筑　波　大　学

博 士 （医 学） 学 位 論 文

Enhancement Patterns Detected by Multidetector Computed Tomography Are Associated with Microvascular Obstruction and Left Ventricular Remodeling in Patients with Acute Myocardial Infarction

（MDCT における遅延造影所見は急性心筋梗塞患者の

微小循環障害や左室リモデリングと関連している）

２０１５

筑波大学大学院博士課程人間総合科学研究科

渡部浩明

ABSTRACT

Aim: This study evaluated the clinical value of myocardial contrast delayed enhancement (DE) with multidetector computed tomography (MDCT) for detecting microvascular obstruction (MVO) and left ventricular (LV) remodeling revealed by DE magnetic resonance imaging (DE-MRI) after acute myocardial infarction (AMI).

Methods and Results: In 92 patients with first AMI, MDCT without iodine reinjection was performed immediately following successful percutaneous coronary intervention (PCI). DE-MRI performed in the acute and chronic phases was used to detect MVO and LV remodeling (any increase in LV end-systolic volume at 6 months after infarction compared with baseline). Patients were divided into 2 groups according to the presence (n=33) or absence (n=59) of heterogeneous enhancement. Heterogeneous enhancement was defined as concomitant presence of hyper- and hypoenhancement within the infarcted myocardium on MDCT. MVO and LV remodeling were detected in 49 (53%) and 29 (32%) patients, respectively. In a multivariate analysis, heterogeneous enhancement and a relative CT density >2.20 were significant independent predictors for MVO (odds ratio [OR] 13.5; 95% confidence interval [CI], 2.15-84.9; P=0.005 and OR 12.0; 95% CI, 2.94-49.2; P<0.001, respectively). The presence of heterogeneous enhancement and relative CT density >2.20 showed a high PPV of 93%, and absence of these two findings yielded a high NPV of 90% for the predictive value of MVO. Heterogeneous enhancement was significantly associated

with LV remodeling (OR 3.97; 95% CI, 1.26-12.60; *P*=0.019).

Conclusions: Heterogeneous enhancement detected by MDCT immediately after primary PCI may provide promising information for predicting MVO and LV remodeling in patients with AMI.

Introduction

Primary percutaneous coronary intervention (PCI) has improved the prognosis of patients with acute myocardial infarction (AMI).[1,2] However, despite successful recanalization of the culprit vessel, left ventricular (LV) remodeling occurs in an appreciable proportion of patients with AMI.[3] LV remodeling following AMI is a major predictor of morbidity and mortality for overt congestive heart failure and life-threatening arrhythmias.[4] LV remodeling is predicted by the extent of transmurality and infarct size after AMI.[5] Late gadolinium-enhanced cardiac magnetic resonance imaging (MRI) is the current clinical standard for the assessment of LV infarct size,[6] microvascular obstruction (MVO),[7] and the prediction of functional recovery.[8]

Myocardial delayed enhancement (DE) on multidetector computed tomography (MDCT) enables the accurate evaluation of infarct size[9] and has comparable results as an alternative technique to MRI in AMI.[10,11] Myocardial DE on MDCT allows the early evaluation of myocardial viability immediately after PCI without additional injection of contrast agent.[12] In our previous study, we showed that contrast DE patterns might be reliably useful in predicting functional recovery of the post-ischemic myocardium and LV remodeling,[13] and myocardial contrast DE size might be a very early predictive marker for future clinical cardiac events in patients with AMI.[14] Recently, Amanieu et al. reported that the presence of a hypoenhanced area had high specificity for the prediction of MVO.[15] MVO, which is an

area of hypoenhancement surrounding hyperenhancement detected by DE-MRI, corresponds to the production of no-reflow regions and reflects myocardial microvascular dysfunction.[16] Furthermore, the extent of MVO has been shown to determine the magnitude of myocardial damage, and it provides an incremental prognostic marker of functional recovery and prognosis beyond that of infarct size.[5,7,17] Therefore, we hypothesized that the presence of hypoenhanced areas detected on DE-MDCT in AMI patients may have a similar potential to predict LV remodeling. The aim of this study was to evaluate the clinical value of myocardial contrast DE with MDCT for detecting MVO and LV remodeling revealed by DE-MRI after AMI.

Methods

Study Population

Between June 2012 and March 2014, 98 consecutive patients with first AMI were initially assessed for inclusion into the study. The inclusion criteria for AMI patients were as follows: 1) chest pain >30 min in duration with presentation within 24 h after onset of symptoms; 2) ST-segment elevation >0.1 mV within 2 contiguous electrocardiograph leads; and 3) elevated creatine kinase-myocardial band (CK-MB) isoenzymes within 24 h of chest pain. Exclusion criteria were a history of previous MI, cardiogenic shock, or renal insufficiency (creatinine >1.5 mg/dl). Cardiac rupture caused the death of one patient, re-infarction occurred in one

patient due to acute stent thrombosis, cerebrovascular disorder occurred during follow-up in two patients, and two patients refused to give their informed consent. Thus, the remaining 92 patients (77 men and 15 women; mean age, 63±12 years) represent the study population. All patients underwent 64-slice MDCT without administration of additional contrast media immediately following successful PCI. The study protocol was approved by our institutional review board, and all the patients enrolled gave their informed consent.

