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CORONARY MAGNETIC RESONANCE ANGIOGRAPHY FOR THE DETECTION OF CORONARY STENOSES

W. YONG KIM, M.D., PH.D., PETER G. DANIAS, M.D., PH.D., MATTHIAS STUBER, PH.D., SCOTT D. FLAMM, M.D., SVEN PLEIN, M.D., EIKE NAGEL, M.D., SUSAN E. LANGERAK, M.Sc., OLIVER M. WEBER, PH.D., ERIK M. PEDERSEN, M.D., PH.D., MATTHIAS SCHMIDT, M.D., RENÉ M. BOTNAR, PH.D., AND WARREN J. MANNING, M.D.

ABSTRACT

Background An accurate, noninvasive technique for the diagnosis of coronary disease would be an important advance. We investigated the accuracy of coronary magnetic resonance angiography among patients with suspected coronary disease in a prospective, multicenter study.

Methods Coronary magnetic resonance angiography was performed during free breathing in 109 patients before elective x-ray coronary angiography, and the results of the two diagnostic procedures were compared.

Results A total of 636 of 759 proximal and middle segments of coronary arteries (84 percent) were interpretable on magnetic resonance angiography. In these segments, 78 (83 percent) of 94 clinically significant lesions (those with a ≥ 50 percent reduction in diameter on x-ray angiography) were also detected by magnetic resonance angiography. Overall, coronary magnetic resonance angiography had an accuracy of 72 percent (95 percent confidence interval, 63 to 81 percent) in diagnosing coronary artery disease. The sensitivity, specificity, and accuracy for patients with disease of the left main coronary artery or three-vessel disease were 100 percent (95 percent confidence interval, 97 to 100 percent), 85 percent (95 percent confidence interval, 78 to 92 percent), and 87 percent (95 percent confidence interval, 81 to 93 percent), respectively. The negative predictive values for any coronary artery disease and for left main artery or three-vessel disease were 81 percent (95 percent confidence interval, 73 to 89 percent) and 100 percent (95 percent confidence interval, 97 to 100 percent), respectively.

Conclusions Among patients referred for their first x-ray coronary angiogram, three-dimensional coronary magnetic resonance angiography allows for the accurate detection of coronary artery disease of the proximal and middle segments. This noninvasive approach reliably identifies (or rules out) left main coronary artery or three-vessel disease. (N Engl J Med 2001;345:1863-9.)

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DESPITE progress in prevention and early diagnosis, coronary artery disease remains the leading cause of death in both men and women in the United States¹ and throughout the Western world. Invasive x-ray coronary angiography remains the gold standard for the identification of clinically significant coronary artery disease. Although numerous noninvasive tests have been developed to assist in the identification of patients with coronary artery disease, a substantial minority of patients referred for elective diagnostic x-ray coronary angiography are found not to have clinically significant coronary stenosis (defined as a reduction in the luminal diameter of at least 50 percent).² A noninvasive test that could directly assess the integrity of the coronary lumen would therefore be desirable.

Coronary magnetic resonance angiography makes possible the noninvasive visualization of the major epicardial coronary arteries in the majority of subjects. Since the first reports by Paulin et al.³ and Edelman et al.,⁴ coronary magnetic resonance angiography has undergone technological advances leading to enhanced spatial resolution and the possibility of imaging while the patient is breathing freely, but assessment of its usefulness has been hampered by the lack

From the Cardiovascular Division, Department of Medicine (W.Y.K., P.G.D., M. Stuber, R.M.B., W.J.M.), and the Department of Radiology (W.J.M.), Beth Israel Deaconess Medical Center and Harvard Medical School, Boston; the Magnetic Resonance Center, Department of Cardiology, and Institute of Experimental Clinical Research, Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark (W.Y.K., E.M.P.); Philips Medical Systems, Best, the Netherlands (M. Stuber, R.M.B.); St. Luke's Episcopal Hospital and the Texas Heart Institute, Houston (S.D.F.); the Yorkshire Heart Centre, Leeds General Infirmary, Leeds, United Kingdom (S.P.); Internal Medicine Cardiology, German Heart Institute, Berlin, Germany (E.N.); the Department of Radiology and Cardiology, Leiden University Medical Center, Leiden, the Netherlands (S.E.L.); the Institute for Biomedical Engineering, University of Zurich, and the Swiss Federal Institute of Technology Zurich, Zurich, Switzerland (O.M.W.); and the Klinik und Poliklinik für Nuklearmedizin der Universität zu Köln, Cologne, Germany (M. Schmidt). Address reprint requests to Dr. Manning at the Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215, or at wmanning@caregroup.harvard.edu.

