Multislice Computed Tomography and Magnetic Resonance Imaging for the Assessment of Reperfused Acute Myocardial Infarction

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OBJECTIVES We evaluated the accuracy of in vivo delayed-enhancement multislice computed tomography (DE-MSCT) and delayed-enhancement magnetic resonance imaging (DE-MRI) for the assessment of myocardial infarct size using postmortem triphenyltetrazolium chloride (TTC) pathology as standard of reference.

BACKGROUND The diagnostic value of DE-MSCT for the assessment of acute reperfused myocardial infarction is currently unclear.

METHODS In 10 domestic pigs (25 to 30 kg), the circumflex coronary artery was balloon-occluded for 2 h followed by reperfusion. After 5 days (3 to 7 days), DE-MRI (1.5-T) was performed 15 min after administration of 0.2 mmol/kg gadolinium-DTPA using an inversion recovery gradient echo technique. On the same day, DE-MSCT (64-slice) was performed 15 min after administration of 1 gI/kg of iodinated contrast material. One day after imaging, hearts were excised, sectioned in 8 mm short-axis slices, and stained with TTC. Infarct size was defined as the hyperenhanced area on DE-MSCT and DE-MRI images and the TTC-negative area on TTC pathology slices. Infarct size was expressed as percentage of total slice area.

RESULTS Infarct size determined by DE-MSCT and DE-MRI showed a good correlation with infarct size assessed with TTC pathology (R² = 0.96 [p < 0.001] and R² = 0.93 [p < 0.001], respectively). The correlation between DE-MSCT and DE-MRI was also good (R² = 0.96; p < 0.001). The relative difference in CT attenuation value of infarcted myocardium compared to remote myocardium was 19±18%. The relative MR signal intensity between infarcted myocardium and remote myocardium was 55±156%.

CONCLUSIONS We demonstrated that DE-MSCT can assess acute reperfused myocardial infarction in good agreement with in vivo DE-MRI and TTC pathology. (J Am Coll Cardiol 2006;48:144–52) © 2006 by the American College of Cardiology Foundation

Acute myocardial infarct size is a predictor of long-term left ventricular function and geometry and clinical outcome in patients who have suffered acute myocardial infarction (1,2). Delayed-enhancement magnetic resonance imaging (DE-MRI) is a well established noninvasive imaging modality that allows assessment of myocardial infarct size (3–5). In recent years, multislice computed tomography (MSCT) technology has made great strides, and noninvasive assessment of coronary artery stenosis is now feasible with high diagnostic accuracy using a 64-slice scanner (6,7). Delayed-enhancement multislice computed tomography (DE-MSCT) has been proposed as an alternative noninvasive imaging modality for the detection of myocardial infarction. However, different imaging protocols have been proposed at different time points after myocardial infarction, and the diagnostic accuracy is currently unclear (8–11). We performed DE-MSCT and DE-MRI in a porcine model of reperfused acute myocardial infarction at a mean of five days after infarction. We evaluated the accuracy of in vivo DE-MSCT and DE-MRI for the assessment of acute reperfused myocardial infarct size and used postmortem viability staining with triphenyltetrazolium chloride (TTC) as standard of reference.

METHODS

Animal model. Fourteen Yorkshire-landrace pigs (2 to 3 months old, 25 to 30 kg) were sedated (ketamine 20 mg/kg intramuscular and midazolam 1 mg/kg intramuscular), anesthetized (thiopental, 12 mg/kg intravenously), intubated, and mechanically ventilated (mixture of oxygen and nitrogen 1:2). Anesthesia was maintained with fentanyl (12.5 μg/kg/h). All pigs then received a sheath in a carotid artery to allow coronary X-ray angiography. Under fluoroscopy guidance, balloon occlusion of the left circumflex coronary artery was performed. In 2 pigs, the balloon was deflated after 15 min of occlusion to produce severely ischemic but reversible injured (stunned) myocardium. In 12 pigs, the balloon was deflated after 2 h of occlusion to allow reperfusion of the infarcted area. Reperfusion was proven by coronary angiography. Of the animals who underwent 2 h...
of occlusion, one pig died after 1 day and one pig died after 3 days after balloon occlusion. The study complied with the regulations of the animal care committee of our hospital and the National Institutes of Health publication “Guide for the Care and Use of Laboratory Animals” (1996).