Sixty-Four-Slice Multidetector Computed Tomography Scanning Procedure

Scanning was performed using prospective ECG triggering with a 64×0.625 mm slice collimation CT scanner (LightSpeed VCT, GE Healthcare, Milwaukee, WI) with a gantry rotation speed of 350 ms/rotation. Scanning was performed using a tube energy of 120 kV and effective tube current of 200 mA at a table feed of 20 mm/gantry rotation with beam pitch of 0.2 and a radiation dose of 2.0 ± 1.0 mSv. Acquisition of CT data and an ECG trace were automatically started during a 9- to 12-second breath-hold. Effective radiation doses were estimated by multiplying the dose-length product reported by the scanner by a conversion factor of 0.014mSv/mGy・cm according to standard methodology outlined in the recent guidelines.[18]

Reconstruction and Analysis of 64-Slice MDCT Images

Analysis of the scans was performed on a ZIOSTATION workstation (ZIOSOFT Inc., Tokyo, Japan). The original axial CT images and multiplanar reformations were used for analysis of the myocardium. The images used for interpretation and for quantitative analysis were reconstructed at a slice thickness of 2 mm. Extent of hyperenhancement was judged as transmural if ≥75% of the LV wall thickness in each segment of the axial, short-axis, and long-axis multiplanar images was visually involved and as subendocardial if <75%. Infarct area was defined as a hyperenhancement with signal intensity (SI) greater than 2 standard deviations (SD) above the mean SI of remote normal myocardium[19] and was adjusted by manual tracing of the suspected area in 3 dimensions. Infarct size was calculated on the basis of graphics displayed by SI histogram thresholding using a step-based algorithm to detect voxels within the defined SI range in the 3 dimensions and to define clusters of voxels that meet the hyperenhancement definition. Using this method, the dedicated software determined the mean SI of the hyperenhancement in Hounsfield units (HU) and calculated total myocardial contrast DE size in grams. We defined heterogeneous enhancement (HE) as the concomitant presence of hyper- and hypoenhancement areas within the infarcted myocardium. We included both the hypoenhanced area surrounded by the hyperenhanced layer, which is a typical finding of MVO on DE-MRI (Figure 1A) and patchy enhancement areas with hyper- and hypoenhancement segments (Figure 1B) in heterogeneous enhancement. Figure 1C showed no heterogeneous enhancement. The CT density values of the contrast-enhanced

myocardium and non-enhanced myocardium in the remote area were measured from at least 3 regions of interest (ROI) with the dimension of myocardial thickness (Figure 2). Then, to normalize the CT values, the relative CT density was calculated as the rate of average density of contrast-enhanced myocardium to that of non-enhanced myocardium.[15]

MRI Protocol

DE-MRI was performed in the acute phase (median 6 days after AMI onset) and chronic phase (median 198 days [median 6 months] after onset). All MRI studies were performed with the patient in the supine position in a 1.5-T clinical scanner (MAGNETOM Avanto, Siemens, Erlangen, Germany) using a dedicated six-element phase-array cardiac coil. The ECG-gated images were acquired during repeated breath-holds of varying duration depending on the heart rate. Cine images were obtained using steady-state free-precession cine MRI in the two-chamber, four-chamber, and short-axis views. In the cardiac short-axis direction, the LV was completely encompassed by contiguous 8-mm-thick slices with a 2-mm interslice gap. Next, T2-weighted MRI was performed in the cardiac short-axis direction using a dark-blood T2-weighted short-tau inversion-recovery (STIR) fast-spin echo sequence. Finally, 5 to 10 minutes after injection of 0.2 mmol/kg gadopentetate dimeglumine (Gd-DTPA; Magnevist, Bayer, Berlin, Germany), delayed contrast-enhanced images were acquired in the same orientation as the cine images using a segmented inversion-recovery gradient-echo pulse

sequence.

MRI Analysis

Analysis of the scans was performed using Argus viewing software (Siemens). End-diastolic volume, end-systolic volume, ejection fraction (EF), and myocardial mass were obtained from short-axis cine-MR images. Late gadolinium-enhancement images were assessed both for infarct area and MVO area. T2-weighted STIR images were used to determine the presence of myocardial hemorrhage in the ischemic myocardium. Infarct area was defined on late contrast images as a hyperintense area. Areas of hyperenhancement were defined as myocardium with a signal intensity greater than 2 SD above the mean signal intensity of remote normal myocardium.[19] MVO was defined as a late hypoenhancement signal within the myocardial wall surrounded by a hyperenhanced region. Myocardial hemorrhage was defined as a hypointense area in the center of the infarct area on T2-weighted images.[20] The MDCT and MRI images were analyzed by two independent observers to calculate inter- and intra-observer agreements.

Coronary Angiography and PCI Procedure

Experienced interventional cardiologists performed coronary angiography (CAG) through the radial or femoral approach with 6-7F catheters. The culprit coronary artery was defined on

the basis of ECG and CAG results. All patients underwent PCI with both aspirin and a loading dose of 300 mg clopidogrel. A glycoprotein IIb/IIIa receptor inhibitor is not yet available in Japan, so no patient received this drug.

Before the start of the procedure, 6000-10000 units of heparin were given intravenously, and the activated clotting time was maintained at >300 sec. The contrast agent used was iopamidol 370 mg I/ml (Schering AG, Berlin, Germany). Post-procedural optimal coronary flow was defined as a TIMI flow grade of ≥3, and incomplete reperfusion or lack of procedural success was defined as a TIMI flow grade of 0 to 2.[21] Time to reperfusion was defined as the period from time of onset of symptoms to time of reperfusion. Total contrast volume and time from last coronary injection to initiation of the CT scan were also measured.

Study Endpoints

Study endpoints were defined as the incidence of MVO detected by MRI and the occurrence of LV remodeling. LV remodeling was defined as any increase in LV end-systolic volume (LVESV) at chronic phase after infarction compared with baseline.[20] Study endpoints were blinded to the findings of CT imaging.

Cardiac events were defined as cardiac death, hospitalization for worsening heart failure, or sustained ventricular tachycardia / ventricular fibrillation. After hospital discharge, all patients were followed up every month at our outpatient clinic of our hospital up to the 6

months. Cardiac events were documented by clinical visits, standardized follow-up phone calls to the patients or their families, and followed by a review of medical records, electrocardiogram, and cardiac enzyme data. To establish the diagnosis of cardiac events, an outcome panel of 2 experienced cardiologists reviewed patient data forms containing prospectively collected information as well as medical records pertaining to the hospital admission.