of standardized hardware, software, and scanning protocols. The results from single-center studies therefore vary considerably.⁵⁻¹⁴ Coronary magnetic resonance angiography^{15,16} performed while the patient is breathing freely has reached sufficient technical maturity to allow more widespread application with a standardized protocol. Therefore, we conducted a prospective, international, multicenter study to determine the clinical usefulness of coronary magnetic resonance angiography in the diagnosis of native-vessel coronary artery disease.

METHODS

Participating Institutions

The subjects were recruited from seven institutions: Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark (7 subjects), the German Heart Institute, Berlin, Germany (18 subjects), Beth Israel Deaconess Medical Center, Boston (18 subjects), St. Luke's Episcopal Hospital, Houston (25 subjects), Leeds General Infirmary, Leeds, United Kingdom (23 subjects), Leiden University Medical Center, Leiden, the Netherlands (9 subjects), and the University and Eidgenoessische Technische Hochschule Zurich, Zurich, Switzerland (9 subjects). The review board at each institution approved the study, and written informed consent was obtained from all subjects. In all cases, coronary magnetic resonance angiography was performed before x-ray angiography.

Patients

The study population consisted of 109 subjects who were consecutively enrolled between June 24, 1999, and October 18, 2000. The subjects could be of either sex and had to be at least 21 years of age with sinus rhythm and with a body weight of 100 kg or less and to be scheduled to undergo elective x-ray coronary angiography for suspected coronary artery disease within 14 days. The exclusion criteria were a contraindication to magnetic resonance imaging¹⁷ (for example, a pacemaker, intraauricular implants, or intracranial clips), previous x-ray coronary angiography or thoracotomy, claustrophobia, orthopnea, and inability to take sublingual nitroglycerin (as a result, for example, of aortic stenosis or obstructive cardiomyopathy).

Protocol for Magnetic Resonance Angiography

Each center performed coronary magnetic resonance angiography according to a standard protocol¹⁶ with use of common hardware and software on a 1.5-T system (Gyrosan ACS-NT, Philips Medical Systems, Best, the Netherlands) equipped with Power-Trak 6000 gradients (23 mT per meter, 219 μ sec rise time). The subjects were examined with a commercial five-element cardiac synergy receiver coil during uncoached free breathing. To compensate for artifacts due to respiratory motion, a right hemidiaphragmatic navigator¹⁸ with real-time slice correction¹⁹ and a 5-mm end-expiratory gating window were used. For cardiac synchronization and monitoring, three or four²⁰ electrodes were placed on the left anterior hemithorax of the subject with the R wave of the electrocardiogram used as a trigger for image acquisition. All coronary images were acquired in mid-diastole.¹⁹

Magnetic Resonance Localization Scans

The first magnetic resonance localizing scan (approximately one minute) employed a multistack and multislice, segmented k-space gradient-echo sequence for localization of the heart and diaphragm in three orthogonal planes (transverse, sagittal, and coronal).^{15,16} From the coronal data set, a navigator-gated transverse three-dimensional segmented echo localizing planar scan (approximately two minutes) with 40 slices was acquired around the base of the heart to cover the region extending from the apex of the left ven-

tricle to the pulmonary artery.¹⁶ This allowed identification of the course of the major right and left coronary arteries. With the use of a three-point planscan tool,¹⁶ a plane through the major axis of the proximal and middle segments of the right coronary artery was subsequently prescribed.

