Can CT Be Reliably Used for Plaque Characterization and Vessel Wall Imaging?

Authors [1] Zahi A. Fayad, PhD

[1, 2] Alexander W. Leber, MD

Correspondence to: Zahi A. Fayad, PhD, FAHA
Mount Sinai School of Medicine
One Gustave L. Levy Place
Imaging Science Laboratories
Box 1234
New York, NY 10029
Fax: 240-368-8096 and 212-534-2683
Telephone: 212-241-6858
E-mail: zahi.fayad@mssm.edu

Affiliations:

[1]Imaging Science Laboratories. Departments of Radiology and Medicine (Cardiology). The Zena and Michael A. Wiener Cardiovascular Institute. The Marie-Josée and Henry R. Kravis Cardiovascular Health Center. Mount Sinai School of Medicine, New York, NY.

[2]Klinikum Grosshadern
Dept. of Cardiology
Ludwig Maximilians University of Munich
Germany

Introduction:

Despite advances in our understanding of the pathogenesis of atherosclerosis, coronary heart disease is still the leading cause of death in western societies. Approximately 50% of all myocardial infarctions occur in patients with no prior symptoms. It is well established that the risk for plaque rupture is predicated by plaque burden and plaque composition {Naghavi, 2003 #77}. Reliable and accurate assessment of the composition of coronary atherosclerosis can currently achieved mainly by invasive methods like intracoronary ultrasound or angioscopy {Schoenhagen, 2003 #27}. Since these are invasive procedures they are not suitable for preventive investigations in asymptomatic patients. Electron beam tomography and multidetector computed tomography enable an accurate noninvasive identification and quantification of calcified coronary plaques {Agatston, 1990 #78}. Although calcified plaques reflect only a small proportion of the entire plaque burden and the proportion of lesions containing calcium reveals a broad variability among humans it is suggested that the extent of coronary calcium is a surrogate marker for total plaque burden. It has been demonstrated that future coronary events may be predicted on the basis of the calcium score derived by various CT-modalities{Arad, 2000 #89; Shaw, 2003 #51}. However myocardial infarction is initiated by rupture or superficial erosion of vulnerable coronary plaques and these plaques are not necessarily calcified as calcium is considered to be a frequent feature of stable lesions{Naghavi, 2003 #77}. Further there are several potential morphologic features such as lipid-cores that constitute potential targets for noninvasive imaging in particular for Multislice CT and Magnetic Resonance Imaging. Hence for risk

stratification and guidance of anti-atherosclerotic therapies, a noninvasive tool that can identify both calcified and non-calcified plaques would be of great interest.

Clinical value of coronary atherosclerosis imaging:

Coronary atherosclerosis starts very early in life and early stages of atherosclerotic lesions are already present in young adults under 20 years of age. In general the disease remains clinically silent for years. 50% of acute myocardial infarctions occur in previously asymptomatic patients and is the first clinical manifestation of CAD. In other patients the first clinical sign of CAD is typically stable angina pectoris, which is due to myocardial ischemia due to a high grade coronary lumen obstruction. The reason for the late development of clinical symptoms is the fact that plaque accumulation within the vessel wall leads to compensatory diameter expansion, a process called coronary vessel remodeling {Glagov, 1987 #90}. Therefore diagnostic tests targeting the detection of myocardial ischemia due to high-grade coronary stenosis identify only the late development stage of coronary atherosclerosis. Currently, catheter based invasive modalities like intravascular ultrasound (IVUS) and angioscopy are almost exclusively used for identification of coronary atherosclerosis in a preclinical stage. IVUS has been shown to allow an accurate determination of coronary plaque burden and plaque composition (compared with histology). From post mortem histopathologic studies investigating the coronaries of victims of myocardial infarction it is known that the responsible culprit lesion in most cases reveals typical characteristics: It is an eccentric plaque containing a large lipid core which is covered by a very thin fibrous cap with an abundance of inflammatory cells (macrophages) on the shoulders. Calcium is not necessarily present {Virmani, 2002 #91}. In accordance to these histologic criteria IVUS has shown that plaque rupture initiating myocardial infarction occurred most frequently in

plaques with a large plaque volume with hypoechoic tissue revealing echolucent zones and presenting extensive compensatory vessel remodeling {Yamagishi, 2000 #125}. Interestingly most of these plaques caused no significant luminal obstruction on initial angiograms.

