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ORIGINAL CONTRIBUTION

Impact of atherosclerotic plaque composition on coronary microembolization during percutaneous coronary interventions

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Abstract *Background* Cardiac marker release after percutaneous coronary interventions (PCI) reflects myocardial necrosis which is usually the result of periprocedural (micro)embolization of atherothrombotic debris and associated with impaired left ventricular function and adverse outcome. *Methods* In this prospective study, we examined 55 patients treated by direct stenting of single de-novo lesions to assess the relationship between plaque composition, as determined by preinterventional intravascular ultrasound (IVUS) with radiofrequency data (IVUS-RF) analysis (so-called Virtual Histology) versus coronary microembolization, as determined by serial measurement of cardiac markers. IVUS was performed with an electronic system and 20-MHz IVUS catheters. Serum creatine kinase (CK) and cardiac troponin I (CTnI) were determined before PCI and after 6, 12, and 24 hours. *Results* Plaques had a volume of 99 ± 63 mm^3 and were composed of fibrous (61 ± 9%) and fibro-fatty tissue (27 ± 12%), dense calcium (4 ± 3%), and necrotic core (NC) (8 ± 6%). NC volume per se, volume per 10 mm of segment length, and volume % were correlated ($r = 0.64$, 0.66, and 0.52 respectively; all $P < 0.01$) with the maximum increase in cardiac markers (CK 55.4 ± 55.7 U/l; CTnI 0.49 ± 0.68 ng/ml). Patients in the 4th quartile of NC volume (>10.8 mm^3) had a particularly high increase in markers ($P < 0.001$). In contrast, total plaque volume and plaque components other than NC had no relation with cardiac markers (ns). *Conclusions* Patients with large NC in culprit lesions may experience more myocardial injury from peri-interventional microembolization. IVUS-RF assessment

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before PCI has the potential to identify lesions at particular high risk which may help to tailor PCI.

Key words intravascular ultrasound – radiofrequency – virtual histology – plaque composition – microembolization

Introduction

Microembolization of atherothrombotic material, as observed in patients with spontaneously ruptured coronary plaques, may result in impairment of the myocardial microcirculation, as demonstrated by various clinical observations and experimental studies [2, 5, 7, 8, 20–22, 33]. Data on coronary and myocardial perfusion as well as the assessment of coronary morphology helped to identify the source and consequences of coronary microembolization [7, 8, 14, 25, 29, 39, 45]. Percutaneous coronary interventions (PCI) may also cause microembolization, which can lead to (1) an impaired flow reserve and/or a no-reflow phenomenon, (2) myocardial microinfarcts with cardiac marker release and impaired left ventricular function, and (3) significantly impaired clinical outcome [4, 9, 15–18, 33, 41]. Coronary stenting, currently the standard PCI technique for the treatment of significant coronary lesions, causes less cardiac marker release than atheroablative techniques [10, 11, 17, 19, 45]. Direct stenting may have a lower risk of coronary microembolization than stenting after predilation [19].

Intravascular ultrasound (IVUS) permits accurate measurement of coronary plaque dimensions in vivo [3, 28, 32, 43]. The ability of conventional IVUS to identify specific plaque components with conventional grey-scale IVUS is very limited [28]. Therefore, novel IVUS techniques such as IVUS Virtual Histology (VH) focus on the analysis of radiofrequency (RF) signals (IVUS-RF) to identify and quantify various plaque components such as the necrotic core (NC) [6, 12, 30, 31, 33, 34, 35]. The correlation between the amount of NC and the release of small embolic particles during PCI has been shown previously [23]. Even in patients with an acute coronary syndrome, the necrotic core was correlated to an ST-segment re-elevation after PCI [24]. Nevertheless, results of the impact of coronary plaque composition on the increase of cardiac markers after PCI are pending.

In the present prospective study we examined patients treated by direct stent implantation to assess the relation between the incidence and severity of PCI-induced coronary microembolization (as determined by serial measurement of cardiac markers) versus atherosclerotic plaque composition (as assessed by the analysis of IVUS-RF data).

Methods

Patient population

In this study, we prospectively enrolled from July 2005 to March 2007 a total of 55 patients with single de-novo non-bifurction coronary lesions suitable for treatment by direct implantation of a single stent. Further inclusion criteria were (1) presence of stable angina pectoris; (2) significance of the stenosis defined by an angiographic diameter stenosis >50% or a fractional flow reserve <0.75 (as measured with an intracoronary pressure wire); (3) angiographic reference diameter between 2.5 and 4 mm; (4) vessel anatomy suitable for high-quality IVUS imaging (no extreme tortuosity of proximal coronary segment and no excessive calcifications); (5) absence of angiographic evidence of thrombus formation; and (6) absence of known heart failure with significant left ventricular impairment. To avoid interference with the assessment of microembolization, the protocol intended the exclusion of patients with a (angiographically visible) PCI-related occlusion of a side branch, intermittent occlusion of the target vessel, and/or prolonged balloon inflations >3 min. Nevertheless, no such event occurred and accordingly, no patient had to be excluded following the PCI procedure. The present study was approved by the Local Council on Human Research, and all patients signed a written informed consent form as approved by the Local Medical Ethics Committee.

Cardiac catheterization

Cardiac catheterization was performed in the Cardiac Catheterization Laboratory of the West-German Heart Center of the University Duisburg-Essen according to international standards using the femoral approach, intracoronary injections of 200 μg nitroglycerin, and 6F or 8F guiding catheters. All patients were on 100 mg aspirin and 75 mg clopidogrel (loading dose of 300 mg one day before the intervention, if required) and received adequate doses of unfractionated heparin intravenously. During the entire interventional procedure, online quantitative coronary angiography (Siemens, Erlangen, Germany) could be used according to standard methodology on end-diastolic frames, using the guiding catheter for calibration.

