Heart Vessels (2013) 28:166–172
DOI 10.1007/s00380-012-0236-7

ORIGINAL ARTICLE

The maximum necrotic core area is most often located proximally to the site of most severe narrowing: a virtual histology intravascular ultrasound study

Michiel A. de Graaf · Joella E. van Velzen · 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

Received: 8 August 2011 / Accepted: 20 January 2012 / Published online: 18 February 2012

Abstract Previous angiographic studies have shown that almost two-thirds of vulnerable plaques are located in non-obstructive lesions. Possibly, the maximum necrotic core (Max NC) area is not always identical to the site of most severe stenosis. Therefore, the purpose of this study was to evaluate the potential difference in location between the maximum necrotic core area and the site of most severe narrowing as assessed by virtual histology intravascular ultrasound (VH IVUS). Overall, 77 patients (139 vessels) underwent VH IVUS. The Max NC site was defined as the cross section with the largest necrotic core area per vessel. 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 virtual histology-thin cap fibroatheroma (VH-TCFA) was assessed. The mean difference (mm) between the MLA site and Max NC site was 10.8 ± 20.6 mm ($p < 0.001$). Interestingly, the Max NC site was located at the MLA site in seven vessels (5%) and proximally to the MLA site in 92 vessels (66%). Importantly, a higher percentage of VH-TCFA was demonstrated at the Max NC site as compared to the MLA site (24 vs. 9%, $p < 0.001$). In conclusion, the present findings demonstrate that the Max NC area is rarely at the site of most severe narrowing. Most often, the Max NC area is located proximal to the site of most severe narrowing.

Keywords Coronary artery disease · Atherosclerosis · Virtual histology intravascular ultrasound · Vulnerable plaque

Introduction

Previous angiographic studies have shown that almost two-thirds of vulnerable plaques are located in non-obstructive atherosclerotic lesions [1, 2]. Furthermore, the extent of atherosclerosis is similar in non-culprit vessels as compared to vessels with a culprit lesion [3]. However, interventional strategies are mainly targeted towards management of acute coronary syndromes (ACS) 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 [4]. Using spectral analysis of radio frequency backscatter signals, this technique has the ability to evaluate four 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

M.A. de Graaf and J.E. van Velzen share first authorship.

M. A. de Graaf · J. E. van Velzen · F. R. de Graaf · J. D. Schuijf · J. J. Bax · M. J. Schalij · E. E. van der Wall · J. W. Jukema (✉)
Department of Cardiology, Leiden University Medical Centre, Postal zone: C5-P, PO Box 9600, 2333 ZA Leiden, The Netherlands
e-mail: j.w.jukema@lumc.nl

J. E. van Velzen · E. E. van der Wall · J. W. Jukema
The Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

J. Dijkstra · J. H. C. Reiber
Division of Image Processing, Department of Radiology, Leiden University Medical Centre, Leiden, The Netherlands

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 [4, 5]. Recently, a large prospective multi-center study by Stone et al. [6] showed a strong predictive value of the presence of virtual histology-thin cap fibroatheroma (VH-TCFA) on VH IVUS. In a cohort of 697 patients, the presence of VH-TCFA on VH IVUS was demonstrated to be an independent predictor of major adverse cardiovascular events. Moreover, Rodrigues-Granillo et al. [7] demonstrated, in 55 patients, that almost two-thirds of lesions classified as VH-TCFA were located in the first 20 mm of a coronary artery.

The aim of the present study was to improve understanding of the spatial relationship between the location of the maximum necrotic core (Max NC) area and the location of most severe narrowing. Therefore, we performed a vessel-based analysis to compare the location of the Max NC area with the location of the minimum lumen area (MLA) (site of most severe narrowing) with VH IVUS.