Evidence from recent investigations suggests that plaque rupture is a systemic coronary process rather than a focal event. In a multi-vessel IVUS study of patients with myocardial infarction, Riofoul et. al{Rioufol, 2002 #126} identified multiple silent plaque ruptures in vessels distinct from the culprit lesion. Similar observations were made by angioscopy where multiple yellow (lipid-rich) lesions were found in patients with acute coronary syndromes whereas in patients with stable coronary artery disease the predominant plaque type was a white (fibrotic, calcified) plaque {Asakura, 1998 #136}. Goldstein et al. reported from the presence of multiple complex lesions in patients with acute myocardial infarction{Goldstein, 2000 #137}. In accordance Leber et al. found significantly more noncalcified and less calcified lesions by multislice CT in patients with acute myocardial infarction if compared to patients with stable coronary artery disease{Leber, 2003 #63}. Those studies indicate that it may not be sufficient to identify the one vulnerable plaque that will cause MI in future because patients at risk have several of them. Moreover it is necessary to identify the vulnerable patient on the basis of the “pan-coronary” morphology of atherosclerosis.

The reasons for the sudden rupture of multiple plaques are currently not totally understood. It is suggested that systemic inflammatory factors play a key role in the development of vulnerable plaques and their progression to rupture. Therefore, a combined approach of determining plaque burden and plaque composition in

conjunction with the determination of biomarkers like CRP or s-CD40 ligand will play an important role for risk-stratification in the future.

Plaque imaging by CT -Technical aspects:

In contrast to other organs imaging of the heart is particular challenging due to the rapid heart motion that causes severe artifacts. In the past CT failed to generate diagnostic quality images because of its restricted temporal resolution. Former spiral-CT technology needed at least 500ms to obtain one tomographic slice. With the introduction of Electron Beam CT (EBCT) and its fast acquisition time of 100ms, the first motion free images of the coronaries were obtained. Albeit the excellent temporal resolution motion artifacts can only be avoided in a certain phase of the heart cycle during diastole. Thus irrespective of the heart rate it is mandatory to generate images at identical time points of the R-R interval, which is achieved by using an ECG-trigger. With the introduction of Multidetector CT (MDCT) a temporal resolution of 83-250 ms is now available. In addition to the faster gantry rotation the major advantage of this technology compared to conventional mechanical spiral CT scanners is the fact that it consists of 4-32 detector rows, which allow to generate 4-64 slices simultaneously. For coronary applications the whole volume of the heart is covered in the spiral technique with simultaneous digital registration of the ECG-signal. Using this approach, images can be reconstructed after data acquisition retrospectively at every time point of the ECG-cycle. That makes this technique more robust against extra systoles and arrhythmias. Furthermore, different trigger points can be used for each coronary vessel. 16- and 64-slice CT scanners offer a very high spatial resolution and generate very thin slices allowing the acquisition of isotropic voxels. This has already led to a major advance in noninvasive coronary

angiography. For visualizing noncalcified plaques (unlike Calcium-Scoring) contrast agent has to be administered intravenously and the protocols for coronary angiography are applied. To obtain diagnostic image quality with MDCT it is essential to reduce heart rates below 65bpm. This is generally done by administering oral or intravenous Beta-Blockers. In a recent study it was demonstrated that despite beta-blockade in 15% of patients a sufficient heart rate reduction could not be achieved {Leber, 2004 #58}. Furthermore patients with renal insufficiency or those allergic to contrast agent cannot be investigated by MDCT. Therefore it is not suitable for a considerable number of patients.

