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Congenital Heart Disease:

Cardiovascular MR Imaging by Using an Intravascular Blood Pool Contrast Agent[1]

Marcus R. Makowski, MD[2]
Andrea J. Wiethoff, PhD
Sergio Uribe, PhD
Victoria Parish, MD
René M. Botnar, PhD
Aaron Bell, MD
Christoph Kiesewetter, MD
Philipp Beerbaum, MD
Christian H. P. Jansen, MD
Reza Razavi, MD
Tobias Schaeffter, PhD
Gerald F. Greil, MD

Purpose: To compare the image quality and diagnostic performance of a contrast agent–specific inversion-recovery (IR) steady-state free precession (SSFP) magnetic resonance (MR) imaging sequence performed by using an intravascular contrast agent (gadofosveset trisodium) with those of a commonly used T2-prepared SSFP sequence performed by using an extravascular (gadopentetate dimeglumine) and an intravascular (gadofosveset trisodium) contrast agent in patients with congenital heart disease (CHD).

Materials and Methods: The local ethics committee and the United Kingdom Medicines and Healthcare products Regulatory Agency approved this study. Patient informed consent was obtained. Twenty-three patients with CHD were examined by using a 1.5-T MR imaging unit and a 32-channel coil. Gadopentetate dimeglumine and gadofosveset trisodium were used in the same patient on consecutive days. Vessel wall sharpness, contrast-to-noise ratios (CNRs), image quality, and diagnostic performance achieved by using the IR SSFP sequence with gadofosveset trisodium were compared with those achieved by using the T2-prepared SSFP sequence with gadopentetate dimeglumine and gadofosveset trisodium and with those achieved at respective contrast material–enhanced MR angiographic examinations. The Wilcoxon rank sum test was used to compare categoric variables; *t* tests were used to compare continuous variables.

Results: Use of the IR SSFP sequence with gadofosveset trisodium significantly improved vessel wall sharpness, CNRs, and image quality ($P < .05$ for all) for all investigated intra- and extracardiac structures compared with the T2-prepared SSFP sequence with gadopentetate dimeglumine and gadofosveset trisodium and the respective contrast-enhanced MR angiographic examinations. With use of the IR SSFP sequence with gadofosveset trisodium, new, unsuspected diseases (five [22%] of 23) were diagnosed, while other diseases could be excluded (15 [65%] of 23). Information available from echocardiography ($n = 23$), conventional angiography ($n = 4$), and/or surgery ($n = 1$) confirmed all diagnoses.

Conclusion: IR SSFP with gadofosveset trisodium improved image quality and diagnostic performance, allowing a more accurate and complete assessment of cardiovascular anatomy in patients with CHD compared with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations.

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[1] From the Division of Imaging Sciences, King's College London British Heart Foundation Centre, Biomedical Research Centre of Guy's and St. Thomas' Hospital, King's College London, National Health Service Foundation Trust, Lambeth Place Road, London SE1 7EH, England (M.R.M., A.J.W., S.U., V.P., R.M.B., A.B., C.K., P.B., C.H.P.J., R.R., T.S., G.F.G.); and Philips Healthcare, Guildford, England (A.J.W.). Received November 24, 2010; revision requested January 10, 2011; revision received March 1; accepted March 11; final version accepted March 24. Supported in part by Bayer Schering Pharma and by the Department of Health through the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's & St Thomas' National Health Service (NHS) Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. G.F.G. supported by the Well Child Foundation (Cheltenham, England). **Address correspondence to** G.F.G. (e-mail: *gerald.greil@kcl.ac.uk*).

[2] **Current address:** Department of Radiology, Charité, Berlin, Germany.

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Owing to modern surgical and medical treatments, there have been major improvements in the prognosis of patients with congenital heart disease (CHD), meaning that there is an increasing prevalence of CHD among adults (1). Serial lifelong follow-up is essential in this patient population. Echocardiography is widely available, but image acquisition is operator and acoustic window dependent. Conventional cardiac angiography is a two-dimensional invasive procedure that is associated with radiation exposure. Even though procedure-related mortality and complication rates have been reduced to very low levels over the past decades, further risk reduction achieved by using noninvasive alternatives would be desirable (2).

Cardiovascular magnetic resonance (MR) imaging is an established, radiation-free noninvasive tool for diagnosis in and follow-up of patients with CHD (3,4). For example, non–electrocardiographically (ECG) gated breath-hold first-pass contrast material–enhanced MR angiography performed by using extravascular contrast agents like gadopentetate dimeglumine has become widely accepted in the diagnosis of vascular disease over the past years (5). Therefore, diagnostic cardiac conventional angiography can frequently be avoided (6). First-pass techniques are limited because of the relatively fast diffusion of currently used contrast agents into the extravascular space. Alternatively, free-breathing high-spatial-resolution three-dimensional (3D) data sets of the thorax and upper abdomen can be acquired by using navigator-gated and ECG-triggered 3D steady-state free precession (SSFP) sequences with a T2 preparation prepulse (4). Because these sequences are corrected for cardiac and respiratory motion, they are an attractive diagnostic approach in this group of patients. They have been previously successfully used without contrast agents (4,7). However, this technique would benefit from increased blood pool contrast, as detailed imaging of small cardiovascular structures such as coronary arteries or parts of the pulmonary vasculature is hampered by limited contrast between the blood pool and extravascular tissue or fluid (4,7). Gadofosveset trisodium is an intravascular MR imaging contrast agent that potentially allows imaging of vascular structures with higher contrast-to-noise ratios (CNRs) (8).

