Journal of Cardiology 75 (2020) 302–308

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Myocardial delayed enhancement on dual-energy computed tomography: The prevalence and related factors in patients with suspicion of coronary artery disease

Natsuko Mukai-Yatagai (MD)[a,*], Yasutoshi Ohta (MD, PhD)[b], Ryosuke Amisaki (MD)[a], Naoko Sasaki (MD)[a], Toshihiko Akasaka (MD)[a], Tomomi Watanabe (MD, PhD)[a], Junichi Kishimoto[c], Masahiko Kato (MD, PhD, FJCC)[a], Toshihide Ogawa (MD, PhD)[d], Kazuhiro Yamamoto (MD, PhD, FJCC)[a]

[a] Division of Cardiovascular Medicine, Endocrinology and Metabolism, Department of Molecular Medicine and Therapeutics, Faculty of Medicine, Tottori University, Yonago, Japan
[b] Division of Radiology, Department of Pathophysiological Therapeutic Science, Faculty of Medicine, Tottori University, Yonago, Japan
[c] Department of Clinical Radiology, Tottori University Hospital, Yonago, Japan
[d] Division of Radiology, Kurashiki Heisei Hospital, Kurashiki, Japan

ARTICLE INFO

Article history:
Received 1 March 2019
Received in revised form 17 July 2019
Accepted 3 August 2019
Available online 7 September 2019

Keywords:
Coronary artery disease
Tomography
X-ray computed
Radiology
Dual-energy scanned projection
Myocardium

ABSTRACT

Background: We aimed to assess the prevalence of myocardial delayed enhancement (MDE) in patients with suspected obstructive coronary artery disease (CAD), and to investigate factors related to the presence or absence of MDE.
Methods: We retrospectively evaluated 191 consecutive patients who underwent coronary computed tomography angiography (CCTA) with MDE imaging for clinical suspicion of CAD from December 2014 to December 2016. The presence of MDE on iodine-density images using dual-energy CT was assessed by two independent readers. Multivariable logistic regression analyses were used to determine factors associated with the presence of MDE.
Results: MDE was detected in 58 (30%) patients. Male gender, hypertension, prior heart failure (HF) hospitalization, and CCTA-detected CAD were independent factors related to the presence of MDE. When CCTA-detected CAD was excluded to narrow down the analysis to factors obtainable before CCTA, interventricular septum thickness (IVST) $\geq$12 mm was added as another independent factor. The combination of the following four factors: female gender, no history of hypertension, no history of prior HF hospitalization, and IVST $<$ 12 mm demonstrated high specificity (98.3%) and positive predictive value (96.2%) for predicting the absence of MDE.
Conclusions: Male gender, hypertension, prior HF hospitalization, and CAD were independently associated with the presence of MDE in patients with suspected CAD. The combination of female gender, no history of hypertension, no history of prior HF hospitalization, and IVST $<$ 12 mm is likely to be a helpful predictor in discriminating patients without MDE before CCTA.
© 2019 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.

Introduction

Myocardial delayed enhancement on cardiac magnetic resonance imaging (MRI-MDE) is widely used for the assessment of myocardial tissue characterization. Evaluation of MDE is helpful in diagnosing cardiomyopathy, and MDE is associated with adverse cardiac mortality in patients with ischemic or non-ischemic cardiomyopathy [1,2].

MDE by single-energy computed tomography (SECT) using iodinated contrast medium reliably represents myocardial fibrosis [3–6]. However, because the contrast-to-noise ratio (CNR) of MDE using SECT is much lower than that of MRI-MDE [7], the *in vivo* diagnostic performance depicting myocardial lesions is inferior to MRI-MDE. Dual-energy computed tomography (DECT) is clinically

* Corresponding author at: Division of Cardiovascular Medicine, Endocrinology and Metabolism, Department of Molecular Medicine and Therapeutics Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago, Tottori 683-8503, Japan.
E-mail address: natsukomukai@tottori-u.ac.jp (N. Mukai-Yatagai).

https://doi.org/10.1016/j.jjcc.2019.08.004
0914-5087/© 2019 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.

available, and low diagnostic performance with SECT has been attenuated by the improvement in CNR using a combination of low energy images and iodine density images (IDIs). Our recent study demonstrated the excellent agreement of MDE of DECT with MRI-MDE [8], suggesting that MDE of DECT is a valid alternative method. Coronary CT angiography (CCTA) is widely used for the noninvasive diagnosis of coronary artery disease (CAD). Since the combination of CCTA and MDE imaging results in a large accumulation of information, the rapid diagnosis of cardiovascular diseases, as well as their severity, may be feasible with DECT.

Compared to MRI-MDE, MDE imaging using CT has the disadvantage of increments of radiation exposure and additional iodinated contrast medium use. The proportion of elderly people and patients with chronic kidney disease (CKD) were higher in patients with CAD than in those with malignant tumors [9,10]. Therefore, it is necessary to consider the addition of contrast medium in patients with CAD. To avoid excessive contrast medium use, it is useful to clarify related factors of the presence or absence of MDE and to distinguish patients with a high necessity of MDE imaging.

In this study, we elucidated the prevalence of MDE in patients with suspected CAD and investigated factors related to the presence or absence of MDE. Such factors may be helpful in discriminating patients who do not require delayed imaging from those who are highly suspected to have MDE.