CT-Imaging of non-calcified plaques:

Plaque Composition

Current developments in particular CT allows noninvasive imaging of coronary vessels. Recent investigations report very high accuracies for determining coronary stenoses. From studies investigating atherosclerotic plaques of the aorta and the carotid arteries we know that CT permits to detect and classify atherosclerotic lesions. The CT attenuation of plaque components correlates well with the echogenicity of ultrasound and even histopathologic criteria. However, only limited data concerning CT-imaging of coronary plaque exists. Becker et al recently demonstrated in an ex vivo study showing that advanced stages of coronary plaques in heart specimens can be detected by MDCT (Figure1){Becker, 2003 #156}. In their comparison with the histologic Stary-classification, they found that CT could visualize type III to type VI plaque, whereas early stages (type I and II) were not detectable. In a 4-slice CT study, Schroeder and colleagues found a good correlation between the CT-attenuation measured within

coronary plaques and the echogenicity of plaques on IVUS {Schroeder, 2001 #158}.In another recent study, Leber et al. using a 16-slice CT demonstrated that non-calcified lesions could be detected with a reasonable sensitivity of 78% (Table 1). However they found that the ability of 16-slice CT to identify non-calcified plaques is restricted to larger more advanced lesions (with a plaque diameter of at least 1.5mm) that are located in proximal and middle coronary segments, which is explained by the given limitations due to temporal resolution {Leber, 2004 #144}. Quantitative characteristics of MDCT detected vs. non detected coronary plaques are shown in Table 2. Similar results were also reported by Achenbach et al{Achenbach, 2004 #164}.

In accordance with previously reported results, Leber et al. also found a good correlation between CT-density measurements within plaques and echogenicity on IVUS. Hypoechoic plaques on IVUS that represented lipid-rich plaques had a significant lower density than fibrotic plaques. Corresponding longitudinal and axial IVUS and MDCT images are shown in Figure 2. However, as in ex vivo studies they also observed a wide overlap of density values among fibrous and soft plaques, making the differentiation of these lesions very difficult. There are several reasons for this observation: 1. Even by IVUS analysis, the separation between lipid-rich and fibrous tissue is difficult as the echogenicity differences between these plaques are relatively small. 2. Density values measured within plaques vary depending on the CT-attenuation within the lumen. The optimal luminal contrast enhancement for plaque differentiation has been found to be located within 200 and 250 HU. This value however cannot be consistently achieved in the clinical situation. 3. Coronary plaques are rarely composed only from fibrous, calcified or lipid-rich tissue. In the majority of cases all kinds of tissue

can be observed. CT-Density values for hypo echoic, hyper echoic and calcified plaques are shown in Figure 3.

Vessel remodeling

As mentioned in the introduction, positive coronary vessel remodeling is supposed to be a characteristic feature of vulnerable plaques. Schoenhagen et al. have demonstrated that MDCT offers the opportunity to visualize this compensatory diameter expansion {Schoenhagen, 2003 #26}. Achenbach et al. have also demonstrated that in highly selected patients the16-slice CT can determine positive and negative vessel remodeling and it is feasible to accurately determined plaque areas {Achenbach, 2004 #37}. The limitation of all these quantitative CT-analysis however is that they were all exclusively performed in patients with high CT-image quality. This high quality could only achieved in approximately 75% of patients. Nevertheless these study-results indicate that MDCT provides a unique opportunity to identify several morphologic features associated with plaque vulnerability like plaque composition, plaque volume and positive vessel remodeling. Although the prognostic impact of these features is unknown so far and the first follow up studies are just underway, evidence from first clinical studies underline the predictive potential of MDCT. In a clinical study MDCT-derived plaque morphology of patients with acute myocardial infarction and stable angina pectoris was compared. In this population, patients with stable angina had significantly more calcified and less non-calcified lesions than patients with myocardial infarction. As a consequence, total plaque burden of patients with myocardial infarction would have been significantly underestimated by calcium scoring alone. Moreover in 10% of patients with AMI only non-calcified lesions were present. These observations imply that non-calcified lesions

may be involved in the process leading to unstable coronary disease.

