Imaging of coronary atherosclerosis and vulnerable plaque

Velzen, J.E. van

CHAPTER 4

The Site of Greatest Vulnerability is Most Often Located Proximally to the Site of Most Severe Narrowing: A Virtual Histology Intravascular Ultrasound Study

Joëlla E. van Velzen, Michiel A. de Graaf, Fleur R. de Graaf, Joanne D. Schuijf, Jouke Dijkstra, Jeroen J. Bax, Johan H.C. Reiber, Martin J. Schalij, Ernst E. van der Wall, J.Wouter Jukema

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ABSTRACT

Background: Previous angiographic studies have shown that almost two-thirds of vulnerable plaques are located in non-obstructive lesions. Possibly, the site of greatest vulnerability is not always located at the site of most severe stenosis. Therefore, the purpose of this study was to evaluate the difference in location between the site of greatest vulnerability and the site of most severe narrowing as assessed by virtual histology intravascular ultrasound (VH IVUS).

Methods: Overall, 77 patients (139 vessels) underwent VH IVUS. The site of greatest vulnerability was defined as the cross-section with the largest necrotic core area per vessel, the maximum necrotic core (Max NC) site. The site of most severe narrowing was defined as the minimum lumen area (MLA). Per vessel the distance from both the Max NC site and MLA site to the origo of the coronary artery was evaluated. In addition, the presence of a thin cap fibroatheroma (TCFA) was assessed.

Results: The mean difference (mm) between the MLA site and Max NC site was 10.8±20.6mm ($P<0.001$). Interestingly, the Max NC site was located at the MLA site in 7 vessels (5%) and proximally to the MLA site in 92 vessels (66%). Importantly, a higher % of TCFA was demonstrated at the Max NC site as compared to the MLA site (24% versus 9%, $P<0.001$).

Conclusion: The present findings demonstrate that the site of greatest vulnerability is rarely at the site of most severe narrowing. Most often, the site of greatest vulnerability is located proximally to the site of most severe narrowing.

INTRODUCTION

Previous angiographic studies have shown that almost two-thirds of vulnerable plaques are located in non-obstructive atherosclerotic lesions.[1 2] Nevertheless, at present, interventional strategies are mainly targeted towards management of acute coronary syndromes at the site of most severe luminal narrowing. Whether this approach adequately covers the more vulnerable regions remains uncertain. Thus far, the spatial relationship between the location of most severe narrowing and vulnerable rupture sites has not been fully elucidated.

Virtual histology intravascular ultrasound (VH IVUS) is a promising tool for the assessment of plaque composition.[3] Using spectral analysis of radiofrequency backscatter signals, this technique has the ability to evaluate 4 plaque components, namely fibrotic, fibro-fatty, necrotic core and calcified tissue. The accuracy of VH IVUS for the determination of plaque components has been validated against histopathology in human coronary arteries and was 90.4% for fibrous, 92.8% for fibro-fatty, 89.5% for necrotic core and 90.9% for dense calcium.[3 4] Recently, a large prospective multi-centre study by Stone et al. showed a strong predictive value of the presence of thin cap fibroatheroma (TCFA) on VH IVUS.[5] In a cohort of 697 patients, the presence of TCFA on VH IVUS was demonstrated to be an independent predictor of major adverse cardiovascular events.

The aim of the present study was to improve understanding of the spatial relationship between the location of the site of greatest vulnerability and the location of most severe narrowing. Therefore, we compared the location of the maximum necrotic core area (site of greatest vulnerability) with the location of the minimum lumen area (site of most severe narrowing) with VH IVUS.

METHODS

Patients

The study population consisted of 77 patients with chest pain referred for invasive coronary angiography (ICA). Patients were clinically referred for invasive coronary angiography because of known or suspected coronary artery disease (CAD). 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. Both patients presenting with stable chest pain and acute coronary syndrome (ACS) were evaluated. Patients with ACS included unstable angina and non-ST-segment elevation myocardial infarction defined according to the guidelines of the European Society of Cardiology[6] and the American College of Cardiology (ACC)/American Heart Association.[7] Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Contra-indications for VH IVUS were severe vessel tortuosity, severe luminal narrowing or (subtotal) vessel occlusion. In each patient the presence of CAD risk factors

such as diabetes, hypertension, hypercholesterolemia, positive family history, smoking and obesity, was recorded.

