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# Simultaneous Assessment Beyond Coronary Stenosis by Multislice Computed Tomography

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## 1. Introduction

Whereas in the past computed tomography (CT) of the coronary arteries could detect only calcifications, recently multislice computed tomography (MSCT) has been already accepted as an efficient noninvasive tool for the detection of coronary artery stenosis, providing good sensitivity, specificity, and very high negative predictive value. However, it must be recognized that these good results are obtained when technically inadequate scans or patients with rapid heart rates, arrhythmia, or severe calcification were excluded. Therefore, for patients who already have a clinical indication for coronary angiography by MSCT in a real world, it would be a clinically important advantage if the same MSCT data could be used to gain additional information about the coronary artery disease (CAD). It has been reported that MSCT enables the analysis of the coronary plaques, left ventricular (LV) function, left atrial volume, myocardial enhancement, aortic valve, and the thoracic aorta, besides the assessment of the coronary stenosis. In this chapter, we focus on the additional information obtained simultaneously from the same data for coronary angiography by MSCT.

## 2. Assessment of myocardial contrast enhancement concomitantly with an assessment of coronary stenosis

MSCT has reached a spatial and temporal resolution that is high enough to visualize not only coronary arteries but also infarcted and non-infarcted myocardium (Paul et al., 2003). Nevertheless, coronary arteries with severely calcified plaques can still be difficult to evaluate by MSCT angiography (Leschka et al., 2005) because blooming artifacts and beam hardening effects can lead to misinterpretation of the luminal area.

Here, we analyzed first-pass myocardial enhancement by 64-MSCT, evaluated its use for detecting significant stenosis and compared the results with quantitative coronary angiography (QCA) (Yoshida et al., 2009). In our study, myocardial contrast enhancement is quantified by deriving the signal density (SD) from the Hounsfield units (HU) values of the CT images. Data from 70 patients with single-vessel disease who underwent 64-MSCT followed by catheter-based coronary angiography were analyzed. After an evaluation of coronary stenosis, early- and late-diastolic (at 60% and 90% of the RR interval, respectively)

short-axis images at 3 levels of the LV (basal, mid and apical), were analyzed. The SD in segments of the LV wall supplied by coronaries with and without stenosis was assessed. In this study, the SD of the LV cavity and remote myocardium was used as a reference for quantifying impaired myocardium. A region of interest of approximately 50 mm<sup>2</sup> was drawn over each myocardial segments and LV cavity. A standardized SD was then calculated from the SD of the myocardium and the SD of the LV cavity according to the following formula:

$$\text{Standardized SD} = \frac{\text{the SD of the myocardium}}{\text{the SD of the LV cavity}} \times 100\%$$

The reduction in the percent SD between the myocardium surrounding a stenotic lesion and non-impaired myocardium away from a stenotic lesion was then defined as:

$$\%SD = \frac{\text{standardized SD stenosis} - \text{standardized SD no - stenosis}}{\text{standardized SD no - stenosis}} \times 100\%$$

In total, 48 patients had 70 atherosclerotic lesions (83 segments) detected by QCA: 35 segments were categorized as a calcified plaque, and the other 48 segments were categorized as a non-calcified plaque. Forty-six segments were found to have more than 50% coronary stenosis by QCA. Diagnosis of significant stenosis by MSCT coronary angiography (segment-based analysis) had a sensitivity, specificity and accuracy for segments without calcified lesions of 92%, 100% and 99.7%, respectively, and 95.2%, 50%, and 77.1%, respectively, for calcified lesions. The standardized SD and %SD values in patients with a significant stenosis (more than 50% stenosis as determined by QCA) were significantly lower than those in patients without a stenosis. A similar trend was observed in patients with more than 75% stenosis. These values did not change during the early to late diastolic phase of the cardiac cycle. Taking into account the myocardial enhancement by calculating the decrease of the %SD, a sensitivity, specificity and accuracy of diagnosis of significant stenosis could be improved to 95.2%, 85.7% and 91.4%, respectively, for segments with calcified lesions. The analysis of the %SD reduction improved the diagnostic performance of MSCT for stenosis of coronaries with calcified plaques. The present study is a clinically essential investigation of first-pass myocardial enhancement by MSCT. Because the same image data that were used for MSCT coronary angiography were also used for the first-pass myocardial enhancement analysis, the patient was neither subjected to additional radiation exposure nor additional administration of contrast agent.