Materials and methods

Study population

We retrospectively evaluated 317 consecutive patients who underwent CCTA and MDE imaging for suspected CAD from December 2014 to December 2016 in our institution; of these patients, three patients underwent CCTA but not MDE imaging because of renal dysfunction.

A flow diagram for the study participants is shown in Fig. 1. The inclusion criteria for the suspicion of CAD were as follows: (1) new/worsening chest pain, or equivalent symptoms suspicious for clinically significant CAD, (2) no previous diagnosis for these symptoms in other hospitals, (3) planned non-invasive testing for diagnosis, (4) age ≥40 years, (5) estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 within the past 90 days, and (6) without suspected acute coronary syndrome requiring emergent coronary intervention. The indication of CCTA examination adhered to the latest guideline [11]. The exclusion criteria were as follows: (1) History of prior revascularization or myocardial infarction (n = 40), (2) no echocardiography (n = 53), (3) insufficient echocardiography data (n = 22). Finally, 202 patients were assessed, including 128 men (mean age ± SD, 71 ± 10 years) and 74 women (mean age, 71 ± 11 years) ($p = 0.613$). Sixteen of the 202 patients were included in our previous study [8].

The study was approved by the local ethics committee, and written informed consent was obtained from all patients before CT. The requirement for written informed consent for the retrospective analysis was waived in accordance with the Declaration of Helsinki. Instead, a public announcement was made in accordance with the request from the local ethics committee and Japanese Clinical Research Guidelines [12].

Computed tomography image acquisition

All CT examinations in this study were performed using rapid kilovolt-peak switching DECT (Discovery CT750 HD, Freedom Edition; GE Healthcare, Milwaukee, WI, USA). CCTA was performed by helical scan mode using retrospective electrocardiogram (ECG) triggering above 60 beats per minute (bpm), or axial scan mode using prospective ECG triggering at 75% R-R interval either at or below 60 bpm (Snap Shot Pulse, GE Healthcare). Other acquisition parameters were as follows: Tube voltage, 120 kV; tube current, 600 mA (with tube current modulation technique for helical acquisition); rotation time, 0.35 s; collimation, 64 × 0.625 mm. The scan was started 3 s after the peak time on test injection. A bolus of iodinated contrast medium [weight (kg) × 0.72 ml/kg/sec, Iopamidol, 370 mgI/ml, Bayer, Osaka, Japan] was injected using an injector (Dual shot GX7, Nemoto Kyorindo, Tokyo, Japan) from the antecubital vein for a duration of 13 s, followed by a 25 ml saline flush.

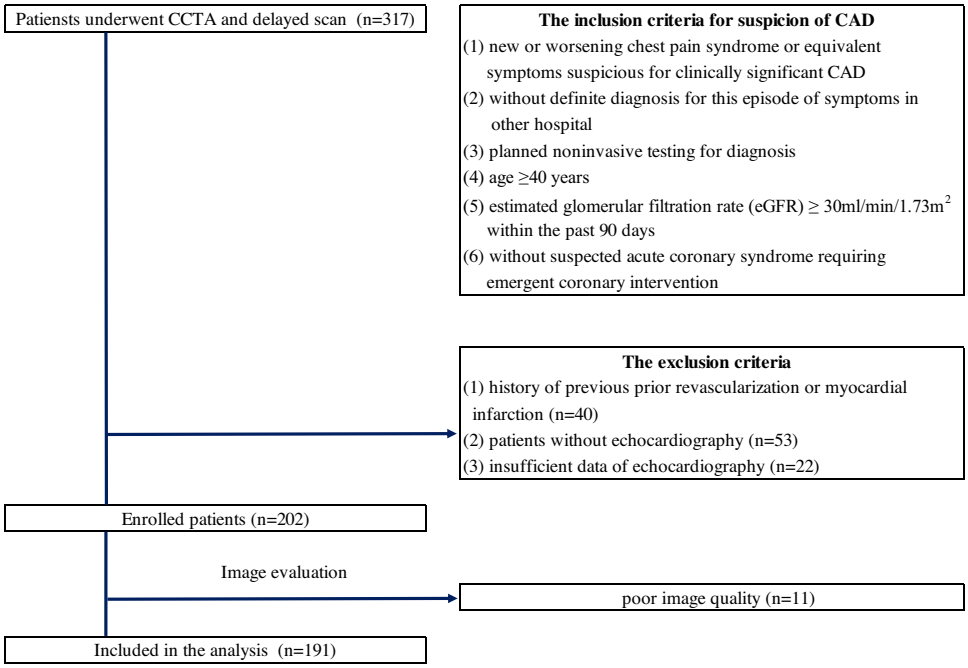

Fig. 1. Flow diagram of enrolled study participants, the inclusion criteria for suspicion of CAD, and the exclusion criteria from analysis.
CCTA, coronary computed tomography angiography; CAD, coronary artery disease.

All patients were administered with sublingual nitroglycerin (Myocoal spray, Toa-eiyo, Tokyo, Japan) 5 min before the scan. β-blocker (metoprolol tartrate 20 mg) was orally administered in patients with a heart rate above 60 bpm 1 h before the CT examination; however, they were not administered in patients with contraindications to β-blockers (bradycardia, bronchial asthma, etc.).