Three-Dimensional Magnetic Resonance Angiography

Coronary magnetic resonance angiography was performed, after sublingual administration of isosorbide dinitrate (2.5 mg), with the use of a three-dimensional segmented k-space gradient-echo sequence (echo time, 2.2 msec; repetition time, 7.7 msec) during free breathing (for about 10 to 15 minutes).^{15,16} For contrast enhancement between blood and the surrounding myocardium and epicardial fat, a T₂-weighted preparation prepulse and a frequency-selective fat-saturation prepulse were applied.¹⁵ For the right coronary artery, a double-oblique three-dimensional volume was imaged with use of the coordinates prescribed by the three-point planscan tool. For the left main, left anterior descending, and left circumflex coronary arteries, a double-oblique transverse three-dimensional volume with anterior-posterior and left-right angulations (5 degrees each) was imaged with the volume centered on the origin of the left main coronary artery (as defined from the second localizing scan). For both the left and the right coronary systems, the three-dimensional volumes were reconstructed to 20 slices, with an individual slice thickness of 1.5 mm. A field of view of 360 mm and a 512-by-360 matrix yielded an in-plane voxel size of 0.7 by 1.0 mm. No signal averaging was performed.

Analysis of Coronary Magnetic Resonance Angiograms

Source coronary magnetic resonance angiograms were evaluated at each site (before x-ray angiography) and again by consensus of two experienced investigators (from the core magnetic resonance imaging laboratory at the Beth Israel Deaconess Medical Center) who were blinded to the patients' clinical data and the x-ray data. The original source images were analyzed by scrolling through individual slices from the three-dimensional data set with the use of a commercial software package (EasyVision 4.0, Philips Medical Systems, Best, the Netherlands). Seven coronary segments were evaluated: the left main coronary artery and the proximal and middle segments of the left anterior descending coronary artery (0 to 2 cm and 2 to 4 cm), the left circumflex coronary artery (0 to 1.5 cm and 1.5 to 3 cm), and the right coronary artery (0 to 2 cm and 2 to 5 cm). For each segment, image quality was visually graded²¹ as 1, indicating poor or uninterpretable (coronary artery visible, with markedly blurred borders or edges); 2, good (coronary artery visible, with moderately blurred borders or edges); 3, very good (coronary artery visible, with mildly blurred borders or edges); or 4, excellent (coronary artery visible, with sharply defined borders or edges). If the segments were not imaged or if the image quality was graded as poor or uninterpretable (grade 1), no further evaluation was performed. Segments that were not visualized or that were graded as poor or uninterpretable were not included in the subsequent analysis. Images of good, very good, and excellent quality (grades 2, 3, and 4) were further classified according to the visual assessment of the coronary-artery lumen as having no coronary artery disease, minimal disease, or clinically significant disease (if there was prominent attenuation of the coronary-lumen signal).

Acquisition and Analysis of Coronary X-Ray Angiograms

Conventional x-ray coronary angiography was performed by standard techniques²² and in multiple projections after sublingual administration of isosorbide dinitrate (2.5 mg). An experienced invasive cardiologist at the institution where angiography was performed analyzed each x-ray angiogram without knowledge of the magnetic resonance data. Each coronary vessel was assessed, and the visual estimation of the segment and the maximal percentage reduction of the luminal diameter for each lesion were reported. In addition, in 99 patients (91 percent), quantitative x-ray angiographic analysis was performed by an independent core laborato-

ry (Brigham and Women's Hospital Angiographic Core Laboratory, Boston) without access to the magnetic resonance data. Quantitative angiographic analysis was performed according to a standard algorithm,²³ with clinically significant disease defined as stenosis of at least 50 percent of the vessel diameter. For 10 subjects for whom quantitative analysis was not performed because of administrative issues (e.g., images could not be located or were unreadable), the visual evaluation reported from the site was used for the analyses.

Statistical Analysis

The data were retained at the Beth Israel Deaconess Medical Center, and the primary data analysis was performed by one of us. For each individual vessel and for each patient, the sensitivity, specificity, and accuracy (percentage of segments correctly classified) were determined, as well as the positive and negative predictive values for coronary magnetic resonance angiography as compared with x-ray coronary angiography. All data are reported as means ±SD or rates with 95 percent confidence intervals.

RESULTS

All subjects completed coronary magnetic resonance angiography without complications. Of the 109 subjects, 69 percent were men (Table 1). The majority of the subjects had a history of chest pain, smoking, and hypercholesterolemia. Sixty-four of the subjects (59 percent) had x-ray angiographic evidence of coronary artery disease, including 12 percent with three-vessel disease (Table 1).

