Prediction of Acute Coronary Syndrome by Using Multislice Computed Tomography

– Can We Predict the Onset of Acute Coronary Syndrome? (Pro) –

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Predicting the occurrence of acute coronary syndrome (ACS) is a major clinical challenge for cardiologists. Multislice computed tomography (CT) has enabled easy detection and assessment of atherosclerotic coronary plaque, and therefore has considerable potential in the prevention of ACS. The recent development of 64-slice cardiac CT enables detailed information on both plaque properties and characteristics to be obtained with excellent diagnostic accuracy. Cardiac CT therefore has great potential for detecting the unstable plaques that are prone to result in ACS. (*Circ J* 2011; **75**: 2013–2018)

Key Words: Acute coronary syndrome; Magnetic resonance imaging; Multislice computed tomography; Unstable plaque

A major clinical challenge for cardiologists, particularly those specializing in interventional cardiology, is the detection and prevention of acute myocardial infarction and other acute coronary syndromes (ACS). With the advent of multislice computed tomography (CT) in 2002, the quality of imaging of the coronary artery improved dramatically, with this new technology enabling easy detection of atherosclerotic plaque and assessment of its composition and mechanical properties. As a consequence, there is considerable hope that cardiac CT will be an effective means of detecting and preventing ACSs.^{1,2}

In this review of the recent literature, we evaluate the prospect of cardiac CT being used to predict ACS.

The Concept of Unstable Coronary Plaque

In their review in 2003, Naghavi et al³ discussed the concept of unstable coronary plaque, and proposed different types of “vulnerable” plaque as the cause of ACS and sudden cardiac death (Figure 1). Generally, rupture-prone vulnerable plaque is recognized as having the morphological characteristics of unstable plaques that lead to ACS.

The morphology of unstable coronary plaques that are prone to develop into ACS have been well defined using pathological examinations: a large necrotic core >25% of plaque area, vessel remodeling, large plaque causing >50% occlusion in 4/5, intraplaque hemorrhage, neovascularization and a thin fibrous cap (thickness ≤65 μm) heavily infiltrated with macrophages.⁴ With increased volume, these positively remodeled plaques are vulnerable to rupture, thereby increas-

ing the risk of ACS.⁵

On the other hand, it is well known that approximately 70% of ACS cases develop from mild to moderate coronary stenosis with ≤50% diameter stenosis as measured by coronary angiography (CAG) (Figure 2).⁶ In the early stage of coronary atherosclerosis, the coronary arteries enlarge relative to plaque area and functionally important lumen stenosis may be delayed until the lesion is occupying 40% of the internal elastic lamina area (ie, compensatory enlargement). We therefore conclude that the preservation of a near-normal lumen cross-sectional (CS) area even in the presence of a large plaque should be taken into account when using CAG to evaluate atherosclerotic disease. In other words, a large volume of plaque may have already formed in patients with a near-normal to moderate stenotic lesion, as assessed by CAG. It is also well known that multiple plaque disruptions may occur asymptotically in ACS patients.⁷

Coronary Plaque Imaging by Cardiac CT

The 64-slice cardiac CT scanners are used mainly in the clinical setting and have a high spatial resolution of 0.5–0.6 mm. In routine procedures, plaques are identified by curved multiplanar reconstruction images, with CS images being used to examine the in-depth plaque morphology. These images provide the data of the remodeling index (RI), CT densities (in Hounsfield units [HU]) and calcium volume, parameters that are used to evaluate plaque properties. In addition, plaque components can be discriminated by color-coded mapping according to CT density, which provides easy-to-read visual

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Figure 1. Different types of vulnerable plaque. (Reproduced with permission from Naghvi et al. *Circulation* 2003.³)

Figure 2. Myocardial infarction develops most frequently from plaques that were only mildly to moderately obstructive, months to years before infarction. (Reproduced with permission from Falk et al. *Circulation* 1995.⁶)

information on plaque characteristics.²

A representative case of plaque evaluation is shown in **Figure 3**.

Diagnostic Accuracy of Cardiac CT for Coronary Artery Disease

The excellent diagnostic accuracy of cardiac CT for detecting coronary artery disease is well established.⁸ In a recent study, the diagnostic accuracy of 64-slice cardiac CT for diagnosing obstructive coronary artery disease with $\geq 50\%$ luminal stenosis was reported as 89% sensitivity, 96% specificity, 76% positive predictive value, and 98% negative predictive value.⁹ This high diagnostic accuracy plays a crucial role in early detection of patients who are predisposed to ACS.

Cardiac CT Findings Suggestive of Unstable Plaque

In a recent cardiac CT study of the morphological comparison of culprit lesions obtained in patients with ACS or stable angina, Motoyama et al characterized the ACS culprit lesions as follows: positive vascular remodeling (RI > 1.10), non-calcified plaque (NCP) with a CT density < 30 HU, and the presence of spotty calcification (**Figure 4**).¹⁰ These characteristics are similar to the pathological characteristics. Matsumoto et al also reported that NCPs with a low CT density on cardiac CT provided prognostic information on ACS.¹¹ Previous studies have repeatedly shown that plaque with these characteristics corresponds closely to the rupture-prone soft plaque identified by either intracoronary ultrasound¹²⁻¹⁶ or coronary angiography.¹⁴ Moreover, Kitagawa et al¹⁷ reported that patients with ACS had a higher prevalence of NCP with vulnerable characteristics (minimum CT density < 40 HU, RI

Figure 3. Plaque evaluation of a representative case of unstable angina pectoris. A curved multiplanar reconstruction image clearly shows a severe obstructive lesion with positively remodeled plaque (A). Cross-sectional image of the lesion: (B) presence of soft plaque with lipid cores characterized by low CT density (-38 and -15 HU); (C) positively remodeled coronary plaque (RI 1.69) with 95.3% AS. Color-coded mapping according to CT density provides visual information on plaque components (D). HU, Hounsfield unit; RI, remodeling index; AS, area stenosis.