Schroeder et al.[19] have demonstrated that the prevalence of non-calcified lesions is inhomogeneous even among a patient selection with a similar high-risk profile, which might reflect different prognostic outcomes. They observed in 14% of patients only non-calcified lesions, in 50% calcified and non-calcified lesions and in 36% of patients only calcified lesions. However future prospective studies have to prove whether patients with detectable non-calcified lesions are prone to develop adverse coronary events when compared to patients with predominant calcified lesions.

Finally, In a recent paper Leber et al.[20] performed contrast-enhanced 64-slice CT in 59 patients scheduled for coronary angiography due to stable angina pectoris. In a subset of 18 patients, IVUS of32 vessels was part of the catheterization procedure. In 55 of 59 patients, 64-slice CT enabled the visualization of the entire coronary tree with diagnostic image quality (American Heart Association 15-segment model). The overall correlation between the degree of stenosis detected by quantitative coronary angiography compared with 64-slice CT was r= 0.54. Sensitivity for the detection of stenosis 50%, stenosis 50%, and stenosis 75% was 79%, 73%, and 80%, respectively, and specificity was 97%. In comparison with IVUS, 46 of 55 (84%) lesions were identified correctly. The mean plaque areas and the percentage of vessel obstruction measured by IVUS and 64-slice CT were 8.1mm2 versus 7.3mm2 ($p < 0.03$, $r = 0.73$) and 50.4% versus 41.1% ($p < 0.001$, $r = 0.61$), respectively.

Future and Conclusions – CT Imaging:

Due to a rapid improvement of the new generation sub-millimeter multislice CT-technology, noninvasive tomographic imaging of the coronary vessel wall has no w

become a reality. First clinical studies have shown the ability of 16-slice CT to determine plaque burden, plaque composition and compensatory vessel-wall remodeling. These novel findings already constitute an important step forward in assessing coronary atherosclerosis non-invasively in a detailed manner that opens promising new opportunities for a better understanding and risk stratification of coronary atherosclerosis. Current limitations, mainly the insufficient accuracy to detect small lesions in distal coronary segments, might be overcome by improved spatial and temporal resolution of the next generation of CT scanners operating with 64 and more detectors.

Table 1: Sensitivity of MDCT in the detection of different coronary plaques in vessels (58/68) and specificity to exclude coronary lesions.

	soft	**Fibrous**	**Calcified**	**Total**
	sensitivity	***sensitivity***	***sensitivity***	***specificity***
RCA	(12/16)	(27/34)	(49/49)	94/102
	75%	79%	100%	92%
	(48-92%)	(62-91%)	n.a.	(85-97%)
LAD	(44/54)	(47/62)	(76/83)	294/315
	81%	76%	92%	93%
	(69-91%)	(63-86%)	(83-97%)	(90-96%)
RCX	(6/10)	(13/16)	(25/26)	96/108
	60%	82%	96%	89%
	(26-88%)	(54-95%)	(80-99%)	(81-94%)
Total	(62/80)	(87/112)	(150/ 158)	484/525
	78 %	78 %	95%	92%
	(67- 86%)	(69- 85%)	(90- 98%)	(89-94%)

Values are (n), %, (95% confidence interval)

Table2: Quantitative characteristics of by MDCT detected vs. non detected coronary plaques

	Detected	**Not detected**
Plaque thickness	1.5 mm ± 0.3	0.9 mm ± 0.3
Vessel size (EEM CSA)	4.5 mm ± 1.2	3.6 mm ± 1.1
% Plaque cross sectional area	42% ± 16%	22 ± 5%

