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High-Resolution Magnetic Resonance Coronary Angiography of the Entire Heart Using a New Blood-Pool Agent, NC100150 Injection: Comparison with Invasive X-Ray Angiography in Pigs

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ABSTRACT

Recent developments of novel magnetic resonance intravascular contrast agents with low T1 in blood and a long intravascular half-life will rapidly position magnetic resonance coronary angiography (MRCA) at the threshold of clinical application. This article describes the use of one such intravascular contrast agent for noninvasive coronary angiography and comparison with routine invasive x-ray angiography. Six domestic farm pigs with an artificial stenoses at the left circumflex were studied. NC100150 Injection, a new ultrasmall superparamagnetic iron oxide (Nycomed Amersham Imaging, Oslo, Norway), was injected using a dose of 5.0 mg Fe/kg body weight. Scanning was done using a 1.5-T Gyroscan ACS-NT. A high-resolution electrocardiogram-triggered scan covering the entire heart was applied. Navigator echoes were used for respiratory triggering. In all animals the location of the stenoses detected with MRCA correlated well with x-ray angiography. The correlation factor between the grade of stenoses determined by MRCA and x-ray angiography was 0.993. MRCA using NC100150 Injection can depict the major coronary arteries and branches well. Decreases in vessel caliber detected by MRCA correlate well with x-ray angiography. The use of such intravascular contrast agents show great promise for clinical applications for noninvasive detection of coronary artery disease in humans.

KEY WORDS: *Contrast media; Coronary disease; Magnetic resonance imaging.*

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INTRODUCTION

Noninvasive delineation of the presence and severity of coronary artery disease in patients represents a major thrust of research in magnetic resonance imaging. Over 1.5 million invasive cardiac catheterizations are performed yearly in the United States alone, and approximately half of those have no subsequent intervention performed, indicating that substantial cost savings in health care could be achieved if a robust noninvasive screening test were available. Magnetic resonance imaging appears to offer such a tool because it yields excellent images of cardiac anatomy, function, valve flow, and even perfusion. However, its use for noninvasive coronary angiography is a key to its ultimate clinical acceptance as a routine diagnostic method.

Magnetic resonance coronary angiography (MRCA) relies on the inflow of blood into coronary arteries during the acquisition (1–8) to produce high signal in the coronary arteries. In areas of very slow flow, however, saturation of the signal may occur, leading to an overestimation of stenoses. Recently, initial trials with both extracellular (9) and intravascular (10) contrast agents have been reported for MRCA. The use of contrast agents alters the approach for MRCA because the signal from blood no longer relies on inflow of blood but rather on the presence of the contrast agent itself. The use of extracellular contrast agents constrains the data acquisition to occur during the first pass of the injection because the contrast agent leaks into the interstitial space very quickly, limiting both spatial resolution and the extend of vessel coverage. Intravascular contrast agents allow longer acquisition times and thereby higher resolution larger volumes to be covered because the half-life of some of these agents can be several hours (11). Simulations have shown that the T1 in blood has to be short to make a significant improvement in MRCA (12). This article describes the use of a new intravascular contrast agent with short T1 in blood and a long intravascular half-life that permits high-resolution MRCA of the entire heart.

METHODS

The study protocol was approved by the institutional animal studies committee. Six domestic farm pigs ranging in weight from 26 to 45 kg were studied. Approximately 1 week before imaging a 3-mm hydraulic cuff constrictor (13) (In Vivo Metric, Healdsburg, CA) was placed surgically around the left circumflex (LCX) via a left thoracotomy at the fifth intercostal space. The placement of the balloon constrictor around the LCX produced an inflammatory response in the tissue surrounding the artery due to the manipulation of the artery and underlying tissue, resulting in a partial stenosis at rest in some cases. The balloon was not actively inflated during any of the measurements. NC100150 Injection (11), a new ultrasmall superparamagnetic iron oxide (Nycomed Amersham Imaging) was injected in an ear vein at a dose of 5.0 mg Fe/kg body weight. Scanning was performed 5 min after injection to allow the contrast agent to reach a steady state within the blood pool. All MR imaging was performed at a 1.5-T Gyroscan ACS-NT (Philips Medical Systems, Best, The Netherlands). The pigs were mechanically ventilated and anesthetized during the examination using 2–3% isoflurane with oxygen. A three-dimensional gradient-echo sequence with a TR/TE = 7.8/2.7 msec and a resolution of 0.9 × 0.9 × 0.9 mm was acquired using an 18-cm circular radiofrequency coil. Spectral fat suppression was applied. The data acquisition was electrocardiogram-triggered to mid-diastole using an acquisition window of 40–60 msec depending on cardiac frequency. A flip angle sweep was applied, optimized to maintain a maximum constant signal of blood during the acquisition (12). Navigator echoes were used for respiratory triggering during continuous ventilation (10–15 cycles/min). A total of 40–50 slices were scanned depending on the size of the heart and the total scan time varied between 10 and 22 min depending on cardiac and respiratory frequency. The wide range in scan times was primarily due to differences in the acceptance rate of the navigator technique, due to individual variation in the range of diaphragm motion.

