



Coronary Artery Imaging in Patients with Congenital Heart Disease: Improved Image Quality Using an Intravascular Contrast Agent and Specific Magnetic Resonance Sequence Design

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Abstract

Background: In patients with congenital heart disease (CHD) imaging of coronary artery origin and course can be crucial for preoperative planning. A novel intravascular contrast agent Gadofosveset trisodium (GdT) has demonstrated to be superior for angiography due to improved intravascular contrast compared to the currently used extravascular contrast agent Gadopentetate dimeglumine (GdD).

The aim of this study was to compare conventional post-contrast coronary magnetic resonance angiography (CMRA) using GdT or GdD to an optimized imaging sequence combined using only the novel agent, GdT.

Methods: Ten patients with CHD (age range 22 to 40 years; mean 31 years) were scanned at a 1.5 T clinical MR scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a 32-element cardiac coil. An extravascular contrast agent (GdD) was administered first using a standard T2-prepared SSFP sequence. Within 72 hours patients were re-scanned using an intravascular contrast agent (GdT) and IR SSFP additional to the standard T2-prepared SSFP MR Sequence. Image quality was graded from 0 (non-diagnostic) to 4 (best image quality). The left anterior descending (LAD), the left circumflex (LCX) and the right coronary artery system (RCA) were assessed separately. Contrast-to-noise ratio (CNR), Signal-to-noise ratio (SNR), blood-to-myocardial contrast (BMC) and image quality were analyzed for the three techniques. A p-value ≤ 0.05 indicated statistical significance.

Results: The intravascular contrast agent GdT showed significantly improved CNR and BMC when combined with an optimized IR SSFP sequence. There was a trend towards being able to image longer segments of the LAD and RCA and towards improved vessel sharpness but the level of significance was not reached. As expected, coronary artery diameter and image quality, were not significantly different since we imaged the same individuals.

Conclusion: The combination of a novel intravascular contrast agent (GdT) and the addition of an adapted inversion recovery whole heart sequence design seems to provide improved contrast of the coronary artery system compared to currently available extravascular contrast agents and conventional sequence design.

Keywords

Congenital heart disease, Coronary artery angiography, Whole heart imaging, Intravascular contrast agent, Inversion recovery steady-state-free-precession

Introduction

Major improvements in the last decades in CHD diagnosis and treatment have led to an increased patient survival up to approximately 85% to adulthood [1,2]. Consequently, with this continuously growing and aging population, physicians are facing new diagnostic challenges. Knowledge about coronary anatomy can be essential for long-term follow-up of these patients. Examples are patients after surgical repair of transposition of the great arteries [3,4] and patients requiring a pulmonary homograft or transcatheter valve implantation to exclude abnormal course of the coronaries [1,5-8]. Imaging of coronary arteries with echocardiography is challenging in young children and becomes extremely difficult in older patients due to poorer acoustic windows. Catheter-based angiography is invasive, costly and entails radiation, which carries the risk of cancer especially in patients who need regular follow-up exams including cardiac imaging [3,4,9]. Therefore, MRI as a radiation free non-invasive diagnostics tool represents a great advantage for these patients. Classically the standard MR angiography (MRA) for assessment of arterial and venous anomalies in congenital heart disease is performed using a 3-dimensional (3D) single- or multiphase first-pass MRA sequence with an extracellular

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contrast agent without cardiac gating during at least one breath hold. Unfortunately this entails limited spatial resolution related to the limited capacity of breath holding of sick patients or limited compliance in young children or infants. Moreover, this approach generally does not include ECG gated sequences or respiratory motion compensation and is therefore quite prone to artifacts.

Whole heart coronary MR angiography (CMRA) has been previously used in adults and children with congenital heart disease [2,7,10]. This free-breathing high spatial resolution three-dimensional sequence allows acquisition of extensive cardiac data via a navigator-gated ECG-triggered T2-prepared SSFP sequence. Good diagnostic accuracy (up to 84% according to Tangcharoen et al.) [7,11] and extensive details on cardiac anatomy, volumes as well as function assessment, via a single and easy to apply sequence have been demonstrated [12-16].