Statistical Analysis

All data are expressed as the mean ± SD or median and interquartile range for non-normally distributed data. Comparisons of continuous variables were analyzed by unpaired *t*-test or Mann-Whitney U test according to the data distribution. Comparisons of categorical variables between groups were performed by the chi-square test without correction for multiplicity. Inter- and intraobserver agreements were performed by intraclass correlation coefficients for continuous variables and kappa (κ) test for categorical variables. Receiver-operating characteristic (ROC) analysis was used to determine optimal cutoff values of relative CT density for prediction of MVO. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and diagnostic accuracy of the CT characteristics alone or in combination were calculated for prediction of MVO. We performed comparison

between 2 groups about various parameters in MVO and LV remodeling respectively, and we used the significantly different parameters for the univariable analysis. Multivariable logistic regression analysis was then developed to calculate odds ratios and 95% confidence intervals. We assessed collinearity for multivariable models by Peason's correlation and excluded the parameters which had collinearity. We performed stepwise forward selection considering any valuables with values of $P<0.05$ to identify potential risk factors for MVO and LV remodeling. A P value of <0.05 was considered to indicate statistical significance.

Results

Patient, Lesion, and Procedural Characteristics

MVO was detected in 49 (53%) patients and LV remodeling was detected in 29 (32%) patients. Patients were divided into 2 groups according to the presence (n=33) or absence (n=59) of heterogeneous enhancement detected by MDCT. The median time delay between last injection of contrast medium and MDCT scanning was 17±8 min (range 5 to 34 min). During the 6-months follow-up periods, 3 cardiac events (1 rehospitalization for worsening heart failure and 2 sustained ventricular tachycardia / ventricular fibrillation) were observed in HE group, but none in non HE group (P=0.042). Baseline patient characteristics, procedural characteristics, and medications are summarized in Table 1. There were no statistically significant differences in sex, coronary risk factors, onset to reperfusion time,

stent size, stent length, contrast volume, culprit lesion, and TIMI flow between the two groups, whereas age was higher in the non HE group. Peak level of CK and its MB fraction and BNP level at 7 days were higher in the group with heterogeneous enhancement. Killip class 2 or greater heart failure and beta-blocker therapy were more commonly observed in the HE group.

MDCT and MRI Measurements

Representative images from the groups of patients with and without HE are presented in Figures 3 and 4. The intra- and inter-observer intraclass correlation coefficients for relative CT density were 0.90 (95% CI 0.81-0.95) and 0.89 (95% CI 0.78-0.94), infarct size on MDCT were 0.93 (95% CI 0.85-0.96) and 0.94 (95% CI 0.88-0.97), ESV in the acute phase were 0.99 (95% CI 0.98-0.99, P<0.001) and 0.97 (95% CI 0.85-0.99), and ESV in the chronic phase on MRI were 0.99 (95% CI 0.94-0.99) and 0.99 (95% CI 0.96-0.99), respectively, and inter- and intra-observer agreement (κ) for the interpretation of the presence of heterogeneous enhancement was 0.91 and 0.81, respectively, and the with all values indicating good intra- and inter-observer agreement. CT and MRI findings are summarized in Table 2. The CT value of the DE area, relative CT density, transmural enhancement, and myocardial contrast DE size were significantly higher in the patients with HE pattern than in those without this pattern. On MRI, LVEF was lower, and end-diastolic and end-systolic volumes were

significantly larger, in the heterogeneous group. These differences were consistently significant in both the acute and chronic phases. The incidences of MVO, myocardial hemorrhage, and LV remodeling were significantly more frequent in the heterogeneous group.

Predictors of MVO

According to the ROC analysis, the area under the curve of relative CT density for predicting the presence of MVO was 0.889 (95% CI 0.825-0.968). When the cutoff value of 2.20 was applied, sensitivity was 86 (95% CI 72.1-94.7)% and specificity was 82 (95% CI 65.7-89.8)%. According to the univariable analysis (Table 3), EF <40%, peak CK >4000 IU/ml, the presence of heterogeneous enhancement,relative CT density >2.20 and transmural enhancement were significantly associated with the presence of MVO. In the multivariable logistic regression analysis, the presence of heterogeneous enhancement, relative CT density >2.20 and transmural enhancement were significant predictors for the presence of MVO after adjustment for multiple confounders. With regard to diagnostic accuracy of CT characteristics for predicting MVO, presence of heterogeneous enhancement and relative CT density >2.20 showed a high PPV of 93 (95%CI 75.7-99.1) % and absence of these two findings yielded a high NPV of 90 (95% CI 76.9-97.3) % for the predictive value of MVO.

Predictors of LV Remodeling

According to the univariable analysis, the presence of heterogeneous enhancement and peak CK >4000 and relative CT density were were significantly associated with the occurrence of LV remodeling. In the multivariable logistic regression analysis, the presence of heterogeneous enhancement was the only significant independent predictor for the occurrence of LV remodeling after adjustment for multiple confounders (Table 4).

Discussion

The major important findings of the study are as follows. First, the presence of heterogeneous enhancement and high relative CT density were significant predictors of MVO detected by MRI. For prediction of MVO, the presence of both heterogeneous enhancement and high relative CT density showed a high PPV of 93%, and their absence offered a high NPV of 90% for the detection of MVO. Furthermore, the presence of heterogeneous enhancement was significantly associated with adverse LV remodeling in the chronic phase. Thus, in the setting of traditional prognostic markers, detection of heterogeneous enhancement on MDCT images may provide promising information for prediction of MVO and LV remodeling.