The mean total magnetic resonance scanning time (including scout imaging) was 70 minutes (median, 66; range, 33 to 145). The median interval between the performance of coronary magnetic resonance angiography and x-ray angiography was 1 day (mean, 3; range, 0 to 14), with no clinical cardiac events reported between the examinations. Right coronary x-ray angiography was not performed in two subjects. Thus, 759 coronary segments were potentially available for analysis. Of these, 636 (84 percent) could be assessed by coronary magnetic resonance angiography; the proportions of segments for which images could be assessed ranged from 68 percent (for the middle left circumflex coronary artery) to 93 percent (for the proximal and middle right coronary artery) (Table 2). Coronary segments were not interpretable by magnetic resonance angiography when scans were not obtained because of time constraints (39 segments), when image quality was poor (grade 1, 58 segments), or when the three-dimensional volume did not include the segment (26 segments).

In the magnetic resonance angiographic assessment of diagnostic accuracy for each individual vessel, we included all vessels for which the proximal segment was graded as having an image quality of at least 2 (good or better). In the analyses for any coronary artery disease and for left main coronary artery or three-vessel disease, 103 subjects (94 percent) were eligible according to the consensus readings, and 101 (93 percent) were eligible according to the readings at the sites. Patients were considered eligible if clinically significant coronary artery disease identified on

TABLE 1. DEMOGRAPHIC, CLINICAL, AND X-RAY ANGIOGRAPHIC CHARACTERISTICS OF THE 109 STUDY PATIENTS.

CHARACTERISTIC	VALUE
Female sex — no. (%)	34 (31)
Age — yr	
Mean ±SD	59±10
Range	27–75
Chest pain — no. (%)	86 (79)
Prior myocardial infarction — no. (%)	26 (24)
History of systemic hypertension — no. (%)	54 (50)
Current or prior cigarette smoking — no. (%)	58 (53)
Cholesterol >200 mg/dl (5.2 mmol/liter) — no. (%)	67 (61)
Diabetes — no. (%)	19 (17)
Family history of premature coronary artery disease — no. (%)*	43 (39)
Family history of any coronary artery disease — no. (%)†	64 (59)
Findings on x-ray angiography — no. (%)	
One-vessel disease	31 (28)
Left anterior descending coronary artery	12 (11)
Left circumflex coronary artery	4 (4)
Right coronary artery	15 (14)
Two-vessel disease	20 (18)
Three-vessel disease	13 (12)

*A family history was defined as a history of myocardial infarction or angina in a first-degree relative before the age of 65 years.

†A family history was defined as a history of myocardial infarction or angina in a first-degree relative.

TABLE 2. NUMBER OF INTERPRETABLE CORONARY-ARTERY SEGMENTS AND QUALITY OF THE IMAGE ON CORONARY MAGNETIC RESONANCE ANGIOGRAPHY.

SEGMENT	SEGMENTS WITH IMAGE QUALITY ≥2*	IMAGE QUALITY mean (±SD) grade
	no./total no. (%)	
Left main coronary artery	96/109 (88)	2.7±0.7
Left anterior descending coronary artery		
Proximal	93/109 (85)	2.7±0.7
Middle	88/109 (81)	2.6±0.7
Left circumflex coronary artery		
Proximal	85/109 (78)	2.4±0.8
Middle	74/109 (68)	2.5±0.7
Right coronary artery†		
Proximal	100/107 (93)	2.7±0.6
Middle	100/107 (93)	2.8±0.6
Total	636/759 (84)	2.6±0.7

*Image quality was graded as 1, poor or uninterpretable; 2, good; 3, very good; or 4, excellent.

†X-ray angiography was not performed on the right coronary artery in two patients.

x-ray angiography was found in any coronary artery segment with a readable magnetic resonance image.

The overall image quality was 2.6 ± 0.7 (Table 2). Individual segment lengths are shown in Figure 1. An example of a coronary magnetic resonance angiogram and a corresponding x-ray contrast angiogram for a patient with left and right coronary artery disease are shown in Figure 2.