The use of a conventional extravascular contrast agent like Gadopentetate dimeglumine (GdD) has been widely described in MR angiography [13,17]. However, first pass techniques carry limitations due to the fast diffusion of GdD into the extravascular space. For visualization of small structures such as coronary arteries, this technique would benefit from increased and longer blood pool contrast compared to the extravascular tissue or fluid [12,13,18].

The novel intravascular contrast agent, Gadofosveset trisodium (GdT) has the potential to increase intravascular contrast to improve image quality and therefore diagnostic performance for the coronary arteries [19].

Furthermore IR SSFP provides enhancement of contrast between tissues with different T1-relaxation times through the addition of a 180° inversion pre-pulse [20], with a determined tissue signal being specifically nulled by selecting an optimal inversion time. Originally this technique was developed and used to detect myocardial infarction [21,22] but it has since then been extended to other cardiac diagnosis *i.e.* cardiomyopathies, myocarditis, amyloidosis, Anderson-Fabrydisease etc.

The aim of this study was to compare conventional post-contrast CMRA using GdT or GdD to an optimized imaging sequence combined using only the novel agent, GdD.

Materials and Methods

The study was approved by the local ethics committee (Guy's and St. Thomas' NHS Research Ethics Committee, London, England) and was registered with the United Kingdom Medicines and Healthcare Products Regulatory Agency.

Ten patients with CHD agreed to take part in the study (eight men, two women, age range 22 to 40 years, mean 31 years, table 1). Written consent was obtained and medical history was assessed in all patients. Only patients with a history of CHD who were scheduled for a routine MR imaging examination were included in this study. Patients with significant renal dysfunction were excluded (defined as estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m²). All patients had follow up clinical appointments after the scan and at 1 year post MRI.

MRI technique

Patients were scanned on 2 occasions at a 1.5 T clinical MR scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a 32-element cardiac coil. During the first scan, gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Berlin, Germany) was administered at a dose of 0.2 mmol per kilogram of body weight (maximum volume, 40 mL) and patients were scanned using a standard commercially available respiratory navigator-gated and ECG-triggered T2-prepared SSFP sequence. During the second scan (within 72 h), a dose of 0.03 mmol per kilogram of body weight gadofosveset trisodium (Vasovist; Bayer Schering Pharma, Berlin, Germany) was injected and all patients were re-scanned using a IR preparation- pre-pulse SSFP sequence additional to the standard T2-prepared SSFP MR sequence.

Table 1: Patients characteristics.

Patient	Sex	Age at MRI (years)	Diagnosis
1	M	30	TGA (Mustard procedure)
2	M	28	Coarctation
3	M	26	Coarctation
4	M	40	PAPVD
5	M	36	VSD with infundibular stenosis
6	F	22	TA (Fontan procedure)
7	F	28	TOF
8	M	34	Coarctation
9	M	34	Coarctation
10	M	29	Coarctation

TGA: Transposition of the Great Arteries, PAPVD: Partial Anomalous Pulmonary Venous Drainage, VSD: Ventricular Septal Defect, TA: Tricuspid Atresia, TOF: Tetralogy Of Fallot

Table 2: MR imaging parameters for contrast-enhanced 3D sequences.

Parameter	T2-prepared SSFP	IR SSFP
Repetition time/echo time (msec)	4.7/2.4	4.5/2.1
Flip angle (degrees)	90	90
Bandwidth (Hz/pixel)	542	542
Field of view (mm)	340 × 340	340 × 340
Voxel size (mm)	1.4 × 1.4 × 1.4	1.4 × 1.4 × 1.4
Acceleration factor for SENSE	4	4
Acquisition time (sec)	240-255	230-248
Navigator efficiency (%)	52 ± 8	53 ± 9

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.

*Acquired as over contiguous sections.

The optimal inversion time to suppress extravascular tissue was determined by a Look-Locker sequence [1,2,23]. In this study, it was used to determine the optimal inversion time (approximately 260-280 msec) to minimize signal from extravascular tissue (Table 2).

Images analysis

Image processing, reformatting and analysis were performed with commercially available software (View Forum, Philips Healthcare, Best, The Netherlands), as well as a specialised custom-made coronary analysis software ("Soap bubble") [1-8,10]. Two experienced investigators analysed the images independently (DL with 8 years and ND with more than 2 years' experience in cardiac MRI). Consensus reading was performed in case of disagreement.