Detection of MVO by MDCT

The presence of MVO after PCI for AMI corresponds to the angiographic no-reflow

phenomenon and is assessed as a hypointense infarct core on late gadolinium enhancement by MRI.[16] We showed that the presence of heterogeneous enhancement and high relative CT density were significant predictors of MVO detected by MRI. A previous report studying DE-CT explained that the hyperenhancement area on MDCT is caused by the penetration of iodine molecules to the myocardial cells caused by sarcolemmal membrane dysfunction after myocyte necrosis, and the hypoenhanced area is caused by the death and subsequent blockage of intramyocardial capillaries by cellular debris.[9] Another study investigating occlusion, microembolization, and reperfusion in an animal model of AMI showed patchy microinfarcts and large infarcts with both hyperenhanced and hypoenhanced areas by MDCT. Histopathologically, these areas showed patchy microinfarcts adjacent to large infarcts and intramyocardial hemorrhage.[22] These reports indicate the possibility that heterogeneous enhancement is associated with distal embolization and myocardial hemorrhage. In fact, the incidence of myocardial hemorrhage was significantly more frequent in the patients with heterogeneous enhancement than in those without heterogeneous enhancement in our study. Besides, these findings are almost consistent with the findings of MVO. Robbers et al. reported that the infarct core of MVO contained extensive necrosis and erythrocyte extravasation without intact vasculature, and the surrounding gadolinium-enhanced area of MVO contained granulation tissue, leucocyte infiltration, and necrosis with morphologically intact microvessels containing microthrombi without erythrocyte extravasation.[23]

The relative CT density was calculated by the average CT values of at least 3 ROIs for infarcted and remote areas. It has components of both intensity and transmurality of the enhancement. As described above, histopathologically, an area of hyperenhancement represents the penetration of iodine molecules into the myocardial cell.[9] Therefore, we consider that a high relative CT density area reflects the magnitude of myocardial damage and might also reflect myocardial hemorrhage. In our study, the patients with MVO and myocardial hemorrhage detected by MRI showed significantly higher relative CT density than those without (2.67±0.70 vs 1.70±0.58, $P<0.001$ and 2.81±0.79 vs 1.92±0.63, $P<0.001$, respectively). Histopathologically, hemorrhage is likely to be present in areas of MVO,[24] and therefore, these finding suggests the possibility that relative CT density is associated with myocardial hemorrhage. in that the presence of a low-density area and high relative CT density is an important marker for predicting MVO.

Relation between Heterogeneous Enhancement and LV Remodeling

Heterogeneous enhancement was significantly associated with adverse LV remodeling in the chronic phase, indicating the clinical usefulness of myocardial contrast DE. The major predictors of adverse LV remodeling in AMI patients are reported to be anterior infarct location, peak CK, perfusion status, LVEF, and infarct size.[3,4] MVO and myocardial hemorrhage are predictors of LV remodeling on MRI.[5,17,20] As explained above,

heterogeneous enhancement is a significant predictor of MVO, and histopathologically, it has the potential to be associated with distal embolization and hemorrhage as with MVO.[9,22] Compared with the patients without heterogeneous enhancement, those with heterogeneous enhancement were associated with higher peak CK, larger infarct size, lower LVEF, greater numbers of transmural pattern, hemorrhage, and MVO. Therefore, it is natural that heterogeneous enhancement should be a predictor of LV remodeling. In addition, previous reports have shown that the presence of MVO and/or myocardial hemorrhage is a stronger independent predictor of LV remodeling or infarct zone contractile recovery than transmural extent of infarction or overall infarct volume.[18,24] The present study similarly showed heterogeneous enhancement to be an independent predictor of LV remodeling than adjusted by transmural extent of infarction or overall infarct volume.

Clinical Implications

Contrast-enhanced MRI is well established for the assessment of myocardial viability without ionizing radiation and injection of nephrotoxic contrast material. However, the facts that MDCT can be performed with a short examination times and that it is generally available and easily performed are considered important advantages in comparison with contrast-enhanced MRI.

MDCT immediately after PCI provides information on transmurality of infarction,

infarct size, and future cardiac events, as does MRI. Furthermore, in this study we showed that heterogeneous enhancement detected by MDCT might provide an early predictive marker for predicting MVO and LV remodeling in patients with AMI. LV remodeling is an important predictor of morbidity and mortality for overt congestive heart failure and life-threatening arrhythmias.[4] Therefore, if heterogeneous enhancement can be detected with MDCT, it would be necessary to plan for prevention of adverse patient outcomes through early treatment interventions and careful follow-up.

Study Limitations

First, because of our relatively small sample size, we acknowledge that our findings should be confirmed in a larger number of patients. Second, as the incidence of MVO was high in this study, an imbalance between cases and samples might occur in analysis of MVO. Third, there is a difference in timing between the DE-MRI and DE-CT examinations. AMI is associated with myocardial edema, and therefore, this might also influence the extent of myocardial contrast DE. A previous study similarly showed that MRI in the very early days after infarction overestimated the true extent of irreversibly injured myocardium because of myocardial edema.[25] Therefore, it is possible that there is a small difference in the extent of DE size and transmurality between DE-MRI and DE-CT. Furthermore, the definition of hyperenhancement was not standardized in DE-CT, and so there were the limitations due to a

global classification. The definition of optimal threshold for infarct area in DE-CT was also not standardized, and therefore standardized analysis using this threshold will further increase reproducibility and facilitate (semi) automated quantification. Fourth, the patients receive additional radiation exposure from the CT scan after primary PCI. However, we make efforts to reduce the radiation exposure by performing low-dose scanning to the extent possible and using prospective ECG triggering methods. In doing so, the radiation exposure of the patients was reduced to 2.0±1.0 mSv. Furthermore, if we can use a high-specification CT system such as a dual-energy scanner or 320-slice MDCT, the better assessment will be provided and the radiation exposure will be reduced even further. Finally, the lack of pathological correlation might leave the mechanism of these phenomena unclear. Therefore, we consider it necessary to investigate the relation between the MDCT images and histopathology and to confirm the correspondence between these imaging characteristics and histopathological findings.