X-ray angiography was performed within a few hours before the MRCA, in the same anesthesia session. Curved image reformats along the vessels were performed by manual identification of the vessel's trajectory in three-dimensional space and then generating a slice along the defined trajectory using standard software on an Easy Vision workstation (Philips Medical Systems). The visible lengths of the left anterior descending, LCX, and right coronary artery were measured by a reviewer blinded to the x-ray angiography results. The x-ray and MR angiography images were compared qualitatively with respect to the position of the constrictor. The percentage of stenosis in x-ray images was classified by an experienced observer blind to the MRCA results (S.A.W.) into one of the following ranges for x-ray angiography: 0–25%, 26–50%, 51–75%, 76–99%, and 100%. The percent stenosis was also measured in the x-ray images using a single plane caliper measurement. For the MRCA, the percentage stenosis was measured using a caliper with the reference diameter measured in a normal vessel segment 10 mm from the stenosis. The correlation

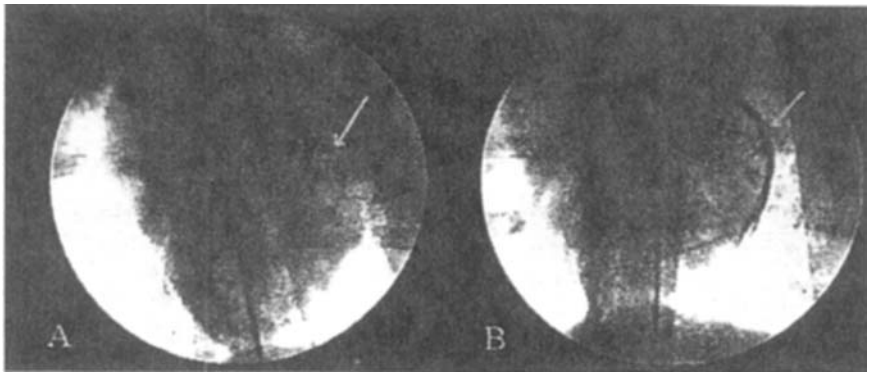

Figure 1. Images showing x-ray angiography of the left coronary system from two pigs.

coefficient between the stenoses measured in x-ray and MR angiography was calculated.

RESULTS

Figure 1 shows a view of the x-ray angiography for two pigs and Fig. 2 the same segments by MRCA. Note that also branches of the main coronary arteries are well visualized with MRCA. For all pigs, the position of the vessel constrictor correlated well between MRCA and x-ray angiography. In both MRCA and x-ray angiography, the location of the balloon constrictor is visualized as a stenosis in the vessel lumen. On MRCA, the location also was detected as signal voids on either side of the vessel caused by the air inside the balloon.

The severity of stenosis correlated well between the MRCA and x-ray angiography as shown in Table 1. The correlation coefficient between the two measurements was 0.993. In all cases except pig 6, the MRCA showed the stenosis within the range classified on x-ray angiography. Pig 6's stenosis was classified to be 76–99% and was measured to be 69% on MRCA. The mean vessel diameter 10 mm from the constrictor was 2.7 ± 0.7 mm.

The visible length (mean ± SD) of the main coronary arteries is shown in Table 2, which indicates excellent coverage of the main coronary arteries.