p-values < 0.05 for all categories

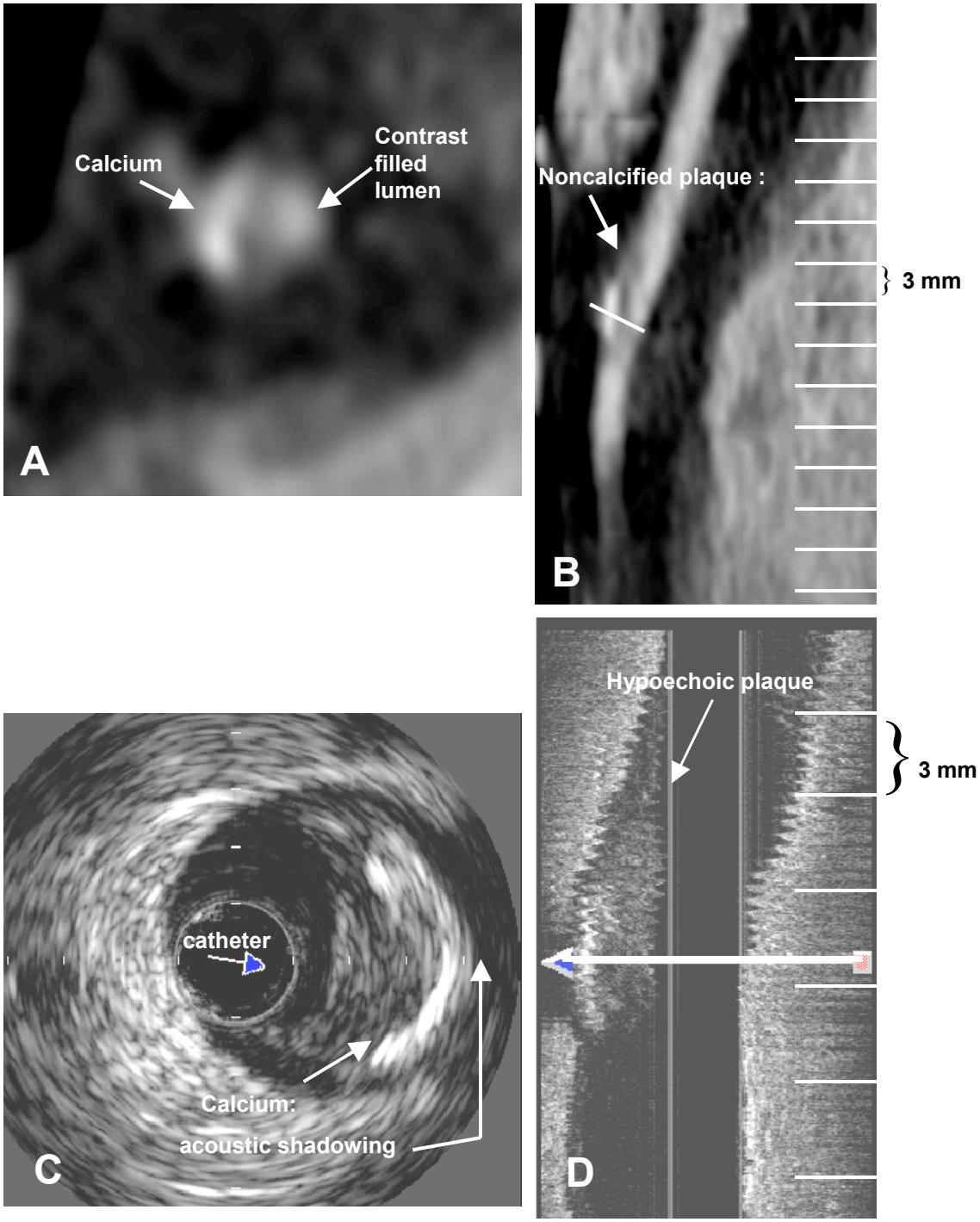

Figure 1 Figure 1: For analysis of IVUS- and MDCT-data the coronary arteries were divided in 3 mm sections. White lines indicate 3 mm intervals of the RCA in the longitudinal view of IVUS (D) and MDCT (B). A: Axial MDCT view of a calcified plaque. B: Longitudinal MDCT view

of the RCA containing a partly calcified and non-calcified plaque, the level of image A is indicated by the white line. C: Corresponding axial IVUS view. D: Longitudinal IVUS view of the RCA, the level of the axial image C is indicated by the arrow.