Conclusion

The present study showed that the presence of heterogeneous enhancement on MDCT was significantly associated with MVO and LV remodeling in patients with AMI. We consider that MDCT images acquired immediately after primary PCI may provide promising information for predicting MVO and LV remodeling in patients with AMI.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet. 2003;361:13-20.

2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2014;35:2541-619.

3. Bolognese L. Left ventricular remodeling after primary coronary angioplasty: Patterns of left ventricular dilation and long-term prognostic implications. Circulation. 2002;106:2351-2357

4. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990;81:1161-1172

5. Tarantini G, Razzolini R, Cacciavillani L, Bilato C, Sarais C, Corbetti F, Marra MP, Napodano M, Ramondo A, Iliceto S. Influence of transmurality, infarct size, and severe microvascular obstruction on left ventricular remodeling and function after primary coronary angioplasty. Am J Cardiol. 2006;98:1033-1040

6. Wagner A, Mahrholdt H, Thomson L, Hager S, Meinhardt G, Rehwald W, Parker M,

Shah D, Sechtem U, Kim RJ, Judd RM. Effects of time, dose, and inversion time for acute myocardial infarct size measurements based on magnetic resonance imaging-delayed contrast enhancement. J Am Coll Cardiol. 2006;47:2027-2033

7. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS, Lima JAC. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation. 1998;97:765-772

8. Beek AM, Kühl HP, Bondarenko O, Twisk JWR, Hofman MBM, van Dockum WG, Visser CA, van Rossum AC. Delayed contrast-enhanced magnetic resonance imaging for the prediction of regional functional improvement after acute myocardial infarction. J Am Coll Cardiol. 2003;42:895-901

9. Lardo AC, Cordeiro MA, Silva C, Amado LC, George RT, Saliaris AP, Schuleri KH, Fernandes VR, Zviman M, Nazarian S, Halperin HR, Wu KC, Hare JM, Lima JA. Contrast-enhanced multidetector computed tomography viability imaging after myocardial infarction: Characterization of myocyte death, microvascular obstruction, and chronic scar. Circulation. 2006;113:394-404

10. Gerber BL, Belge B, Legros GJ, Lim P, Poncelet A, Pasquet A, Gisellu G, Coche E, Vanoverschelde JL. Characterization of acute and chronic myocardial infarcts by multidetector computed tomography: Comparison with contrast-enhanced magnetic resonance. Circulation. 2006;113:823-833

11. Baks T, Cademartiri F, Moelker AD, Weustink AC, van Geuns RJ, Mollet NR, Krestin GP, Duncker DJ, de Feyter PJ. Multislice computed tomography and magnetic resonance imaging for the assessment of reperfused acute myocardial infarction. J Am Coll Cardiol. 2006;48:144-152

12. Habis M, Capderou A, Ghostine S, Daoud B, Caussin C, Riou JY, Brenot P, Angel CY, Lancelin B, Paul JF. Acute myocardial infarction early viability assessment by 64-slice computed tomography immediately after coronary angiography: Comparison with low-dose dobutamine echocardiography. J Am Coll Cardiol. 2007;49:1178-1185

13. Sato A, Hiroe M, Nozato T, Hikita H, Ito Y, Ohigashi H, Tamura M, Takahashi A, Isobe M, Aonuma K. Early validation study of 64-slice multidetector computed tomography for the assessment of myocardial viability and the prediction of left ventricular remodelling after acute myocardial infarction. Eur Heart J. 2008;29:490-498

14. Sato A, Nozato T, Hikita H, Akiyama D, Nishina H, Hoshi T, Aihara H, Kakefuda Y, Watabe H, Hiroe M, Aonuma K. Prognostic value of myocardial contrast delayed enhancement with 64-slice multidetector computed tomography after acute myocardial infarction. J Am Coll Cardiol. 2012;59:730-738

15. Amanieu C, Sanchez I, Arion S, Bonnefoy E, Revel D, Douek P, Boussel L. Acute myocardial infarction: Early ct aspects of myocardial microcirculation obstruction after percutaneous coronary intervention. Eur Radiol. 2013;23:2405-2412

16. Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. Circulation. 1996;94:3318-3326

17. Weir RA, Murphy CA, Petrie CJ, Martin TN, Balmain S, Clements S, Steedman T, Wagner GS, Dargie HJ, McMurray JJ. Microvascular obstruction remains a portent of adverse remodeling in optimally treated patients with left ventricular systolic dysfunction after acute myocardial infarction. Circ Cardiovasc Imaging. 2010;3:360-367

18. Larke FJ, Kruger RL, Cagnon CH, Flynn MJ, McNitt-Gray MM, Wu X, Judy PF, Cody DD. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. AJR Am J Roentgenol. 2011;197:1165-9.

19. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100:1992-2002

20. Ganame J, Messalli G, Dymarkowski S, Rademakers FE, Desmet W, Van de Werf F, Bogaert J. Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. Eur Heart J. 2009;30:1440-1449

21. The thrombolysis in myocardial infarction (timi) trial. Phase i findings. Timi study group. N Engl J Med. 1985;312:932-936

22. Saeed M, Hetts SW, Do L, Wilson MW. Assessment of microembolization

associated with revascularization in acute myocardial infarction: Mdct cardiac perfusion and function study. Int J Cardiovasc Imaging. 2013;29:1861-1869

23. Robbers LF, Eerenberg ES, Teunissen PF, Jansen MF, Hollander MR, Horrevoets AJ, Knaapen P, Nijveldt R, Heymans MW, Levi MM, van Rossum AC, Niessen HW, Marcu CB, Beek AM, van Royen N. Magnetic resonance imaging-defined areas of microvascular obstruction after acute myocardial infarction represent microvascular destruction and haemorrhage. Eur Heart J. 2013;34:2346-2353

24. Kidambi A, Mather AN, Motwani M, Swoboda P, Uddin A, Greenwood JP, Plein S. The effect of microvascular obstruction and intramyocardial hemorrhage on contractile recovery in reperfused myocardial infarction: Insights from cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2013;15:58

25. Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Timing of cardiovascular mr imaging after acute myocardial infarction: Effect on estimates of infarct characteristics and prediction of late ventricular remodeling. Radiology. 2011;261:116-126

Figure 1.