Signal to noise and contrast to noise

For quantitative image analysis, regions of interest (ROIs) were defined in areas of myocardium, the intra-aortic blood-pool close to coronary ostia, and in a region anterior to the chest wall, where no respiration-induced motion artifacts were visually identified. Signal-to-noise (SNR) was defined as the mean signal intensity found in a ROI divided by the standard deviation found in the ROI anterior to the chest wall [3,4,9] (Equation 1).

SNR was evaluated using the following formula:

$$SNR = \frac{S_{Mean}}{SDEV_{Mean}} \quad (1)$$

S_{Mean} in [1] denotes the mean signal intensity in the user defined region of interest and $SDEV_{Mean}$ relates to the standard deviation of the mean of the signal intensity anterior to the chest (parallel imaging was used: sensitivity encoding for fast MR imaging [Philips specific]) [2,5-8,10].

At the same anatomical level, SNR was also quantified in the blood-pool of ascending aorta. SNR of the muscle signal was determined in the muscle of the LV anterolateral wall at the level of proximal RCA.

Table 3: Image Quality Assessment (from McConnell [10,13]).

Score	Grading	Description
1	poor	Coronary artery visible with markedly blurred borders/edges
2	good	Coronary artery visible with moderately blurred borders/edges
3	very good	Coronary artery visible with mildly blurred borders/edges
4	excellent	Coronary artery visible with sharply defined borders/edges

Contrast to noise ratio (CNR) was defined as the difference of the mean signal intensities in two user specified ROIs divided by the standard deviation found in the ROI anterior to the chest wall [4,7,9,11] (Equation 2). The CNR between blood and muscle was defined as

$$CNR = \frac{S_{Mean,Blood} - S_{Mean,Muscle}}{0.5 * (SDEV_{Mean,Muscle} + SDEV_{Mean,Blood})} \quad (2)$$

Blood to myocardium contrast: BMC

BMC was defined as the mean signal intensity of the blood divided by the mean intensity of the myocardium in the previously described chosen ROIs.

$$BMC = \frac{S_{MeanBlood}}{S_{MeanMuscle}}$$

Vessel sharpness, length and diameter measurements

For the quantitative image analysis of coronaries vessel wall sharpness, length and area a custom-made analyzing tool (“Soap Bubble”) was used [2,7,10,12-14]. As previously described by Botnar at al. [10,13,17,24] vessel sharpness can be obtain using a Deriche algorithm [7,11-13,18]. Briefly, this algorithm allows the calculation of an edge image by using a first-order derivative of the input image; the local value in a Deriche image, which 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.

Each one of the main coronary arteries (LAD, LCX and RCA) were analysed for the use of the extracellular (T2-prepared SSFP) contrast agent and intracellular (T2-prepared SSFP and IR-SSFP) contrast agent (Figure S1 and Figure S2).

Visual scoring of the quality of the coronary images

For qualitative image analysis, after coronary reformat using Soap Bubble software, image quality was graded from 0 (non-diagnostic) to 4 (best image quality) [12-14,19] for each vessel of the main coronary system using GdD (T2-prepared SSFP) and GdT (T2-prepared SSFP and IR-SSFP) -image quality assessment (from McConnell et al. [13,17,20] (Table 3).

Statistical analysis

For statistical comparison, non-parametric methods using statistics software (IBM SPSS Statistics Version 20) were applied. In light of the small sample size we checked the preconditions for parametric testing, using Kolmogorov-Smirnov tests. Since variables were not normally distributed, we conducted the non-parametric Wilcoxon tests for dependent variables. A p-value ≤ 0.05 was considered to indicate statistical significance.

Results

Ten patients completed the study protocol (Table 1: patient characteristics) without any complications. All indications for MRI were part of the clinical follow-up, and all patients agreed to undergo a second scan for research purposes. One of these patients had an abnormal origin of the LCX. None of them experienced any side effects of the MRI scan as well as contrast agent administration.

