and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet* 2001;357:21–8.
- Prakash A, Powell A, Krishnamurthy R, et al. Magnetic resonance imaging evaluation of myocardial perfusion and viability in congenital and acquired pediatric heart disease. *Am J Cardiol* 2004;93:657–61.
- Manginas A, Voudris V, Pavlides G, et al. Effect of plaque burden on coronary vasoreactivity in early atherosclerosis. *Am J Cardiol* 1998;81:401–6.
- Papadakis M, Manginas A, Cotileas P, et al. Documentation of slow coronary flow by TIMI frame count in patients with coronary artery ectasia. *Am J Cardiol* 2001;88:1030–2.
- Flacke S, Setser R, Barger P, et al. Coronary aneurysms in Kawasaki's disease detected by magnetic resonance coronary angiography. *Circulation* 2000;101:156–7.
- Mavrogeni S, Manginas A, Papadakis E, et al. Correlation between magnetic resonance angiography (MRA) and quantitative coronary angiography (QCA) in ectatic coronary vessels. *J Cardiovasc Magn Reson* 2004;6:17–23.
- Swaye PS, Fisher LD, Litwon P, et al. Aneurysmal coronary artery disease. *Circulation* 1983;67:134–8.
- Fujiwara M, Yamada TN, Ono Y, et al. Magnetic resonance imaging of old myocardial infarction in young patients with a history of Kawasaki disease. *Clinical Cardiol* 2001;24:247–52.