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# Intravascular ultrasound for morphological assessment of napkin-ring sign detected on multidetector computed tomography

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ABSTRACT

*Background:* Although napkin-ring sign (NRS) plaques assessed by multidetector computed tomography (MDCT) is identified as a high-risk feature, the detailed morphological features are still unknown. The purpose of this study was to elucidate the morphological features of the MDCT-assessed NRS using intravascular ultrasound (IVUS).

*Methods:* We evaluated 204 plaques in 193 patients with non-ST-elevation acute coronary syndrome who were diagnosed using 128-slice MDCT and were assessed using IVUS prior to coronary intervention. Morphology was compared between plaques with and without MDCT-assessed NRS. Severe IVUS-assessed attenuation was defined as an attenuation angle >180°.

*Results:* NRS was detected in 49 lesions. MDCT-assessed plaque attenuation was lower ($p < 0.0001$), and cross-sectional plaque areas at lesion sites, remodeling index, and the prevalence of positive remodeling were greater, in lesions with NRS ($p < 0.005$, $p < 0.0001$, and $p < 0.0001$, respectively). Furthermore, the IVUS-assessed remodeling index and prevalence of severe attenuation and speckled echo appearance were significantly greater in lesions with NRS ($p < 0.01$, $p < 0.0001$, and $p < 0.0001$, respectively). Using multivariate analysis, IVUS-assessed speckled echo appearance was identified as an independent predictor of MDCT-assessed NRS (odds ratio, 3.59; 95% confidence interval, 1.49–8.66; $p < 0.005$).

*Conclusion:* MDCT assessment of NRS may be associated with larger heterogeneous necrotic cores and greater positive remodeling.

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## 1. Introduction

Multidetector computed tomography (MDCT) has allowed the non-invasive assessment of coronary artery stenosis and culprit coronary plaque characteristics [1–5]. Coronary flow deterioration (no-reflow/slow flow) is an issue during primary percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS), because no-reflow has been shown to predict larger infarct size and consequently poor clinical outcomes [6]. Previous studies have demonstrated that the presence of the napkin-ring sign (NRS), also termed ring-like enhancement or signet ring-like appearance, on MDCT is useful for detecting plaque disruption identified using IVUS or angioscopy [7,8] and for predicting transient no-reflow during PCI [9,10]. Furthermore, the presence of NRS on MDCT has been demonstrated as an important sign of thin-cap fibroatheroma identified using optical coherence tomography [11]. Previous studies have shown that NRS is strongly associated with future acute coronary events [12,13], and recent reviews have identified NRS as a high-risk coronary plaque feature that is associated with the probability of ACS [14,15]. In a previous postmortem histological study on NRS [16], the outer portion of NRS plaques was found to contain a significant amount of fibrous plaque tissue, correlating with the high attenuation rim observed on MDCT. Moreover, histopathological analyses revealed significant degrees of vasa vasorum.

Detailed plaque assessment using intravascular ultrasound (IVUS) is useful for the prediction of transient no-flow phenomenon [17–20]. Atherosclerotic plaques with ultrasonic attenuation may be associated with transient deteriorations in coronary flow and consequently with greater infarct size and higher incidence of fatal arrhythmia following

*Abbreviations:* ACS, acute coronary syndrome; HDL, high-density lipoprotein; HU, Hounsfield units; IVUS, intravascular ultrasound; MDCT, multidetector computed tomography; NRS, napkin-ring sign; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RI, remodeling index; TIMI, thrombolysis in myocardial infarction.

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PCI in patients with ACS. These assessments may aid the selection of lesions suitable for distal protection devices. Previous studies have demonstrated that CT density values measured within plaques reflect plaque composition observed using IVUS [21–23].

The purpose of this study was to elucidate the morphological features of MDCT-assessed NRS using IVUS.

## 2. Methods

### 2.1. Study population

This study included patients with non-ST-elevation ACS who were admitted to Hiroshima City Asa Hospital between March 2010 and July 2015. All patients presented with ischemic chest discomfort, and significant coronary stenosis was identified using 128-slice MDCT prior to admission. Patients with myocardial infarction or coronary artery bypass grafting were excluded. Myocardial infarction was diagnosed by the serum troponin value using international criteria [24]. Patients with heavily calcified lesions, left main coronary artery disease, tortuous lesions expected to cause difficulty in advancing IVUS catheters, and lesions with thrombolysis in myocardial infarction (TIMI) flow grade <2 were also excluded. We identified MDCT-assessed plaques based on coronary angiography and evaluated each plaque using IVUS.

Patients were divided into two groups based on the presence or absence of NRS at culprit coronary plaques identified using MDCT. We assessed patient characteristics, including age, gender, body mass index, waist circumference, the presence of coronary risk factors (hypertension, diabetes mellitus, hyperlipidemia, current smoking, and ischemic family history), and medications. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or anti-hypertensive drug usage. Hyperlipidemia was defined as serum low-density lipoprotein level ≥140 mg/dl, fasting serum triglyceride level ≥150 mg/dl, or anti-hyperlipidemic drug usage. Diabetes mellitus was defined as any of the following: fasting serum glucose level ≥126 mg/dl, non-fasting glucose level ≥200 mg/dl, self-reported usage of diabetes medications, or a self-reported previous diagnosis by another physician.