VH IVUS acquisition

VH IVUS was performed according to standard clinical protocol during ICA using a novel dedicated IVUS-console (s5^{tm} Imaging system, Volcano Corporation, Rancho Cordova, CA, USA). After local intracoronary admission of 200 µg nitroglycerin, VH IVUS was performed with a 20 MHz, 2.9 F phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA). The IVUS catheter was positioned distally in the coronary artery and motorized automated IVUS pullback was performed using a speed of 0.5 mm/s until the catheter reached the guiding catheter. Images were obtained at the R-wave peak on the ECG. At an average heart rate of 60/min, the incremental distance between frames was approximately 0.5 mm. Cine runs were performed to record the starting position of the VH IVUS catheter. Images were stored on DVD for further offline analysis.

VH IVUS analysis

Images were analyzed offline using specially developed dedicated software for images acquired on the s5^{tm} IVUS Imaging system (QCU- CMS 4.59, Medis, Leiden, The Netherlands). Vessels without evidence of major atherosclerotic plaque (plaque burden <40%) or with previous stent placement were excluded from further analysis. All IVUS examinations were evaluated by two experienced observers. First, the IVUS run was visually assessed to confirm that the pullback had been performed at a constant speed.

Second, contour detection of the external elastic membrane (EEM) and lumen was performed. The area enclosed by the contours of EEM and lumen was defined as plaque area. Percentage plaque burden was calculated as plaque cross-sectional area (CSA) plus media CSA divided by EEM CSA multiplied by 100 according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS).[8] Subsequently, using radiofrequency backscatter analysis, four plaque components were differentiated into color codes as validated previously.[3] Accordingly, fibrotic tissue was labeled in dark green, fibro-fatty in light green, dense calcium in white and necrotic core in red.

The site of most severe narrowing was defined as the cross-section with the smallest cross-sectional lumen area in the entire vessel, the minimum lumen area site (MLA). Multiple definitions are available to define the site of greatest vulnerability on VH IVUS. As amount of necrotic core is quantifiable on VH IVUS, the site of greatest vulnerability was defined as the cross-section with the largest necrotic core area per vessel, the maximum necrotic core (Max NC) site. Subsequently, per vessel, the maximum necrotic core (Max NC) site and MLA site were identified. First, in each vessel the distance from both the Max NC site and MLA site to the ostium of the coronary artery was measured with a dedicated software tool in the longitudinal IVUS view. Distances were calculated based on the pullback speed of motorized automated pullback at a rate of 0.5 mm/s. Difference between both sites was calculated as distance from MLA site to origo minus distance from Max NC

site to origo. Furthermore, classification of plaque type and composition was performed at both the Max NC site and MLA site. Plaque components were reported as absolute values and percentages of plaque area. In addition, visual plaque type classification was obtained according to the following categorization:[9, 10]

1. Pathological intimal thickening; defined as a mixture of fibrotic and fibro-fatty tissues, a plaque burden ≥40% and <10% necrotic core and dense calcium.
2. Fibroatheroma; defined as having a plaque burden ≥40% and a confluent necrotic core occupying 10% of the plaque area or greater in three successive frames with evidence of an overlying fibrous cap.
3. TCFA; defined as a lesion with a plaque burden ≥40%, the presence of confluent necrotic core of >10%, and no evidence of a large fibrous cap.
4. Fibrocalcific plaque; defined as a lesion with a plaque burden ≥40%, with dense calcium >10% and a percentage necrotic core of <10% (higher amount accepted if necrotic core was located exclusively behind the accumulation of calcium).