The aim of this study was to test the following hypothesis: A contrast agent–specific sequence design (inversion-recovery [IR] SSFP) in combination with an intravascular contrast agent (gadofosveset trisodium) brings together the advantages of first-pass imaging with high signal intensity from the intravascular contrast agent bolus and motion-compensated high-spatial-resolution isotropic MR imaging performed by using T2-prepared SSFP sequences.

The purpose of this study was to compare the image quality and diagnostic performance achieved by using a contrast agent–specific IR SSFP sequence in combination with an intravascular contrast agent (gadofosveset trisodium) with those achieved by using a commonly used T2-prepared SSFP sequence with an extravascular (gadopentetate dimeglumine) and an intravascular (gadofosveset trisodium) contrast agent in patients with CHD.

Advances in Knowledge

- A steady-state free precession (SSFP) MR imaging sequence can be combined with an inversion-recovery (IR) prepulse after the injection of gadofosveset trisodium for imaging cardiovascular structures.
- Gadofosveset trisodium in combination with IR SSFP significantly improves vessel wall sharpness, contrast-to-noise ratios, and image quality compared with the commonly used T2-prepared SSFP sequence after the injection of gadopentetate dimeglumine and gadofosveset trisodium.

Implications for Patient Care

- Gadofosveset trisodium in combination with an IR SSFP sequence can be effective in imaging complex cardiovascular anatomy in patients with congenital heart disease (CHD).
- An IR SSFP sequence with gadofosveset trisodium improved image quality, allowing the exclusion and confirmation of cardiovascular diseases in patients with CHD, compared with a T2-prepared SSFP sequence with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations.

Materials and Methods

This study was supported in part by Bayer Schering Pharma, including provision of contrast agents and imaging time. Bayer Schering Pharma had no control of inclusion of any data and information that might present a conflict of interest.

Study Design and Population

The study was approved by the local ethics committee (Guy's NHS Research Ethics Committee, London, England) and was registered with the United Kingdom Medicines and Healthcare products Regulatory Agency. Twenty-seven patients with CHD (20 men and seven women) were prospectively enrolled (all patients: age range, 21–60 years; median age, 32 years; men: age range,

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Abbreviations:
CHD = congenital heart disease
CNR = contrast-to-noise ratio
ECG = electrocardiography
IR = inversion recovery
SSFP = steady-state free precession
3D = three-dimensional

Author contributions:
Guarantors of integrity of entire study, M.R.M., G.F.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, G.F.G.; clinical studies, M.R.M., A.J.W., S.U., V.P., R.M.B., A.B., C.K., P.B., C.H.P.J., R.R., T.S., G.F.G.; statistical analysis, C.H.P.J., G.F.G.; and manuscript editing, A.J.W., S.U., V.P., R.M.B., P.B., C.H.P.J., R.R., T.S., G.F.G.

Potential conflicts of interest are listed at the end of this article.

21–60 years; median age, 32 years; women: age range, 24–48 years; median age, 33 years). No significant difference in age was found between the male and female patient population by using an unpaired *t* test ($P > .05$). Written consent was obtained and medical history was assessed in all patients. Only individuals with a history of CHD who were scheduled for a routine MR imaging examination and who therefore had no contraindication to MR imaging were included in this study. All patients had no contraindications to the use of MR imaging contrast agents. Patients were given a take-home informed consent form for the administration of MR imaging contrast media. Within a follow-up period of more than 1 year, no side effects were noted in any patient. Four patients declined to take part in the second MR imaging examination without stating a reason.

Patients (Table E1 [online]) were examined twice. On day 1, gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Berlin, Germany) was administered to a maximum dose of 0.2 mmol per kilogram of body weight (maximum volume, 40 mL), and on day 2 (>24 hours after but within 6 days after administration of gadopentetate dimeglumine), a dose of 0.03 mmol/kg gadofosveset trisodium (Vasovist; Bayer Schering Pharma) was injected. All examinations were performed by using a 1.5-T clinical MR imaging unit (Achieva; Philips Healthcare, Best, the Netherlands) with a 32-element cardiac coil.

Morphologic Imaging

After contrast agent injection (gadopentetate dimeglumine on day 1 and gadofosveset trisodium on day 2) at a flow rate of 2 mL/sec, contrast-enhanced MR angiography was performed by requesting the patient to suspend breathing (end expiration) for first-pass data acquisition (Table 1). This examination was followed by a respiratory navigator–gated and ECG-triggered T2-prepared SSFP sequence (Table 1). On day 2, the same examinations were repeated, and an additional IR preparation–prepulse SSFP sequence that was comparable to sequences previously described for coronary MR angiography (9,10) was used.