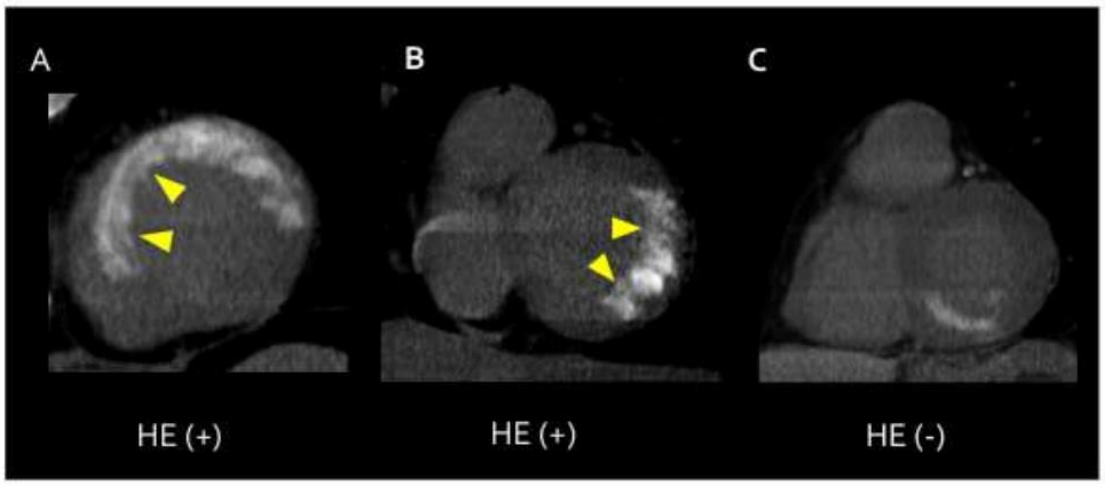

Figure 1. Short-axis DE-CT in 3 patients with acute myocardial infarction. Panels A and B show the presence of HE, and Panel C shows no heterogeneous enhancement. Panel A shows transmural contrast-delayed enhancement in the anterior wall and a hypoenhanced area surrounded by a hyperenhanced layer (arrows), which is a typical finding of microvascular obstruction on DE-MRI. Panel B shows transmural contrast-delayed enhancement in the lateral wall and a patchy enhancement area with hyper- and hypoenhancement segments (arrowheads). Panel C shows subendocardial contrast-delayed enhancement in the inferior wall and no HE. DE-CT indicates delayed-enhancement computed tomography; DE-MRI, delayed-enhancement magnetic resonance imaging; and HE, heterogenous enhancement.

Figure2

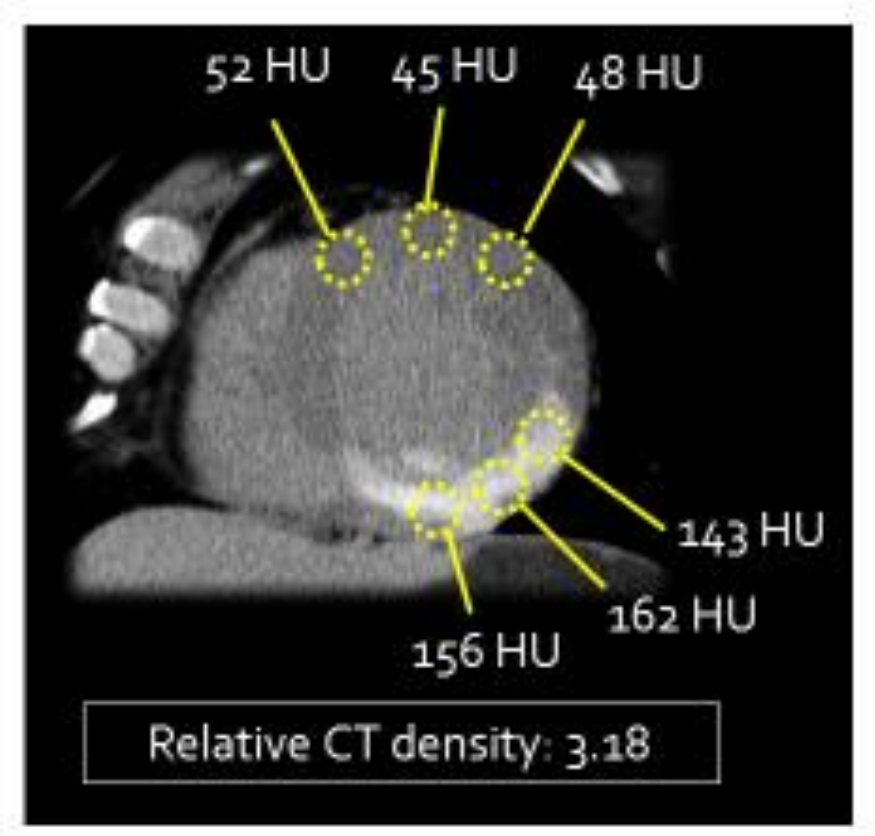

Figure 2. Short-axis DE-CT of a 49-year-old man. The CT density values of the contrast-enhanced myocardium and non-enhanced myocardium were measured from at least 3 ROIs with the dimension of myocardial thickness. To normalize the CT values, the relative CT density was calculated as the rate of average density of contrast-enhanced myocardium to that of non-enhanced myocardium. In this image, the relative CT density was calculated to be 3.18.