Statistical analysis

Statistical analyses were performed using SPSS (version 17.0, SPSS Inc., Chicago, IL, USA). First, the spatial relationship (in mm) between Max NC and MLA site was assessed. In a sub-analysis, the impact of clinical presentation (patients with stable CAD versus patients with ACS) and the difference in length between the Max NC and MLA site was evaluated. Furthermore, differences in plaque composition and type between both the Max NC and MLA site were compared. When normally distributed, continuous variables were expressed as mean (± standard deviation) and compared with independent sample t-test for unpaired samples or the dependent t-test for paired samples. If not normally distributed, variables were presented as median and interquartile range. Unpaired samples were analyzed using non-parametric Mann-Whitney test and paired variables were analyzed with Wilcoxon signed rank tests. Categorical variables were expressed as numbers and percentages, and compared with the Chi-square test. A p-value of $p<0.05$ was considered significant.

RESULTS

Overall, 77 patients were evaluated. Patient characteristics are presented in Table 1. In total, 169 vessels were analyzed with VH IVUS, in 30 vessels (18%) previous PCI was performed and these vessels were therefore excluded. Thus, 139 vessels were included for further analysis.

The spatial relationship between the Max NC and MLA site is demonstrated in Figure 1. Interestingly, the Max NC site was located in the same location as the MLA site in only 7 vessels (5%). In the remaining vessels, the Max NC site was located proximally to the

Table 1. Patient characteristics of study population.

	n (%)
Age (years)	59 ± 10
Gender (% male)	64 (70%)
Risk factors for CAD	
Obesity (Body mass index ≥ 30 kg/m^2)	21 (23%)
Diabetes	27 (29%)
Hypertension†	54 (59%)
Hypercholesterolemia‡	47 (51%)
Family history of CAD	44 (48%)
Smoking	32 (35%)
Aspirin use	49 (53%)
Statin use	60 (65%)
Previous PCI	25 (27%)
Previous myocardial infarction	17 (19%)
Presentation with ACS	62 (67%)

Data are absolute values, percentages or means ± standard deviation.
†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.
Abbreviations: CAD, coronary artery disease; ACS, acute coronary syndrome, PCI, percutaneous coronary intervention.

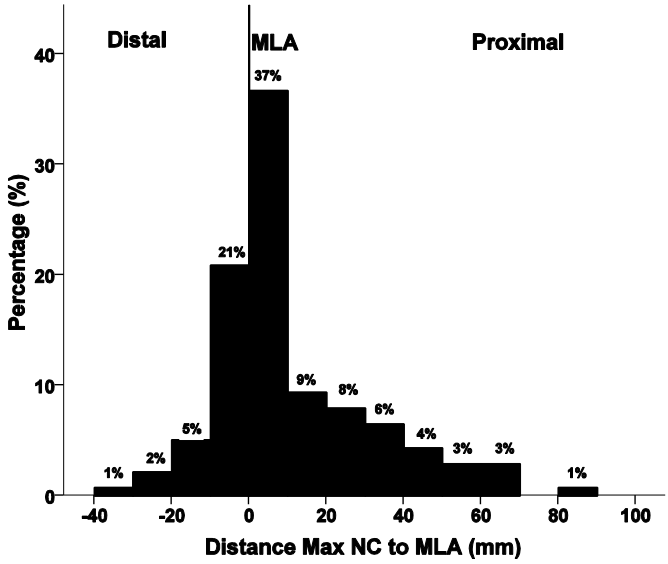

Figure 1. Spatial relationship of the maximum necrotic core site (Max NC) as compared to minimal lumen area (MLA). In the majority of vessels the site of Max NC is located proximal to site of MLA.

MLA site in 92 vessels (66%) and located distally from the MLA site in 40 vessels (29%). Accordingly, the mean difference (mm) between the MLA site and Max NC site was 10.8 ± 20.6 mm (P<0.001). Regarding the more proximally located Max NC sites, the mean difference between Max NC and MLA site was 19.6 ± 19.7 mm (P<0.001). Concerning the more distally located Max NC sites, the mean difference between Max NC site and MLA was 7.4 ± 7.8 mm (P<0.001). The differences in distance between Max NC site and MLA site were assessed between patients with ACS (n=52) and patients with stable CAD (n=25). Interestingly, no difference in distance between Max NC and MLA was observed (10.7 ± 20.5 mm for stable CAD vs. 10.9 ± 20.8 mm for patients with ACS, P=0.699). Figure 2 shows an example of a vessel with the site of greatest vulnerability located proximal to the MLA site.