Seventy-eight of 94 clinically significant coronary stenoses (83 percent) identified on x-ray angiography were correctly identified on magnetic resonance angiography. The sensitivity of coronary magnetic resonance angiography for identifying a patient as having clinically significant coronary artery disease, according to the consensus of the two interpreters, was 93 percent (95 percent confidence interval, 88 to 98 percent) (Table 3). All four patients who had clinically significant coronary artery disease that was not diagnosed by coronary magnetic resonance angiography had isolated single-vessel disease, with two (50 percent) having isolated left circumflex artery disease. In the consensus interpretation, the overall diagnostic accuracy of coronary magnetic resonance angiography in identifying a patient as having any coronary artery disease was 72 percent (95 percent confidence interval, 63 to 81 percent), increasing to 87 percent (95 percent confidence interval, 81 to 93 percent) for the identification of a patient with left main coronary artery or three-vessel disease. The prevalence, sensitivity, specificity, and positive and negative predictive values for individual coronary vessels and patients according to the consensus and the site-reported interpretations are summarized in Table 3.

DISCUSSION

In this prospective, multicenter study comparing noncontrast coronary magnetic resonance angiography with x-ray angiography among patients referred for a first elective coronary angiogram, we found that coronary magnetic resonance angiography had a high sensitivity, negative predictive value, and overall accuracy for detecting coronary artery disease, especially in subjects with left main coronary artery disease or three-vessel disease. Coronary magnetic resonance angiography is not exercise-dependent, and its high negative predictive value suggests that it may have a role in ruling out clinically significant coronary disease in this population of patients, among whom the prevalence of disease is intermediate. Indeed, 41 percent of study subjects had no clinically significant coronary artery disease, a prevalence similar to that in previously published data,² a fact that emphasizes the need for an accurate, noninvasive technique that can rule out clinically significant disease before invasive x-ray coronary angiography. On the basis of the finding of no clinically significant disease on magnetic resonance angiography, x-ray angiography could have been avoided in 18 subjects (according to the consensus

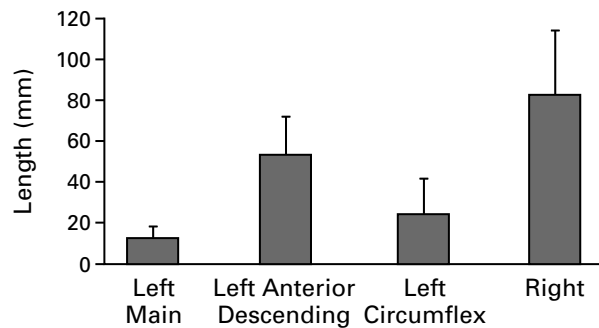


Figure 1. Mean (+SD) Lengths of Segments of Coronary Vessels Visualized by Coronary Magnetic Resonance Angiography.

reading) or 25 subjects (according to the site reading) — those with true negative results (Table 3), or 42 to 58 percent of subjects without clinically significant coronary artery disease. With the use of standardized technology and a standardized scanning protocol, all patients with left main coronary artery or three-vessel disease were identified as having clinically significant coronary artery disease. These data therefore support the use of coronary magnetic resonance angiography to identify (or rule out) left main coronary artery disease or three-vessel disease reliably. Such information is clinically relevant, since surgical revascularization in patients with such disease is associated with a more favorable long-term survival benefit.²⁴

The protocol for three-dimensional, noncontrast, free-breathing coronary magnetic resonance angiography facilitated visualization of the vast majority of the proximal and middle segments of the left main, left anterior descending, and right coronary arteries. Coronary magnetic resonance angiography would detect 94 percent of all patients with any coronary artery disease or with left main coronary artery or three-vessel disease. The left circumflex artery was less reliably visualized, but isolated disease of this artery was found in only 4 percent of subjects, suggesting that the absence of clinically significant disease in the remaining coronary system makes left circumflex artery disease unlikely. This observation is in agreement with other reports.²⁵ The accuracy of coronary magnetic resonance angiography for the detection of coronary disease in the left circumflex artery was also low in prior single-center studies.^{5,6,9,13} This poor accuracy may be due to the relatively small caliber and posterior location of the circumflex artery, which results in a lower signal-to-noise ratio because of the increased distance from the artery to the receiver coils.