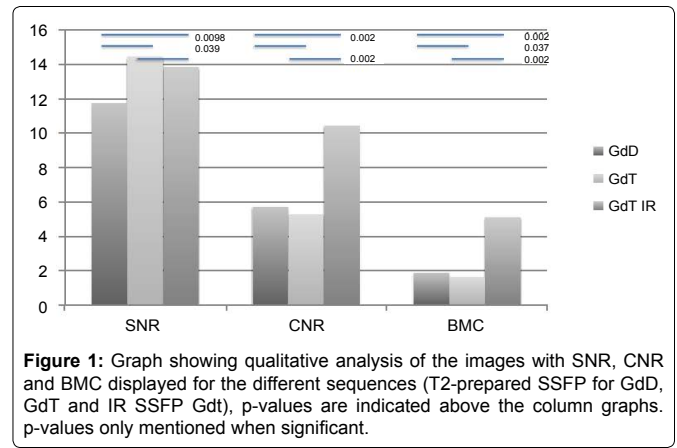


Figure 1: Graph showing qualitative analysis of the images with SNR, CNR and BMC displayed for the different sequences (T2-prepared SSFP for GdD, GdT and IR SSFP GdT), p-values are indicated above the column graphs. p-values only mentioned when significant.

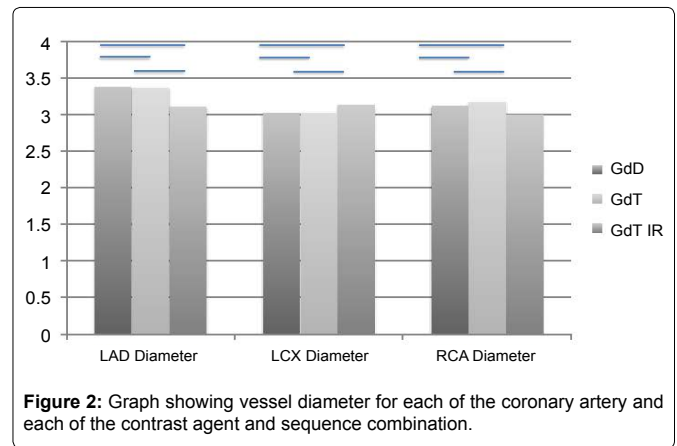


Figure 2: Graph showing vessel diameter for each of the coronary artery and each of the contrast agent and sequence combination.

Quantitative analysis

SNR, CNR and BMC: The use of IR SSFP with GdT resulted in significantly improved CNR and blood to myocardial contrast (BMC) when compared with the conventional T2-prepared SSFP sequence using GdT (p = 0.002 for CNR and BMC) as well as GdD (p = 0.002 for CNR and BMC). Furthermore GdT improved SNR significantly using T2-prepared SSFP (p = 0.039) and IR SSFP (p = 0.0098) when compared to GdD (Figure 1).

Vessel length and vessel diameter: We did not find any statistically significant difference in vessel diameter when comparing the two contrast agents and three different imaging protocols. This indicates that, as expected, neither the contrast agent nor the sequences let to a difference in vessel diameter within each of the scanned individuals (Figure 2).

Despite not reaching statistical significance, there was a trend towards increased length of LAD or RCA imaged when using IR SSFP with GdT (Figure 3).

Vessel sharpness: Mean vessel sharpness was measured (GdD T2-prepared SSFP, GdT T2-prepared SSFP, GdT IRSSFP respectively) for LAD (0.44, 0.43 and 0.45), LCX (0.39, 0.42 and 0.48) and RCA (0.46, 0.46 and 0.48). Once again these results seem to indicate a trend in favour of IRSSFP with GdT for the LAD and RCA compared to the conventional T2-prepared SSFP sequence but did not reach statistical significance (Figure 4).

Qualitative image analysis

Image quality was scored for the RCA, left main, LAD, and LCX artery according to McConnell et al. [12,13,18,21,22] as stated in table 3. Mean image scoring (GdD T2 prepared SSFP, GdT T2-prepared SSFP, GdT IR SSFP respectively) was for LAD (3.3, 3.35 and 3.05) for LCX (1.95, 3.0 and 2.7) and for RCA (2.3, 3.2 and 2.7) respectively and did not reach statistical significance (Figure 5).