Immediately after CCTA, additional contrast material (0.5 ml/kg) was infused for 60 s. In total, 1.4 ml/kg of iodinated contrast material (not exceeding 100 ml throughout the examination) was used [8,13,14]. The MDE image with dual-energy acquisition was obtained 7–8 min after CCTA [15–17]. The following examination parameters were used for MDE acquisition: Prospectively ECG-gated axial scan at mid-diastolic phase; tube voltage, 80 kV and 140 kV rapid-kilovolt switching (GSI cardiac, GE Healthcare); tube current, 600 mA; rotation time, 0.35 s. Effective radiation doses were calculated as the product of the dose length product (DLP) and a chest conversion coefficient [k = 0.014 mSv/(mGy × cm)] [18].

Computed tomography image reconstruction

CCTA images were reconstructed with a dedicated workstation (Advantage workstation 4.6: GE healthcare).

For evaluating MDE, IDIs were reconstructed for its high diagnostic performance in detecting MDE compared to MRI-MDE [8]; images were given by the amount of iodine density in a voxel (mg/ml). The adaptive statistical iterative reconstruction (ASiR; GE Healthcare) was used to improve the signal to noise ratio and the CNR of IDI with the ASiR intensity of 80% [19]. Images of 8 mm in slice thickness of the left ventricular (LV) short axis from base to apex were reconstructed for image analysis.

Computed tomography image analysis

Coronary artery stenosis (CAS) on CCTA images was evaluated by radiologists and cardiologists with more than 6 years of experience in cardiac radiology, and all segments were categorized according to the Coronary Artery Disease-Reporting and Data system (CAD-RADS™) lexicon [20]

The CT-MDE images were independently reviewed by a radiologist and a cardiologist (13 and 8 years of experience in cardiac imaging, respectively), who were blinded to the other results.

The presence of MDE was defined as apparent high attenuation in the myocardium on IDIs (Fig. 2) [21]. Although the image window width and level were initially set at standard values automatically predetermined for the IDI series, they could be adjusted to best visualize late enhancement. The patterns of MDE were defined by modifying the MRI-MDE patterns reported by Mahrholdt et al. [22] as follows: subendocardial, transmural, midwall, epicardial, and global endocardial. Subendocardial or transmural enhancement was classified as an ischemic pattern, and isolated midwall or epicardial hyperenhancement was classified as a non-ischemic pattern. When a patient had two or more MDE patterns, the pattern with the largest MDE area was adopted. Discrepancies between the readers were resolved by discussion after both reading sessions were completed, and we confirmed that the IDIs showed excellent interobserver agreement in our previous study [8].

Echocardiographic examination

Echocardiography was performed by experienced sonographers or cardiologists, and each parameter was measured as previously described [23].

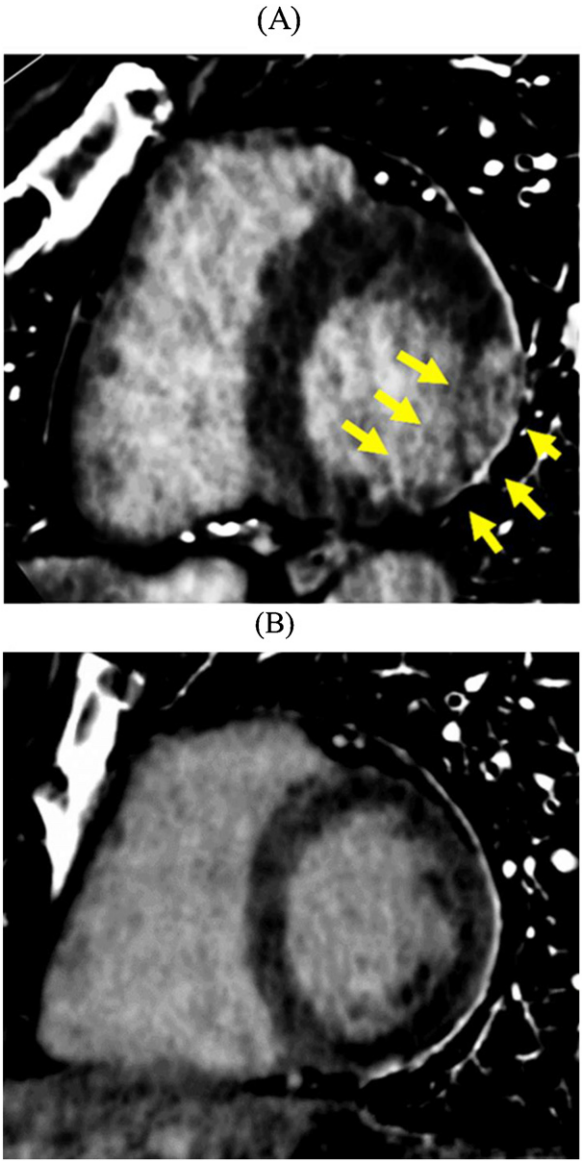

Fig. 2. Two patients with presence of MDE (A) and absent of MDE (B) with iodine density image. (A) MDE image of a midventricular short-axis slice demonstrating transmural hyperenhancement with ischemic pattern (yellow arrows). (B) MDE image of a midventricular short-axis slice demonstrating no apparent hyperenhancement.
MDE, myocardial delayed enhancement.