All pigs were anesthetized as described above before imaging. First, DE-MRI was performed, and 93 ± 23 min later DE-MSCT imaging. The two pigs that underwent 15 min of balloon occlusion underwent imaging at 3 and 4 days, respectively, after induction of ischemia. Of the 10 remaining pigs that underwent the 2-h occlusion protocol, 2 pigs were imaged at 3 days, 6 at 5 days, and 2 at 7 days after reperfusion. One day after the DE-MSCT and DE-MRI imaging session, all animals were euthanized and their hearts excised. The ex vivo hearts were stiffened using alginate impression material (Cavax Holland, Haarlem, the Netherlands). The myocardium of the left ventricle was then sectioned in 8 mm consecutive slices in short-axis view perpendicular to the long axis of the left ventricle using a commercially available meatslicer. To obtain a viability staining, the slices were embedded in a solution of 1% triphenyltetrazolium chloride (TTC) and 0.2 mol/l Sorensen’s buffer (pH 7.4) at 37°C for 15 min, followed by fixation in 4% formalin. Slices that showed a TTC-negative area were photographed digitally after 24 h of exposure to formalin. Exposure to formalin allows delineation between necrotic but hemorrhagic myocardium (which has a red appearance due to the presence of blood) and viable tissue (which stains red owing to the conversion of TTC to the bright red formazan stain). By exposing the TTC-stained tissue to formalin, the hemorrhagic necrotic areas acquire a dark brown color, whereas the red formazan precipitate remains bright red (Fig. 1). Unfortunately, a limitation of this approach was the asymmetric shrinkage (causing the slices to bend) in 9 out of a total of 67 slices (in 10 animals), hampering the accurate assessment of infarct size in these slices, which were excluded from analysis for this reason.

**DE-MSCT.** A 64-slice clinical CT scanner was used for imaging (Sensation 64; Siemens, Forchheim, Germany) with the following characteristics: number of detector rows 32 × 2 (oversampling in the z-axis obtained with flying focal spot [12]); individual detector width 0.6 mm; gantry rotation time 330 ms; effective temporal resolution 165 ms. The delayed-enhancement protocol was performed 15 min after administration of 1 gI/kg of iodinated contrast agent through an ear vein at an injection speed of 1.5 ml/s (400 mgI/ml Iomeprol; Iomeron, Bracco, Italy). The following scan parameters were used: tube voltage 120 kV; tube current 900 mA; table feed per rotation 3.84 mm; scan direction craniocaudal and retrospective electrocardiographic gating. Voxel size at acquisition was 0.3 × 0.3 × 0.4 mm. The estimated radiation dose if applied in humans was calculated with dedicated software as 15/21 mSv for male/female (WinDose; Institute of Medical Physics, Erlangen, Germany). Mean heart rate decreased to 51 ± 9 beats/min after administration of zatebradine (10 mg/kg intravenously). An instrumented breath hold was applied to minimize the influence of respiratory motion on data collection. The DE-MSCT datasets were reconstructed at −300 ms, −350 ms, and −400 ms before the next R-wave (end-diastolic phase of the cardiac cycle). From the dataset with optimal image quality, axial slices with a slice thickness of 1 mm and an increment of 0.5 mm were reconstructed using a field of view of 150 × 150 mm, a 512² reconstruction matrix, and a medium smooth convolution filter (B30f). The MSCT short-axis slices with a slice thickness of 1 mm were then reconstructed perpendicular to the long axis of a double-oblique true four-chamber view using a dedicated software platform with multiplanar capabilities (Leonardo; Siemens).

**DE-MRI.** A clinical 1.5-T MRI scanner with a dedicated cardiac four-element phased-array receiver coil was used for imaging (Signa CV/i; GE Medical Systems, Milwaukee, Wisconsin). Repeated instrumented breath-holds and gating to the electrocardiogram were applied to minimize the influence of cardiac and respiratory motion on data collection. No medication was administered to control heart rate. Cine-MRI was performed with a steady-state free-precession technique (Fiesta; Medical Systems) with the following imaging parameters: 24 temporal phases per slice, voxel size 1.8 × 1.5 × 8 mm; repetition time 3.4 ms; time to echo 1.4 ms; flip angle 45° bandwidth 83 kHz; number of averages 0.75. To cover the entire left ventricle, six to eight consecutive slices of 8 mm were planned in short-axis view perpendicular to the long axis of a double-oblique true four-chamber view.