Figure 3

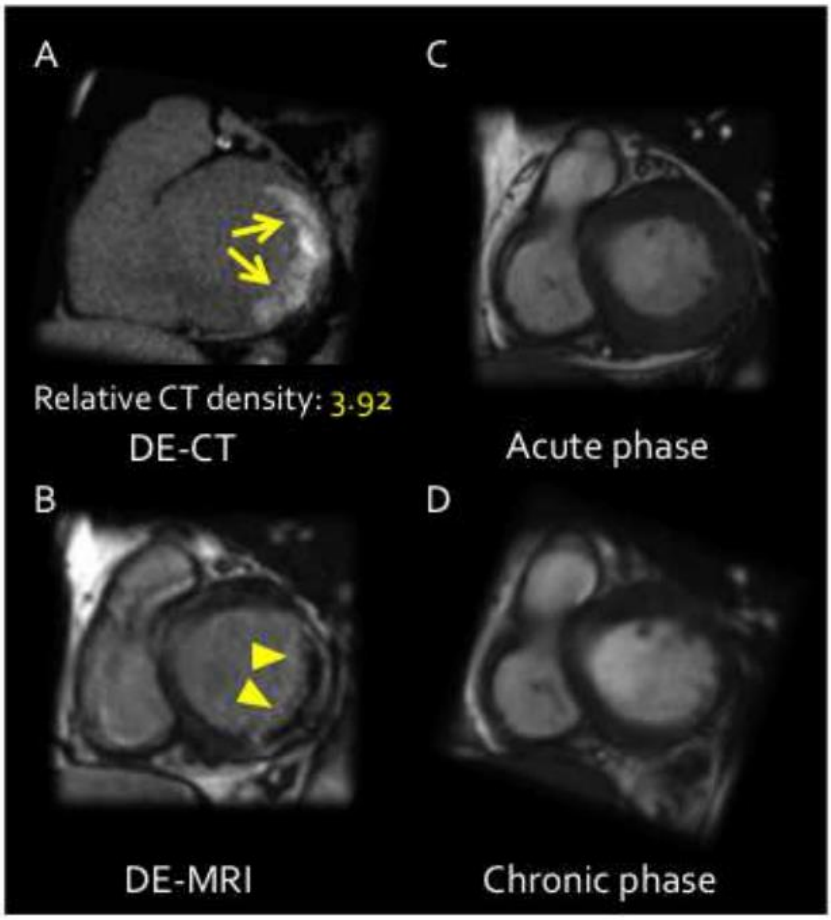

Figure 3. A 64-year-old man from the group of patients with heterogeneous enhancement. Short-axis DE-CT imaging (A), DE-MRI at 1 week (B), and cine magnetic resonance imaging (end-systolic time frame) at 1 week (C), and at 6 months (D). DE-CT imaging (A) shows complete transmural contrast-delayed enhancement with heterogeneous enhancement (arrows) and high relative CT density. DE-MRI at 1 week (B) shows complete transmural enhancement of the left ventricular lateral wall with microvascular obstruction (arrowheads). On cine magnetic resonance imaging (C and D), the left ventricular lateral wall was

obviously thinned at 6 months. Left ventricular end-systolic volume was increased from 150 ml at 1 week to 170 ml at 6 months.

Figure 4

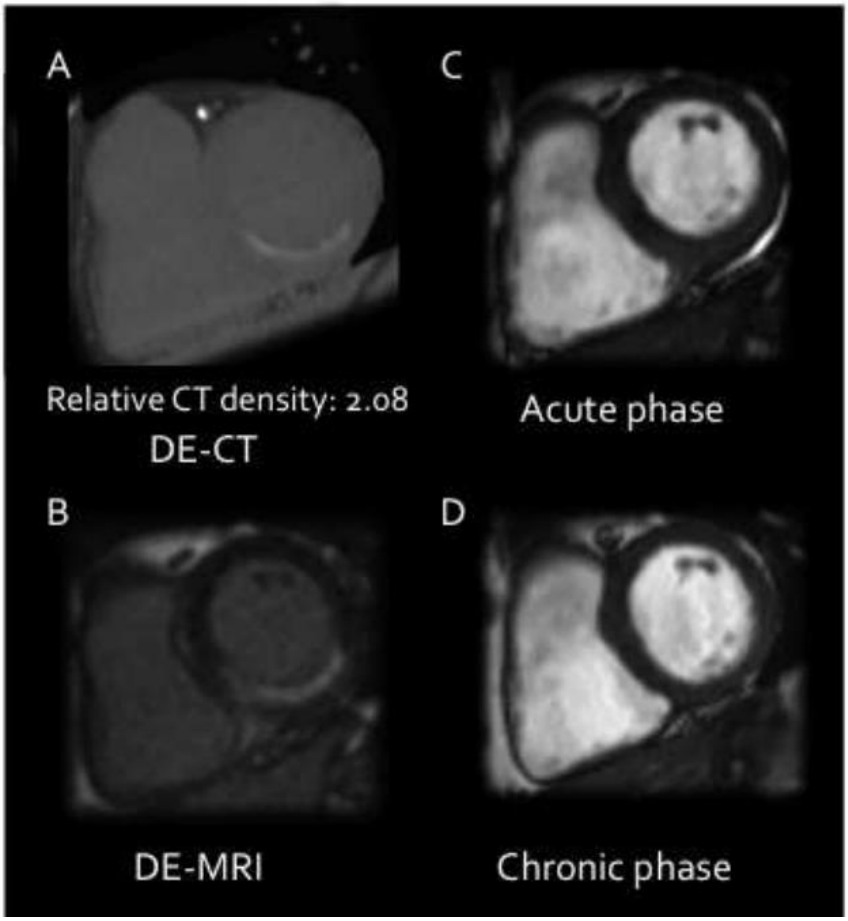

Figure 4. A 64-year-old man from the group without heterogeneous enhancement. Short-axis DE-CT imaging (A), DE-MRI at 1 week (B), and cine magnetic resonance imaging (end-systolic time frame) at 1 week (C), and at 6 months (D). DE-CT imaging (A) shows subendocardial contrast-delayed enhancement without heterogeneous enhancement and with low relative CT density. DE-MRI at 1 week (B) shows subendcardial enhancement of the left ventricular inferior wall without microvascular obstruction. On cine magnetic resonance imaging (C and D), left ventricular end-systolic volume was reduced from 82 ml at 1 week to 58 ml at 6 months.