Statistical analysis

Statistical analysis was performed using SPSS (version 23; IBM, Armonk, NY, USA). All data are expressed as mean ± standard deviation (SD) for normally distributed data, or median and interquartile range for non-normally distributed data. Comparisons of continuous variables were analyzed by unpaired *t*-test or Man-Whitney's U test, according to the data distribution. Categorical variables were compared between groups using the chi-square test without correction for multiplicity.

We compared various parameters in MDE between two groups and used the significantly different parameters for the univariable analysis. The presence of obstructive CAD was defined as at least one lesion with a CAD-RADS™ category ≥4 on CCTA images, and prior heart failure (HF) hospitalization was defined as HF hospitalization in the 6 months before CCTA. The categorical variables of echocardiography were determined by the upper limit

Table 1
Baseline characteristics.

	MDE(+) n = 58	MDE(−) n = 133	P value
Male	46 (79%)	77 (57%)	0.04
Age, years	69 ± 11	71 ± 10	0.27
Body mass index, kg/m^2	22.3 ± 3.0	22.3 ± 3.5	0.9
Risk factors			
Hypertension	44(75%)	67(50%)	<0.01
Diabetes mellitus	26(43%)	25(18%)	<0.01
Dyslipidemia	25(43%)	49(36%)	0.41
Current smoking	24(41%)	38(28%)	0.08
Hyperuricemia	9(15%)	12(9%)	0.18
Laboratory findings			
eGFR, ml/min/1.73 m^2	67 ± 15	74 ± 20	0.02
Medications			
Diuretics	23 (39%)	18 (13%)	<0.01
β-blocker	19 (32%)	24 (18%)	0.025
ACEI/ARB	38(65%)	41(30%)	<0.01
Ca blocker	22(37%)	48(36%)	0.8
Statin	19(32%)	38(28%)	0.56
Parameters of echocardiography			
LVEF, %	51.3 ± 14.6	60.6 ± 11.4	<0.01
IVST, mm	10.0 ± 2.2	8.8 ± 1.4	<0.01
LVDd, mm	50.4 ± 8.1	47.0 ± 6.2	<0.01
LAVI, ml/m^2	39.8 ± 15.3	33.0 ± 15.9	<0.01
Septal e', cm/s	4.7 ± 1.6	5.2 ± 1.8	0.08
E/e'	16.3 ± 8.6	13.2 ± 5.4	0.016
Clinical background			
Prior HF hospitalization	25(43%)	14(10%)	<0.01
CAD (CAD-RADS^{TM} ≥ 4)	33(56%)	20(15%)	<0.01

Data are mean ± SD or n (%); ACEI/ARB: Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker; CAD: coronary artery disease; CAD-RADS: Coronary Artery Disease Reporting and Data System; E: peak early diastolic transmitral flow velocity; e': early diastolic velocity of the mitral annulus at the septum; eGFR: estimate glomerular filtration rate; IVST: interventricular septum thickness; LAVI: left atrial volume index; HF: heart failure; LVDd: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MDE: myocardial delayed enhancement.

of normal values according to the current guidelines [24], and the ejection fraction (EF) <40% was determined by the definition of HF with reduced EF [25]. The eGFR ≤44 ml/min/1.73 m^2 was determined as worse than CKD stage G3b [26].

Multivariable logistic regression analysis was used to calculate the odds ratio (OR). Stepwise forward selection, considering any variables with values of $p < 0.05$, was performed to identify related factors for MDE in the following two models. Model 1 included all variables that were significantly associated with MDE in the univariable logistic regression analysis, with the exception of CAD (CAD was added to model 2) since model 1 aimed to only carry out analysis with the factors known before CCTA. A p-value of <0.05 was considered to indicate statistical significance.

Agreement between observers in assessing the presence of MDE was evaluated with simple linear regression analysis, and determined by the Cohen kappa coefficient for diagnostic performance.

Results

Baseline patient characteristics

In 11 of 202 patients, the CT quality was insufficient to evaluate CAS, because of motion artifacts (n = 5) and calcification (CAD-RADS = N) (n = 5), or to evaluate MDE, due to artifacts (n = 1). Among the remaining 191 patients, MDE was detected in 58 (30%) patients. The baseline characteristics of the patients with and without MDE are shown in Table 1.

Compared to patients without MDE, patients with MDE were characterized by a higher prevalence of males, hypertension, diabetes mellitus, lower eGFR and left ventricular ejection fraction (LVEF), higher left ventricular end-diastolic dimension (LVDd), left atrial volume index (LAVI), interventricular septum thickness (IVST), and E/e' (E: peak early diastolic transmitral flow velocity/e': early diastolic velocity of the mitral annulus at the septum). They were also treated more frequently with diuretics, β-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and had a higher prevalence of CCTA-detected CAD and prior HF hospitalization.

The patterns of myocardial delayed enhancement

Of the 58 patients with MDE, 31 had an ischemic pattern and 27 had a non-ischemic pattern. The pattern was subendocardial in 18 patients, transmural in 13, epicardial in 4, midwall in 21, and global endocardial in 2 (Fig. 3). In 31 patients with an ischemic pattern, 29 patients had CCTA-detected CAD. In all of 29 cases, the region with MDE coincided with that of CAS. The remaining two patients were diagnosed with radiation-induced cardiomyopathy and LV noncompaction.