The optimal inversion time (260–280 msec) to suppress extravascular tissue was determined by using a Look-Locker sequence (11). The Look-Locker technique is an MR imaging pulse sequence for the measurement of spin-lattice T1 relaxation times. It is used in combination with IR sequences (clinically used for myocardial infarction imaging) to optimize the contrast between the signal from the contrast agent and the surrounding tissue. In this study, it was used to determine the optimal inversion time (260–280 msec) to minimize signal from extravascular tissue.

Image Analysis

Image processing and reformatting were performed (by G.F.G., with more than 10 years of experience) with commercially available analysis software (View Forum; Philips Healthcare).

Quantitative image analysis of CNRs.—Regions of interest (ROIs) were defined to determine the signal *(S)* from blood (S_{Blood}) and reference tissue ($S_{Myocardium}$). Noise *(N)* was determined by the standard deviation in the respective ROIs, as parallel imaging was used (sensitivity encoding for fast MR imaging [vendor specific] [12]). CNR was assessed at several levels of the aorta (ROI dimensions and levels are given in Table E2 [online]) and the left pulmonary artery (mean ROI dimension: 2.1 $cm^2 \pm 0.8$ [standard deviation]); measurements were performed by one author (M.R.M., with 3 years of experience).

CNR was defined by using the following equation (13): $CNR = (S_{Blood} - S_{Myocardium})/0.5 \cdot (N_{Blood} + N_{Myocardium})$, where all variables are means.

Quantitative image analysis of vessel wall sharpness, length, and area.—To compare data from vascular structures obtained with different imaging techniques, a custom-made analyzing tool ("Soap Bubble") was used (9,14). This tool allows comparison of data sets for objective quantitative analysis of CNR, vessel length, sharpness, and area. As earlier described by Botnar et al (9), the local vessel sharpness can be obtained by using a Deriche algorithm (14). In brief, this algorithm calculates an edge image by using a first-order derivative of the input image. The local value in a Deriche image represents the magnitude of local change in signal intensity. A vessel sharpness of 100% refers to a maximum signal intensity change at the vessel border. A lower edge value is consistent with inferior vessel sharpness. For the identification of the vessel edges along the path, a semiautomatic vessel tracking algorithm is used. By using this algorithm, the location of the vessel border and the sharpness of the user-specified vessel segment are defined semiautomatically.

For quantitative assessment of the pulmonary artery and aorta, images were first reformatted by using the Soap Bubble tool (15). The aorta and the left pulmonary artery were chosen for analysis because these vascular structures were imaged with all of the imaging sequences (contrast-enhanced MR angiography, IR SSFP, and T2-prepared SSFP) and both of the contrast agents (gadopentetate dimeglumine and gadofosveset trisodium) investigated in this study. Additionally, the aorta and the pulmonary vasculature are frequently imaged in patients with CHD.

Vessel wall sharpness of the aorta and the left pulmonary artery were measured as previously described (9). Furthermore, the maximal true visible length of the left pulmonary artery was assessed in each subject. Cross-sectional areas were measured at different corresponding levels of the aorta for each sequence used.

Qualitative image analysis.—The image grading system we used, which was applied in a previous study for assessment of vascular malformations in CHD (16), was modified from that used by McConnell et al (17) (Table 2). Consensus reading was performed for image quality scoring by two readers. Prior to the analysis, a trial assessment of five separate MR images (from all MR imaging sequences) for quality assurance was performed by the two readers together. Subsequently, the two readers (G.F.G. and A.B., with more than 10 and more than 5 years of experience in pediatric cardiology and pediatric cardiac MR

imaging, respectively) analyzed all images independently in a blinded and random order. Disagreements were discussed before a single final grade was given. Visual inspection of image quality was performed for intracardiac and extracardiac arterial and venous structures. The presence of any cardiac or vascular abnormality, artifact, or incidental finding was recorded for each cardiac segment.

Diagnostic information.—Consensus reading, as described above, was also performed to determine diagnostic information. Diagnostic information derived from images obtained with the IR SSFP sequence with gadofosveset trisodium was compared with that derived from images obtained with the currently used T2-prepared SSFP sequence with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations.

The following two groups of diagnostic information were defined: *(a)* that related to the exclusion of diseases (ie, all clinically relevant diseases that could be excluded with diagnostic image quality [image quality score, 3–5] [Table 2]) and *(b)* that related to new, unsuspected diseases (ie, all new diagnoses based on images with diagnostic image quality [image quality score, 3–5] that were relevant to the patient's assessment regarding CHD).

Information available from echocardiography ($n = 23$), conventional angiography ($n = 4$), or surgery ($n = 1$) was used to confirm all diagnoses.

Statistical Analysis

Variables are reported as means ± standard deviations. Paired and unpaired t tests were used to compare continuous variables, as appropriate. The Wilcoxon rank sum test was used to compare categoric variables. $P < .05$ was considered to indicate a statistically significant difference.

Results

Twenty-seven patients were enrolled in the study protocol. Twenty-three patients completed both imaging sessions. Four patients declined to take part in the second MR imaging examination without stating a reason.

