Non-Invasive Assessment and Clinical Strategy of Stable Coronary Artery Disease by Magnetic Resonance Imaging, Multislice Computed Tomography and Myocardial Perfusion SPECT

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Coronary multislice computed tomography (MSCT) angiography and magnetic resonance angiography (MRA) have emerged as new diagnostic techniques that allow direct visualization of the coronary artery. These new modalities have both advantages and disadvantages concerning radiation exposure, the use of contrast medium, ability of visualizing heavily calcified artery lumens, and spatial and temporal resolution. However, these modalities only provide anatomical information of the coronary artery. Functional assessment of the severity of coronary artery disease (CAD) is essential for the management of patients with known or suspected CAD in practical clinical settings. Myocardial perfusion single-photon emission computed tomography is thought to be the most suitable diagnostic procedure for the determination of therapeutic strategy when coronary MSCT and MRA show significant and also insignificant coronary artery lesions. (Circ J 2010; 74: 34–40)

Key Words: Coronary artery disease; Magnetic resonance imaging; Multislice computed tomography; Prognosis; SPECT

REVIEW

Recent development in non-invasive imaging modalities, such as multislice computed tomography (MSCT) and magnetic resonance imaging (MRI), have gained great attention in the field of diagnostic cardiology, especially in the diagnosis of coronary artery disease (CAD). These imaging modalities have clinical advantages over other imaging techniques including stress echocardiography and stress single-photon emission computed tomography (SPECT), because they permit direct visualization of the coronary artery rather than showing indirect evidence of CAD, such as stress-induced wall motion abnormalities and myocardial perfusion defects. Moreover, MSCT provides additional information to conventional coronary angiography, that is, the coronary artery plaque texture. However, coronary MSCT angiography is not a totally non-invasive method because it requires radiation exposure and contrast medium, which might be harmful in a certain number of patients.1 However, coronary magnetic resonance angiography (MRA), which requires no radiation exposure or contrast medium can be performed safely, and it has potential to become a routine screening tool for participants with low likelihood of CAD, but currently available equipments do not provide information of coronary artery plaques so far. In this review, we discuss advantages and disadvantages of coronary MSCT angiography and MRA. We also discuss the role of myocardial perfusion imaging using myocardial perfusion SPECT in the determination of therapeutic strategies.

Coronary MSCT Angiography

Detection of Coronary Artery Stenoses and Occlusions

We have shown, for the first time in Japan, that MSCT has potential to become the first choice of diagnostic modality for patients with suspected CAD and that MSCT would replace diagnostic coronary angiography.2,3 The sensitivity and specificity of the first generation of MSCT (4 detector-row equipment) for the detection of angiographically significant CAD was 94% and 97%, respectively. In the era of 64 detector-row MSCT, the diagnostic accuracy was increased because of improvements in spatial and temporal resolution; the accuracy had a sensitivity of 95–97% and specificity of 93–98%.4–7 On segment-based analysis, 8 to 12% of coronary segments were not assessable due to heavily calcification, arrhythmia and motion artifacts.8–9 However, coronary MSCT angiography has several shortcomings. First, evaluation of severely calcified coronary artery lesions is sometimes difficult because of overestimation of the size of calcium deposit due to partial volume effect, leading to overestimation of coronary artery stenosis. Dual-energy CT equipments that provide 2 different X-ray energy sources might allow clear...
visualization of heavily calcified coronary arteries. Second, limited temporal resolution results in deterioration of image quality in patients with high heart rates. Dual-source CT, which provides 75 ms temporal resolution, allows acceptable images for interpretation without decreasing heart rates by β-blockers. In addition, recently introduced CT equipments that provide faster gantry rotation (0.27–0.30 s/rotation) might also allow improved temporal resolution of 135–150 ms when half reconstruction is applied and 67.5–75 ms when 2-segment reconstruction is applied. Third, MSCT requires radiation exposure (approximately 10–12 mSv in case of helical CT scanners) and injection of contrast medium. The use of contrast becomes particularly important in patients with chronic kidney disease, elderly patients and patients with diabetes mellitus. With recent development of new technology, a 320-detector-row CT allows reduced amount of contrast medium for routine MSCT examinations. Other CT equipments that provide non-helical scan mode can also decrease radiation exposure to 2–3 mSv. These non-helical scanners can increase signal to noise ratio and permit visualization of heavily calcified coronary arteries and stents.