In patients with a non-ischemic pattern, additional diagnoses were as follows: Dilated cardiomyopathy (8 patients), hypertrophic cardiomyopathy (3 patients), cardiac transthyretin amyloidosis (2 patients), cardiac sarcoidosis (2 patients), hypertensive cardiomyopathy (2 patients), valvular disease (2 patients), and LV diastolic dysfunction (3 patients). The remaining 5 patients had no apparent cardiac disease. Although global endocardial MDE coincided with cardiac amyloidosis, there was no specific relationship between the other MDE patterns and cardiomyopathies.

The median DLP and mean effective radiation dose of CCTA and MDE imaging were 241.1 ± 38.5 mGycm, 3.37 ± 0.53 mSv, 738.9 ± 453.3 mGycm, and 10.34 ± 5.89 mSv, respectively. The kappa values for the agreement of detecting MDE between the two readers was 0.88.

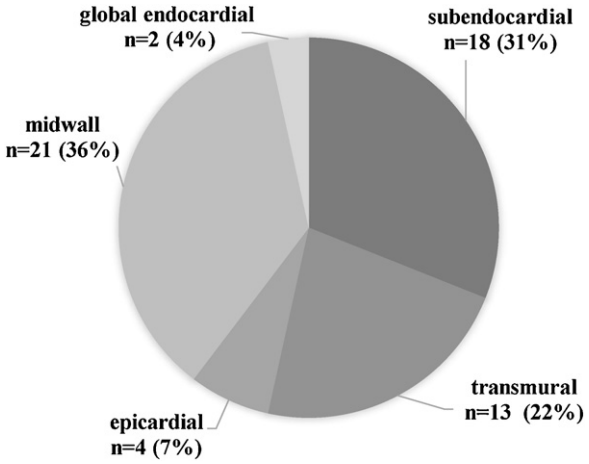

Fig. 3. The percentage of each MDE patterns of 58 patients with MDE. MDE, myocardial delayed enhancement.

Factors associated with myocardial delayed enhancement

In the univariate analysis, male gender, hypertension, diabetes mellitus, current smoking, diuretics, ACEI/ARB, IVST ≥ 12 mm, LVDd ≥ 55 mm, LAVI ≥ 34 ml/m^2, EF < 40%, prior HF hospitalization, and CCTA-detected CAD were significantly associated with MDE (Table 2).

In the multivariable logistic regression analysis, male gender, hypertension, IVST ≥ 12 mm, and prior HF hospitalization were independent factors after adjustment for multiple confounders, which narrowed down the analysis to factors obtainable before CCTA (in model 1) (Table 2). In model 2, male gender, hypertension, prior HF hospitalization, and CCTA-detected CAD were independent factors related to the presence of MDE.

Based on the result of model 1, we examined whether the combination of all associated factors would predict the presence of MDE. Among 191 patients, only 5 cases met all 4 criteria, and MDE was observed in all 5 cases. As a predictor of the presence of MDE, the combination of these 4 factors showed a high specificity (100%) and positive predictive value (PPV) (100%), but low sensitivity (8%) (Table 3a).

Next, we examined whether the combination of all of female gender, no history of hypertension, IVST < 12 mm, and no history of prior HF hospitalization, would predict the absence of MDE. Among 191 patients, 26 cases met all four criteria, and MDE was not observed in 25 of 26 cases. As a predictor of the absence of MDE, the combination of these four factors showed high specificity (98.3%) and high PPV (96.2%) (Table 3b).

Discussion

In the current study, MDE was observed in 30% of the study subjects. Male gender, hypertension, prior HF hospitalization, and CAD on CCTA were independent factors related to MDE, and prior HF hospitalization showed the highest OR. Among the patient characteristics obtainable before CT examination, male gender, hypertension, prior HF hospitalization, and LV hypertrophy were independently associated with the presence of MDE. The combination of female gender, no hypertension, no prior HF hospitalization, and no LV hypertrophy, predicted the absence of MDE with high PPV.

Men, hypertension, CAS, and prior HF hospitalization are well known as risk factors for poor prognosis [11]. Previous studies have reported that MRI-MDE is a stronger predictor of cardiovascular events in patients with suspected CAD [27–29], given that MRI-MDE reflects myocardial fibrosis [30]. MDE imaging can evaluate the infarct lesion and myocardial viability in patients with ischemic cardiomyopathy [31,32]. In the case of non-ischemic cardiomyopathy, the pattern and extent of MDE is helpful for diagnostic process in non-ischemic cardiomyopathy [8,21]. A previous study reported that the combination of CCTA and MDE imaging can identify the underlying etiology of patients with LV

Table 2
xxx.