Table 1

MR Imaging Parameters for Contrast-enhanced 3D Sequences

Parameter	Contrast-enhanced MR Angiography	T2-prepared SSFP	IR SSFP
Repetition time /echo time (msec)	4.2/1.3	4.7/2.4	4.5/2.1
Flip angle (degrees)	40	90	90
Bandwidth (Hz/pixel)	434	542	542
Field of view (mm)	340 × 269	340 × 340	340 × 340
Voxel size (mm)*	1.8 × 1.8 × 1.8	1.4 × 1.4 × 1.4	1.4 × 1.4 × 1.4
Acceleration factor for sensitivity encoding acquisition	4	4	4
Acquisition time (sec)	12	240–255	230–248
Navigator efficiency (%)	NA	52 ± 8	53 ± 9

Note.—Acquisition parameters relevant to image analysis were identical for the T2-prepared SSFP and IR SSFP sequences. The inversion time for the IR SSFP sequence was 260–280 msec. The acquisition window of the navigator was 5 mm. Two consecutive phases were acquired at contrast-enhanced MR angiography. NA = not applicable.

* Acquired as overcontiguous sections.

Table 2

Image Quality Scoring System

Score	Description
1	Poor-quality information; nondiagnostic (nondiagnostic)
2	Structures visible but markedly blurred; diagnosis suspected but not established (nondiagnostic)
3	Anatomy visible with moderate blurring; able to establish diagnosis (diagnostic)
4	Minimal blurring; good-quality diagnostic information with definite diagnosis (diagnostic)
5	Sharply defined borders; excellent-quality diagnostic information (diagnostic)

Quantitative Image Analysis

The use of IR SSFP with gadofosveset trisodium resulted in improved CNR and vessel wall sharpness (Fig 1; Figs E1, E2 [online]; Table E2 [online]) compared with the use of T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium. For IR SSFP with gadofosveset trisodium, image acquisition was independent from bolus timing, as needed for the contrast-enhanced MR angiographic examinations (Fig 1, Fig E1 [online]). Cross-sectional areas of the aorta were compared between all 3D imaging techniques (contrast-enhanced MR angiography, T2-prepared SSFP, and IR SSFP). Comparable results were found for T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and IR SSFP with gadofosveset trisodium using respiratory navigator gating and ECG triggering (Table E2 [online]). Areas were larger in breath-hold non–ECG-triggered contrast-enhanced MR angiographic images (Table E2 [online], $P < .05$ for all).

Qualitative Image Analysis

All qualitative image analysis results are summarized in Table E3 (online). At comparison of all 3D imaging techniques, the lowest values for image quality were found for breath-hold first-pass non–ECG-triggered contrast-enhanced MR angiography, without significant differences between gadopentetate dimeglumine (day 1) and gadofosveset trisodium (day 2). Gadopentetate dimeglumine and gadofosveset trisodium were compared by using T2-prepared SSFP; no significant differences could be found.