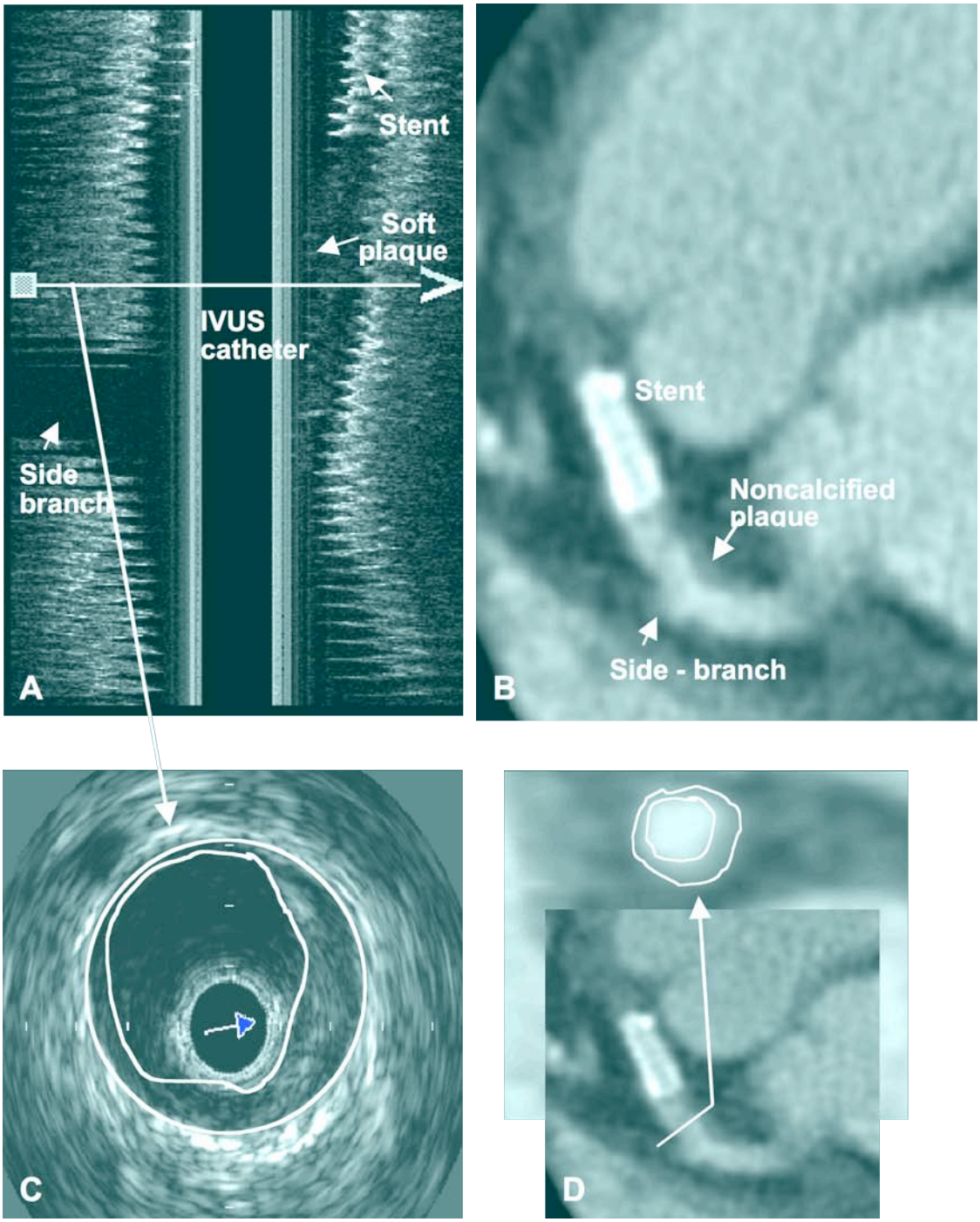

Figure 2: CT-Density values for hypo echoic, hyper echoic and calcified plaques: Each box describes the distribution of density values within one standard deviation, the whiskers above and below each box are describing the range between the lowest and highest observed density value.

The differences of the mean CT-density values between hypo echoic, hyper echoic and calcified plaques were significant with a p value <0.02.