DISCUSSION

The long intravascular half-life and short T1 in blood obtained with the intravascular contrast agent NC100150 Injection (11,14) facilitates the depiction of the major

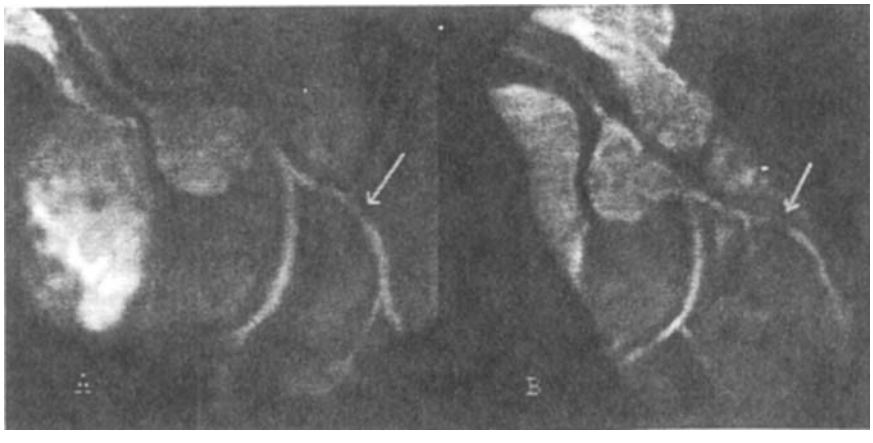

Figure 2. Images showing magnetic resonance coronary angiography curved reformats of left and right coronary system from the same pigs as in Fig. 1.

Table 1

Percent Stenosis X-Ray vs. MRCA

Pig	Stenosis Classified in X-Ray Angiography (%)	Stenosis Measured in X-Ray Angiography (%)	Stenosis Measured in MR Angiography (%)
1	51–75	72	60
2	0–25	14	10
3	51–75	70	63
4	26–50	38	30
5	0–25	0	6
6	76–99	82	69

coronary arteries and their branches by three-dimensional MRCA with high spatial resolution. The long intravascular half-life (more than 1 hr in pigs with a T1 less than 100 msec) and preserved contrast-to-noise ratio (11,14) also facilitates repeated measurements or measurements targeted to small areas of the coronary tree in addition to a full heart coverage measurement without losing contrast to noise. Decreases in vessel caliber detected by MRCA correlated well with those measured and estimated by x-ray angiography. A feature with MRCA is the possibility to see the entire vascular tree in the same image. This is possible because the data acquisition is performed when the contrast agent has reached steady state in the blood pool. Thus, the contrast agent reaches vascular areas with very slow flow but remains at a high concentration, whereas x-ray angiography relies on first-pass imaging and therefore the vessels with slow flow are shown somewhat later in the acquisition. During first-pass x-ray angiography, reduction of the concentration of the contrast agent may also occur in areas of constricted vessels and therefore produce less contrast than that possible with MRCA.

Figure 2 shows not only the left coronary system but also the right coronary system. The fact that vascular tree from the entire heart is acquired in the same acquisition is one of the advantages of three-dimensional MRCA.

Table 2

Visible Length of Main Coronary Arteries in MRCA

	Visible Length (mm)
Left anterior descending	82.6 ± 12.6
LCX	65.5 ± 5.30
Right coronary artery	83.1 ± 21.1

Values are means ± SD.

This is possible because the concentration of the contrast agent is the same in the entire blood pool during the steady-state acquisition.

The resolution used for this study is enough to detect small changes in caliber of the vessels at these diameters (2.7 ± 0.7 mm). Greater accuracy in quantification of stenoses may require even higher resolution. This possibility is perhaps manifest in the slight underestimation of the stenosis in pig 6 by MRCA, because the vessel diameter at the stenoses was smaller than the MR pixel size (0.9 mm). There is a trend that the higher grade stenoses is underestimated in MRCA as seen not only in pig 6 but also in pigs 1 and 3. In patients we can expect the vessel diameter of the major coronary arteries to be larger, although higher resolution may still be required for MRCA. This could be achieved by using even more efficient sampling strategies such as echo planar or spiral imaging.

The average length of the coronary arteries visualized in these small pigs (26–45 kg) indicates that it should be possible to depict at least the proximal 100 mm of the coronary arteries in humans. The contrast-to-noise ratio could be improved further by using a prepulse to null the signal of the myocardium. In the present study, the high heart rate (100–150 beats/min) precluded the use of a prepulse because it would also affect the blood signal, leading to reduced signal to noise. However, this strategy should be possible in humans.

One advantage of MRCA is the capability to collect three-dimensional information. Availability of isotropic three-dimensional data permits curved planar reformatting that is not possible with two-dimensional projections as acquired in x-ray angiography. Previous studies in peripheral angiography have shown that three-dimensional tomographic acquisition with MR imaging improves the accuracy for quantifying stenoses (15).

One limitation of the current study is that the location

of the stenosis in each animal is clearly identified from the signal void due to the air in the vascular constrictor. Furthermore, the x-ray angiography measurements were made in a single plane only. The main purpose of the study, however, was to demonstrate feasibility, not to perform a comprehensive evaluation of sensitivity and specificity for detection of coronary artery stenoses.