Aside from these disadvantages, performing coronary MSCT angiography can be justified when patients are symptomatic and having multiple coronary risk factors. The representative case with high-grade coronary artery stenosis is demonstrated in Figure 1.

**Evaluation of Coronary Artery Plaques**

The role of coronary MSCT angiography in the diagnosis of CAD is not only in the detection of significant coronary artery luminal narrowing, but also in the assessment of coronary artery plaque texture. Since acute coronary syndrome (ACS), including acute myocardial infarction and unstable angina, occurs mainly in coronary arteries with stenosis less than 70%, detecting non-obstructive, vulnerable coronary artery plaques is of utmost importance in the management of high-risk patients. In a retrospective study, we have demonstrated that patients with ACS have lower CT densities within the plaque and larger vessel area in the culprit coronary artery lesions than those with stable angina. Furthermore, plaque CT densities are higher in non-culprit, remote coro-
Coronary artery in patients with ACS than in those with stable angina. In a prospective study, we have shown that patients with CT low-dense plaques are more likely to have ACS events than those without CT low-dense plaques during the 5-year follow-up period (Figure 2). Motoyama et al also focused on the presence of positive vessel remodeling and low-attenuation plaque for the prognostic evaluation. They documented that positively remodeled coronary segments with low-attenuation plaques on MSCT angiography were at a high risk for future ACS events.

Evaluating plaque texture and vessel size by coronary MSCT angiography permits not only prediction of future cardiac events, but also the detection of ongoing ACS, which could not be diagnosed by conventional non-invasive methods, such as electrocardiography, echocardiography and cardiac enzymes. In addition, coronary MSCT angiography allows non-invasive evaluation of changes in the plaque size after lipid-lowering therapy by statins.

Clinical Indications of MSCT Angiography
For the patients with both any symptoms and intermediate pretest likelihood of CAD (roughly 30–70%), MSCT angiography might become a first choice of imaging modality. If those patients did not show either any coronary stenoses or calcification and plaques, the probability of CAD is very low. The group of intermediate likelihood of CAD without cardiac symptoms might as well perform coronary calcium scanning. If the coronary calcium score was 0, further scanning with contrast medium might be unnecessary for avoiding inappropriate radiation exposure. Those patients without coronary calcification showed extremely good prognosis. Conversely, critical stenosis in the left main coronary artery, which might be overlooked by myocardial perfusion SPECT, correlated with high cardiac event rates. When MSCT findings did show equivocal or mildly abnormal in patients without high coronary risks, the next recommendations are so far uncertain. Furthermore, we do not have enough data whether or not the information of MSCT angiography improve patients’ outcome.
Coronary MRA

Recent introduction of MRI, which allows whole heart, 3-dimensional navigator free-breathing imaging, has gained an enormous amount of attention because this technique is totally non-invasive without radiation exposure or contrast medium. The sensitivity and specificity of coronary MRA to detect angiographically significant CAD (coronary stenosis ≥50%) are 82% and 90–91%, respectively. On patients’ basis, 13–14% of unsuccessful rate has been reported. The failure is mainly due to irregular breathing or drift of the diaphragm position during data acquisition. However, because of limited spatial resolution of MRA (1.1 mm), coronary arteries with the diameter less than 1.5 mm are not well visualized and diagnostic accuracy of distal coronary artery lesions is inferior to coronary MSCT angiography, which provides temporal resolution of 0.4 mm. Besides, currently available MRI equipments do not provide information of coronary artery plaques and lesions after stent implantation. However, advantages of coronary MRA over coronary MSCT angiography are the ability of assessing heavily calcified coronary arteries and better temporal resolution, which does not require premedication that lowers heart rates. Because of its non-invasive nature, MRA might be the most feasible imaging modality for the detection of CAD in patients with chronic kidney disease, in young patients and asymptomatic patients. In particular, coronary MRA has been shown to be effective in detecting congenital coronary artery anomalies. The representative case of stable angina has been shown in Figure 3.