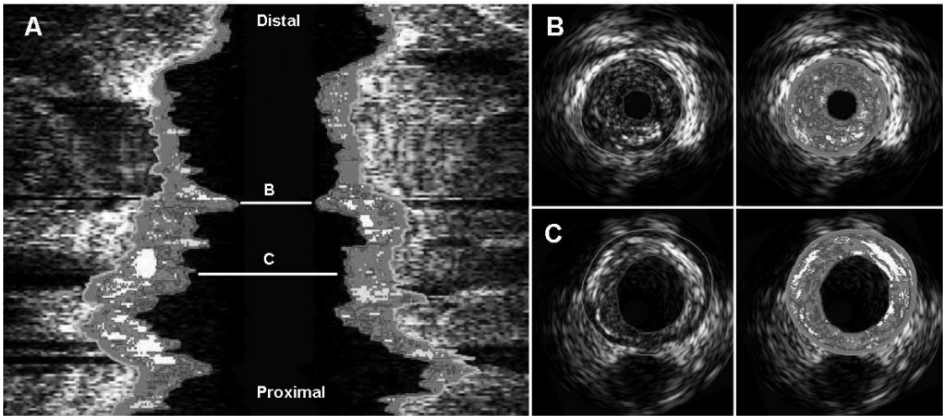

Figure 2. Example of a coronary artery with the site of maximum necrotic core (Max NC) located proximal from the minimal lumen area (MLA) site. Panel A demonstrates a longitudinal view of the intravascular ultrasound (IVUS) images. As demonstrated, the Max NC site (C) is not located at the minimum lumen area (MLA) site (B), but 16.4 mm proximal of the MLA site. Panel B shows the grayscale cross-sectional slices and the corresponding virtual histology IVUS images of the MLA site. Panel C shows the grayscale cross-sectional slices and the corresponding virtual histology IVUS images for the Max NC site. Interestingly, although the MLA site has significant luminal narrowing (lumen area of 2.1 mm2) the Max NC site demonstrated a thin cap fibroatheroma (TCFA).

The differences in absolute and relative plaque composition between the Max NC and MLA site are demonstrated in Table 2. As expected, the Max NC site contained significantly more necrotic core as compared to the MLA site (31% (23 - 40%) versus 19% (10 - 19%), P<0.001). Moreover, the MLA site contained significantly more fibrotic tissue than the Max NC site (57% (47 - 65%) versus 49% (41 - 57 %), P<0.001). Furthermore, the MLA site contained significantly more fibro-fatty tissue than the Max NC site (13% (6 - 24%) versus 6% (3 - 12%), P<0.001). Lastly, plaque burden was significantly larger at the MLA site than at Max NC site (63% (54 - 74%) versus 59% (43 - 68%), P<0.001).

Table 2. Comparison of plaque composition between maximum necrotic core (Max NC) site and minimum lumen area site (MLA).

VH IVUS plaque composition	Max NC site	MLA site	P-value
Lumen area (mm^2)	7.3 (5.1 - 10.9)	4.3 (3.1 - 6.9)	<0.001
Vessel area (mm^2)	18.7 (14.9 – 23.8)	14.0(10.4 - 17.4)	<0.001
Plaque area (mm^2)	11.2 (8.5 - 13.6)	8.9 (6.1 - 11.2)	<0.001
Plaque burden	59% (49 – 68%)	63% (54 – 74%)	<0.001
Fibrotic (mm^2)	3.8 (2.6 - 4.9)	3.2 (2.1 - 4.6)	0.01
Fibro-fatty (mm^2)	0.5 (0.2 - 1.0)	0.7 (0.2 - 1.5)	<0.001
Necrotic core (mm^2)	2.3 (1.5 - 3.1)	1.2 (0.5 - 1.8)	<0.001
Dense calcium (mm^2)	0.8 (0.3 - 1.3)	0.3 (0.1 - 0.8)	<0.001
Fibrotic	49% (41 – 57%)	57% (47 – 65%)	<0.001
Fibro-fatty	6% (3 – 12%)	13% (6 – 24%)	<0.001
Necrotic core	31% (24 – 40%)	19% (9 – 28%)	<0.001
Dense calcium	10% (5 – 16%)	6% (1 – 12%)	<0.001