Discussion

The present study evaluated the impact of an intravascular

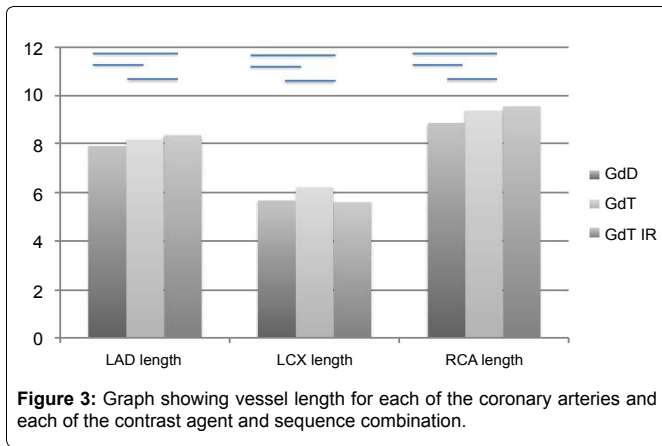


Figure 3: Graph showing vessel length for each of the coronary arteries and each of the contrast agent and sequence combination.

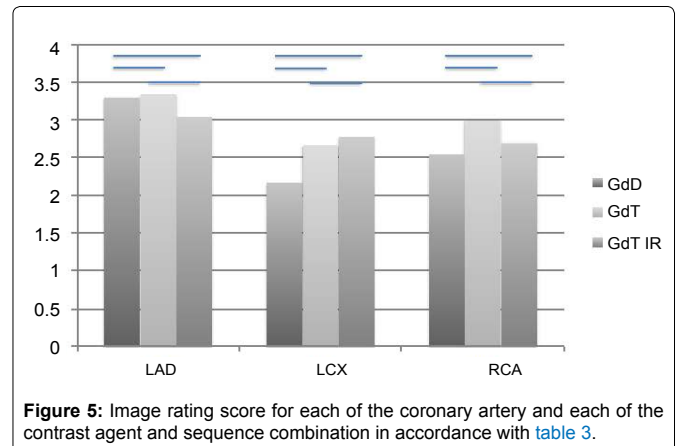


Figure 5: Image rating score for each of the coronary artery and each of the contrast agent and sequence combination in accordance with table 3.

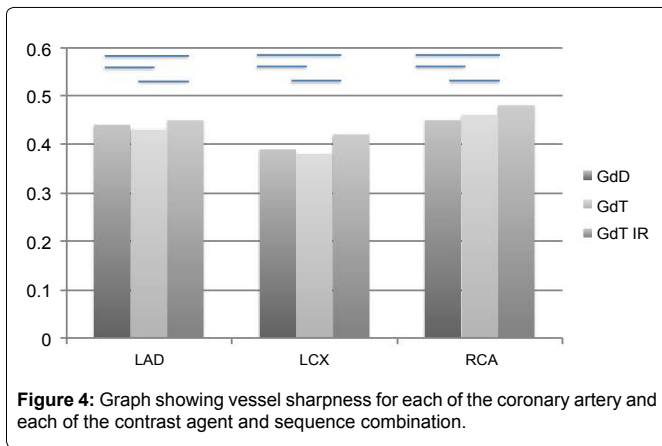


Figure 4: Graph showing vessel sharpness for each of the coronary artery and each of the contrast agent and sequence combination.

contrast agent on whole-heart MR angiography for characterization of origin and course of coronary arteries as well as the identification of possible coronary abnormalities. Additionally IR SSFP in combination with GdT was evaluated. Whole heart MR angiography enables visualization of the majority of cardiovascular structures of the thorax, assessing simultaneously venous and arterial anomalies including the coronary artery system with a free breathing acquisition [1,12,19]. If the data are acquired isotropic, the complete coronary artery system can be reformatted from a single whole heart dataset by post-processing software applications. Currently, a whole heart T2-prepared SSFP sequence is the most commonly used approach [3,20,25-28].

Unfortunately, some of the disadvantages of the whole-heart CMRA are the relatively long acquisition time; the dependence of an adequate navigator efficiency to compensate for breathing motion artifacts and the reduced contrast between vascular structures and surrounding tissues or fluids [1,5,7,8,12,21,22]. In that context, intravascular contrast agents may provide a significant advantage compared to extravascular contrast agents. Since GdD is an extravascular contrast agent its binding capacity to albumin is relatively low. On the contrary, GdT has a non-covalent, transient and reversible but much stronger binding to albumin, that results in a prolonged intravascular enhancement [3,9,23,29-32].