Figure 4. Plaque characteristics of culprit lesions in ACS and target lesions in SAP groups. Positive remodeling, NCP <30HU, and spotty calcification are seen more frequently in culprit ACS lesions. ACS, acute coronary syndrome; SAP, stable angina pectoris; NCP, noncalcified plaque; HU, Hounsfield unit. (Reproduced with permission from Motoyama et al. *JACC* 2007.¹⁰)

>1.05, and adjacent spotty calcification) than patients with a stable clinical presentation. Motoyama et al also confirmed that plaques with those characteristics were a high-risk for ACS, with approximately 22% leading to subsequent occurrence of ACS during a follow-up period of longer than 2 years (Figure 5).¹⁸ These studies suggest that cardiac CT has considerable potential for detecting unstable plaques that are prone to develop into ACS.

Representative Case of the Development of ACS

A representative case of the development of ACS is shown in Figure 6. The patient was male, aged approximately 70 years, with multiple coronary risk factors (hypertension, diabetes mellitus, and hypercholesterolemia). He sometimes felt atypical chest discomfort and was therefore referred to hospital for screening of coronary artery disease by cardiac CT. The

cardiac CT at that initial visit showed no significant stenosis, but positively remodeled plaque (RI 2.17) with an 81.7% plaque area (PA), low CT density (minimum CT density -21 HU) and spotty calcification in the proximal right coronary artery. One year later, he underwent a second cardiac CT because of recurrent chest pain and this time there was narrowing of the lumen area because of increased plaque volume (PA 86.9%) with an ulcer also being observed. Unfortunately, the patient had an acute myocardial infarction 12 days later. Intravascular ultrasound confirmed markedly remodeled plaque with extensive ultrasound attenuation, which indicated lipid-rich rupture-prone soft plaque as the culprit lesion.

The positively remodeled NCPs with low CT density are recognized as having the characteristics of unstable plaque and are thought to be in the well-matured stage of plaque pro-

gression, with compensatory remodeling.¹⁹ Such NCPs are easy to detect by cardiac CT.

Limitations for Cardiac CT-Based Prediction of ACS

Mechanical limitations, such as spatial resolution and density resolution, in cardiac CT imaging may preclude detection and identification of several important factors used to characterize unstable plaques. These factors include a thin fibrous cap (<65 μ m) and necrotic core, intraplaque hemorrhage, and neovascularization. In addition, cardiac CT-based assessment of early-stage plaques is often subject to error because of small plaque volumes and other factors that affect intra-plaque CT density.^{20,21} Therefore, with early-stage immature plaque, it may be difficult to predict the future occurrence of ACS based on morphological characteristics. Moreover, as reported by Motoyama et al,¹⁸ 78% of 2-featured positive plaques do not develop into ACS, indicating that a high proportion of false-positive results will be obtained when plaque morphology on cardiac CT images is used to predict ACS.

Expectation of Coronary Magnetic Resonance Imaging (MRI) Detecting Unstable Plaque

Imaging unstable plaque using MRI is a well-known technique for carotid artery disease.²² Unstable carotid plaques are shown as high-signal areas on inversion recovery-based 3-dimensional T1-weighted MRI. Recently, this technique was used to successfully describe a high-signal area in the coronary artery, similar to those observed in the carotid artery. More recently, our group observed high-signal areas, termed “hyperintense plaque” (HIP), in the area corresponding to the positively remodeled coronary plaque with low-CT density seen on multislice CT. These HIPs have been observed more frequently in the culprit lesions of ACS patients.^{23,24} In addition, Oei et al reported that these HIPs may correlate with intraplaque hemorrhage and they concluded that this plaque imaging technique may emerge as a valuable tool for detecting “active coronary lesions”.²⁵ On the basis of its ability to provide excellent soft-tissue contrast, MRI appears to be the superior modality for characterizing unstable plaque components.

Conclusions

Cardiac CT-based prediction of ACS occurrence still has several limitations. However, cardiac CT imaging, which has the ability to detect the presence of unstable plaque that may eventually develop into ACS, provides an opportunity for aggressive lipid-lowering and other pharmacotherapies in susceptible patients. The future prospects for this diagnostic modality are therefore considerable and have exciting potential. Because of the rapid technological improvement in cardiac CT imaging, we anticipate that CT-based diagnosis will allow more accurate prediction and better prevention of ACS in the near future. Finally, it is possible that by combining cardiac MR and cardiac CT imaging, the diagnostic accuracy for detecting unstable plaque prone to develop into ACS may be further improved.

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Authors' Comments on the Con-Side Author

Can we predict the onset of ACS? Regarding this issue, Dr Kihara emphasized that elucidation of CT coronary images and comparison with pathological examination has not been achieved.²⁶ In addition, radiation dosage and administration of contrast media are matters of concern for its routine application.

We agree that there are some limitations to predicting the onset of ACS. Certainly, elucidating the relationship between CT coronary imaging and pathological investigation using CT is required.

Cardiac CT-based assessment of early-stage plaques is often subject to error because of small plaque volumes and other factors that affect intra-plaque CT density, but the adverse effects of radiation/contrast media will be decreased along with future advances in radiographic technology.

Compared with cardiac CT imaging, in some cases MRI is more accurate for detecting unstable plaque in the coronary artery. As Oei et al reported, these hyperintense plaques may correlate with intraplaque hemorrhage and therefore this plaque imaging technique may emerge as a valuable tool for detecting “active coronary lesions”.²⁵ We expect the combination of cardiac MRI and CT imaging to be used for assessing coronary plaque in the future.²⁶