Methods

The study population consisted of 77 patients who presented with chest pain. Patients were referred for invasive coronary angiography (ICA) in combination with VH IVUS based on the patient's clinical presentation and/or imaging results to further evaluate the extent and severity of CAD. During ICA, an experienced interventional cardiologist decided whether IVUS studies should be performed [8, 9]. Our institutional review board does not require its approval and written informed consent for retrospective technical analysis of data, as was the case in this study. Both patients presenting with stable chest pain and 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 [10] and the American College of Cardiology (ACC)/American Heart Association [11]. 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.

Invasive coronary angiography was performed according to standard clinical protocols. Vascular access was obtained through the femoral approach with the use of a 6-F or 7-F sheath. Quantitative coronary angiography (QCA) analysis was performed by an observer unaware of VH-IVUS findings with the use of Q-Angio XA version 7.2 (Medis, Leiden, The Netherlands). First, per vessel, the two best orthogonal projections were chosen on which measurements were performed, to minimize foreshortening. Prior to measuring stenosis degree, images were calibrated with use of the contrast-filled catheter. Subsequently, the highest percent diameter stenosis as measured by QCA was reported for each lesion. For vessels with wall irregularities, a fixed stenosis degree of 30% was used.

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.

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 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) [12]. Subsequently, using radiofrequency backscatter analysis, four plaque components were differentiated into color codes as validated previously [4]. 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 MLA site. The Max NC site was defined as the cross section with the largest necrotic core area per vessel. Subsequently, per vessel the 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, plaque type was visually assessed. At present, multiply definitions are available for plaque type on VH IVUS [13–15]. For the current paper, the following categorization was used [15]:

1. 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.
2. VH-TCFA; defined as a lesion with a plaque burden ≥40%, the presence of confluent necrotic core of >10%, and arc of NC in contact with the lumen for >36° along lumen circumference.
3. 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).
4. Other; a lesion that could not be classified as one of the aforementioned plaque types.

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 vs. 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. Subsequently, the correlation between the difference in Max NC and MLA site and the angiographical degree of stenosis was assessed. 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. Correlations were calculated using Pearson correlations coefficient. 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. Overall, 139 vessels were included for further analysis. In 121 vessels, the degree of stenosis was assessed using QCA. The median angiographical degree of stenosis was 41% (30–65%). In the remaining 18 vessels, QCA could not be performed due to diffuse atherosclerosis.

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

Table 1 Patient characteristics of study population ($n = 77$)

	n (%)
Age (years)	57 ± 10
Gender (% male)	53 (69%)
Risk factors for CAD	
Obesity (body mass index ≥30 kg/m^2)	20 (26%)
Diabetes	24 (31%)
Hypertension[a]	46 (60%)
Hypercholesterolemia[b]	43 (56%)
Family history of CAD	40 (52%)
Smoking	28 (36%)
Aspirin use	40 (52%)
Statin use	49 (64%)
Previous PCI	18 (23%)
Previous myocardial infarction	13 (17%)
Presentation with ACS	52 (68%)

Data are absolute values, percentages, or means ± standard deviation

CAD coronary artery disease, *ACS* acute coronary syndrome, *PCI* percutaneous coronary intervention

[a] Defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication

[b] Serum total cholesterol ≥ 230 mg/dl or serum triglycerides ≥ 200 mg/dl or treatment with lipid-lowering drugs

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 Max NC area located proximal to the MLA site.

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%) vs. 19% (10–19%), $p < 0.001$]. Moreover, the MLA site contained significantly more fibrotic tissue than the Max NC site [57% (47–65%) vs. 49% (41–57%), $p < 0.001$]. Furthermore, the MLA site contained significantly more fibro-fatty tissue than the Max NC site [13% (6–24%) vs. 6% (3–12%), $p < 0.001$]. Lastly, plaque burden was significantly larger at the MLA site than at Max NC site [63% (54–74%) vs. 59% (43–68%), $p < 0.001$].