Univariate analysis			Multivariate analysis			
			Model 1: not included CAD		Model 2: included CAD	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	p-value
Age	0.98(0.86–1.08)	0.33				
BMI	0.96(0.95–1.01)	0.57				
Male	2.78(1.35–5.72)	0.005	3.18(1.39–7.25)	0.006	2.79(1.18–6.56)	0.019
Hypertension	3.09(1.55–6.17)	0.01	3.20(1.44–7.06)	0.004	3.01(1.28–7.04)	0.011
Diabetes Mellitus	3.08(1.54–6.05)	0.001	Not selected		Not selected	
Hyperlipidemia	1.29(0.69–2.43)	0.42				
Smoking	1.76(0.92–3.36)	0.09				
Hyperuricemia	1.85(0.73–4.67)	0.21				
Diuretics	4.19(2.03–8.65)	0.001	Not selected		Not selected	
β-blocker	2.21(1.09–4.47)	0.03	Not selected		Not selected	
ACEI/ARB	4.26(2.21–8.2)	0.001	Not selected		Not selected	
Ca blocker	1.08(0.57–2.04)	0.87				
Statin	1.21(0.62–2.36)	0.6				
eGFR ≤ 44 ml/min/1.73 m^2	1.02(0.30–3.45)	0.97				
IVST ≥ 12 mm	4.51(1.76–11.60)	0.002	3.08(1.05–9.00)	0.04	Not selected	
LVDd ≥ 55 mm	3.26(1.49–7.11)	0.003	Not selected		Not selected	
LAVI ≥ 34 ml/m^2	1.99(1.06–3.72)	0.039	Not selected		Not selected	
E/e' ≥ 15	1.70(0.89–3.23)	0.13				
LVEF ≤ 39	4.99(2.17–11.45)	0.001	Not selected		Not selected	
Prior HF hospitalization	6.43(3.01–13.76)	0.008	7.33(3.13–17.15)	<0.001	8.48(3.41–21.09)	<0.001
CAD (CAD-RADS™ ≧ 4)	7.45(3.68-15.08)	0.001			6.73(3.02–14.96)	<0.001

BMI: Body mass index; ACEI/ARB: Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker; CAD: coronary artery disease; CAD-RADS: Coronary Artery Disease Reporting and Data System; E: peak early diastolic transmitral flow velocity; e': early diastolic velocity of the mitral annulus at the septum; eGFR: estimate glomerular filtration rate; IVST: interventricular septum thickness; LAVI: left atrial volume index; HF: heart failure; LVDd: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; OR: odds ratio.

Table 3a
The predictive performance for the presence of MDE of the combination of four factors: male, history of hypertension, LV hypertrophy and history of prior HF hospitalization.

Sensitivity	Specificity	PPV	NPV	Accuracy
8.6 (5/58)	100.0 (133/133)	100.0 (5/5)	71.5 (133/186)	72.2 (138/191)

MDE: myocardial delayed enhancement, HF: heart failure, NPV: negative predictive value, PPV: positive predictive value. Parenthesis shows actual number.

Table 3b
The predictive performance for the absence of MDE of the combination of four factors: female, no history of hypertension, no LV hypertrophy and no history of prior HF hospitalization.

Sensitivity	Specificity	PPV	NPV	Accuracy
18.8 (25/133)	98.3 (57/58)	96.2 (25/26)	34.5 (57/165)	42.9 (82/191)

MDE: myocardial delayed enhancement, HF: heart failure, NPV: negative predictive value, PPV: positive predictive value. Parenthesis shows actual number.

dysfunction similarly to MRI-MDE and coronary angiography [33]. Our recent study has also shown that the MDE imaging on DECT is compatible with MRI-MDE [8]. Thus, MDE on CT is likely to reflect myocardial fibrosis and predict poor prognosis as well as MRI-MDE. Furthermore, our current findings that male gender, hypertension, CAS, and prior HF hospitalization were independently related to MDE on CT can be explained by the fact that all of these parameters are associated with poor clinical outcomes.

Although MRI provides high CNR without radiation exposure and is a first-line diagnostic tool for noninvasive myocardial tissue characterization, MRI-MDE has various disadvantages compared with cardiac CT, including nephrogenic systemic fibrosis in patients with severe renal dysfunction, higher cost, longer scanning times, and restriction of indication in patients with mechanical devices. Compared to MRI, CCTA is widely used for noninvasive diagnosis of CAD, and it is possible to simultaneously evaluate myocardial properties by including MDE imaging; although this combination has not yet been generalized, our recent study suggested that it may be as useful in the diagnosis of cardiomyopathy and the assessment of its severity as MRI-MDE [8]. However, MDE imaging on CT has the disadvantage of increments of radiation exposure and additional use of iodinated contrast medium. Patients with CAD are more elderly and often associated with CKD, and thus, we have to be careful in adding contrast agents to them.

One of the strategies to resolve these issues is to predict patients without MDE before CT and to avoid the unnecessary exposure to additional radiation and the unnecessary injection of additional contrast medium in association with the delayed imaging in such patients. Although we elucidated the factors that are independently related to MDE, information regarding coronary arteries cannot be obtained during the short timeframe between initial and delayed imaging. Therefore, multivariable logistic regression analysis was conducted excluding information relating to coronary arteries (model 1). We found that male gender, hypertension, prior HF hospitalization, and LV hypertrophy were independently related to MDE. Our findings are partly compatible with previous studies that have reported that LV dilatation, LV hypertrophy, and LV systolic dysfunction are associated with MRI-MDE in non-ischemic cardiovascular diseases [34–36]. Furthermore, IVST $\geq$ 12 mm, LVEF $<$ 40%, and LVDd $\geq$ 55 mm were significantly associated with MDE on CT (Table 2), and IVST $\geq$ 12 mm was selected as an independent predictor of MDE from multivariable logistic regression analysis. Although reduced LVEF and increased LVDd were not selected as independent predictors, this may be because that the etiology of heart diseases was not restricted in the study subjects, in contrast to previous studies. The current study demonstrated that the combination of female gender, no hypertension, no LV hypertrophy, and no prior HF hospitalization predicted the absence of MDE with high PPV, and may be useful in discriminating patients who have low necessity of delayed imaging. Another strategy is to discriminate patients with a highly likely presence of MDE. In contrast, the combination of male gender, hypertension, LV hypertrophy, and prior HF hospitalization was considered insufficient to predict the presence of MDE before CCTA examination, due to its low sensitivity. Prior HF hospitalization showed the highest OR in both models, and MDE was detected in 63% of patients with prior HF hospitalization. It was possible to obtain clues leading to diagnose hidden cardiomyopathy in patients with non-ischemic MDE patterns. These results suggest that MDE imaging is required in patients with prior HF hospitalization, and that MDE imaging can help to reveal the cause of HF. Furthermore, CAD on CCTA showed a high OR in model 2, indicating that MDE imaging is also necessary for patients both with a high risk, and prior history, of CAD. Future studies are necessary to validate these proposals.