In contrast, IR SSFP with gadofosveset trisodium resulted in a significantly

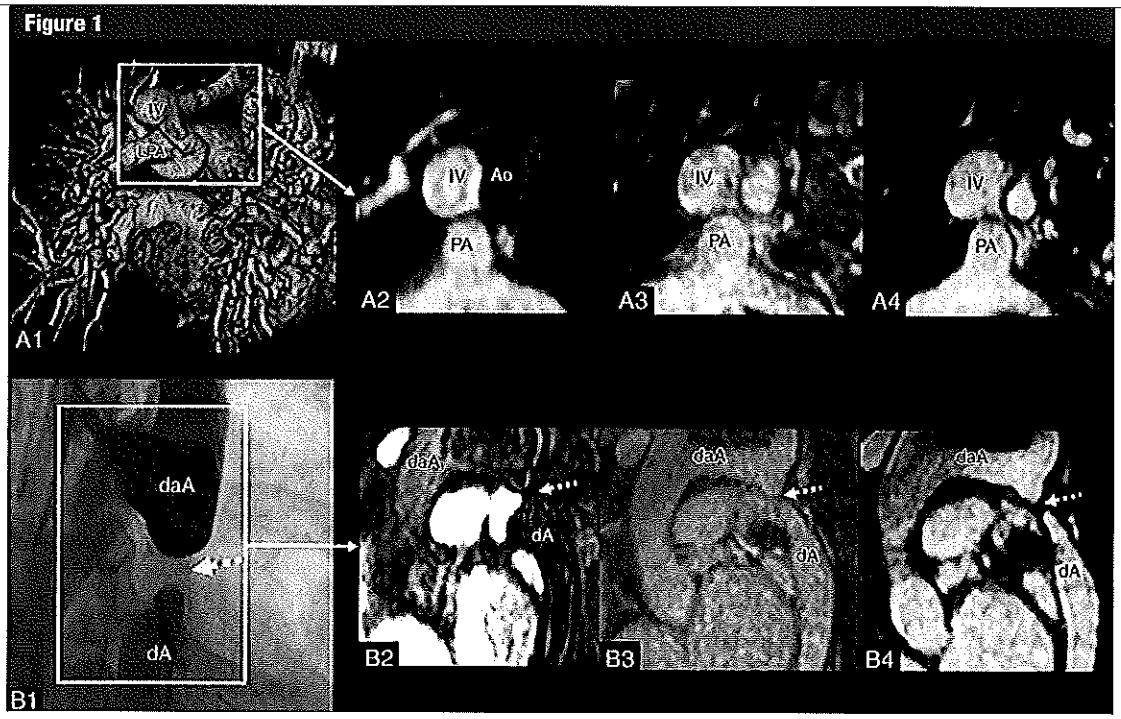

Figure 1: Images in 43-year-old patient with atretic aortic arch and drainage of the left and right upper pulmonary veins to the innominate vein. *A1*,Volume-rendered image obtained in pulmonary phase of first-pass contrast-enhanced MR angiography with gadofosveset trisodium shows drainage of stenotic left upper pulmonary vein curling around the left pulmonary artery *(LPA)* to the innominate vein. *A2*, Multiplanar reformatted plane through white box in *A1*. The same stenotic area is displayed on, *A3*, a multiplanar reformatted image obtained with T2-prepared SSFP sequence. *A4*, IR SSFP image shows that highest contrast from the blood pool was achieved by using this technique. *B1*, Conventional anglogram. Dotted arrow = atretic distal aortic arch. On, *B2*, contrast-enhanced MR angiogram of area in white box in *B1*, the atretic distal aortic arch is insufficiently imaged owing to bolus timing and an insufficient breath hold. *B3*, T2-prepared SSFP image shows the atretic segment of the aorta. However, the highest contrast from the blood pool was achieved by using, *B4*, IR SSFP. *Ao* = aorta, *dA* = descending aorta, *daA* = distal aortic arch, *IV* = innominate vein, *PA* = pulmonary artery.

higher image quality for all evaluated structures compared with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations (Table E3 [online], $P < .05$ for all).

If IR SSFP was applied in combination with an extravascular contrast agent with only a short blood half-life, like gadopentetate dimeglumine (8), the compound rapidly extravasated into the extravascular space during image acquisition (FigE3 [online]). Therefore, IR SSFP was used only with gadofosveset trisodium.

Diagnostic Information

The diagnostic information gained by using IR SSFP with gadofosveset trisodium was compared with that gained by using T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and the respective contrast-enhanced MR angiographic examinations (Figs 1, 2; Figs E1, E2 [online]; Table 3).

Exclusion of relevant diseases.—In 15 patients, relevant diseases related to CHD could be excluded for optimal treatment planning (Figs 1, 2; Figs E1, E2 [online]; Table 3). An example of this was a patient in whom severe aortic coarctation was suspected (Fig 1). IR SSFP with gadofosveset trisodium could not only delineate a complete obstruction of the aortic arch but also showed a continuity of the aorta in this area (Fig 1). This gave reassurance to the interventionalist in perforating the aortic arch obstruction with a guidewire in the cardiac angiography laboratory and inserting a covered stent. T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations were not able to provide this information (Fig 1). IR SSFP with gadofosveset trisodium also showed advantages (Fig 1, Table 3) for assessing the pulmonary vascular system owing to better discrimination of pulmonary arteries and veins. The spatial relationship between arterial and venous structures and adjacent nonvascular structures such as myocardium or pericardial fluid was clearly delineated by using an intravascular contrast agent with an IR prepulse. This improved image quality, particularly for exclusion of sinus venosus defects (15 [65%] of 23 [Fig 2]). Other examples include imaging of the semilunar valves (nine [39%] of 23).

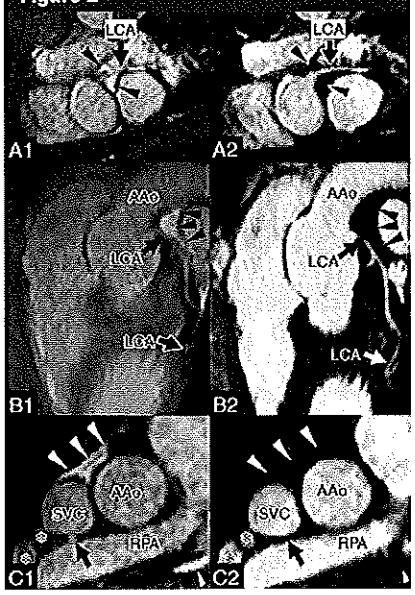

Figure 2: Multiplanar reformations of left coronary artery *(LCA)* and proximal pulmonary vessels obtained by using, *A1, B1, C1,* T2-prepared SSFP MR imaging sequence and, *A2, B2, C2,* IR SSFP MR imaging sequence with gadofosveset trisodium. *A1, B1,* Pericardial fluid and extravascular tissue (arrowheads) obscured the clear definition of the origin of the LCA. *A2, B2,* Suppression of perivascular fluid and tissue (arrowheads) with the IR SSFP sequence allowed clear delineation of the course of the LCA. *C1, C2,* Images show an axial plane of the ascending aorta *(AAo),* superior vena cava *(SVC),* right pulmonary artery *(RPA),* and right upper pulmonary veins (*). *C1,* The presence of perivascular fluid (arrowheads) mimics connections between the SVC, RPA, and right upper pulmonary vein (arrow in *C1* and *C2*). *C2,* Owing to suppression of perivascular fluid (arrowheads), these connections could be excluded.