Informed consent was obtained from all patients participating in the study.

### 2.2. MDCT scanning and imaging protocol

MDCT was performed using a 128-slice dual source detector CT (SOMATOM Definition Flash Dual Source 128-slice scan, Siemens, Forchheim, Germany). All patients received sublingual nitroglycerin (0.3 mg) immediately prior to scanning. Patients with heart rate >100 beats/min received intravenous landiolol (0.125 mg/kg). For contrast-enhanced scanning, a 0.7 ml/kg bolus of contrast medium (Iopamidol, 370 mg I/ml, Bayer Healthcare, Berlin, Germany) was intravenously injected at a flow rate of 0.07 ml/kg/s, followed by a 50-ml injection of saline at the same flow rate. We acquired contrast-enhanced data during an inspiratory breath hold. Volume data sets were acquired in helical mode (128 × 0.6 mm, collimation; rotation time, 280 ms; tube voltage, 120 kV). The estimated radiation dose ranged from 1 to 10 mSv.

#### 2.2.1. Image analysis of coronary arteries using MDCT

Image reconstruction was performed using image-analysis software on a dedicated computer workstation (Virtual Place Raijin plus, AZE, Tokyo, Japan). Analysis of MDCT image data was performed by two experienced readers.

Outer vessel area and arterial remodeling index (RI) were assessed using cross-sectional images. RI was calculated as the ratio of the outer vessel cross-sectional area at the plaque site to the mean cross-sectional area of the proximal and distal reference sites in a normal-appearing vessel segment. Positive remodeling was defined as RI > 1.10 [10,25]. Plaque CT attenuation values, expressed in Hounsfield units (HU), were measured at five points, and the lowest values at three points were averaged. Low attenuation plaques were defined as those with CT attenuation values <50 HU. Plaques were classified as non-calcified plaques (plaques with lower density than contrast-enhanced vessel lumens without any calcification), calcified plaques (plaques with high density), or mixed plaques (plaques with non-calcified and calcified elements within a single plaque) [13,26]. Specifically, any discernible structure that could be assigned to the coronary artery wall, but with a CT density below the contrast-enhanced coronary lumen and above the surrounding connective tissue, was defined as a noncalcified coronary atherosclerotic plaque [1]. Any hyperdense structure that could be visualized separately from the contrast-enhanced coronary lumen and could be assigned to the coronary artery wall was defined as a calcified atherosclerotic plaque [1]. A second qualitative reading was performed to describe the attenuation pattern of non-calcified plaques in cross-sectional images previously classified as non-calcified plaques or mixed plaques. Plaque cross-sections were classified as homogenous if no variation in attenuation was observed. NRS was defined as the presence of low CT attenuation at the center of plaques close to the lumen surrounded by a rim of higher attenuation (Fig. 1, panels A and B) [13,16]. Thus, the plaque attenuation pattern classification scheme comprised four categories: calcified plaques, homogenous plaques, heterogeneous non-NRS plaques, and NRS heterogeneous plaques. The prior three plaque patterns were classified as non-NRS plaques.

#### 2.2.2. Interventional protocol

Oral aspirin (100 mg/day), clopidogrel (75 mg/day), or prasugrel (3.75 mg/day), along with intravenous heparin (5000 U), were administered prior to coronary intervention. Coronary angiography was performed according to the standard Judkins technique, using a 6-F sheath and catheters. Images were analyzed as previously described, and substantial lesions (vessel diameter narrowing >50%) were quantitatively measured [27].

The location of the culprit lesion was determined by correlating the presence of a complex lesion with electrocardiographic and wall motion abnormalities. In each patient, the coronary vasculature was reviewed to identify any anatomically remote complex lesions. An anatomically remote lesion was defined as a lesion in an artery different from that containing the culprit lesion, in a different branch of the same artery, or in the same branch but at least 5 cm from the culprit lesion and with an intervening disease-free segment. Angiograms were analyzed by two independent angiographers. Results were compared, and a final decision was made by consensus when there was disagreement.

Direct stenting was performed in the majority of patients, and pre- and post-dilatation was performed according to the operator's discretion. Stent diameters and balloon inflation pressures were recorded. The slow flow phenomenon was defined as coronary flow of TIMI flow grade 0–2 with ST-segment elevation on ECG during the procedure, except in cases of dissection, spasm, thrombus, or residual stenosis [28,29]. TIMI flow grade was assessed by two experienced cardiologists.

#### 2.2.3. Intravascular ultrasonographic image acquisition and image analysis

Immediately prior to PCI, culprit lesions were observed using IVUS (VISIWAVE, Terumo, Tokyo, Japan). IVUS examination was performed using an anatomic pullback device at a rate of 0.5 mm/s.

All images were digitally recorded and analyzed by two independent investigators who were blinded to the clinical presentation. Corresponding images from IVUS were identified according to observed distances from two landmarks such as side branches. In cases of discordance between observers, a consensus reading was obtained. Attenuated plaques were identified according to the absence of an ultrasound signal behind the plaque that was either hypoechoic or isoechoic compared with the reference adventitia but contained no

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