The difference in plaque type between MLA and Max NC sites was assessed. Lesions at the Max NC site were more often classified as a fibroatheroma than lesions at the MLA site (71 vs. 60%, $p = 0.04$). Furthermore, the percentage of fibrocalcific plaque was similar at both the MLA site and Max NC site (5 vs. 4%, $p = 0.78$). Importantly, as demonstrated in Fig. 3, a significantly higher percentage of VH-TCFA was present at Max NC site as compared to the MLA site (24 vs. 9%, $p < 0.001$). Moreover, if VH-TCFA was identified at the Max NC site, only in 33% of cases the MLA site also demonstrated a VH-TCFA. Furthermore, no significant correlation between angiographical degree of stenosis and distance between de Max NC and MLA site was demonstrated $r = 0.04$ ($p = 0.67$).

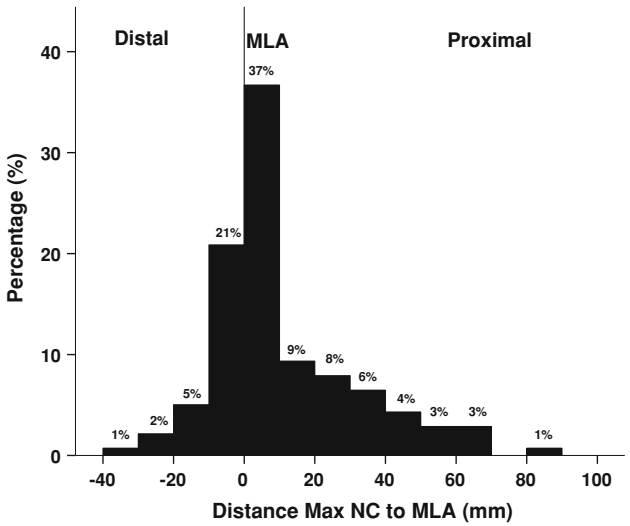

Fig. 1 Spatial relationship of the maximum necrotic core site (Max NC) as compared to minimal lumen area (MLA). In the majority of vessels, the site of Max NC is located proximal to site of MLA

Discussion

The present study evaluated the spatial relationship between the site of most severe narrowing and Max NC