The Role of Nuclear Cardiology in the Era of Coronary MSCT Angiography and MRA

Before the era of coronary MSCT and MRA, stress myocardial perfusion SPECT and stress echocardiography were the first choice of diagnostic modalities for the detection of CAD. The sensitivity and specificity of myocardial perfusion SPECT for the detection of significant CAD are 82–84% and 90–97% in our institute. Since myocardial perfusion SPECT detects myocardial ischemia due to hemodynamically significant CAD, it is only natural that the sensitivity for detecting mild coronary artery stenosis is inferior to that derived from coronary MSCT angiography. However, myocardial perfusion SPECT has been shown to be important in therapeutic decision-making in patients with stable angina. For example, patients with inducible myocardial ischemia greater than 10% of the left ventricle benefit from coronary artery interventions in terms of future cardiac events, including ACS and cardiac death, whereas intensive medical treatment is effective for those with myocardial ischemia less than 10%. In addition, myocardial viability can be easily evaluated by analyzing the redistribution status of the tracer (201Tl) after 24 h. Thus, unnecessary invasive interventions to the arteries supplying the non-viable myocardium can be avoided.

Another advantage of myocardial perfusion SPECT over coronary MSCT angiography and MRA is the potential to predict future cardiac events. We prospectively identified 2,170 consecutive patients who underwent dual-isotope (rest 201Tl and stress 99mTc-Tetrofosmin) SPECT with either exercise or pharmacological stress test. In this large scale, we prospectively have demonstrated that cardiac event rates are successfully stratified by summed stress score (SSS), which were calculated by adding perfusion scores at stress using a 20-segment model of the left ventricle with a 5-point scale (Figures 4, 5). Normal SPECT group (SSS <4) indicates very low annual ACS event rate (acute myocardial infarction; 0.2%/year, unstable angina; 0.7%/year). In addition, multivariate Cox proportional hazard regression analysis showed that inducible ischemia (summed difference score: SDS, which was derived from the subtraction between stress and rest scores) and hypertension were the independent predictors of ACS events. Multivariate Cox proportional hazard analysis also revealed that the best predictor of cardiac death was age, followed by SSS. SDS was a weak but significant predictor of cardiac death. Although the cardiac event rate in the present study was lower than that in the American population, predictors of ACS and cardiac death that were determined by multivariate Cox proportional hazard regression analysis are also in good agreement with those of previous studies. In the subgroup analysis, we have also shown that the decrease in post-stress left ventricular ejection fraction (EF) has an incremental prognostic value to myocardial perfusion abnormality for the prediction of future ACS. According to those approaches, annual event rates of ACS in subgroups are depicted in Figure 6. There was statistical significance of the annual ACS rate between the group with small ischemia (SDS <4; 0.9%/year) and the group with relatively high SDS (SDS ≥13; 4.8%/year).
large ischemia (SDS ≥ 4; 2.6%/year). There was also statistical significance of the annual ACS rate between the group with normal post-stress function (EF ≥ 45%; 0.9%/year) and the group with impaired post-stress function (EF < 45%; 2.9%/year) using 8-frame electrocardiogram (ECG)-gating technique. We also showed the combined assessment of significant myocardial ischemia and low post-stress EF was the best predictor than myocardial ischemia alone or low post-stress EF alone (Figure 7).

