Imaging of coronary atherosclerosis and vulnerable plaque

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CHAPTER 8

Positive Remodeling on Coronary Computed Tomography as a Marker for Plaque Vulnerability on Virtual Histology Intravascular Ultrasound

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ABSTRACT

Background: Coronary computed tomography angiography (CTA) allows direct evaluation of the vessel wall and thus positive remodeling, which is a marker of vulnerability. The purpose of this study was to assess the association between positive remodeling on CTA and vulnerable plaque characteristics on virtual histology intravascular ultrasound (VH IVUS).

Methods: A total of 45 patients (78% male, age 58 ±11 years) underwent CTA followed by VH IVUS. On CTA, the remodeling index (RI) was determined for each lesion by a blinded observer using quantitative analysis. Positive remodeling was defined based on RI ≥1.0. Percentage necrotic core and presence of thin-capped fibroatheroma (TCFA) were used as markers for plaque vulnerability on VH IVUS.

Results: In total, 99 atherosclerotic plaques were evaluated, of which 37 lesions (37.4%) were identified as having positive remodeling on CTA. Higher levels of plaque vulnerability were identified in lesions with positive remodeling as compared to lesions without positive remodeling. Percentage necrotic core was significantly higher in lesions with positive remodeling (15.7% ±7.8%) as compared to lesions without this characteristic (10.2% ±7.2%) ($p<0.001$). Furthermore, significantly more TCFA lesions were identified in positively remodeled lesions (n=16; 43.2%) than in lesions without positive remodeling (n=3; 4.8%) ($p<0.001$).

Conclusion: Lesions with positive remodeling on CTA are associated with increased levels of plaque vulnerability on VH IVUS, including a higher percentage necrotic core and a higher prevalence of TCFA. Accordingly, evaluation of remodeling on CTA may provide a valuable marker for plaque vulnerability.

INTRODUCTION

Non-invasively, coronary computed tomography angiography (CTA) has emerged as a promising modality to detect coronary atherosclerosis. The technique allows for direct evaluation of the coronary artery vessel wall, thereby enabling to some extent non-invasive evaluation of plaque morphology and composition.[1] Due to technical restrictions, CTA cannot provide detailed visualization of fibrous cap thickness or necrotic core size. However, the presence of positive remodeling, which is an important surrogate marker of vulnerability,[2 3] can be reliably assessed.[4-6] Moreover, previous studies have demonstrated a relation between positive remodeling as assessed on CTA and presentation with acute coronary syndrome (ACS).[5 6] However, a direct comparison of plaque remodeling on CTA and plaque characteristics on virtual histology intravascular ultrasound (VH IVUS) has not yet been performed. The purpose of this study was to assess the association between positive remodeling on CTA and vulnerable plaque characteristics on VH IVUS.

METHODS

Patient population

The patient population consisted of 45 patients who underwent both CTA and invasive coronary angiography in combination with VH IVUS. Patients were clinically referred for CTA because of known or suspected coronary artery disease (CAD), followed by invasive coronary angiography and VH IVUS. Referral for invasive coronary angiography was based on clinical presentation and/or imaging results. VH IVUS was performed to further evaluate the extent and severity of disease in order to determine further management more precisely and elucidate possible discrepancies between non-invasive and invasive angiographic findings. Contra-indications for CTA were (1) (supra) ventricular arrhythmias, (2) renal insufficiency (glomerular filtration rate<30ml/min, (3) known allergy to iodinated contrast agents, (4) severe claustrophobia, (5) pregnancy. Exclusion criteria for IVUS were severe vessel tortuosity, severe stenosis or vessel occlusion. Risk factors for CAD were derived from existing patient medical record data. For this retrospective evaluation, patients with good to moderate image quality on CTA and available quantitative analyses were selected from an ongoing registry.[7]

CTA and VH IVUS acquisition

CTA was performed using either a 64-detector row (n=34) helical scanner or a 320-detector row (n=11) volumetric scanner (Aquilion 64 or Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) as previously described.[8,9] Patients with an elevated heart rate (≥65 beats/min) were administered beta-blockers (oral metoprolol 50 or 100mg, single dose, 1 hour before examination), if not contra-indicated. Unless contra-indicated, nitroglycerin 0.4mg sublingual was administered immediately before contrast injection. During the CTA examination the mean heart rate was 57 ±8 beats per minute. An initial data set was

reconstructed at 75% of the R-R interval, with a slice thickness of 0.50 mm and a reconstruction interval of 0.25 mm. In case of motion artifacts, additional reconstructions were explored to obtain images with most optimal image quality for evaluation. For processing and evaluation CTA data were transferred to an off-line workstation.