Myocardial distribution of delayed enhancement was studied 15 min after administration of Gadolinium-DTPA (0.2 mmol/kg; Magnevist, Schering, Germany). A two-dimensional T1-weighted inversion-recovery segmented fast gradient-echo sequence with the following imaging parameters was used: voxel size 1.1 × 1.5 × 8 mm; repetition time 7.3 ms; time to echo 1.6 ms; flip angle 20°; inversion pulse 180°; number of averages 1; bandwidth 17.9 kHz; inversion time 180 to 300 ms; data acquisition every second R-R interval. The trigger delay was adjusted per pig to acquire data in mid- to end-diastole, and the inversion time was adjusted per pig to null the signal of remote myocardium. Slice locations for delayed-enhancement imaging were copied from slice locations of short-axis cine-imaging.

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Figure 1. Acute reperfused myocardial infarction can be assessed accurately with delayed-enhancement multislice computed tomography (DE-MSCT) and delayed-enhancement magnetic resonance imaging (DE-MRI) compared with postmortem triphenyltetrazolium chloride (TTC) pathology. The left ventricle is shown from base (Slice 1) to apex (Slice 6). The MSCT images represent 1-mm slices compared with the photographed TTC pathology slices and the MRI slices of 8 mm.
Data analysis. The DE-MSCT, DE-MRI, and TTC pathology images were coregistered using anatomical landmarks like the insertion of the right ventricle to the septum and the presence of papillary muscles. Infarct size per slice was calculated by dividing the infarcted area by the total slice area of left ventricular myocardium. The digitalized TTC pathology slices were loaded in a separate workstation with a commercially available analysis package (SigmaScan Pro 5.0). The TTC negative area (including the dark-brown subendocardial area) was considered to be the infarcted area and was segmented manually. Reconstructed DE-MSCT images and DE-MRI images were exported and transferred to a separate workstation with dedicated software (Cine Tool 3.4; GE Medical Systems). Image quality was evaluated on a per-slice basis and classified as good (defined as the absence of any image-degrading artifacts related to motion or miss-triggering), adequate (presence of image-degrading artifacts but evaluation possible), or poor (presence of image-degrading artifacts but evaluation possible with moderate confidence). The region with delayed hyperenhancement was segmented manually by two different observers (T.B. and A.M.) blinded to the results of the other imaging modality and TTC pathology. Regional wall thickening was assessed on cine-MRI images at the core of the infarction and in remote noninfarcted myocardium of the septum using dedicated software based on the centerline method (CAAS MRV 2.1, Pie Medical Imaging, Maastricht, the Netherlands). CT attenuation values (expressed in Hounsfield Units [HU]) were measured using the scanner software by drawing three 10-mm² regions of interest in delayed enhanced myocardium, remote myocardium and the left ventricular cavity in a short axis slice located at the center of the infarction of each pig (11). Noise was considered to be the standard deviation of the CT value in a region of interest of 25 mm² placed in the descending thoracic aorta. The MRI signal intensity values (expressed in arbitrary units [AU]) were measured using the scanner software by drawing 30 mm² regions of interest in delayed enhanced and remote myocardium (13). Signal intensity of the left ventricular blood pool was measured by drawing a >100 mm² region of interest in the left ventricular cavity. Noise was considered to be the standard deviation of the signal measured in a region of interest >300 mm² placed in the imaged air outside of the pig.

Statistical analysis. All data are presented as mean ± standard deviation. The relation between infarct size assessed with DE-MSCT, DE-MRI, and TTC pathology was evaluated with univariate linear regression analysis. Agreement between DE-MSCT, DE-MRI, and TTC pathology for the assessment of infarct size and intra- and interobserver variability was determined with Bland-Altman analysis. Differences in regional wall thickening were tested with an unpaired t test. Differences in CT attenuation values and MR signal intensity values between infarcted myocardium, remote myocardium, and left ventricular blood pool were tested with one-way analysis of variance followed by post hoc Bonferroni correction to adjust for multiple comparisons.