Data are presented as medians and interquartile range

The difference in plaque type between MLA and Max NC sites was assessed. Interestingly, pathological intimal thickening was most often observed at the MLA site as compared to the Max NC site (26% versus 1%, P<0.001). In addition, lesions at the Max NC site were more often classified as a fibroatheroma than lesions at the MLA site (71% versus 60%, P=0.04). Furthermore, the percentage of fibrocalcific plaque was similar at both the MLA site and Max NC site (5% versus 4%, P=0.78). Importantly, as demonstrated in Figure 3, a significantly higher percentage of TCFA was present at Max NC site as compared to the MLA site (24% versus 9%, P<0.001). Moreover, if TCFA was identified at the Max NC site, only in 33% of cases the MLA site also demonstrated a TCFA. No significant differences were observed between plaque type and composition between proximal and distal Max NC sites (Table 3).

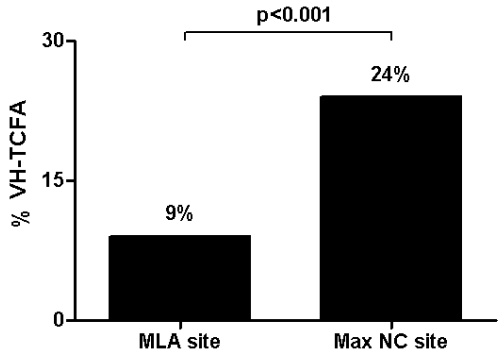

Figure 3. Difference in presence of thin cap fibroatheroma (TCFA) between minimum lumen area (MLA) site and maximum necrotic core (Max NC) site. As demonstrated, TCFA was significantly more often observed at the Max NC site as compared to the MLA site.

Table 3. Comparison of plaque composition and type between the maximum necrotic core (Max NC) site located proximal and distal from the minimum lumen area (MLA).

VH IVUS characteristics	Max NC site proximal to MLA site	Max NC site distal from MLA site	P-value
Plaque composition			
Fibrotic	49% (41 - 56%)	49% (39 - 58%)	0.96
Fibro-fatty	6% (3 – 12%)	5% (3 - 10%)	0.40
Necrotic core	31% (24 - 40%)	34% (24 - 39%)	0.74
Dense calcium	10% (6 – 14%)	10% (4 - 19%)	0.91
Plaque type			
Pathological intimal thickening	0 (0%)	1 (1%)	0.51
Fibroatheroma	32 (24%)	63 (48%)	0.18
Thin cap fibroatheroma	7 (5%)	23 (17%)	0.35
Fibrocalcific plaque	1 (1%)	5 (4%)	0.46

Data are presented as numbers, percentages, medians and interquartile range

DISCUSSION

The present study evaluated the spatial relationship between the site of most severe narrowing and greatest vulnerability with the use of invasive VH IVUS. Interestingly, it was demonstrated that the site of greatest vulnerability (defined as maximum necrotic core area) was rarely located at the site of most severe narrowing (defined as the minimum lumen area). Most often (in 66% of vessels), the site of greatest vulnerability was located proximal from the site of most severe narrowing. Of particular interest was the finding that a higher percentage of TCFA (plaque phenotype with high-risk of rupture) was demonstrated at the site of greatest vulnerability.