IVUS examination

Conventional IVUS and RF ultrasound backscatter IVUS signals were acquired after intracoronary injection of nitroglycerin (but before stenting) with a commercially available electronic IVUS catheter (Eagle-Eye^{TM} 20 MHz catheter and R-100 pullback device, Volcano Corporation, Rancho Cordova, CA, USA). The IVUS transducer was automatically withdrawn using the continuous motorized pullback device at a speed of 0.5 mm/s. Pullbacks were started as distal as possible, distal to an anatomical landmark, and at least 10 mm distal to the target segment. Then the entire artery was imaged up to the aorto-ostial junction. After the motorized pullback was finished, the operator was free to perform additional manual interrogations of the lesion. A final motorized IVUS run was performed at the end of the PCI procedure. IVUS-RF data were acquired with ECG gating at the time of the R-top; accordingly, the frame rate depended on the heart rate. Both, conventional grayscale IVUS and IVUS-RF data were collected in a dedicated console (InVision Gold^{TM}, Volcano Corp.) and were stored on the hard disk for offline analysis. In this study, there were no procedural or post-procedural in-hospital complications related to IVUS and/or the PCI.

Stent implantation

Implantation of balloon-expandable stents was performed according to standard clinical practice using balloon pressures between 14 and 18 atm. According to the study protocol, only direct stenting was performed. The choice between drug-eluting stents (DES) and bare-metal stents (BMS) was left to the investigator's discretion. The stent diameter was chosen, aiming at an angiographic stent-to-artery ratio of 1.1–1.15. Both, angiography and IVUS information from the preinterventional run were used to determine the optimal stent size. If required, additional heparin was administered during the procedure to maintain an activated clotting time >250 s. The final PCI result was assessed (1) by angiography in the "worst angiographic view" (by visual assessment) and (2) with quantitative IVUS from a motorized pullback run that was performed at 0.5 mm/s at the end of the PCI.

IVUS analysis

All IVUS runs were interpreted by three interventional cardiologists. The IVUS analysis was performed with dedicated software (pcVH2.1, Volcano Corp.) by a single operator, who was experienced in the analysis of IVUS but blinded to clinical details, the result of the PCI, and the results of the laboratory analysis.

Spectral Analysis of RF Ultrasound Backscatter IVUS Signal: VH uses spectral analysis of IVUS-RF data to build tissue maps that are correlated with a tissue specific spectrum of the radiofrequency signal, permitting in this way a detailed assessment of plaque composition. Validation of this technique in explanted human coronary segments has been reported [26, 27]. The IVUS B-mode images were reconstructed from the RF data by the customized software (pcVH^{TM}2.1, Volcano Corp.). Cross-sectional frames and longitudinal views were displayed, which allowed to automatically determine the interface between media-adventitia (total vessel dimensions) and the lumen-plaque interface (lumen dimensions); then the automatically detected contours could be manually edited. Volumetric data on lumen, total vessel, and plaque plus media dimensions were provided; plaque plus media dimensions were calculated as total vessel minus lumen dimensions.

For each IVUS frame, geometrical and compositional plaque characterization was obtained within these borders. "Blind Deconvolution"—an iterative algorithm for normalization—was used to account for the catheter transfer function from the backscatter and therefore for catheter-to-catheter variability. The software differentiated between tissue types and assigned color codes to them (Fig. 1): fibrous tissue (labeled green), fibro-fatty tissue (labeled greenish-yellow), necrotic core (labeled red), and dense calcium (labeled white). In order to provide comparable volumetric data, we present for each individual plaque component not only the absolute volume, but also the proportion of the total plaque volume (%) and the volume normalized for 10 mm of segment length.

The PCI result was assessed on the grayscale images of an IVUS run at 0.5 mm/s at the end of the PCI. Conventional IVUS measurements of stent and lumen dimensions at the site of the minimal stent lumen cross-sectional area and at the reference segments (within 10 mm from the stent edges) were performed according to international standards [27, 28].

Laboratory analyses

Venous blood samples were collected before and 6, 12 and 24 h after PCI from a peripheral vein; all samples were analyzed in the central laboratory of the University Duisburg-Essen according to international standards. Immediate serum marker analysis was performed by an enzymatic assay (Bayer Diagnostics, Leverkusen, Germany) for determining total creatine kinase (CK) activity. The upper limit of normal was

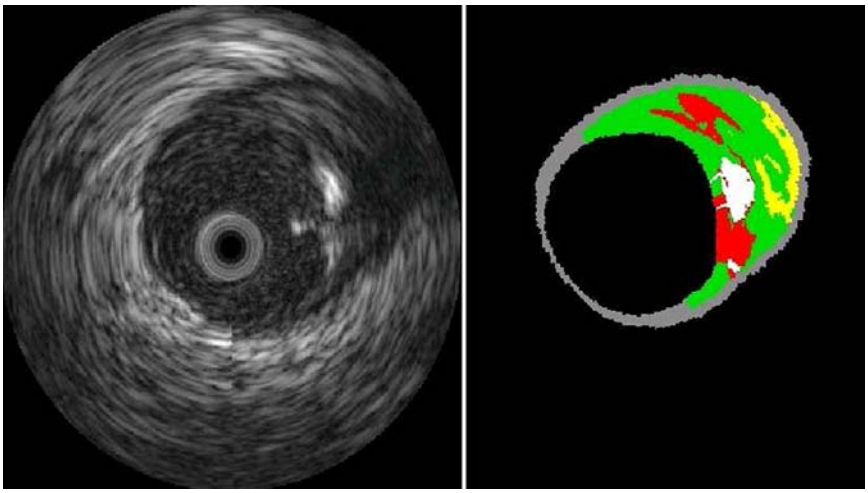

Fig. 1 Conventional IVUS grayscale image and color-coded visualization of plaque composition obtained from IVUS VH analysis. Fibrous tissue is displayed in green and fibro-fatty tissue is greenish-yellow; the necrotic core is encoded in *red*, and dense calcium is *white*