RESULTS

The two pigs that underwent 15 min of balloon occlusion of the circumflex coronary artery showed hypokinesia of the lateral wall on echocardiography performed 20 min after reperfusion, indicating the presence of stunned myocardium. The DE-MSCT and DE-MRI imaging demonstrated no regions with delayed enhancement. The TTC staining confirmed that there was no infarcted myocardium.
Figure 3. (A) The relation between infarct size assessed with DE-MSCT, DE-MRI, and postmortem TTC pathology. (B) Bland-Altman analyses show the excellent agreement between infarct size assessed with DE-MSCT, DE-MRI, and postmortem TTC pathology. Abbreviations as in Fig. 1.
In 10 pigs that underwent 2-h balloon occlusion of the circumflex coronary artery, acute reperfused myocardial infarction was accurately detected by both DE-MSCT and DE-MRI (Figs. 1 and 2). The DE-MSCT image quality was classified as good in 83% (48 of 58), moderate in 10% (6 of 58), and poor in 7% (4 of 58) of slices. The DE-MR image quality was classified as good in 75% (43 of 58), moderate in 17% (10 of 58), and poor in 8% (5 of 58) of slices. No delayed enhancement was seen in myocardium outside the perfusion territory of the circumflex coronary artery. Mean infarct size was 21 ± 15% on DE-MSCT images, 22 ± 16% on DE-MR images, and 20 ± 15% on TTC pathology images. Infarct size assessed with DE-MSCT correlated well with infarct size measured on TTC pathology slices (R^2 = 0.96; p < 0.001). Also, infarct size assessed with DE-MRI correlated well with infarct size measured on TTC pathology slices (R^2 = 0.93; p < 0.001). Accordingly, infarct size assessed with DE-MSCT correlated well with infarct size assessed with DE-MRI (R^2 = 0.96; p < 0.001) (Fig. 3A). Bland-Altman analyses demonstrated a good agreement for the assessment of infarct size between DE-MSCT, DE-MRI, and TTC pathology (Fig. 3B). The intraobserver variability for the assessment of infarct size was 1.0 ± 3.9% for DE-MSCT and 0.5 ± 4.6% for DE-MRI. The interobserver variability for the assessment of infarct size was 2.1 ± 5.6% for DE-MSCT and 3.0 ± 5.9% for DE-MRI. Regional wall thickening was significantly decreased in infarcted myocardium of the lateral wall compared with remote noninfarcted myocardium of the septum (0 ± 14% vs. 50 ± 14%; p < 0.001) (Fig. 4).

Mean CT attenuation value of delayed-enhanced myocardium was significantly different from CT attenuation value of remote myocardium (126 ± 20 HU vs. 66 ± 6 HU; p < 0.001; three pair-wise comparisons) (Fig. 5). The relative difference in CT attenuation value between delayed-enhanced and remote myocardium was 191 ± 18%. Noise measured in the descending aorta was 17 ± 3 HU. Mean MR signal intensity value of delayed-enhanced myocardium was significantly higher than MR signal intensity of remote myocardium (154 ± 37 AU vs. 28 ± 6 AU; p < 0.001; three pairwise comparisons) (Fig. 5). Relative MR signal intensity value of delayed-enhanced myocardium compared with remote myocardium was 554 ± 156%. Noise measured in the air outside the pig was 6 ± 1 AU.

**DISCUSSION**

Our results demonstrate that DE-MSCT can assess acute reperfused myocardial infarction in good agreement with in vivo DE-MRI and postmortem TTC pathology. **Delayed-enhancement imaging.** Delayed-enhancement imaging is feasible with MSCT and MRI because both iodinated contrast agents and gadolinium chelates passively diffuse into the increased extracellular matrix of infarcted myocardium (14). Higgins et al. (15) demonstrated elevated concentrations of iodinated contrast material in infarcted tissue compared with uninfarcted tissue if assessed more than 5 min after administration of these contrast materials. Rehwald et al. (16) showed significantly higher concentrations of gadolinium chelates in infarcted myocardium compared with remote myocardium after a delay of 10 min. Because accumulation of contrast agents in necrotic myocardium is a passive process, the timing between adminis-
tration of contrast agents and imaging may be crucial to accurately assess infarct size. Amado et al. (17) performed DE-MRI between 6 and 30 min after administration of gadolinium chelates and observed no difference in measured infarct size. The optimal time delay for performing DE-MSCT after administration of iodinated contrast agents remains to be determined, because no data are available for DE-MSCT in infarctions more than 2 days old. The pharmacokinetic behavior of gadolinium chelates and iodinated contrast agents is relatively similar, but differences in molecule size may influence the rate of diffusion in infarcted myocardium (18).