Other minimally invasive imaging methods have recently been advocated for coronary-artery imag-

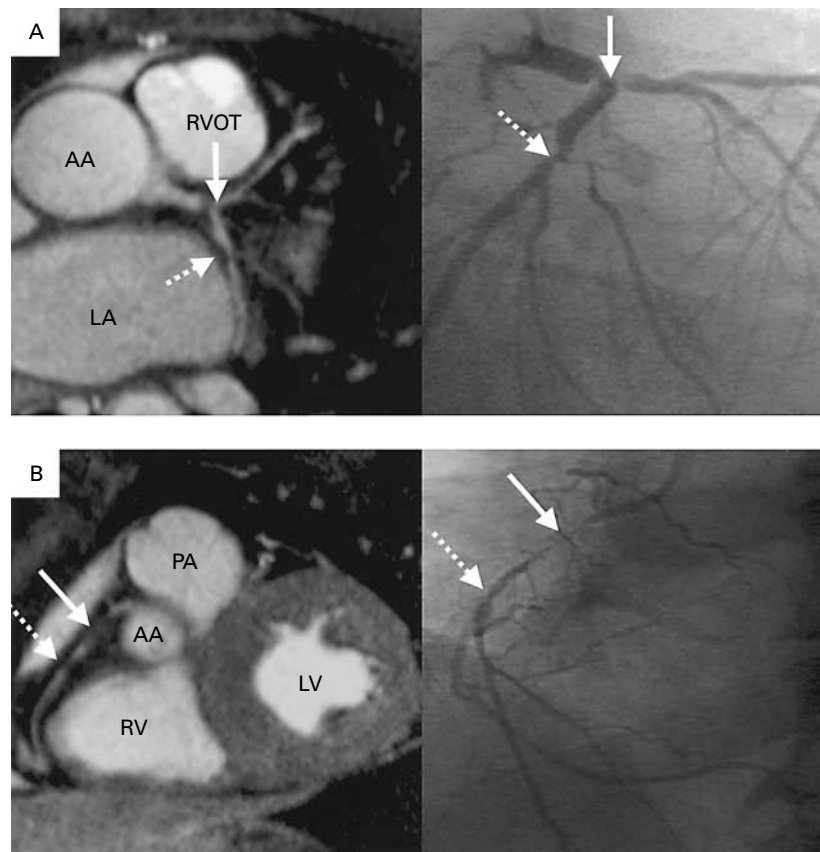


Figure 2. Coronary Angiography in a 53-Year-Old Man with Exertional Chest Pain.

Panel A shows a coronary magnetic resonance angiogram (left) and a corresponding x-ray coronary angiogram (right) indicating a severe lesion at the bifurcation of the left anterior descending coronary artery and the left circumflex coronary artery, involving the left main coronary artery (solid arrows), and a more distal focal stenosis of the left circumflex coronary artery (broken arrows). Panel B shows a coronary magnetic resonance angiogram (left) and a corresponding x-ray angiogram (right) indicating two stenoses of the proximal (solid arrows) and middle (broken arrows) right coronary artery. AA denotes ascending aorta, LA left atrium, RVOT right ventricular outflow tract, PA pulmonary artery, RV right ventricle, and LV left ventricle.

ing. Electron-beam computed tomography is a highly sensitive technique for detecting calcium in the coronary arteries.² Recent studies using multislice computed tomography in combination with iodinated contrast medium to visualize the coronary-artery lumen demonstrated very good diagnostic accuracy for detecting coronary artery disease when image quality was adequate (that is, when 70 to 80 percent of images could be assessed).²⁶⁻²⁸ A potential advantage of this method is the acquisition of a complete data set during a single, though prolonged, breath-holding period (30 to 40 seconds). As compared with computed tomography, the magnetic resonance approach has the advantage of requiring no exposure to ionizing radiation or injection of a contrast agent, and it allows for more comfortable free breathing

during the entire examination. Both the magnetic resonance²⁹ and computed tomographic approaches are safe in patients with intracoronary stents, but interpretation is difficult.