Impaired myocardial blood flow and clinically unrecognized myocardial injuries could lead to reduced enhancement on MSCT images of the myocardium. First, the intra-myocardial coronary capillaries make up more than 90% of the microcirculation of the myocardium and the cross-connections serve to homogenize the myocardial pressure and flow distribution (Kassab et al., 1994, 1999). In myocardium supplied by healthy coronary arteries, increased capillary outlet pressure produces pressure dispersion and local flow reversal (Mittal et al., 2005) during systole, whereas during diastole, the rapidly decreasing capillary outlet pressure promotes the washout of contrast agent. In contrast, stenotic epicardial coronary stenosis fails to supply optimal coronary blood flow (Gould et al., 1974) to the intra-myocardial coronary capillary inlets and as a result, enhancement of CT images of the myocardium appears to be reduced. Impaired myocardial blood flow resulting from more

than 75% stenosis has already been visualized by myocardial contrast echocardiography with power Doppler imaging (Masugata et al., 2000). However, unrecognized myocardial injuries are also a possible cause for reduced myocardial enhancement, as has been shown by other studies in which myocardial injuries in patients with a clinical suspicion of CAD, but without known myocardial infarction, were detected by cardiac magnetic resonance imaging. We have shown that myocardial enhancement might be represented in the resting condition by the combination of reduced myocardial blood flow and unrecognized myocardial injuries. The advantage of MSCT imaging is that epicardial coronary stenosis can be analyzed concomitantly with an assessment of myocardial enhancement. It is important to note that an analysis of the degree of coronary stenosis and risk areas of the myocardium can be performed without additional radiation exposure or contrast injections. The introduction of myocardial assessment by first-pass scan protocols into clinical practice is easy without additional stress and cost, because of post-hoc analysis.

### 3. Assessment of the atherosclerosis and sclerosis in the aorta

Atherosclerosis consists of two pathological processes: atherosclerosis characterized by morphologic atheromatous lesions appearing in the intima, and sclerosis characterized by an increase in stiffness of the vessel walls. Aortic stiffness is known to increase with age (Tomochika et al., 1999), but it is also correlated with various diseases such as CAD (Herrington et al., 2003) and hypertension (Laurent et al., 2003), or hypercholesterolemia (Tomochika et al., 1999). So far, atherosclerosis and sclerosis of the descending thoracic aorta (DTA) could be observed and analyzed during transesophageal echocardiography performed for other indications than CAD (Tomochika et al., 1999; Sugioka et al., 2002). Typical indications are cardiac embolism, valvular disease and atrial fibrillation, and transesophageal echocardiography is not performed for assessing aortic atherosclerosis in patients with CAD. A patient study with the latter aim would pose ethical problems, in particular since transesophageal echocardiography causes some discomfort.

In contrast, for patients who already have an indication for coronary angiography by MSCT, which is non-invasive, it would be a clinically important advantage if the same MSCT data could be used to gain additional information about the CAD through the analysis of the aorta at multiple locations. A time-resolved, electrocardiographic (ECG)-gated CT technique to derive the aortic distensibility from cyclic cross-sectional area changes has already been validated in a phantom set-up with porcine aortic specimens (Ganten et al., 2005). Ganten et al reported the negative correlation between abdominal aortic distensibility and aging with the use of this method albeit 4- or 16-slice CT (Ganten et al., 2007). The distensibility however depends on the blood pressure, whereas the stiffness  $\beta$  is considered to be independent of the blood pressure (Hayashi et al., 1980; Hirai et al., 1989).