Table 3

Results of Comparison of Diagnostic Information Yielded by IR SSFP Sequence with Gadofosveset Trisodium with That Yielded by Other Sequences or Examinations

Diagnostic Group and Instances	Finding(s)
Exclusion of relevant diseases (15 [65%] of 23)	
15 (65)	Exclusion of sinus venosus defects
12 (52)	Exclusion of muscular or membranous ventricular septal defects
9 (39)	Exclusion of coronary artery abnormalities
9 (39)	Exclusion of aortic or pulmonary valve leaflet abnormalities
1 (4)	Exclusion of aortic arch interruption in functional occluded aortic arch
New, unsuspected diseases (five [22%] of 23)	
3 (13)	Bicuspid aortic valve
1 (4)	Partial anomalous pulmonary venous return of right and left upper pulmonary veins
1 (4)	Ventricular septal defect

Note.—Data are numbers of patients in whom the IR SSFP sequence in combination with gadofosveset trisodium provided additional information with diagnostic image quality (image quality score, 3–5) for the analyzed region compared with the T2-prepared SSFP sequence and contrast-enhanced MR angiography with gadopentetate dimeglumine and gadofosveset trisodium (image quality score, 1 or 2). Findings were differentiated into *(a)* those relating to exclusion of relevant diseases and *(b)* those revealing new, unsuspected diseases. All findings were compared with those at commonly used ECG-triggered and respiratory navigator–gated T2-prepared SSFP and contrast-enhanced MR angiographic examinations with gadopentetate dimeglumine and gadofosveset trisodium. Information from echocardiography ($n = 23$), conventional angiography ($n = 4$), and/or surgery ($n = 1$) was used to confirm all diagnoses.

Extravascular fluids and the blood pool both show high signal intensity on images obtained with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium. Therefore, in some patients, a clear diagnostic delineation of the origin and course of the coronary arteries was only possible by using IR SSFP with gadofosveset trisodium (nine [39%] of 23 [Fig 2]) as pericardial fluid was fully suppressed. If the ventricular septum was evaluated, IR SSFP with gadofosveset trisodium allowed for imaging with diagnostic image quality owing to the full suppression of the myocardium or membranous part of the ventricular septum while generating strong signal from the blood pool. The image quality provided by T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium was in some cases not diagnostic and did not allow the exclusion of ventricular septal defects (12 [52%] of 23) (Fig E2 [online]). Similar results for assessment of the interatrial tunnel were observed in patients who had undergone the Mustard or Fontan operation (two [8%] of 23 [Table 3]). Information available from other modalities (echocardiography [$n = 23$], conventional angiography [$n = 4$], and/or surgery [$n = 1$]) was used to confirm all diagnoses.

New, unsuspected diseases.—In five of the examined patients (22%), a previously undetected diagnosis was found by using IR SSFP with gadofosveset trisodium (Table 3). Previously unexpected bicuspid aortic valves (three [13%] of 23) and a ventricular septal defect (one [4%] of 23) (Fig E2 [online]) were imaged by using IR SSFP with gadofosveset trisodium but could not be delineated by using T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations. Results were consecutively confirmed at echocardiography. A partial anomalous pulmonary venous return (PAVPR) of the right and left upper pulmonary veins was diagnosed by using IR SSFP with gadofosveset trisodium but was missed at first-pass contrast-enhanced MR angiography owing to suboptimal timing of the contrast agent bolus in a patient who had difficulties holding her breath. The diagnosis was also missed at conventional cardiac angiography as it was targeted to image an aortic arch obstruction. Images obtained with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium raised suspicion of the diagnosis of PAPVR, but owing to limited delineation of the intrapulmonary vasculature (Fig 1), definitive diagnosis was provided only by using IR SSFP with gadofosveset trisodium. Repeated contrast-enhanced MR angiographic examinations with optimal contrast agent bolus timing to the

pulmonary phase and subsequent cardiac conventional angiography confirmed the diagnosis (one [4%] of 23 [Fig 1]).

Information available from other modalities (echocardiography [n = 23], conventional angiography [n = 4], and/or surgery [n = 1]) was used to confirm all diagnoses.

Discussion

In this prospective study, we proposed a single injection of an intravascular contrast agent (gadofosveset trisodium) in combination with an IR SSFP sequence for improved assessment of cardiovascular morphology in patients with CHD. IR SSFP with gadofosveset trisodium improved image quality and diagnostic performance compared with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations. No qualitative or quantitative differences were found between the two contrast agents in the same patient with the T2-prepared SSFP and contrast-enhanced MR angiography sequences.

First-pass contrast-enhanced MR angiography is an approach used in clinical practice to image intrathoracic vessels. One of its main advantages is the high contrast generated by the intravascular contrast agent bolus while the signal from extravascular tissue is suppressed. However, there are several limitations: Acquisition time is restricted to one breath hold, limiting the spatial resolution (usually nonisotropic voxels) and field of view (16). This is also relevant if multiphase imaging is used. Contrast-enhanced MR angiography relies on patients holding their breath to compensate for respiratory motion. If patients cannot fully comply with breathing commands, artifacts from chest motion can result. Owing to the requirement for optimal patient-specific bolus timing while investigating highly complex cardiovascular anatomy, standardization and reproducibility of follow-up MR imaging examinations can be challenging (18). Bolus injection should not be repeated because of the limited amount of contrast agent that should be given. Imaging of intracardiac structures is limited, as contrast-enhanced MR angiographic sequences are not triggered to cardiac motion.