There are several limitations to this study. First, this was a retrospective single-center study, with a low sample number. Second, MRI examination was not routinely performed as a reference for the presence of MDE on CT. Third, since the quantitative assessment of iodine density has not been established, visual assessment was performed by physicians to detect MDE on CT. Fourth, 22 of 317 cases were excluded because of inadequate echocardiography data, mainly due to poor image quality or record omission. Fifth, although all patients were suspected of CAD, in some patients with reduced LVEF but without regional wall motion abnormality, non-ischemic cardiomyopathy was more suspected, and CCTA was conducted only to exclude the possibility of CAD. The ratio of this group to the study subjects may have affected the factors related to MDE. In addition, the ratio of etiologies of non-ischemic cardiomyopathies in the study population may have also influenced the factors. Sixth, due to the small sample size, detailed analyses based on the classification of MDE into ischemic vs. non-ischemic type was not performed to identify factors related to each pattern. Seventh, our conclusion that female patients without LV hypertrophy, hypertension and prior HF hospitalization are highly unlikely to have MDE was not validated in different study subjects. Finally, we have not investigated the relationship between the presence of MDE and cardiac prognosis.

Conclusions

The present study showed that MDE was detected in 30% of patients with suspected CAD. Male gender, hypertension, prior HF hospitalization, and CCTA-detected CAD were independently associated with the presence of MDE on CCTA, and prior HF hospitalization and CCTA-detected CAD showed the highest ORs. Among the factors obtainable before CCTA, male gender,

hypertension, prior HF hospitalization, and LV hypertrophy were independent factors related to MDE.

At CCTA, the necessity of the delayed imaging for the assessment of myocardial tissue characterization might be low in female patients without hypertension, LV hypertrophy, and prior HF hospitalization to avoid additional radiation exposure and additional injection of contrast medium. However, delayed imaging should be obtained in patients with prior HF hospitalization in order to accurately assess the prognostic severity and determine the underlying causes for HF.

Funding

This study was supported by a grant from Tottori University Hospital.

Disclosures

The authors declare no conflict of interest.

Acknowledgments

This research was supported by patients and staff in the Cardiology and Radiology Departments, Tottori University Hospital.