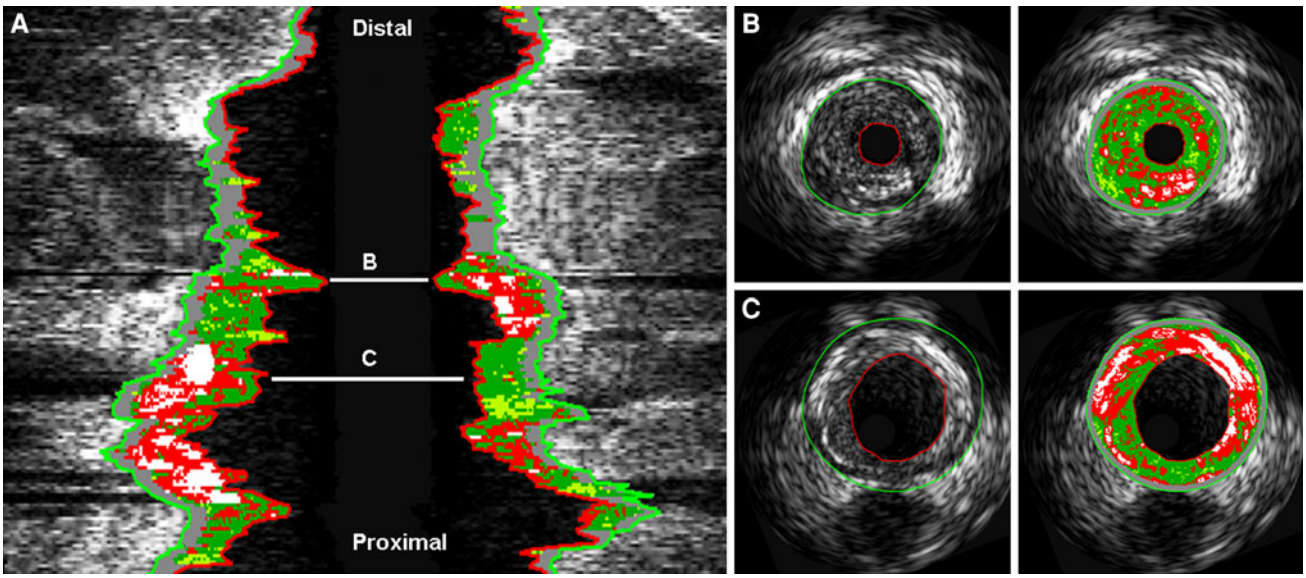

Fig. 2 Example of a coronary artery with the site of maximum necrotic core (Max NC) located proximal from the minimal lumen area (MLA) site. **a** Longitudinal view of the intravascular ultrasound (IVUS) images. As demonstrated, the Max NC site (*C*) is not located at the minimum lumen area (MLA) site (*B*), but 16.4 mm proximal of the MLA site. **b** Grayscale cross-sectional slices and the corresponding virtual histology IVUS images of the MLA site. **c** 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 mm^2) the Max NC site demonstrated a virtual histology-thin cap fibroatheroma (VH-VH-TCFA)

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

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)	NA
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

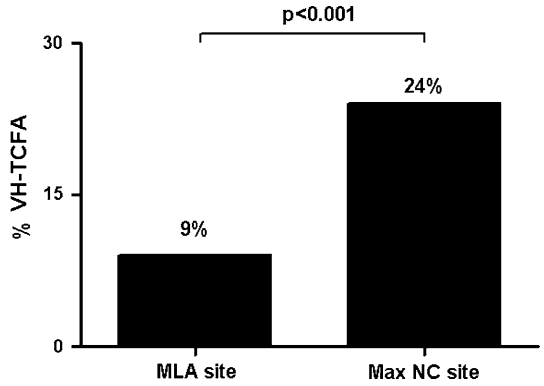

Fig. 3 Difference in presence of virtual histology-thin cap fibroatheroma (VH-TCFA) between minimum lumen area (MLA) site and maximum necrotic core (Max NC) site. As demonstrated, virtual histology-thin cap fibroatheroma was significantly more often observed at the Max NC site as compared to the MLA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

with the use of invasive VH IVUS. It was demonstrated that the site with the Max NC area was rarely located at the site of most severe narrowing (defined as the MLA). Most often (in 66% of vessels), the Max NC area site was located proximal from the site of most severe narrowing. Of particular interest was the finding that a higher percentage of VH-TCFA (plaque phenotype with high risk of rupture) was demonstrated at the site with Max NC area. In addition, there was no significant correlation between angiographical degree of stenosis and distance between the Max NC site and the MLA site.

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 [14, 16]. Indeed, the rupture of a VH-TCFA is thought to be the primary cause of an ACS [17]. Moreover, several landmark angiographic studies have reported that the presence of plaque rupture was poorly related to angiographic degree of luminal narrowing [1, 18, 19]. 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 the site with the largest amount of necrotic core using VH IVUS have demonstrated comparable findings [20–22]. García-García et al. [23] investigated the relation between plaque size and necrotic core and showed that large plaque size was positively correlated with the amount of necrotic core. Moreover, Rodriguez et al. [22] performed VH IVUS in 40 patients and assessed the difference in plaque characteristics between plaque rupture site and site of most severe narrowing. 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. [21] 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. 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 [24, 25]. Also, during in vivo VH IVUS studies, a similar connection between positive remodeling and plaque composition has been reported [25, 26]. However, with traditional ICA, lesions with outward (positive) remodeling are frequently missed. ICA 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 [27]. As a consequence, coronary angiography alone will not detect the exact location of the Max NC area in the majority of patients. Furthermore, due to the difference in location between the site of most severe narrowing and the Max NC area, 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 [28, 29]. Therefore, identification of the Max NC area, in addition to the site of most severe narrowing, could possibly be of importance for clinical management and outcome. Potentially, plaque-stabilizing medication can be subscribed for patients with a hemodynamically non-significant vulnerable plaque. However, no consensus exists regarding the type of treatment for vulnerable regions. Systemic anti-atherosclerotic measures (statins) are currently preferred. In addition, PCI is most often performed in flow-limiting lesions in order to relieve chest pain symptoms. Nevertheless, studies are ongoing evaluating other alternatives (e.g., bio-absorbable stents) for effective treatment of vulnerable plaque regions [30].