Thus, GdT's non-covalent binding to albumin not only contributes to slower renal excretion but also increases T1 relaxivity up to 6 to 10 times when compared to GdD [7,10,32-35]. The intravascular contrast staying in the blood pool for a longer amount of time allows characterization of all cardiac segments and structures, including arterial and venous phases, with a reduced requirement for precise timing of the contrast bolus. Recently published data has shown that intravascular agents are superior in defining anatomical structures in patients with congenital heart disease [24,36].

Although, Raman et al. demonstrated in a recent study that GdT was associated with an increase in CNR (24%) between arteries and myocardium as well as an improvement in image quality when

compared to GdD, the differences between the 2 groups were not as significant [12,14,37]. It is worth mentioning that this study was conducted on a 3T scanner while our study was performed on a 1.5T scanner. However, these results are similar to the results published by Wagner et al. [38] where GdT whole heart MRA showed a slightly better image quality.

In our study CNR and BMC were significantly better for GdT using the IR SSFP sequence that allows a suppression of fluids and extravascular tissue in the presence of the short T1 values of the blood. As GdT provides short T1 values of the blood for several hours, CNR and BMC values increased significantly when combining GdT and IR-SSFP (Figure 1).

We would have also expected a higher image quality in terms of image rating for IR SSFP when compared to T2-prepared SSFP sequences [23,36]. In our study the LCX seemed to benefit most from higher intravascular contrast and the IR SSFP sequence (Figure 5). As image quality is mainly influenced by respiratory and cardiac motion as well as heart rate variability, but not intravascular contrast, techniques to suppress respiratory and cardiac motion will predominantly influence image quality. Respiratory motion remains a significant impediment in image quality and speed. The standard1D navigator used assumes a constant linear relationship between cardiac and diaphragmatic motion, which is incorrect and not only increases scan time but, on occasion, leads to residual motion artefacts. The recent introduction of 2D and 3D self-navigating result in an improved coronary artery imaging and shorter scanning times [12,18-20,39,40]. These new navigator techniques in combination with GdT and IR-SSFP might therefore offer a significant improvement in imaging the coronary artery system and need to be evaluated in future studies.

Regarding vessel length, we did not find a statistically significant difference between the two contrast agents. However when using GdT in combination with both IR SSFP and T2-preparedSSFP, the trend is favourable for the intravascular agent for the LAD and RCA. As expected, vessel diameter did not differ between the three groups since we compared the coronary arteries in the same individuals.

Vessel sharpness did not significantly improve with GdT. However, there was a tendency for better vessel wall sharpness of the GdT- IR-SSFP combination (Figure 4). Similar results were reported by Makowski et al. [21,22,36] with better identification and definition of the anatomy of the great vessel using this technique. It is very likely that we could not reach statistical significance due to the small sample size as well as the much smaller vessel size.

Conclusion

A single injection of an intravascular contrast agent in combination with an IR SSFP sequence showed significantly improved CNR and BMC. Although there was a trend towards being able to image longer segments of the LAD and RCA and towards improved vessel sharpness but the level of significance was not reached. Image quality was not significantly different, which could be addressed in the future with novel motion compensation techniques for cardiac and

respiratory motion. Using this technique, also more vessel length of the LAD and RCA could be imaged with improved vessel sharpness for all coronaries, but level of significance was not reached.

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(a)

(b)

(c)