The VH IVUS examinations were performed during invasive coronary angiography. Invasive coronary angiography was performed according to standard protocols. Patients were administered nitroglycerin intracoronary before induction of the IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA). The ultrasound catheter was positioned in the coronary artery, and motorized pull back at a speed of 0.5 mm/s was used until the catheter reached the guiding catheter. The VH IVUS data were stored digitally and assessed offline.

CTA and VH IVUS analysis

The CTA examinations were evaluated by an independent and experienced observer who was blinded to the VH IVUS results, using a dedicated and extended version of the QAngio CT software (QAngio CT 1.1, Medis medical imaging systems, Leiden, The Netherlands).[10] On CTA data sets, the dedicated software was used to detect both lumen and vessel wall contours. According to the modified American Heart Association classification, coronary arteries were divided into 17 segments.[11] Only segments that were available on both VH IVUS and CTA were analyzed. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen.[12] Per segment, coronary plaque was selected at the site of the most severe luminal narrowing. The detected lumen and vessel wall contours were used for automated quantitative measurements of coronary plaques. At the level of the minimal lumen area (MLA), the remodeling index (RI) was calculated by dividing the cross-sectional vessel wall area by the corresponding reference area. The cross-sectional reference area was determined in the normal appearing reference area as close as possible to the respective coronary lesion. The presence of positive remodeling was defined as a RI ≥1.0.[13]

The VH IVUS analysis was performed by two experienced observers who were blinded to baseline patient characteristics and CTA results, with the use of dedicated software (pcVH2.1, Volcano Corporation, Rancho Cordova, CA, USA). The previously described 17-segment model was used to ensure that similar plaques were analyzed with CTA and VH IVUS. Side branches and coronary ostia were used as anatomical markers.

For each lesion identified on both CTA and VH IVUS, MLA and corresponding vessel area were determined. In addition, percentage plaque burden was calculated as plaque cross-sectional area divided by the vessel cross-sectional area multiplied by 100.[14] Four different plaque components, namely fibrotic tissue, fibro-fatty, necrotic core and dense calcium, were differentiated into different color codes. The different plaque components were calculated as percentage of the plaque burden. Plaque type was determined on VH IVUS using a classification based on the differentiation of the four plaque components as described previously.[7] In total, four different plaque types were identified, namely pathological intimal thickening, fibroatheroma, fibrocalcific plaque and thin capped

fibroatheroma (TCFA). TCFA lesions were defined as lesions with a plaque burden ≥40%, the presence of confluent necrotic core of >10%, and no evidence of an overlying fibrous cap.[7] Both the percentage necrotic core and the presence of TCFA were used to determine plaque vulnerability on VH IVUS.[15]

Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS, Inc., Chicago, Illinois). Continuous data are represented as means (±SD). Categorical data are expressed as absolute numbers or percentages. Segments available on both CTA and VH IVUS were included in the lesion-based analysis. Plaque vulnerability on VH IVUS (as defined by the percentage necrotic core and the presence of TCFA) was assessed in lesions with positive remodeling (RI ≥1.0) on CTA and compared to the remaining lesions that did not show positive remodeling (RI <1.0) on CTA. Comparisons were performed by chi-square analysis. A p value of <0.05 was considered statistically significant.

Table 1. Patient characteristics (n=45)

Age (years)	58 ±11
Men/women	35/10
Heart rate during CTA (beats per minute)	57 ±8
Stable angina/Suspected acute coronary syndrome	27/18
At least one stenosis with >50% diameter narrowing on invasive coronary angiography)	32 (71%)
No. of vessels diseased: 1	17 (53%)
No. of vessels diseased: 2	6 (19%)
No. of vessels diseased: 3	9 (28%)
Cardiovascular risk factors	
Diabetes Mellitus	10 (22%)
Hypertension†	29 (64%)
Hypercholesterolemia‡	26 (58%)
Current Smoker	20 (44%)
Obesity¥	8 (18%)

Data are absolute values or means ± standard deviation.
Data in parentheses are percentages.
†Defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.
‡Serum total cholesterol ≥230 mg/dL or serum triglycerides ≥200 mg/dL or treatment with Lipid lowering drugs.
¥Body mass index ≥30 kg/m^2
CTA: coronary computed tomography angiography

RESULTS

In total, 45 patients (78% male, age 57.8 ±11 years) who underwent CTA followed by VH IVUS were enrolled retrospectively. Characteristics of the patient population are provided in Table 1. In all patients CTA and VH IVUS studies were of sufficient imaging quality for analysis. In total, 99 plaques were identified on both CTA and the corresponding available VH IVUS analyses. Of theses 99 atherosclerotic plaques, 37 lesions (37.4%) were classified as positive remodeled (RI ≥1.0) on CTA. In the remaining 62 lesions (62.6%) no positive remodeling (RI <1.0) was observed. On VH IVUS, the most prevalent plaque component was fibrotic tissue (52% ±16%), followed by fibro-fatty tissue (19% ±12%), necrotic core (13% ± 8%) and dense calcium (8% ±9%). Qualitative evaluation of coronary lesions on VH IVUS revealed the presence of pathological intimal thickening, fibroatheroma and fibrocalcific lesions in respectively 37 (37.4%), 30 (30.3%) and 13 (13.1%) of lesions. Finally, TCFA were identified in 19 lesions (19.2%).