174 U/l. Cardiac Troponin I (CTnI) was measured using a specific two-side immunoassay (Dimension Flex, Dade Behring GmbH, Marburg, Germany). The detection range of CTnI was 0.04 to 40 ng/ml; the upper limit of normal was 0.1 ng/ml.

Statistical analysis

Analyses were performed with the SPSS 12.0.1 (SPSS Inc. Chicago, IL) statistical software. Dichotomous data are presented as frequencies. Quantitative data are presented as mean ± 1SD and compared using paired and unpaired Student *t* test, ANOVA, and linear regression analysis. A P-value < 0.05 was considered significant. In addition, a multi-variate analysis was performed to identify plaque components and cardiovascular risk factors that may influence coronary microembolization after PCI.

Results

Demographics and characteristics of patients and procedures

The 55 patients were 64 ± 9 years old, and 71% were males. The culprit vessel was the left anterior descending, right, and left circumflex coronary artery in 37(67%), 10(18%), and 8(15%) patients, respectively. The balloon-expandable coronary stents implanted were 20.1 ± 9.1 mm long and had a nominal diameter of 3.3 ± 0.4 mm. DES were used in 34(62%) patients, BMS in 21(38%) patients. Stents were implanted with a balloon pressure of 15.9 ± 1.7 atm. In all cases, a good angiographic result was achieved with a residual stenosis <10%. Further clinical details, medication, and serum lipid profile are presented in Table 1.

IVUS analysis

The minimal lumen cross-sectional area in the culprit segment was 3.07 ± 0.62 mm^2 before stent and 7.99 ± 1.69 mm^2 after stent implantation. The mini-

Table 1 Patient characteristics, medication, and serum lipid profile

Patients		*n* = 55
Age (years)		64 ± 9
Males		39 (71%)
Angina status	Class I	13 (23%)
	Class II	21 (38%)
	Class III	12 (22%)
	Class IV	9 (16%)
Dyspnea	Class I	18 (33%)
	Class II	29 (53%)
	Class III	8 (15%)
	Class IV	0
Risk factors	Smokers	17 (31%)
	Family history of CAD	26 (59%)
	Hypertension	47 (86%)
	Diabetes	12 (25%)
	Hypercholesterolemia	47 (86%)
Medication	Aspirin	53 (93%)
	Beta-blocker	53 (93%)
	ACE inhibitor	35 (64%)
	AT blocker	16 (30%)
	Calcium channel blocker	11 (20%)
	Diuretics	33 (60%)
Serum lipid profile	Total cholesterol (mg/dl)	178.3 ± 39.5
	HDL cholesterol (mg/dl)	50.9 ± 14.8
	LDL cholesterol (mg/dl)	92.7 ± 25.6
	Triglycerides (mg/dl)	154.8 ± 97.1

Continuous data are expressed as mean ± SD. Frequencies are expressed as absolute and relative frequencies; *n*(%)
CAD coronary artery disease

Table 2 IVUS virtual histology data of target lesion plaques

Plaque volume (segment) [mm^3]	99.6 ± 63.2
Plaque volume/10 mm [mm^3]	49.4 ± 18.9
Fibrous volume (segment) [mm^3]	59.5 ± 37.6
Fibrous volume [%]	60.7 ± 8.3
Fibrous volume/10 mm [mm^3]	29.4 ± 11.1
Fibro-fatty volume (segment) [mm^3]	28.9 ± 27.3
Fibro-fatty volume [%]	27.4 ± 12.1
Fibro-fatty volume/10 mm [mm^3]	14.3 ± 10.0
Dense calcium volume (segment) [mm^3]	3.9 ± 4.9
Dense calcium volume [%]	4.1 ± 3.5
Dense calcium/10 mm [mm^3]	2.0 ± 2.1
Necrotic core volume (segment) [mm^3]	7.2 ± 7.0
Necrotic core volume [%]	7.9 ± 6.4
Necrotic core volume/10 mm [mm^3]	3.7 ± 2.9

Continuous data are expressed as mean ± SD

mal lumen diameter increased from 1.79 ± 0.18 to 3.11 ± 0.36 mm.

Plaque composition by IVUS VH analysis

Table 2 presents the data of the IVUS VH analysis (presenting). Plaques had a volume of 99 ± 63 mm^3 and were composed of fibrous (61 ± 8%) and fibro-fatty tissue (27 ± 12%), dense calcium (4 ± 3%), and necrotic core (NC) (8 ± 6%).

Cardiac markers

Before PCI, CK and CTnI values were 76 ± 35.1 U/l and 0.03 ± 0.03 ng/ml, respectively. The maximum increases in CK and CTnI during 24 h after the PCI were 55.41 ± 55.7 U/l and 0.49 ± 0.68 ng/ml, respectively. The increases in CK and CTnI after 6 h were 12.67 ± 27.19 U/l and 0.07 ± 0.22 ng/ml, after 12 h 34.47 ± 48.42 U/l and 0.34 ± 0.56 ng/ml, after 24 h 49.31 ± 59.2 U/l and 0.44 ± 0.69 ng/ml, respectively.