Conversely, myocardial perfusion SPECT has disadvan-
tages. One of them is radiation exposure, which is estimated to be 10mSv for 99mTc-sestamibi tracer. Another is the high-cost of total examination in Japan.

**Strategy of Non-Invasive Assessment of Stable CAD**

Figure 8 illustrates our conceptual approach for the stable patients with or suspected CAD using MRA, MSCT and SPECT. For patients with low likelihood of CAD, a completely non-invasive modality, i.e., MRA, which does not require gadolinium contrast medium, is recommended because MRA has high negative predictive value in the diagnosis of major coronary artery stenoses and a cost advantage. Patients with significant coronary artery stenosis with MRA scan, will be assigned to coronary MSCT angiography or myocardial perfusion SPECT.

In symptomatic patients with intermediate pretest likelihood of CAD, coronary MSCT angiography is the first choice of diagnostic modality. Because of the value of non-invasive diagnostic modalities is highest in patients with an intermediate likelihood of CAD, these patients are good candidates for MSCT angiography, which provides higher sensitivity and specificity than that in MRA. In patients without either significant coronary artery stenoses or plaques, medical treatment is the first choice. Medical treatment might include lifestyle modification including exercise and diet; the NIPPPONDATA80 group clearly demonstrated the relationship between cardiovascular events and coronary risks. Patients with CT low-dense coronary artery plaques without significant coronary artery stenoses should undergo aggressive lipid-lowering treatments.

When visually significant coronary stenosis is observed, stress ECG-gated myocardial perfusion SPECT is strongly recommended for the evaluation of functional coronary artery stenosis. As mentioned previously, myocardial perfusion SPECT is essential for assessing functional significance of CAD and should be the gatekeeper for the determination of therapeutic strategies. The background of the idea is supported by Hachamovitch et al, who clearly demonstrated that patients will benefit from coronary interventions only when the amount of inducible ischemia is greater than 10% by myocardial perfusion SPECT. In a subset of patients who have inducible ischemia of 5–10%, the necessity of detection of coronary artery plaques by coronary MSCT angiography is under debate even when the patients have multiple risk factors for CAD. Combined assessment of perfusion and cardiac function by ECG-gated myocardial perfusion SPECT contributes incremental prognostic evaluation for those patients’ prognosis.

Myocardial perfusion SPECT, thus, provides additional information to MRA and coronary MSCT angiography concerning patients’ prognosis and therapeutic decision-making, and it is essential in the management of patients with CAD.

When patients had frequent arrhythmia, severe coronary calcification, motion artifact during MSCT or MRA data acquisition and chronic kidney disease, myocardial perfusion SPECT should be recommended for the first choice of diagnostic tool for therapeutic decision-making.

**Conclusion**

With an advent of new non-invasive imaging techniques, diagnostic and therapeutic strategies for patients with CAD have become more complicated than ever. Basically, non-invasiveness is the first priority for patients with low and intermediate risk factors. In this line, coronary MRA would be the first choice of diagnostic modality in asymptomatic patients and in patients with low pretest likelihood of CAD. Coronary MSCT angiography has been established as the routine imaging modality in the past decade, but its use might be limited to patients with middle or high pretest likelihood of CAD because MSCT is not totally non-invasive, but it requires radiation exposure and injection of contrast medium. Both imaging techniques have both advantages and disadvantages as mentioned previously. After the anatomical evaluation by either coronary MRA or coronary MSCT angiography, functional evaluation of CAD by myocardial perfusion SPECT is recommended because it contributes to therapeutic decision-making and predicts patients’ short- and long-term prognosis.

In summary, we described diagnostic and therapeutic management of patients with CAD in the era of new diagnostic imaging modalities. These techniques not only provide assessment of CAD without exposing patients to unnecessary invasive coronary angiography, but also give information for making therapeutic strategy and provide information of patients’ prognosis.

**References**


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