Coronary magnetic resonance angiography has already been demonstrated to be of clinical value for the assessment of anomalous coronary artery disease, and it is often superior to x-ray coronary angiography in delineating the course of the anomalous vessels.³⁰⁻³³ However, coronary magnetic resonance angiography was considered an investigational technique for the assessment of stenotic native-vessel disease in task-force reports from Europe and the United States in 1998.^{34,35} The results of single-center investigations of coronary magnetic resonance angiography that used different hardware, software, and scanning protocols

TABLE 3. DIAGNOSTIC ACCURACY OF CORONARY MAGNETIC RESONANCE ANGIOGRAPHY TO DETECT STENOSES OF ≥ 50 PERCENT.

VARIABLE	LEFT MAIN CORONARY ARTERY	LEFT ANTERIOR DESCENDING CORONARY ARTERY	LEFT CIRCUMFLEX CORONARY ARTERY	RIGHT CORONARY ARTERY	ANY CORONARY ARTERY DISEASE (CONSENSUS/SITE READING)*	LEFT MAIN CORONARY ARTERY OR THREE-VESSEL DISEASE (CONSENSUS/SITE READING)*
No. of true negatives	81	31	49	43	18/25	74/75
No. of true positives	4	29	8	37	56/51	16/15
No. of false negatives	2	4	7	3	4/7	0/1
No. of false positives	9	29	21	17	25/18	13/10
Prevalence (%)	6	41	19	40	59	15
Sensitivity (%)	67	88	53	93	93 (88–98)/88 (82–94)	100 (97–100)/94 (89–99)
Specificity (%)	90	52	70	72	42 (32–52)/58 (48–68)	85 (78–92)/88 (82–94)
Accuracy (%)	89	65	67	80	72 (63–81)/75 (67–83)	87 (81–93)/89 (83–95)
Positive predictive value (%)	30	56	29	69	70 (61–79)/75 (67–83)	54 (44–64)/58 (48–68)
Negative predictive value (%)	98	86	86	94	81 (73–89)/77 (69–85)	100 (97–100)/99 (95–100)

*Values in parentheses are 95 percent confidence intervals.

have been variable.⁵⁻¹⁴ Single-center experience (often including patients who had previously undergone angiography or a coronary intervention) may also be difficult to translate into general clinical practice. Clinical acceptance of coronary magnetic resonance angiography will probably require standardization to ensure optimal test results. The findings of the present multicenter study should reflect the clinical value of coronary magnetic resonance angiography more accurately, because we evaluated a relatively large number of patients at seven international institutions and used common hardware and software and a common scanning protocol. Only one of the seven participating institutions had extensive experience with coronary magnetic resonance angiography. Furthermore, the independent consensus analyses and those reported from individual sites were quite similar (Table 3).

Subgroups of patients who may initially benefit from coronary magnetic resonance angiography are likely to include patients who present with severe left ventricular systolic dysfunction in the absence of a clinical history of myocardial infarction. For these patients, the underlying disease process is either severe multivessel coronary artery disease or nonischemic cardiomyopathy. Conventional stress tests are often inaccurate in this group, resulting in frequent referral for diagnostic coronary angiography. Although this possibility was not directly tested in our study, the data suggest that coronary magnetic resonance angiography may be able to discriminate between these two causes; thus, x-ray angiography could be avoided for those without magnetic resonance evidence of coronary disease. It should be remembered, however, that coronary magnetic resonance angiography

was unable to assess 16 percent of coronary segments and that 6 percent of the study patients could not be assessed for the presence of any coronary disease or for left main coronary artery or three-vessel disease.

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APPENDIX

The following investigators also participated in this study: A.D. Blankholm, Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark; C. Klein, E. Fleck, J. Hug, and A. Bornstedt, German Heart Institute, Berlin, Germany; K.V. Kissinger and L.A. Goepfert, Beth Israel Deaconess Medical Center, Boston; A. Moustapha, M. Pereyra, B. Lambert, J.M. Wilson, and R. Muthupillai, St. Luke's Episcopal Hospital, Houston; M.U. Sivananthan, J.P. Ridgway, T.R. Jones, and T.N. Bloomer, Leeds General Infirmary, Leeds, United Kingdom; A. de Roos, P. Kunz, H. Lamb, J.W. Jukema, and E.E. van der Wall, Leiden University Medical Center, Leiden, the Netherlands; and J. Schwitler, University Hospital, Zurich, Switzerland.

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