Relation between plaque composition and cardiac markers

There was a significant relation between the dimensions of the necrotic core by IVUS VH and the markers of microembolization: NC volume per se, NC volume per 10 mm of segment length, and NC volume % had a significant linear relation ($r = 0.64$, 0.66, and 0.52 respectively; all $P < 0.01$) with the maximum increase in TnI (see Fig. 2). In the multi-variate analysis after adjustment for potentially confounding risk factors, only NC was correlated with the increase of cardiac markers ($P < 0.01$). Total plaque volume and plaque components other than the NC had no relation with the cardiac markers ($r \leq 0.30$; all NS).

Necrotic core volume was divided into quartiles. Figure 3 presents for each quartile the increase in cardiac markers which indicated the extent of microembolization. Patients in the 4th quartile of NC volume (>10.81 mm^3) had a greater increase in cardiac markers ($P < 0.001$).

ECG changes

No relevant ECG changes were recorded during the hospital stay.

Relation between stent design and coronary microembolization

Both, DES(62%) and BMS(38%) were used in this study. There was no significant difference in the increase of cardiac markers after PCI in these two groups (P = NS).

Medication and coronary microembolization

Before PCI, 40 (73%) patients were treated with statins. Patients on statins had lesser increases in CTnI (0.31 ± 0.43 ng/ml vs. 1.02 ± 0.99 ng/ml) and CK (41.8 ± 440.7 U/l vs. 97.6 ± 68.9 U/l). Statistical significance was not reached ($P = 0.065$).

Cardiovascular risk factors and coronary microembolization

The impact of coronary risk factors on microembolization was assed using a multi-variate analysis. An increase of age and diabetes was significantly correlated ($P < 0.05$) with an increase of cardiac markers after PCI.

Discussion

The main finding of our study is a significant relation between the extent of cardiac marker release following stenting Vs. the volume of the NC in the treated lesions. In contrast, the volumes of the total plaque and of other plaque components (other than NC) had no relation with cardiac marker release.

PCI and coronary microembolization

Observations in spontaneously ruptured plaques and experimental studies previously demonstrated that

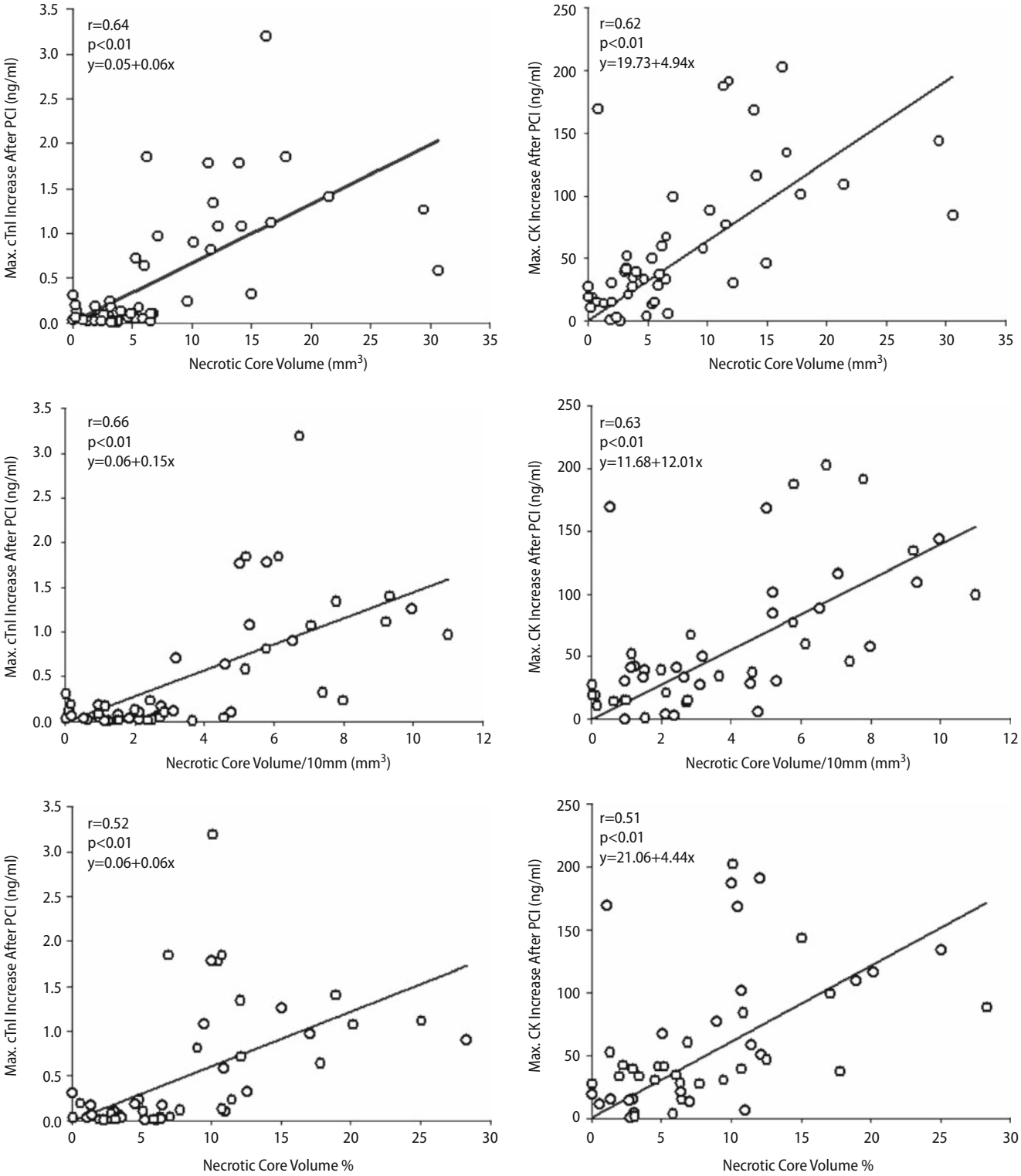

Fig. 2 Correlation between necrotic core size and maximum increase in cardiac markers following PCI

debris is washed out from the atheromatous core and embolized into the distal microvascular bed, which can lead to microinfarcts with regional myocardial dysfunction (even in the absence of a significant epicardial coronary stenosis) [2, 5, 9, 20–22, 39]. During PCI, atheromatous lesions are