Recently, we quantified atherosclerosis and sclerosis of DTA and analyzed differences between patients with and without CAD using MSCT (Okuyama et al., 2008). The population contained 89 patients who underwent ECG-gated MSCT: 40 patients who were suspected of CAD by MSCT underwent invasive coronary angiography, and had documented significant stenoses (CAD group), 49 patients were found without significant stenoses (control group). We quantified atheromatous lesions and stiffness  $\beta$  of DTA. First, twenty cross-sectional images of DTA were reconstructed every 5% (0-95%) of the RR interval, and the largest and

smallest luminal areas were traced at 3 levels of the DTA avoiding sites of severe atheromatous lesion: at the pulmonary artery bifurcation (proximal DTA), below the heart (distal DTA), and in between (middle DTA). The maximum systolic ( $D_{\max}$ ) and minimum diastolic ( $D_{\min}$ ) lumen diameters were calculated from those areas with the assumption that the cross section was circular ( $\text{diameter} = 2 \times [\text{area} / \pi]^{1/2}$ ) (Nakatani et al., 1995). The aortic stiffness  $\beta$  was then calculated according to the formula

$\beta = \ln (BP_{\text{sys}} / BP_{\text{dia}}) / ([D_{\max} - D_{\min}] / D_{\min})$ , where  $\ln$  was the natural logarithm,  $BP_{\text{sys}}$  was the systolic blood pressure, and  $BP_{\text{dia}}$  was the diastolic blood pressure. Next, we assessed the grade of aortic atherosclerosis for each patient. We divided the DTA into 3 segments of 5 cm length (2.5 cm proximal and 2.5 cm distal to each level described above), then continuously assessed the severity of atherosclerosis in the transverse and longitudinal images of each area. We classified the aortic atheromatous lesions into 4 categories and scored each segment according to the severity of atherosclerosis from 0 through 3, as described previously (Tomochika et al., 1999; Dávila-Román et al., 1994). An atheromatous score 0 indicated a normal aortic wall, score 1 indicated mild atherosclerosis (intimal thickening  $<3.0$  mm, without intimal irregularities), score 2 indicated moderate atherosclerosis (intimal thickening  $\geq 3.0$  mm, with intimal irregularities) and score 3 indicated severe atherosclerosis (significantly raised plaques, calcified plaques or raised plaques with ulcer formation).

In our study, the atheromatous score and stiffness  $\beta$  in the CAD group were significantly higher than those in controls. Multivariate analysis revealed that the average atheromatous score was an independent factor associated with CAD ( $p < 0.005$ ). Receiver-operating characteristic analyses were carried out on the average, maximum, and minimum atheromatous score and stiffness  $\beta$  for identifying patients with CAD. The areas under the curves for the average, maximum, and minimum atheromatous score were 0.82 (95% CI, 0.73 to 0.91), 0.82 (95% CI, 0.73 to 0.91) and 0.75 (95% CI, 0.65 to 0.85), respectively. Regarding the average, maximum, and minimum stiffness  $\beta$ , the areas under the curves were 0.75 (95% CI, 0.65 to 0.86), 0.74 (95% CI, 0.64 to 0.85) and 0.75 (95% CI, 0.65 to 0.85), respectively. A cut-off value  $\geq 1.33$  of the average atheromatous score (total atheromatous score  $\geq 4$ ) had a sensitivity of 73%, a specificity of 84%, a positive predictive value of 78%, and a negative predictive value of 79% for detection of CAD. In contrast, regarding the average stiffness  $\beta$ , a cut-off value  $\geq 14$  had a sensitivity of 63%, a specificity of 65%, a positive predictive value of 60%, and a negative predictive value of 68%. Moreover, the combination of the average atheromatous score ( $\geq 1.33$ ) and stiffness  $\beta$  ( $\geq 14$ ) had a sensitivity of 48%, a specificity of 92%, a positive predictive value of 83%, and a negative predictive value of 68% for detection of CAD. In cases with image qualities unsatisfactory for interpretation of coronary stenoses, the additional assessment of atherosclerosis of DTA will be useful for identifying patients with CAD.

#### 4. Assessment of aortic valve area

In industrialized countries the most frequent cause of aortic stenosis (AS) is degenerative changes of valve leaflets, such as the congenital bicuspid aortic valve (AV) and atherosclerotic valves. These changes frequently occur in elderly patients, who are also at risk for CAD. Severe AS (an AV area (AVA) of less than  $1.0 \text{ cm}^2$ ) accompanied by CAD presents problems for surgical decision-making in whether AV replacement should be performed with coronary artery bypass graft surgery.

Transthoracic echocardiography is an important and non-invasive method for assessing the significance of cardiac murmurs, which are derived from diseased heart valves. For diagnosing and evaluating the AVA by 2-dimensional echocardiography in patients with AS, the planimetric method without disturbed visualizations and the Doppler approach using an adequate angle of ultrasound beam are highly sensitive (Caidahl et al., 1998; Okura et al., 1997). The high spatial and temporal resolution of MSCT might allow for detailed images of the AV orifice and measurements of the AVA.