Lesions identified as positive remodeled (RI ≥1.0) on CTA had a significantly higher plaque burden on VH IVUS as compared to lesions without positive remodeling (RI <1.0) as shown in Table 2. Percentage necrotic core was also significantly higher in the positive remodeled lesions (RI ≥1.0) as compared to lesions without positive remodeling (RI <1.0). No differences in relation to the presence or absence of positive remodeling on CTA were observed in the percentage of fibrotic tissue, fibro fatty tissue and dense calcium.

Table 2. VH IVUS characteristics between lesions with and without positive remodeling on CTA

Plaque characteristics on VH IVUS	Presence of positive remodeling on CTA	Absence of positive remodeling on CTA	p value
Minimal lumen area (mm2)	8 ±4	9 ±5	0.38
Vessel area* (mm2)	16 ±6	15 ±6	0.24
Plaque burden (%)	51 ±10	41 ±16	<0.001
Fibrotic (%)	55 ±9	51 ±19	0.18
Fibro-Fatty (%)	20 ±11	18 ±13	0.58
Necrotic core (%)	16 ±8	10 ±7	0.001
Dense calcium (%)	9 ±6	7 ±11	0.25

Data are represented as mean ± standard deviation
*at minimal lumen area
CTA: computed tomography coronary angiography; VH IVUS: virtual histology intravascular ultrasound

Qualitative evaluation of plaque types as shown in Figure 1, revealed an equal distribution of the presence of fibroatheroma (9 (24%) versus 21 (34%), p=0.32) between lesions with positive remodeling (RI ≥1.0) as compared to lesions without positive remodeling (RI <1.0). Furthermore, no significant difference of the presence of fibrocalcific plaques (3 (8%) versus 10 (16%), p=0.36) were observed between the two groups. Pathological

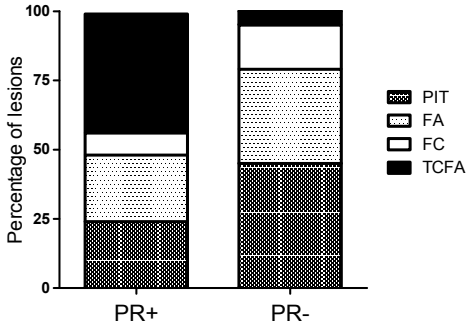

Figure 1. Relative distribution of visually assessed plaque types on VH IVUS between lesions with positive remodeling and lesions without positive remodeling on CTA. Significantly more lesions classified as PIT were present in lesions without positive remodeling. Percentage of FA and FC were not significantly different between lesions with positive remodeling and lesions without positive remodeling. Significantly more TCFA lesions were identified in lesions with positive remodeling on CTA. (Abbreviations: PR+, lesions with positive remodeling (RI ≥1.0) on CTA; PR –, lesions without positive remodeling (RI <1.0) on CTA; PIT, pathological intimal thickening; FA, fibroatheroma; FC, fibrocalcific lesions; TCFA, thin-capped fibroatheroma.)

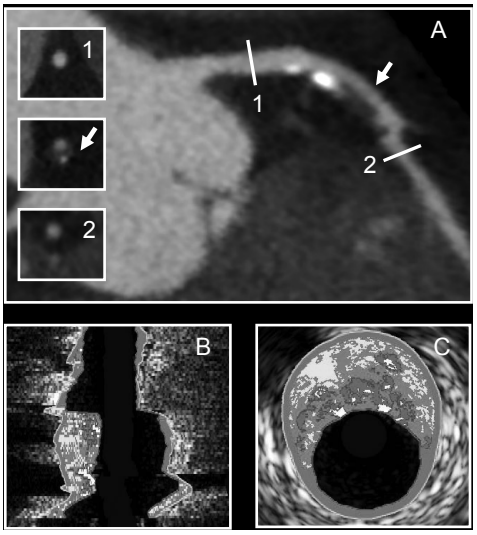

Figure 2. An example of a lesion with positive remodeling on 320-row CTA and corresponding findings on VH IVUS. (A) Curved multiplanar reconstruction of the left anterior descending coronary artery showing a large plaque in the proximal segment of the vessel. The diameter of the vessel at the plaque site is larger as compared to the diameter at the reference sections (1,2), indicating the presence of positive remodeling. (B and C) Corresponding longitudinal (B) and cross-sectional (C) VH IVUS images demonstrate indeed an outward-remodeled lesion, with a large plaqueburden (69%) and a large amount of necrotic core (19%), labeled in red, corresponding to a TCFA lesion.