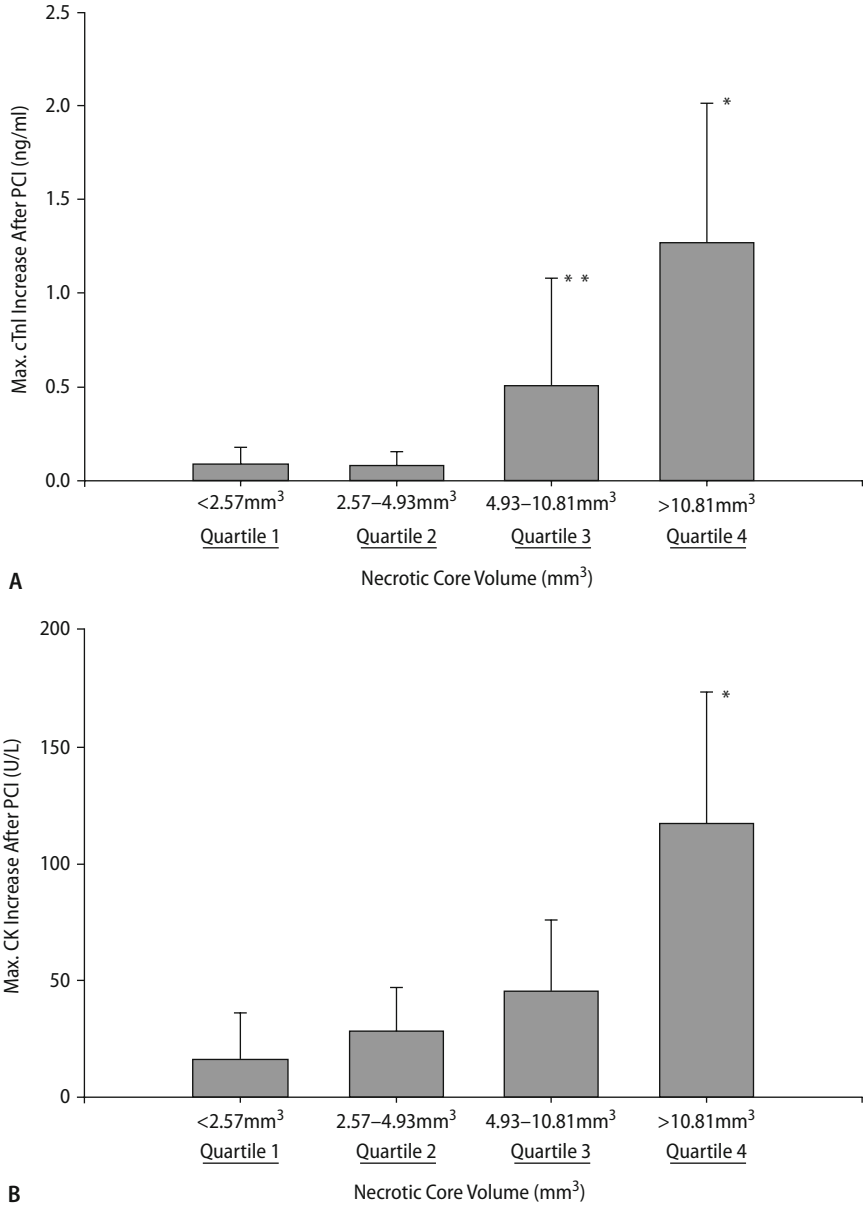

Fig. 3 Maximum rise of cardiac markers in quartiles of necrotic core volume for CK (A) and CTnI (B); (*$P < 0.01$ vs. quartiles 1, 2, and 3; **$P < 0.05$ vs. quartile 2)

compressed and often even fractured or dissected, which can lead to the release of debris from the atheromatous core into the coronary lumen and finally to embolization into the coronary microvasculature.

Cardiac marker release after PCI has previously been related to persistent reduction of relative coronary flow velocity reserve, suggesting procedural microembolization of atherothrombotic debris [1, 14], which may have significant consequences with regards to clinical outcome [7, 15, 17]. Consequently, the increase in CK and CTnI following PCI is considered to reflect coronary microembolization. This applies all the more to the population of the present study, as patients with alternative causes of cardiac marker release (e.g., angiographic evidence of thrombus; PCI-related side branch occlusion; intermittent target vessel occlusion; or prolonged balloon inflations) were excluded.