References

[1] Roes SD, Kelle S, Theodorus AM, Kaandorp AM, Kokocinski T, Poldermans D, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol 2007;100:930–6.
[2] Wu KC, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. JACC 2008;51:2414–21.
[3] Gerber BL, Belge B, Legros GJ, Lim P, Poncelet A, Pasquet A, et al. Characterization of acute and chronic myocardial infarcts by multidetector computed tomography comparison with contrast-enhanced magnetic resonance. Circulation 2006;113:823–33.
[4] Zhao L, Ma X, Delano MC, Jiang T, Zhang C, Liu Y, et al. Assessment of myocardial fibrosis and coronary arteries in hypertrophic cardiomyopathy using combined arterial and delayed enhanced CT: comparison with MR and coronary angiography. Eur Radiol 2013;23:1034–43.
[5] Shiozaki AA, Senra T, Arteaga E, Martinelli FM, Avila LF, Parga JR, et al. Myocardial fibrosis detected by cardiac CT predicts ventricular fibrillation/ventricular tachycardia events in patients with hypertrophic cardiomyopathy. J Cardiovasc Comput Tomogr 2013;7:173–81.
[6] Lardo AC, Cordeiro MA, Silva C, Amado LC, George RT, Saliaris AP, et al. Contrast-enhanced multidetector computed tomography viability imaging after myocardial infarction: characterization of myocyte death, microvascular obstruction, and chronic scar. Circulation 2006;113:394–404.
[7] Nieman K, Shapiro MD, Ferencik M, Nomura CH, Abbara S, Hoffmann U, et al. Reperfused myocardial infarction: contrast-enhanced 64-section CT in comparison to MR imaging. Radiology 2008;247:49–56.
[8] Ohta Y, Kitao S, Yunaga H, Fujii S, Mukai N, Yamamoto K, et al. Myocardial delayed enhancement CT for heart failure evaluation: comparison to MRI. Radiology 2018;288:682–91.
[9] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56–528.
[10] Mamas MA, Sperrin M, Watson MC, Coutts A, Wilde K, Burton C, et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. Eur J Heart Fail 2017;19:1095–104.
[11] Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013;34:2949–3003.
[12] Ethical guidelines for medical and health research involving human subjects. Japanese Ministry of Health,LaborandWelfare. http://www.mhlw.go.jp/file/06-seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf. Published 2015. Accessed March 31, 2015..
[13] Rajiah P, Desai MY, Kwon D, Flamm SD. MR imaging of myocardial infarction. RadioGraphics 2013;33:1383–412.
[14] Rodriguez GA. Delayed enhancement cardiac computed tomography for the assessment of myocardial infarction: from bench to bedside. Cardiovasc Diagn Ther 2017;7:159–70.
[15] Deseive S, Bauer RW, Lehmann R, Kattner M, Kaiser C, Korkusuz H, et al. Dual-energy computed tomography for the detection of late enhancement in reperfused chronic infarction: a comparison to magnetic resonance imaging and histopathology in a porcine model. Invest Radiol 2011;46:450–6.
[16] Wichmann JL, Rauser RW, Doss M, Stock W, Lehnet T, Bodelle B, et al. Diagnostic accuracy of late iodine-enhancement dual-energy computed tomography for the detection of chronic myocardial infarction compared with late gadolinium-enhancement 3-T magnetic resonance imaging. Invest Radiol 2013;48:851–6.
[17] Wichmann JL, Arbaciauskaite R, Kerl JM, Frellesen C, Bodelle B, Lehnert T, et al. Evaluation of monoenergetic late iodine enhancement dual-energy computed tomography for imaging of chronic myocardial infarction. Eur Radiol 2014;24:1211–8.
[18] Valentin J. International Commission on Radiation Protection. Managing patient dose in multi-detector computed tomography (MDCT). ICRP publication 102. Ann ICRP 2007;37:1–79.
[19] Kishimoto J, Ohta Y, Kitao S, Watanabe T, Ogawa T. Image quality improvements using adaptive statistical iterative reconstruction for evaluating chronic myocardial infarction using iodine density images with spectral CT. Int J Cardiovasc Imaging 2018;34:633–9.
[20] Cury RC, Abbara S, Achenbach S, Agaston A, Berman D, Budoff M, et al. CAD-RADS™ coronary artery disease-reporting and data system. An expert consensus document of the society of cardiovascular computed tomography (SCCT), and american college of radiology (ACR) and the north american society for cardiovascular imaging (NASCI). Endorsed by the american college of cardiology. J Cardiovasc Comput Tomogr 2016;10:269–81.
[21] Lee HJ, Im DJ, Youn JC, Chang S, Suh YJ, Hong YJ, et al. Assessment of myocardial delayed enhancement with cardiac computed tomography in cardiomyopathies: a prospective comparison with delayed enhancement cardiac magnetic resonance imaging. Int J Cardiovasc Imaging 2017;33:577–84.
[22] Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischemic cardiomyopathies. Eur Heart J 2005;26:1461–74.
[23] Yamada K, Kinugasa Y, Sota T, Miyagi M, Sugihara S, Kato M, et al. Inspiratory muscle weakness is associated with exercise intolerance in patients with heart failure with preserved ejection fraction: a preliminary study. J Cardiac Fail 2016;22:38–47.
[24] Lang RM, Badano LP, Mor-Avi V, Aflalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. JASE 2015;28:1–39.
[25] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats A, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
[26] Stevens PE, Levin A. Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Ann Intern Med 2013;158:825–30.
[27] Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation 2006;113:2733–43.
[28] Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletas AH, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. JAMA 2012;308:890–6.
[29] Kim HW, Klem I, Shah DJ, Wu E, Meyers SN, Parker MA, et al. Unrecognized non-Q-wave myocardial infarction: prevalence and prognostic significance in patients with suspected coronary disease. PLoS Med 2009;6:1–11.
[30] Hashimura H, Kimura F, Ishibashi-Ueda H, Morita Y, Higashi M, Nakano S, et al. Radiologic-pathologic correlation of primary and secondary cardiomyopathies: MR imaging and histopathologic findings in hearts from autopsy and transplantation. Radiographics 2017;37:719–36.
[31] Machida H, Tanaka I, Fukui R, Shen Y, Ishikawa T, Tate E, et al. Dual-energy spectral CT: various clinical vascular applications. Radiographics 2016;36:1215–32.
[32] Mahnken AH, Koos R, Katoh M, Shen Y, Ishikawa T, Tate E, et al. Assessment of myocardial viability in reperfused acute myocardial infarction using 16-slice computed tomography in comparison to magnetic resonance imaging. JACC 2005;45:2042–7.
[33] le Polain de Waroux J, Pouleur AC, Goffinet C, Pasquet A, Vanoverschelde JL, Gerber B. Combined coronary and late-enhanced multidetector-computed tomography for delineation of the etiology of left ventricular dysfunction: comparison with coronary angiography and contrast-enhanced cardiac magnetic resonance imaging. Eur Heart J 2008;29:2544–51.
[34] Lehke S, Lossnitzer D, Schob M, Steen H, Merten C, Kemmling H, et al. Use of cardiovascular magnetic resonance for risk stratification in chronic heart failure: prognostic value of late gadolinium enhancement in patients with non-ischemic dilated cardiomyopathy. Heart 2011;97:727–32.
[35] Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajua P, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic gadolinium imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail 2010;3:51–8.
[36] Rudolph A, Abdel-Aty H, Bohl S, Boye P, Zagrosek A, Dietz R, et al. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different form of left ventricular hypertrophy. JACC 2009;53:284–91.