We investigated whether the AVA in patients with AS assessed by MSCT corresponds to that by echocardiographic assessment and to evaluate simultaneously the clinical accuracy in detecting CAD with MSCT (Tanaka et al., 2007). The AVA of 29 consecutive AS patients with transthoracic echocardiography and MSCT were analyzed. The AVA was estimated by means of the continuity equation method in 2-dimensional echocardiography. Regarding AVA measurement method by MSCT, initially, one data set was reconstructed with the reconstruction window starting at 10% of the cardiac cycle. If motion artifacts were present in the AV, image reconstruction was repeated with the reconstruction window offset 2% toward the beginning and end of the systole until images without motion artifacts were obtained or until 20 data sets had been created, in which case the data set with the fewest motion artifacts was used for further evaluation for each coronary artery separately. The mid-systolic image data set, which was extracted with reference to the R wave of recorded ECG trace, was used to assess the AV orifice. The AV orifice images were reconstructed with a slice thickness of 2.0 mm in 1.5 mm intervals using the 2-step double-oblique method. The long axis of the transaxial image was obtained at mid-systole, and the next image was oblique at the line connecting the center of the ascending aorta and the AV orifice. Short-axis views of the aortic root were reconstructed as a first step. Further procedures were performed by inclining the short-axis image as a second step. AVA represented as planar images contained AV commissures. Finally, the calculations of the AVA were performed by planimetry. Concomitantly, the severity of the coronary artery stenosis was assessed by MSCT.

In our study, regression analysis showed that the AVA in patients with AS determined by MSCT correlated well with those determined by 2-dimensional echocardiography ( $r=0.96$ ,  $p<0.001$ ). Significant coronary stenosis of more than 50% diameter reduction was present in 48% of the study population. The results of the present study are demonstrated by modern non-invasive technique of MSCT as follows: 1) the morphological appearance of AV orifice was clearly visualized; 2) the measurement of the AVA was accurately estimated to be the same as transthoracic echocardiography assessment; and 3) a moderate incidence of significant coronary stenosis was determined. Current guidelines recommend a diagnostic coronary angiography before surgery in symptomatic patients with AS. Analysis of the severity of AVA concomitant with CAD is important for patients with AS. Therefore, assessment for AS and CAD by MSCT is ideal for realization of these purposes. MSCT can investigate not only the degree of CAD and AS, but also the anatomical assessments of a calcified ascending aorta and patency of graft arteries, such as bilateral internal mammary arteries.

## 5. Assessment of coronary plaque

Although CAD is the leading cause of death in the individuals with coronary risk factors, the majority of these individuals do not actually develop coronary symptoms before the

onset of acute myocardial infarction (AMI) or sudden death. In fact, AMI or sudden death frequently occurs as the first symptom of coronary diseases. Therefore, screening of the patients with unstable plaque is important for prevention of the onset of AMI or sudden cardiac death. Intracoronary thrombus, immediate result of plaque rupture plays key roles in the onset of acute coronary syndromes (ACS) (van der Wal et al., 1994; Moreno et al., 1994). Ruptured plaques are histopathologically characterized by large lipid core and large plaque volumes that are covered by the thin fibrous cap often inflamed with macrophages and T lymphocytes infiltration. Moreover, in recent intravascular ultrasound (IVUS) studies, the term “arterial remodeling” was defined as a change in vessel size, using the ratio of the external elastic membrane area (vessel area) at the culprit lesion site to that at the minimally diseased reference site within the same vessel segment. Most of their studies demonstrate that the vessels are positively remodeled at the site of plaque rupture in patients with ACS (Schoenhagen et al., 2000; Ehara et al., 2004). Various diagnostic techniques have identified the imaging characteristics of vulnerable plaques and proposed that these characteristics may allow recognition of coronary lesions likely to result in ACS.