ECG-triggered and respiratory navigator–gated 3D MR imaging techniques such as T2-prepared SSFP are another approach to image intrathoracic structures and have shown some advantages in the clinical environment. They are easy to plan, as they do not need to be adjusted to specific cardiovascular structures and usually cover the complete thorax. ECG triggering and respiratory navigator gating are applied for compensation of respiratory and cardiac motion. This allows the evaluation of intracardiac structures. Isotropic voxels can be acquired, allowing highly standardized and reproducible evaluation of data sets through postprocessing. Arterial and venous anomalies can be imaged simultaneously, without the need for precise bolus timing (4). A shortcoming of this technique is the reduced contrast between vascular structures and surrounding soft tissues and fluids. This can lead to limitations in imaging structures like the interventricular septum, the pulmonary vasculature, and the coronary arteries (4), as these structures may sometimes not be clearly distinguishable from surrounding tissue, fluids, or blood.

A single injection of an intravascular contrast agent (gadofosveset trisodium) in combination with a contrast agent–specific sequence design (IR SSFP) brings together the advantages of first-pass imaging with high signal intensity from the vasculature and motion-compensated high-spatial-resolution isotropic imaging with T2-prepared SSFP. In this study, IR SSFP with gadofosveset trisodium allowed imaging with high signal intensity from the blood pool, while signal from extravascular tissues and fluids was suppressed. This approach improved the image quality of all investigated intrathoracic structures significantly compared with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations. All cardiac segments, including the course of the coronary artery system, the ventricular septum, and the arterial and venous pulmonary vasculature, were assessed with higher contrast from the blood pool and suppression of extravascular structures like pericardial fluid.

The arterial and venous systems were imaged simultaneously with high intravascular contrast with the IR SSFP sequence with gadofosveset trisodium without the need for precise contrast agent bolus timing. If sequence acquisition fails because of patient movement or technical issues, examinations can be repeated without the need for an additional injection of a contrast agent, owing to the long blood half-life of the intravascular contrast agent ($t_{1/2}\alpha$, approximately 29 minutes; $t_{1/2}\beta$, approximately 16 hours 18 minutes) (8).

Using IR SSFP with gadofosveset trisodium, all information can be obtained during a single high-spatial-resolution isotropic motion-compensated acquisition, independent from bolus timing. The isotropic property of data sets allows reformatting of any desired imaging plane; hence, precise morphologic evaluation may be performed with postprocessing. This can have diagnostic implications. The exclusion or clear delineation of relevant diseases (15 [65] of 23) and the diagnosis of new, unsuspected diseases (five [22] of 23) showed the clinical benefit of using IR SSFP with gadofosveset trisodium. The results of this study demonstrate that IR SSFP with gadofosveset trisodium is superior for diagnosing intra- and extracardiac vascular and cardiac abnormalities in patients with CHD compared with the currently used combination of T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinations. Other investigators confirmed in a retrospective study (19) the superior image quality of navigator-gated and ECG-triggered IR SSFP MR imaging compared with first-pass breath-hold contrast-enhanced MR angiography with gadofosveset trisodium. T2-prepared SSFP and extravascular contrast agents such as gadopentetate dimeglumine were, however, not available for comparison in that study (19).

If IR SSFP is applied in combination with a extravascular contrast agent with only a short blood half-life, like gadopentetate dimeglumine (8), the compound will rapidly extravasate into the extravascular space during image acquisition. Even if the IR pulse is timed to achieve a high intravascular signal after contrast agent injection and imaging is started immediately after contrast agent injection (while the contrast agent is still in the distribution phase), a substantial portion of the contrast agent will have diffused out of the intravascular space before the imaging sequence is complete (8). This will result in a mixed contrast between intra- and extravascular space. The compound may accumulate in, for example, the cardiac valves, scar tissue in the myocardium (myocardial late enhancement), and atherosclerotic vessel walls as a consequence of an increased distribution volume, endothelial permeability, or neovascularization (20).

The improved contrast between intra- and extravascular structures seen with IR SSFP in combination with gadofosveset trisodium may have resulted from the higher relaxivity of gadofosveset trisodium when bound to albumin, in combination with its prolonged intravascular half-life (8) compared with currently used extravascular contrast agents. Additionally, the IR SSFP sequence applied was heavily T1 weighted and thus specifically useful to highlight regions with shortened T1 times. Therefore, this sequence design was well suited for the detection of gadolinium-based contrast agents. The T2-prepared SSFP sequence used was mainly T2 weighted, because of the T2 preparation prepulse applied, and some additional T2/T1 weighting resulted from the SSFP readout. The T2-prepared SSFP sequence used was therefore not highly sensitive for the detection of T1-lowering contrast agents but rather for the detection of fluids, including blood.