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. Thirdly, 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. Lastly, VH-IVUS has limited ability to detect and accurately classify thrombus. Often, thrombus is classified as fibrotic or fibro-fatty, therefore it cannot be excluded that the MLA site was a healed or unhealed ruptured plaque with thrombus [31]. Potentially, both the Max NC site and the MLA site initially presented as a vulnerable plaque but the MLA site had ruptured causing the patient's angina.

In summary, the present findings demonstrate that the Max NC area is rarely at the site of most severe narrowing. Of note, the Max NC area 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.

Acknowledgments This work was supported by the Dutch Heart Foundation (The Hague, The Netherlands) [Grant number 2007B223 to Dr. van Velzen] and the Dutch Technology Foundation STW (Utrecht, The Netherlands) [Grant number 10084 to Dr. de Graaf]. Dr. Jukema has received research grants from and was speaker on (CME accredited) meetings sponsored by Astellas, Astra-Zeneca, Biotronik, Boston Scientific, Bristol Myers Squibb, Cordis, Daiichi Sankyo, Ely Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Orbus Neich, Novartis, Roche, Servier. Dr. Schalij has research grants from Biotronik (Berlin, Germany), Boston Scientific (Natick, Massachusetts) and Medtronic (Minneapolis, Minnesota). Dr. Bax has research grants from Biotronik (Berlin, Germany), Lantheus Medical Imaging (North Billerica, Massachusetts), Boston Scientific (Natick, Massachusetts), Edwards Lifesciences (Irvine, California), GE Healthcare (Buckinghamshire, UK), Medtronic (Minneapolis, Minnesota) and St. Jude Medical (St. Paul, Minnesota).

Reference

1. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V (1988) Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 12(1):56–62
2. Glaser R, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, Detre KM, Wilensky RL (2005) Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. Circulation 111(2):143–149
3. Ishio N, Kobayashi Y, Iwata Y, Kitahara H, Fukushima K, Asano T, Nakayama T, Kuroda N, Komuro I (2010) Ubiquitous atherosclerosis in coronary arteries without angiographically significant stenosis. Heart Vessels 25(1):35–40
4. Nasu K, Tsuchikane E, Katoh O, Vince DG, Virmani R, Surmely JF, Murata A, Takeda Y, Ito T, Ehara M, Matsubara T, Terashima M, Suzuki T (2006) Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. J Am Coll Cardiol 47(12):2405–2412
5. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG (2002) Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation 106(17): 2200–2206
6. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW (2011) A prospective natural-history study of coronary atherosclerosis. N Engl J Med 364(3):226–235
7. Rodriguez-Granillo GA, Garcia-Garcia HM, Mc Fadden EP, Valgimigli M, Aoki J, de Feyter P, Serruys PW (2005) In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. J Am Coll Cardiol 46(11):2038–2042