Necrotic core size and microembolization

Histomorphometric analyses have previously shown that the NC cross-sectional area and the ratio between NC and total plaque size is larger in ruptured plaques than in fibroatheromas or thin-walled atheromas [42]. Accordingly, plaques with larger NC may be at a

higher risk of plaque rupture and to cause microembolization. The findings of our study comply with these histopathologic observations, as the volume of the NC showed a strong relation with the amount of cardiac marker release (i.e. the extent of coronary microembolization) while plaque components other than the NC (fibrous and fibro-fatty tissue, and dense calcium) showed no such relation. In addition, cardiac marker release following PCI was much greater in plaques with a large necrotic core volume (>10.81 mm^3; $P < 0.001$). In addition, these findings agree to a study of Kamamoto et al. in which they demonstrated a correlation between the amount of necrotic core and the release of small embolic particles during PCI [23]. We found a not significant ($P = 0.065$) trend to a lower increase of cardiac markers in patients treated with statins before PCI. This may underline the potential implication of statin therapy to reduce microembolization as shown by Herrmann et al. [18].

PCI techniques and cardiac marker release

Our findings in PCI procedures with *direct stenting* demonstrate that plaque composition – in particular the size of the NC—determines the extent of procedure-related microembolization. This is remarkable, as *direct stenting* (performed in the present study) is considered a PCI technique with relatively low risk of coronary microembolization [19].

One may argue that in PCI procedures with atheroablative techniques, which pose a much greater trauma to the vessel wall, the relation between NC size Vs. microembolization might be even stronger. In the present study, we found no significant relation between the total plaque volume and cardiac marker release after PCI, while in a study by Mehran et al. plaque burden as measured by conventional IVUS showed a significant relation with the elevation of the serum creatine kinase MB fraction after PCI [27]. This contrast may be explained by significant differences in the populations studied. While our study included patients with direct stenting only (and excluded complex lesions, lesions with procedure-related side branch occlusion etc.), Mehran et al. examined an unselected cohort of patients with PCI procedures that were performed with various techniques including atheroablative techniques, which were found to be associated with a particulaly high incidence of cardiac marker release [27].

IVUS assessment of coronary plaque composition

IVUS imaging provides accurate measurements of lumen, total vessel, and plaque dimensions, and facilitates the detection of coronary plaque ruptures and ulcerations [13, 39, 44, 46, 47]. Nevertheless, visual interpretation of grayscale IVUS images is very limited for the evaluation of plaque composition (other than the detection of calcium) [28]. Spectral analysis of IVUS radiofrequency data by so-called Virtual Histology is an emerging tool for the assessment of plaque morphology and composition in-vivo [12, 28, 31, 32, 36], while other promising intracoronary techniques for the detection of vulnerable plaques address mechanical properties of the plaques (e.g., IVUS Palpography), the presence of thin fibrous caps, or local plaque inflammation [37, 38, 40].

As recently shown by Rodriguez-Granillo et al., IVUS VH assessment detects vulnerable plaques with acceptable sensitivity [36]. Previously, these authors demonstrated that IVUS VH characterization of non-culprit vessels shows a significant relation with the clinical presentation [41]. Our present study suggests that IVUS VH quantification of the NC dimensions may be useful to identify vulnerable plaques and to predict the risk of significant microembolization during PCI.

Potential clinical implications

If a population of relatively low-risk patients treated by the most atraumatic PCI technique (direct stenting) shows a strong relation between NC size and release of cardiac markers, it is very likely that the assessment of plaque composition (and in particular of the NC size) may have clinical implications. Only large multicenter trials will be able to evaluate the clinical value of the assessment of plaque composition prior to PCI. Nevertheless, we speculate that the IVUS VH assessment of coronary plaques may result in tailored interventions (i.e., the use of an embolic protection device) [26], and may help to optimize systemic medical therapy (i.e., therapy with very high dose statins [18] or novel antiatherosclerotic drugs). In patients with *stable* angina pectoris and lesions with huge NC, the operator may then even decide to delay PCI in order to permit aggressive medical pretreatment to reduce the risk of PCI-related microvascular damage as a result of microembolization.

Limitations

By most standards, this was a relatively large study with IVUS VH assessment; nevertheless most current studies with IVUS-RF data analysis are limited to a relatively small number of patients. We used strict inclusion criteria in order (1) to be able to relate the treatment of a particular lesion with the corresponding cardiac marker release (e.g., no multivessel PCI;

no patients with acute coronary syndrome and cardiac marker release), and (2) to be able to relate cardiac marker release with microembolization (e.g., exclusion of cases with other potential causes of cardiac marker release). These criteria were inevitable, but accordingly, our findings may not be applicable to patients with severe and diffuse coronary artery disease or complicated coronary lesions. This study was neither designed nor powered to assess clinical outcome. Nevertheless, as such information is of interest, clinical outcome data should be obtained in future multicenter trials. Although histopathology remains the "gold standard" for the assessment of coronary plaques [42], IVUS VH assessment permits interesting information on plaque composition in vivo which may be clinically useful.

Conclusions

Patients with large necrotic cores in culprit lesions, as determined by intravascular ultrasound Virtual Histology assessment, may experience more myocardial injury from microembolization during percutaneous coronary interventions. Even in percutaneous coronary interventions with presumably lower risk of coronary microembolization (such as direct coronary stenting), the size of the necrotic core appear to determine the extent of procedure-related microembolization and microvascular dammage. In principle, intravascular ultrasound Virtual Histology assessment before the intervention has the potential to identify lesions at particular high risk of microembolization which may finally lead to tailored percutaneous coronary interventions in the future.

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Conflict of interest R. Erbel was consultant for Volcano Corp. (Rancho Cordova, US). The other authors have no potential conflict of interest.