Histopathological studies have observed that high-risk plaque features include the presence of a large necrotic core, inflammatory cells at the shoulders of the plaque and a thin fibrous cap.[10 11] Indeed, the rupture of a thin cap fibroatheroma is thought to be the primary cause of an acute coronary syndrome.[12] Moreover, several landmark angiographic studies have reported that the presence of plaque rupture was poorly related to angiographic degree of luminal narrowing.[1 13 14] As demonstrated during the follow up of patients admitted for acute myocardial infarction, almost two thirds of plaques prone to rupture were located in non flow-limiting atherosclerotic lesions, and only a minority were located in severely obstructed lesions.[1] Interestingly, the findings of the current study support this concept, demonstrating invasively with VH IVUS that the more vulnerable sites were not at the site of most severe narrowing, but were located more proximally. Therefore, it could be of importance to identify the presence of a high-risk lesion with either non-invasive or invasive modalities, even at sites without the presence of significant luminal narrowing.

Previous reports exploring the relation between the location of the site of most severe narrowing and site of greatest vulnerability using VH IVUS have demonstrated comparable findings.[15-17] Rodriguez et al. performed VH IVUS in 40 patients and assessed the difference in plaque characteristics between plaque rupture site and site of most severe narrowing.[17] Similar to the current findings, the authors demonstrated a significantly higher percentage of necrotic core at the plaque rupture site (16.8%) as compared with the site of most severe narrowing (11.8%). Consequently, the authors concluded that the plaque rupture sites had a worse plaque phenotype than the site of most severe narrowing. In addition, Konig et al. performed an analysis with VH IVUS in 48 patients and demonstrated that the site of severest stenosis was not always located at the site with the highest percentage necrotic core.[16] However, the aforementioned investigations performed an analysis on a per-lesion basis, whereas the present study investigated the entire vessel with VH IVUS. Indeed, a vessel-based analysis provides a more complete evaluation and relevant vulnerable plaque sites are less likely to be missed.

A possible explanation for the current findings could be the relation between presence of positive remodeling and plaque vulnerability. Indeed, compensatory enlargement of the vessel wall, including eccentric plaque growth, is strongly associated with necrotic core area, macrophage infiltration and the occurrence of acute cardiac events.[18 19] Also during in vivo VH IVUS studies, a similar connection between positive remodeling and plaque composition has been reported.[19 20] However, with traditional invasive coronary angiography, lesions with outward (positive) remodeling are frequently missed. Invasive coronary angiography is only able to show the contrast filled lumen and is unable to visualize atherosclerosis in the arterial wall (with the exception of large calcifications) and reference segments.[21] As a consequence, coronary angiography alone will not detect the exact location of the site of greatest vulnerability in the majority of patients. Furthermore, due to the difference in location between the site of most severe narrowing and the site of greatest vulnerability, percutaneous coronary intervention (PCI) of the high risk lesion will be less accurate. Incomplete coverage of a high-risk lesion can lead to increased rates of in-stent restenosis, dissection and stent thrombosis.[22 23] Therefore, identification of the site of greatest vulnerability, in addition to the site of most severe narrowing, could possibly be of importance for clinical management and outcome. In addition, PCI is most often performed in flow-limiting lesions in order to relieve chest pain symptoms. However, no consensus exists regarding the type of treatment for vulnerable regions and systemic anti-atherosclerotic measures (statins) are currently preferred. Nevertheless, studies are ongoing evaluating other alternatives (e.g. bio-absorbable stents) for effective treatment of vulnerable plaque regions.[24]

The following limitations of the present study should be considered. First, the present study only evaluated 77 patients in a single center. Ideally, a larger patient population should be studied, preferably in a multicenter setting. Secondly, due to acoustic shadowing it is difficult to assess plaque composition behind severe calcifications on VH IVUS. Therefore, possibly small non-calcified elements within the more heavily calcified parts of the plaque may have been missed. Lastly, detection of the thin fibrous cap (<65 μm)

is not yet feasible as VH IVUS has limited radial resolution of only 100 μm. A technique such as optical coherence tomography (OCT) imaging would permit these measurements; however, OCT was not performed in the present study.

Conclusion

The present findings demonstrate that the site of greatest vulnerability is rarely at the site of most severe narrowing. Moreover, the site of greatest vulnerability is frequently located proximal from the site of most severe narrowing. Potentially, due to insufficient identification of the high risk lesion, a vulnerable site might remain concealed.

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