Recently, MSCT has reached a spatial and temporal resolution high enough for assessment not only of coronary artery stenosis but also coronary atherosclerotic plaques. For the first time, Schroeder et al demonstrated that the IVUS-based coronary plaque configuration can be accurately identified by MSCT (Schroeder et al., 2001). They reported that IVUS-based soft plaques showed a mean density of  $14 \pm 26$  HU, intermediated plaques of  $91 \pm 21$  HU, and calcified plaques of  $419 \pm 194$  HU. Similarly, Motoyama et al showed that the corresponding values were  $11 \pm 12$  HU,  $78 \pm 21$  HU, and  $516 \pm 198$  HU (Motoyama et al., 2007). Regarding arterial remodeling determined by MSCT, on the other hand, Achenbach et al reported that cross-sectional vessel areas and remodeling indices measured by 16-slice CT scanner correlated closely to IVUS ( $r = 0.88$  and  $r = 0.91$ , respectively) (Achenbach et al., 2004). More recently, Leber et al provided comparative data of vessel areas, plaque areas, and lumen areas determined by IVUS and 64-slice CT, and reported that the correlation coefficients for these measurements were  $r = 0.88$ ,  $r = 0.73$ , and  $r = 0.81$ , respectively (Leber et al., 2005). Based on these promising studies, the prospective MSCT study was designed by Motoyama et al (Motoyama et al., 2009) to evaluate the role of CT plaque characterization for predicting acute coronary events in 1059 subjects with established or suspected CAD who were followed up for an average of 27 months. They reported that of the 45 patients showing plaque with both positive remodeling and low-attenuation plaques ( $<30$  HU), ACS developed in 10 (22.2%), compared with 1 (3.7%) of the 27 patients with plaques displaying either feature. In only 4 (0.5%) of the 820 patients with neither positive remodeling nor low-attenuation plaques did ACS develop. None of the 167 patients with normal angiograms had acute coronary events. ACS was independently predicted by positive remodeling and/ or low-attenuation plaques. They concluded that the patients demonstrating positively remodeled coronary segments with low-attenuation plaques in CT angiography were at a higher risk of ACS developing over time when compared with patients having lesions without these characteristics. We also demonstrated that in patients with IVUS-based plaque rupture, the prevalence of an ulcer-like enhancement space, a ring-like sign was higher than those in patients without IVUS-based plaque rupture (Tanaka et al., 2008). Thus, MSCT might provide a useful and promising tool for the non-invasive detection of vulnerable plaques and vulnerable patients.

## 6. Conclusion

The diagnostic accuracy of MSCT in the detection of coronary artery stenoses has been reported by many investigators, with a very high specificity and very high negative predictive values. However, most previous studies did not consist of consecutive patients and most studies excluded patient images with image qualities unsatisfactory for interpretation. MSCT scans of the coronary arteries are still associated with a relatively high radiation dose and administration of contrast agent, it is therefore important to obtain as much relevant information as possible from the scan. The simultaneous assessment beyond angiography, which is often possible even in cases with unsatisfactory coronary image quality, could offer a way to increase the diagnostic usefulness of MSCT for CAD patients.

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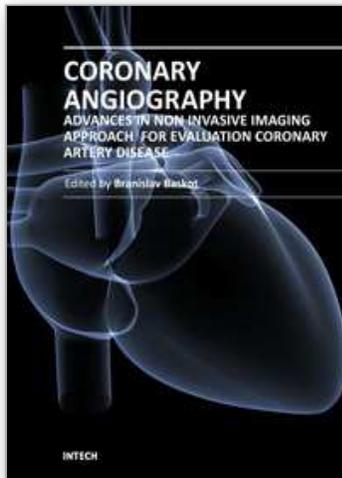
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In the intervening 10 years tremendous advances in the field of cardiac computed tomography have occurred. We now can legitimately claim that computed tomography angiography (CTA) of the coronary arteries is available. In the evaluation of patients with suspected coronary artery disease (CAD), many guidelines today consider CTA an alternative to stress testing. The use of CTA in primary prevention patients is more controversial in considering diagnostic test interpretation in populations with a low prevalence to disease. However the nuclear technique most frequently used by cardiologists is myocardial perfusion imaging (MPI). The combination of a nuclear camera with CTA allows for the attainment of coronary anatomic, cardiac function and MPI from one piece of equipment. PET/SPECT cameras can now assess perfusion, function, and metabolism. Assessing cardiac viability is now fairly routine with these enhancements to cardiac imaging. This issue is full of important information that every cardiologist needs to now.

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