References

1. Bahrmann P, Werner GS, Heusch G, Ferrari M, Poerner TC, Voss A, Figulla HR (2007) Detection of coronary microembolization by Doppler ultrasound in patients with stable angina pectoris undergoing elective percutaneous coronary interventions. Circulation 115:600–608
2. Baumgart D, Liu F, Haude M, Gorge G, Ge J, Erbel R (1995) Acute plaque rupture and myocardial stunning in patients with normal coronary arteriography. Lancet 346:193–194
3. Böse D, Birgelen C von, Erbel R (2007) Intravascular ultarsound for the evaluation of therapies targeting coronary atherosclerosis. J Am Coll Cardiol 49:925–932
4. Califf RM, Abdelmeguid AE, Kuntz RE, Popma JJ, Davidson CJ, Cohen EA, Kleiman NS, Mahaffey KW, Topol EJ, Pepine CJ, Lipicky RJ, Granger CB, Harrington RA, Tardiff BE, Crenshaw BS, Bauman RP, Zuckerman BD, Chaitman BR, Bittl JA, Ohman EM (1998) Myonecrosis after revascularization procedures. J Am Coll Cardiol 31:241–251
5. Davies MJ, Thomas AC (1985) Plaque fissuring—the cause of acute myocardial infarction, sudden ischemic death and crescendo angina. Br Heart J 53:363–373
6. DeMaria AN, Narula J, Mahmud E, Tsimikas S (2006) Imaging vulnerable plaque by ultrasound. J Am Coll Cardiol 47:C32–C39
7. Dietrich T, Perlitz C, Licha K, Stawowy P, Atrott K, Tachezy M, Meyborg H, Stocker C, Gräfe M, Fleck E, Schirner M, Graf K (2007) ED-B fibronectin (ED-B) can be targeted using a novel single chain antibody conjugate and is associated with macrophage accumulation in atherosclerotic lesions. Basic Res Cardiol 102:298–307
8. Erbel C, Sato K, Meyer FB, Kopecky SL, Frye RL, Goronzy JJ, Weyand CM (2007) Functional profile of activated dendritic cells in unstable atherosclerotic plaque. Basic Res Cardiol 102:123–132
9. Erbel R, Heusch G (2000) Coronary microembolization. J Am Coll Cardiol 36:22–24
10. Erbel R, Haude M, Hopp HW, Franzen D, Rupprecht HJ, Heublein B, Fischer K, de Jaegere P, Serruys P, Rutsch W, Probst P (1998) Coronary artery stenting compared with balloon angioplasty. N Engl J Med 339:1672–1678
11. Erbel R, Di Mario C, Bartunek J, Bonnier J, de Bruyne B, Eberli FR, Erne P, Haude M, Heublein B, Horrigan M, Ilsley C, Böse D, Koolen J, Luscher TF, Weissman N, Waksman R; PROGRESS-AMS (Clinical Performance, Angiographic Results of Coronary Stenting with Absorbable Metal Stents) Investigators (2007) Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. Lancet 369:1869–1875
12. Fujii K, Carlier SG, Mintz GS, Wijns W, Colombo A, Böse D, Erbel R, de Ribamar Costa J Jr, Kimura M, Sano K, Costa RA, Lui J, Stone GW, Moses JW, Leon MB (2005) Association of plaque characterization by intravascular ultrasound virtual histology and arterial remodeling. Am J Cardiol 96:1476–1483
13. Ge J, Chirillo F, Schwedtmann J, Gorge G, Haude M, Baumgart D, Shah V, von Birgelen C, Sack S, Boudoulas H, Erbel R (1999) Screening of ruptured plaques in patients with coronary artery disease by intravascular ultrasound. Heart 81:621–627
14. Guethlin M, Kasel AM, Coppenrath K, Ziegler S, Delius W, Schwaiger M (1999) Delayed response of myocardial flow reserve to lipid-lowering therapy with fluvastatin. Ciculation 99:475–481
15. Haude M, Baumgart D, Verna E, Piek JJ, Vrints C, Probst P, Erbel R (2001) Intracoronary Doppler- and quantitative coronary angiography—derived predictors of major adverse cardiac events after stent implantation. Circulation 103:1212–1217