Table 1. Baseline Patient Characteristics, Procedural Characteristics, and Medications

	HE (-) n=59	HE (+) n=33	*P* value
Age (years)	66±12	58±12	0.002
Male (%)	81	88	0.416
Diabetes mellitus (%)	25	33	0.419
Hypertension (%)	59	67	0.486
Dyslipidemia (%)	61	73	0.258
Smoker (%)	51	61	0.367
BMI	24.6±3.0	25±2.9	0.374
Laboratory findings			
CRP (mg/dl)	0.29±0.38	0.25±0.34	0.596
LDL (mg/dl)	126±39	131±37	0.409
Peak CK (IU/ml)	1931±1228	4856±2241	<0.001
Peak CK-MB (IU/ml)	170±101	398±230	<0.001
BNP on day 7 (pg/ml)	145±146	227±188	0.042
Onset-reperfusion time (h)	6.4±6.4	7.4±6.5	0.467
Stent size (mm)	3.3±0.4	3.3±0.3	0.502
Stent length (mm)	26.3±7.6	25.0±7.7	0.439
Contrast volume (ml)	200±58	216±64	0.210
Culprit lesion: LAD (%)	49	64	0.181

LCx (%)	14	18	0.554
RCA (%)	37	18	0.056
First TIMI flow 0 (%)	53	64	0.303
Final TIMI flow (0-2) (%)	8	18	0.169
Killip class ≧2 (%)	3	15	0.041
Medication after on admission			
Aspirin (%)	98	100	0.452
Clopidogrel (%)	98	100	0.452
ACE-inhibitor/ARBs (%)	78	88	0.240
Beta-blockers (%)	73	97	0.004
Statins (%)	98	100	0.452

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body-mass index; BNP, brain natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; HE, heterogeneous enhancement; LAD, left anterior descending artery; and TIMI, Thrombolysis in Myocardial Infarction.

Table 2. CT and MRI Findings

	HE (-) n=59	HE (+) n=33	*P* value
CT			
CT value: DE area (HU)	94±34	127±28	<0.001
CT value: remote area (HU)	49±8	48±7	0.287
Relative CT density	1.9±0.8	2.7±0.6	<0.001
Transmural enhancement (%)	20	73	<0.001
Myocardial contrast DE size (g)	9.0±9.2	36.1±17.2	<0.001
MRI			
LVEF baseline (%)	45±9	38±8	0.001
Chronic phase (%)	49±10	39±8	<0.001
LVEDV baseline (ml)	119±31	143±38	0.002
Chronic phase (ml)	110±32	149±40	<0.001
LVESV baseline (ml)	67±25	90±33	<0.001
Chronic phase (ml)	56±25	93±34	<0.001
MVO (%)	31	94	<0.001
Hemorrhage (%)	19	67	<0.001
LV remodeling (%)	19	55	<0.001

CT indicates computed tomography; DE, delayed enhancement; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HE, heterogeneous enhancement; HU, Hounsfield unit; LV, left ventricular; MRI, magnetic resonance imaging; and MVO, microvascular obstruction.

Table 3. Univariable and Multivariable Logistic Regression Analyses for Prediction of MVO

	Univariable			Multivariable (P<0.050)		
Factor	OR	95% CI	P value	OR	95% CI	P value
Age	0.96	0.93-1.00	0.076			
Sex (male)	1.37	0.45-4.16	0.577			
EF <40%	3.12	1.19-8.14	0.019	1.45	0.33-6.27	0.622
Peak CK >4000 IU/ml	10.66	2.31-49.12	0.002	0.90	0.08-10.10	0.934
HE	25.90	5.61-119.48	<0.001	13.50	2.15-84.90	0.005
Relative CT density >2.2	18.40	5.61-60.00	<0.001	12.00	2.94-49.20	<0.001
Transmural enhancement	29.56	9.34-93.52	<0.001	6.50	1.32-32.00	0.021

CI indicates confidence interval; CK, creatine kinase; CT, computed tomography; EF, ejection fraction; HE, heterogeneous enhancement; OR, odds ratio; and TIMI, Thrombolysis in Myocardial Infarction.

Table 4. Logistic Regression Analysis for Prediction of LV Remodeling

	Univariable			Multivariable (P<0.050)		
Factor	OR	95% CI	P value	OR	95% CI	P value
Age	0.96	0.93-1.00	0.067			
Sex (male)	8.00	0.99-64.10	0.050			
EF <40%	0.57	0.22-1.51	0.264			
Peak CK >4000 IU/ml	3.45	1.32-9.06	0.012	1.44	0.42-4.85	0.561
HE	5.24	2.03-13.51	<0.001	3.97	1.26-12.60	0.019
Relative CT density	1.77	1.01-3.12	0.048	1.14	0.57-2.26	0.708
Myocardial contrast DE size	1.02	0.99-1.05	0.056			
Transmural enhancement	2.14	0.874-5.26	0.096			

CI indicates confidence interval; CT, computed tomography; DE, delayed enhancement; EF, ejection fraction; HE, heterogeneous enhancement; and OR, odds ratio.