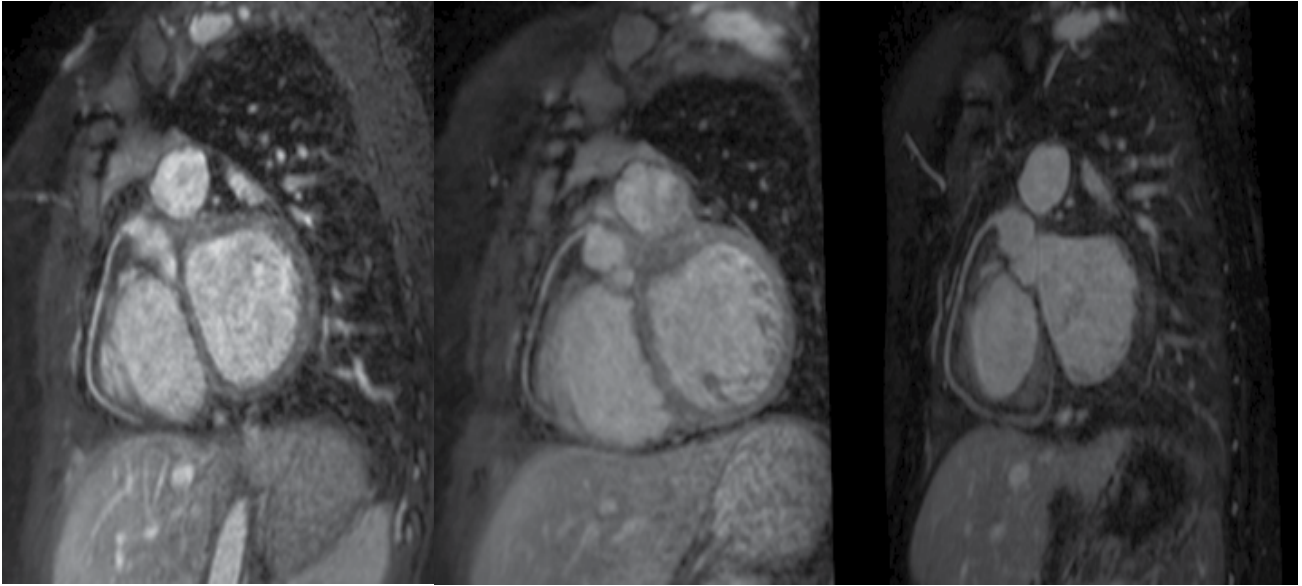


Figure S1: Representative reformatted images of the RCA in the same patient using GdD with a T2-prepared SSFP sequence (a), GdT with a T2-prepared SSFP (b) and GdT with IRSSFP (c).

(a)

(b)

(c)

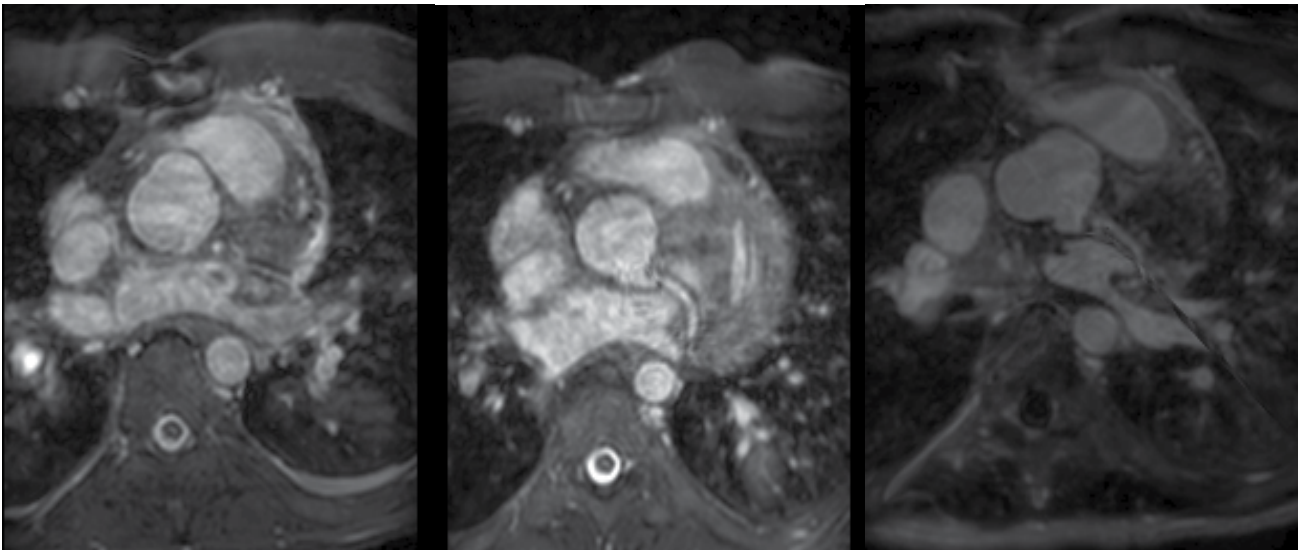


Figure S2: Representative reformatted images of the LCX in the same patient using GdD with a T2-prepared SSFP sequence (a), GdT with a T2-prepared SSFP (b) and GdT with IRSSFP (c).