16. Herrmann J, Haude M, Lerman A, Schulz R, Volbracht L, Ge J, Schmermund A, Wieneke H, von Birgelen C, Eggebrecht H, Baumgart D, Heusch G, Erbel R (2001) Abnormal coronary flow velocity reserve after coronary intervention is associated with cardiac marker elevation. Circulation 103:2339–2345
17. Herrmann J, Von Birgelen C, Haude M, Volbracht L, Malyar N, Eggebrecht H, Konorza TF, Baumgart D, Erbel R (2002) Prognostic implication of cardiac troponin T increase following stent implantation. Heart 87:549–553
18. Herrmann J, Lerman A, Baumgart D, Volbracht L, Schulz R, von Birgelen C, Haude M, Heusch G, Erbel R (2002) Preprocedural statin medication reduces the extent of periprocedural non-Q-wave myocardial infarction. Circulation 106:2180–2183
19. Herrmann J (2005) Periprocedural myocardial injury: 2005 update. Eur Heart J 26:2493–2519
20. Honour AJ, Ross RW (1962) Experimental platelet embolism. Br J Exp Pathol 43:350–362
21. Jorgensen L (1964) Experimental platelet, coagulation thrombi. Acta Pathol Microbiol Scand 62:189–223
22. Jorgensen L, Rowsell HC, Hovig T, Glynn M, Mustard JF (1967) Adenosine diphosphate–induced platelet aggregation and myocardial infarction in swine. Lab Invest 17:616–644
23. Kawaguchi R, Oshima S, Jingu M, Tsurugaya H, Toyama T, Hoshizaki H, Taniguchi K (2007) Usefulness of virtual histology intravascular ultrasound to predict distal embolization for ST-segment elevation myocardial infarction. J Am Coll Cardiol 50:1641–1646
24. Kawamoto T, Okura H, Koyama Y, Toda I, Taguchi H, Tamita K, Yamamuro A, Yoshimura Y, Neishi Y, Toyota E, Yoshida K (2007) The relationship between coronary plaque characteristics and small embolic particles during coronary stent implantation. J Am Coll Cardiol 50:1635–1640
25. Lambertz H, Tries HP, Stein T, Lethen H (1999) Noninvasive assessment of coronary flow reserve with transthoracic signal-enhanced Doppler echocardiography. J Am Soc Echocardiogr 12:186–195
26. Leineweber K, Böse D, Vogelsang M, Haude M, Erbel R, Heusch G (2006) Intense vasoconstriction in response to aspirate from stented saphenous vein aortocoronary bypass grafts. J Am Coll Cardiol 47:981–986
27. Mehran R, Dangas G, Mintz GS, Lansky AJ, Pichard AD, Satler LF, Kent KM, Stone GW, Leon MB (2000) Atherosclerotic plaque burden and CK-MB enzyme elevation after coronary interventions: intravascular ultrasound study of 2,256 patients. Circulation 101:604–610
28. 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 clinival expert consensus document on standards for acquisition, measurements, and reporting of intravascular ultrasound studies (IVUS). J Am Coll Cardiol 37:1478–1492
29. Nagai T, Luo H, Atar S, Lepor NE, Fishbein MC, Siegel RJ (1999) Intravascular ultrasound imaging of ruptured atherosclerotic plaques in coronary arteries. Am J Cardiol 83:135–136
30. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG (2002) Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation 106:2200–2206
31. 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 47:2405–2412
32. Nissen SE, Yock P (2001) Intravascular ultrasound: novel pathophysiological insights and current clinical applications. Circulation 103:604–606
33. Reffelmann T, Kloner RA (2006) The no-reflow phenomenon: a basic mechanism of myocardial ischemia and reperfusion. Basic Res Cardiol 101:359–372
34. 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 remodeling is related to plaque composition. Heart 92:388–391
35. Rodriguez-Granillo GA, García-García HM, Valgimigli M, Schaar JA, Pawar R, van der Giessen WJ, Regar E, van der Steen AF, de Feyter PJ, Serruys PW (2006) In vivo relationship between compositional and mechanical imaging of coronary arteries: insights from intravascular ultrasound radiofrequency data analysis. Am Heart J 151:1025e1–1025e6
36. Rodriguez-Granillo GA, McFadden EP, Valgimigli M, van Mieghem CA, Regar E, de Feyter PJ, Serruys PW (2006) Coronary plaque composition of nonculprit lesions, assessed by in vivo intracoronary ultrasound radio frequency data analysis, is related to clinical presentation. Am Heart J 151:1020–1024
37. Schaar JA, van der Steen AF, Mastik F, Baldewsing RA, Serruys PW (2006) Intravascular palpography for vulnerable plaque assessment. J Am Coll Cardiol 47:C86–C91
38. Schaar JA, Mastik F, Regar E, den Uil CA, Gijsen FJ, Wentzel JJ, Serruys PW, van der Stehen AF (2007) Current diagnostic modalities for vulnerable plaque detection. Curr Pharm Des 13:995–1001
39. Skyschally A, Leineweber K, Gres P, Haude M, Erbel R, Heusch G (2006) Coronary microembolization. Basic Res Cardiol 101:373–382
40. Van Belle E, Lablanche JM, Bauters C, Renaud N, McFadden EP, Bertrand ME (1998) Coronary angioscopic findings in the infarct—related vessel within one month of acute myocardial infarction. Natural history and effect of thrombolysis. Circulation 97:26–33
41. Van Liebergen RA, Piek JJ, Koch KT, de Winter RJ, Lie KI (1998) Immediate and long-term effect of balloon angioplasty or stent implantation on the absolute and relative coronary blood flow velocity reserve. Circulation 98:2133–2140
42. Virmani R, Burke AP, Kolodgie FD, Farb A (2002) Vulnerable plaque: the pathology of unstable coronary lesions. J Interv Cardiol 15:439–446
43. von Birgelen C, Hartmann M, Mintz GS, Baumgart D, Schmermund A, Erbel R (2003) Relation between progression and regression of atherosclerotic left main coronary artery disease and serum cholesterol levels as assessed with serial long-term (≥12 months) follow-up intravascular ultrasound. Circulation 108:2757–2762
44. von Birgelen C, Klinkhart W, Mintz GS, Papatheodorou A, Herrmann J, Baumgart D, Haude M, Wieneke H, Ge J, Erbel R (2001) Plaque distribution and vascular remodeling of ruptured and non-ruptured coronary plaques in the same vessel: an intravascular ultrasound study in vivo. J Am Coll Cardiol 37:1864–1870

45. Wunder A, Klohs J (2008) Optical imaging of vascular pathophysiology. Basic Res Cardiol 103:182–190

46. Wijns W, Verheye S, Manoharan G, Werner GS, Grube E, De Bruyne B, Koolen J, Hamm CW, Medina A, Bech JW, De Feyter PJ; CONVERTIBLE Investigators (2005) Angiographic, intravascular ultrasound, and fractional flow reserve evaluation of direct stenting Vs. conventional stenting using BeStent2 in a multicentre randomized trial. Eur Heart J 26:1852–1859

47. Zamorano J, Erbel R, Ge J, Gorge G, Kearney P, Koch L, Scholte A, Meyer J (1994) Spontaneous plaque rupture visualized by intravascular ultrasound. Eur Heart J 15:131–133