intimal thickening was significantly more often observed in lesions without positive remodeling (RI ≥1.0) on CTA; 28 lesions (45%) without positive remodeling (RI <1.0) on CTA were classified as showing pathological intimal thickening as compared to 9 lesions (24%) with positive remodeling (RI ≥1.0) on CTA (p=0.04). Importantly, as shown in Figure 1, 16 lesions (43.2%) with positive remodeling (RI ≥1.0) on CTA were identified as TCFA. In contrast, only 3 lesions (4.8%) without positive remodeling (RI <1.0) on CTA were classified as TCFA (p<0.001). An example of a lesion with positive remodeling (RI ≥1.0) on CTA and corresponding findings on VH IVUS is provided in Figure 2.

DISCUSSION

In the present study, positive remodeling on CTA was related to vulnerable plaque characteristics on VH IVUS. Lesions with positive remodeling on CTA were shown to have a significantly higher plaque burden on VH IVUS. A larger amount of necrotic core and a higher prevalence of TCFA were found in lesions with positive remodeling on CTA.

The current findings are consistent with previous investigations, showing that compensatory enlargement of the vessel wall, including eccentric plaque growth, is strongly associated with necrotic core area and macrophage infiltration.[15 16] Indeed, histopathological data have confirmed that vulnerable plaques are almost always associated with positive remodeling.[17-19] Also during in vivo VH IVUS studies, a similar connection between positive remodeling and plaque composition has been reported.[20] In 41 patients, Rodriguez-Granillo et al. described a significantly larger percentage of necrotic core in positively remodeled vessels as compared to vessels with negative remodeling. Furthermore, 56% of positively remodeled lesions were classified as TCFA, indicating a higher risk phenotype. In the current study, non-invasive imaging with CTA was used to identify the presence of positive remodeling. Previous studies have shown that reliable assessment of remodeling on CTA is feasible.[4-6 21] Achenbach et al. determined RI in 44 patients with high-quality CTA data sets and observed higher indices in nonstenotic (<50% diameter reduction) as compared to stenotic lesions.[4] In a subset of patients, measurements on CTA were verified against IVUS, revealing a close correlation (r^2=0.82). Consequently, several studies have explored whether the presence of positive remodeling on CTA may indicate an increased likelihood of vulnerability. Interestingly, lower attenuation values on CTA have been observed in lesions with positive remodeling as compared to lesions without this phenomenon.[21] In turn, a correlation between lower attenuation values on CTA and increased lipid-rich and necrotic core content on IVUS has been observed.[12 22] Accordingly, these observations indirectly suggested that positively remodeled lesions on CTA may have a higher proportion of necrotic core, a hypothesis that was tested in the current study. In addition, the presence of positive remodeling on CTA has been related to clinical presentation with ACS.[5 23] Two retrospective studies investigated the differences in coronary plaque features between ACS patients and patients presenting with stable angina pectoris.[5 23] As compared to lesions in stable patients, culprit lesions in ACS displayed more non-calcified plaque, spotty calcifications and higher remodeling indices. Moreover, in a prospective study in 1.059 patients with a follow-up duration of 27 ±10 months, patients with plaques showing both positive remodeling and a low attenuation value on CTA were found to have a higher likelihood of developing ACS over time[6]. In contrast, absence of lesions with these characteristics on CTA conferred an excellent outcome.

Currently, the use of CTA is gradually shifting from assessment of degree of stenosis to evaluation of atherosclerotic plaque burden and risk assessment. The present study showed that lesions identified as positive remodeled on CTA were associated with plaque vulnerability on VH IVUS. Accordingly, more comprehensive assessment of the coronary

artery vessel wall, including evaluation of positive remodeling, may potentially allow more individualized risk stratification, based on CTA.

The following limitations need to be acknowledged. This feasibility study is a retrospective analysis in selected optimal conditions. Only patients with a CTA data set of diagnostic image quality were included and assessment of remodeling may be more difficult in data sets with lower image quality. Accordingly, our current findings are based on a relatively small study population and need to be validated in a larger, more challenging study population. Our observations indicate that with increasing remodeling index, the likelihood of TCFA also increases. However, this observation does not implicate that a lesion with a remodeling index of ≥1.0 is per definition a vulnerable lesion. Possibly, additional markers are needed to predict the presence of a vulnerable lesion with higher accuracy. Of note, other characteristics of vulnerable plaque on CTA were not analyzed in this particular study. Importantly, while the presence of positive remodeling on CTA may have value for risk stratification in addition to clinical characteristics and other CTA variables, the implications of this particular observation for prognosis and therapeutic management remain to be determined. Finally, the radiation exposure associated with CTA currently still restricts its widespread use. Notably however, novel dose-saving algorithms and recent technical improvements have led to substantial dose reductions.[24]

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