8. van Velzen JE, Schuijf JD, de Graaf FR, Nucifora G, Pundziute G, Jukema JW, Schalij MJ, Kroft LJ, de Roos A, Reiber JH, van der Wall EE, Bax JJ (2009) Plaque type and composition as evaluated non-invasively by MSCT angiography and invasively by VH IVUS in relation to the degree of stenosis. Heart 95(24):1990–1996
9. Kroner ES, van Velzen JE, Boogers MJ, Siebelink HM, Schalij MJ, Kroft LJ, de Roos A, van der Wall EE, Jukema JW, Reiber JH, Schuijf JD, Bax JJ (2011) Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. Am J Cardiol 107: 1725–1729
10. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W (2007) Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 28(13):1598–1660
11. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr (2002) ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol 40(7):1366–1374
12. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG (2001) American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 37(5): 1478–1492
13. Carlier SG, Mintz GS, Stone GW (2006) Imaging of atherosclerotic plaque using radiofrequency ultrasound signal processing. J Nucl Cardiol 13(6):831–840
14. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM (2000) Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 20(5):1262–1275
15. Garcia-Garcia HM, Mintz GS, Lerman A, Vince DG, Margolis MP, van Es GA, Morel MA, Nair A, Virmani R, Burke AP, Stone GW, Serruys PW (2009) Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. EuroIntervention 5(2):177–189
16. Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK (2004) Pathologic assessment of the vulnerable human coronary plaque. Heart 90(12):1385–1391
17. Shah PK (2003) Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol 41(4 Suppl S):15S–22S
18. Giroud D, Li JM, Urban P, Meier B, Rutishauer W (1992) Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. Am J Cardiol 69(8):729–732
19. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP (1988) Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 78(5 Pt 1):1157–1166
20. Kaple RK, Maehara A, Sano K, Missel E, Castellanos C, Tsujita K, Fahy M, Moses JW, Stone GW, Leon MB, Mintz GS (2009) The axial distribution of lesion-site atherosclerotic plaque components: an in vivo volumetric intravascular ultrasound radio-frequency analysis of lumen stenosis, necrotic core and vessel remodeling. Ultrasound Med Biol 35(4):550–557
21. Konig A, Bleie O, Rieber J, Jung P, Schiele TM, Sohn HY, Leibig M, Siebert U, Klauss V (2010) Intravascular ultrasound radiofrequency analysis of the lesion segment profile in ACS patients. Clin Res Cardiol 99(2):83–91
22. Rodriguez-Granillo GA, Garcia-Garcia HM, Valgimigli M, Vaina S, van Mieghem C, van Geuns RJ, van der Ent M, Regar E, de Jaegere P, van der Giessen W, de Feyter P, Serruys PW (2006) Global characterization of coronary plaque rupture phenotype using three-vessel intravascular ultrasound radiofrequency data analysis. Eur Heart J 27(16):1921–1927
23. Garcia-Garcia HM, Goedhart D, Serruys PW (2007) Relation of plaque size to necrotic core in the three major coronary arteries in patients with acute coronary syndrome as determined by intravascular ultrasonic imaging radiofrequency. Am J Cardiol 99(6): 790–792
24. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R (2002) Morphological predictors of arterial remodeling in coronary atherosclerosis. Circulation 105(3):297–303
25. Varnava AM, Mills PG, Davies MJ (2002) Relationship between coronary artery remodeling and plaque vulnerability. Circulation 105(8):939–943
26. Rodriguez-Granillo GA, Serruys PW, Garcia-Garcia HM, Aoki J, Valgimigli M, van Mieghem CA, McFadden E, de Jaegere PP, de Feyter P (2006) Coronary artery remodelling is related to plaque composition. Heart 92(3):388–391
27. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, Chuang YC, Bucher TA, Sokolowicz LE, Leon MB (1995) Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol 25(7):1479–1485
28. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB (2005) Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 45(7):995–998
29. Okabe T, Mintz GS, Buch AN, Roy P, Hong YJ, Smith KA, Torguson R, Gevorkian N, Xue Z, Satler LF, Kent KM, Pichard AD, Weissman NJ, Waksman R (2007) Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. Am J Cardiol 100(4):615–620
30. Wykrzykowska JJ, Onuma Y, Serruys PW (2009) Advances in stent drug delivery: the future is in bioabsorbable stents. Expert Opin Drug Deliv 6(2):113–126
31. Nasu K, Tsuchikane E, Katoh O, Vince DG, Margolis PM, Virmani R, Surmely JF, Ehara M, Kinoshita Y, Fujita H, Kimura M, Asakura K, Asakura Y, Matsubara T, Terashima M, Suzuki T (2008) Impact of intramural thrombus in coronary arteries on the accuracy of tissue characterization by in vivo intravascular ultrasound radiofrequency data analysis. Am J Cardiol 101(8): 1079–1083