**DE-MSCT.** Delayed-enhancement CT for the assessment of myocardial infarction was performed as early as the late 1970s, and these initial results were encouraging (19). However, practical use of this technique was hampered by insufficient image quality mainly caused by cardiac motion. Computerized tomography technology has developed rapidly during the last decade, and with the introduction of spiral and later multislice spiral CT a marked increase in temporal and spatial resolution was obtained. Three recent experimental studies demonstrated the excellent diagnostic accuracy of 4-, 16-, and 32-slice CT for the assessment of nonreperfused and reperfused myocardial infarction if performed within 5 h after induction of infarction (10,11,20). However, infarct morphology may change after myocardial infarction with early infarct expansion (<2 days) and late infarct shrinkage (>10 days) (5,21), and the ability of

![Figure 6](image-url)

**Figure 6.** DE-MSCT provides higher spatial resolution than DE-MRI. Image A represents an 8-mm-thick DE-MRI image, and image B represents the similar slice reconstructed from eight different 1-mm-thick DE-MSCT images. Images on the right represent the eight reconstructed 1-mm-thick slices that together form image B. Abbreviations as in Fig. 1.
DE-MSCT to assess infarctions more than 5 h old is currently unknown. To assess infarct size between 2 and 7 days after infarction is clinically relevant, because infarct size predicts long-term left ventricular remodeling and clinical outcome (1,22–24). In the present study, we demonstrated that DE 64-slice CT can assess infarct size between 2 and 7 days after infarction and can differentiate between necrotic myocardium and stunned myocardium with good correlation with in vivo DE-MRI and ex vivo TTC pathology. More studies are needed to demonstrate if DE-MSCT can also show myocardial infarction or scar at a longer time of follow-up after myocardial infarction.

An advantage of MSCT is that it offers high spatial resolution, allowing reconstruction of thin slices and thereby reducing possible partial volume artifacts. High-resolution DE-MSCT imaging also allowed the transmural differentiation of viable and nonviable myocardium. A major disadvantage of MSCT is the limited soft tissue contrast that is obtained. Tissue contrast is related to the radiation dose that is applied and the amount of iodinated contrast material administered. For DE-MSCT imaging, we used the radiation dose that is used for MSCT coronary angiography (15/21 mSv for men/women). We administered 1 gI/kg iodine contrast to the pigs, equivalent to approximately 200 ml iodine contrast to a patient of 70 kg, which is considered a normal dose of contrast during a conventional angiography procedure (25). Technical developments are desirable that reduce radiation exposure and limit the amount of iodinated contrast material needed. Recent developments include tube-current modulation which reduces radiation exposure by nearly one-half by applying radiation only in the mid- to end-diastolic phase of the cardiac cycle (26).

DE-MRI. Delayed-enhancement MRI is an established noninvasive imaging modality that can assess reperfused and nonreperfused myocardial infarction (4). It is safe and patient friendly and can be repeated multiple times to evaluate therapy without causing harm to the patient. No heart rate control is necessary. Excellent soft tissue contrast is obtained with gadolinium chelates that have T1 shortening characteristics. Further improvement in tissue contrast is obtained by applying a nonselective inversion pulse before data acquisition, allowing suppression of signal of remote myocardium (27). We observed a relative signal intensity between hyperenhanced and remote myocardium of 554 ± 156%. A disadvantage of MRI is the limited through-plane resolution, resulting in a slice thickness of 4 to 8 mm (Fig. 6). In the present study, differences in infarct size between postmortem TTC pathology, DE-MSCT, and DE-MRI may have been caused by dissimilarity in slice thickness offered by these different modalities. The DE-MSCT allowed reconstruction of a slice thickness of 1 mm, whereas DE-MRI was performed with a slice thickness of 8 mm, and TTC pathology, the standard of reference, was analyzed on a two-dimensional digital photograph. The accuracy and reproducibility of infarct size measurements with DE-MSCT and DE-MRI may further improve by using a semiautomated quantification software (17).

Conclusions. Delayed-enhancement MRI is a well-established noninvasive imaging modality that allows assessment of myocardial infarct size and has been shown to provide prognostic information in patients who have suffered acute myocardial infarction. We demonstrated that DE-MSCT can assess acute reperfused myocardial infarction in good agreement with in vivo DE-MRI and postmortem TTC pathology. Ongoing technical improvements of the CT scanner have resulted in high diagnostic performance to detect significant coronary stenosis in selected groups of patients without arrhythmia and a heart rate below 70 beats/min (6,7). Together with the assessment of infarct size, this new CT technology may emerge as a clinically valuable tool to comprehensively evaluate post-infarction patients.

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