There were limitations to our study. No conclusion from our data is applicable to patients with cardiac arrhythmia. Motion artifacts cannot be addressed with the improved blood pool signal and sequence design presented in this study. Even though substantial improvement in imaging of cardiac valves was achieved by using gadofosveset trisodium, echocardiography is still considered to be the reference standard method for anatomic imaging (4). The role of intravascular contrast agents in imaging myocardial delayed enhancement is still subject to investigation and was not addressed in this study. In case information on myocardial scar imaging is needed, gadopentetate dimeglumine may be the preferred imaging agent at the moment. As the use of MR imaging method and contrast agent administration were not randomized owing to technical reasons, it could not be determined to what degree the order of administration confounded the power of the method.

In conclusion, a single injection of an intravascular contrast agent (gadofosveset trisodium) in combination with a contrast agent–specific sequence design (IR SSFP) combines the advantages of first-pass contrast-enhanced MR angiography with high signal from the vasculature with the benefits gained from motion-compensated high-spatial-resolution isotropic T2-prepared SSFP sequences. In this study, IR SSFP with gadofosveset trisodium improved image quality and diagnostic performance for the assessment of cardiovascular morphology in patients with complex CHD compared with T2-prepared SSFP with gadopentetate dimeglumine and gadofosveset trisodium and respective contrast-enhanced MR angiographic examinaions. This may broaden the use of cardiac MR imaging and improve follow-up in patients with CHD.

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References

1. Therrien J, Gatzoulis M, Graham T, et al. Canadian Cardiovascular Society Consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease—Part II. Can J Cardiol 2001;17(10):1029–1050.
2. Bergersen L, Gauvreau K, Lock JE, Jenkins KJ. A risk adjusted method for comparing adverse outcomes among practitioners in pediatric and congenital cardiac catheterization. Congenit Heart Dis 2008;3(4):230–240.
3. Geva T, Vick GW 3rd, Wendt RE, Rokey R. Role of spin echo and cine magnetic resonance imaging in presurgical planning of heterotaxy syndrome: comparison with echocardiography and catheterization. Circulation 1994;90(1):348–356.
4. Sørensen TS, Körperich H, Greil GF, et al. Operator-independent isotropic three-dimensional magnetic resonance imaging for morphology in congenital heart disease: a validation study. Circulation 2004;110(2):163–169.
5. Rofsky NM, Adelman MA. MR angiography in the evaluation of atherosclerotic peripheral vascular disease. Radiology 2000;214(2):325–338.
6. Boxt LM, Rozenshtein A. MR imaging of congenital heart disease. Magn Reson Imaging Clin N Am 2003;11(1):27–48.
7. Weber OM, Martin AJ, Higgins CB. Whole-heart steady-state free precession coronary artery magnetic resonance angiography. Magn Reson Med 2003;50(6):1223–1228.
8. Hartmann M, Wiethoff AJ, Hentrich HR, Rohrer M. Initial imaging recommendations for Vasovist angiography. Eur Radiol 2006;16(Suppl 2):B15–B23.
9. Botnar RM, Stuber M, Danias PG, Kissinger KV, Manning WJ. Improved coronary artery definition with T2-weighted, free-breathing, three-dimensional coronary MRA. Circulation 1999;99(24):3139–3148.
10. Bi X, Li D. Coronary arteries at 3.0 T: Contrast-enhanced magnetization-prepared three-dimensional breathhold MR angiography. J Magn Reson Imaging 2005;21(2):133–139.

11. Look DC, Locker DR. Time saving in measurement of NMR and EPR relaxation times. Rev Sci Instrum 1970;41(2):250–251.

12. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. Magn Reson Med 1999;42(5):952–962.

13. Arai AE, Epstein FH, Bove KE, Wolff SD. Visualization of aortic valve leaflets using black blood MRI. J Magn Reson Imaging 1999;10(5):771–777.

14. Deriche R. Fast algorithms for low-level vision. IEEE Trans Pattern Anal Mach Intell 1990;12(1):78–87.

15. Etienne A, Botnar RM, Van Muiswinkel AM, Boesiger P, Manning WJ, Stuber M. "Soap-Bubble" visualization and quantitative analysis of 3D coronary magnetic resonance angiograms. Magn Reson Med 2002; 48(4):658–666.

16. Groil GF, Powell AJ, Gildein HP, Geva T. Gadolinium-enhanced three-dimensional magnetic resonance angiography of pulmonary and systemic venous anomalies. J Am Coll Cardiol 2002;39(2):335–341.

17. McConnell MV, Khasgiwala VC, Savord BJ, et al. Comparison of respiratory suppression methods and navigator locations for MR coronary angiography. AJR Am J Roentgenol 1997; 168(5):1369–1375.

18. Fellows KE, Weinberg PM, Baffa JM, Hoffman EA. Evaluation of congenital heart disease with MR imaging: current and coming attractions. AJR Am J Roentgenol 1992;159(5): 925–931.

19. Naehle CP, Müller A, Willinek WA, et al. First-pass and steady-state magnetic resonance angiography of the thoracic vasculature using gadofosveset trisodium. J Magn Reson Imaging 2009;30(4):809–816.

20. Ibrahim T, Makowski MR, Jankauskas A, et al. Serial contrast-enhanced cardiac magnetic resonance imaging demonstrates regression of hyperenhancement within the coronary artery wall in patients after acute myocardial infarction. JACC Cardiovasc Imaging 2009;2(5): 580–588.