Further studies in patients are needed to demonstrate the clinical potential of this method to detect coronary artery disease in humans. This agent has already been shown to improve blood-myocardial contrast in functional MR imaging of the heart (16), and with the long intravascular half-life of the agent, one could envision using it for both functional and coronary imaging with a single injection. The results presented here confirm that an intravascular contrast agent with a long intravascular half-life and with a short T1 in blood enables high-resolution three-dimensional MRCA of the entire heart.

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REFERENCES

1. Edelman R, Manning W, Burstein D and Paulin S. Coronary arteries: Breath hold MR angiography. *Radiology*, 1991; 181:641–643.
2. Meyer CH, Hu BS, Nishimura DG and Macovski A. Fast spiral coronary artery imaging. *Magn Reson Med*, 1992; 28:401–406.
3. Li D, Paschal CB, Haacke EM and Adler LP. Coronary arteries: Three-dimensional MR imaging with fat saturation and magnetization transfer contrast. *Radiology*, 1993; 187:401–406.
4. Post JC, van Rossum AC, Bronzwaer JG, de Cock CC, Hofman MB, Valk J and Visser CA. Magnetic resonance angiography of anomalous coronary arteries. A new gold standard for delineating the proximal course? *Circulation*, 1995; 92:3163–3171.
5. Wielopolski PA, Manning WJ and Edelman RR. Single breath-hold volumetric imaging of the heart using magnetization-prepared 3D segmented echo-planar imaging. *J Magn Reson Imag*, 1995; 5:401–410.
6. Pennell DJ, Bogren HG, Keegan J, Firmin DN and Underwood SR. Assessment of coronary artery stenosis by magnetic resonance imaging. *Heart*, 1996; 75:127–133.
7. Oshinski JN, Hofland L, Mukundan S, Dixon WT, Parks WJ and Pettigrew RI. Two-dimensional coronary MR angiography without breath holding. *Radiology*, 1996; 201: 737–743.
8. Duerinckx A and Atkinson DP. Coronary MR angiography during peak-systole: Work in progress. *J Magn Reson Imag*, 1997; 7:979–986.
9. Kessler W, Laub G, Ropers D, Achenbach S, Moshage W and Bachmann K. Contrast-enhanced 3D breath-hold MRA for the visualization of the coronary arteries in oblique projection angiograms. Proceedings of the Sixth Annual Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Sydney, Australia, April 18–24, 1998, p. 317.
10. Stuber M, Botnar RM, McConnell MV, Danias PG, Kissinger KV, Edelman RR and Manning WJ. Coronary artery imaging with the intravascular contrast agent MS-325. Proceedings of the Sixth Annual Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Sydney, Australia, April 18–24, 1998, p. 316.
11. Nolte Ernsting C, Adam G, Bücker A, Berges S, Bjornerud A and Günther RW. Abdominal MR angiography with blood pool contrast agents: Comparison of a new superparamagnetic iron oxide nanoparticle and a linear gadolinium polymer. *AJR Am J Roentgenol*, 1998; 171: 107–113.
12. Johansson L, Hofman MBM, Fischer SE, Wickline SA and Lorenz CH. How does T1 reduction in blood affect contrast enhanced magnetic resonance coronary angiography? Proceedings of the First Annual Meeting of the Society for Cardiovascular Magnetic Resonance, Atlanta, Georgia, January 30–February 1, 1998, p. 42.
13. Shoukas A. Construction of hydralic cuff occluders for blood vessels. *Am J Physiol*, 1977; 31:99–100.
14. Bjonerud A, Wendland MF, Johansson L, Ahlstrom HK, Higgins CB and Oksendal A. Use of intravascular contrast agents in MRI. *Acad Radiol*, 1998; 5(Suppl 1): S223–S225.
15. Ho KY, Leiner T, de Haan MW, Kessels AG, Kitslaar PJ and van Engelshoven JM. Peripheral vascular tree stenoses: evaluation with moving-bed infusion-tracking MR angiography. *Radiology*, 1998; 206:683–692.
16. Taylor AM, Panting JR, Keegan J, Gatehouse PD, Jhooti P, Yang GZ, McGill S, Francis JM, Burman ED, Firmin DN and Pennell DJ. Use of the intravascular contrast agent NC100150 injection in spin-echo and gradient-echo imaging of the heart. *J Cardiovasc Magn Reson*, 1999; 1:23–32.