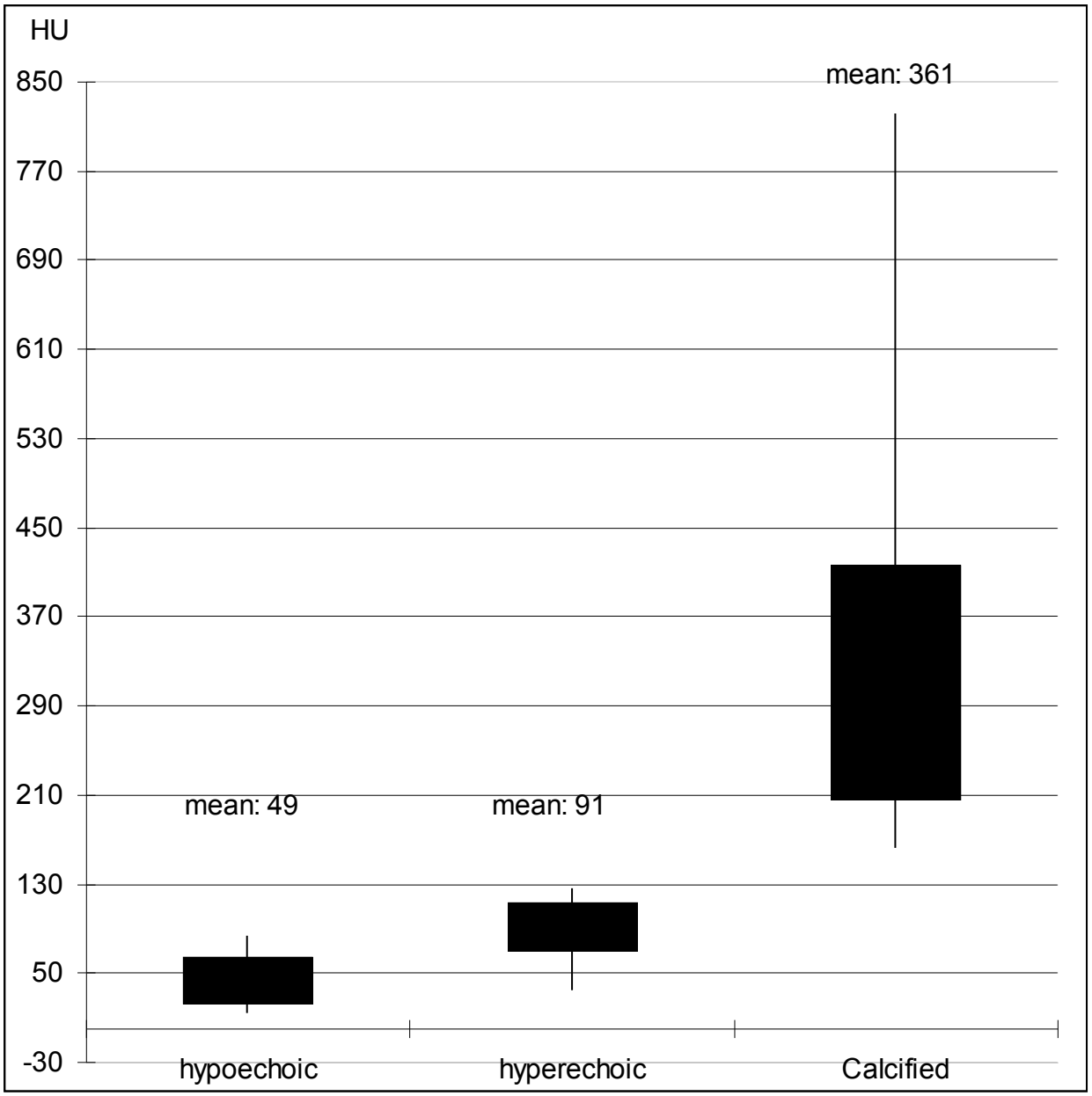

Figure 3: Corresponding longitudinal and axial IVUS and MDCT images:

A: IVUS of a LAD in longitudinal direction containing a hypo echoic plaque adjacent to a stent. B: Corresponding MDCT -reconstruction using maximum intensity projection. C: Axial tomographic view of the hypo echoic plaque on the level of the arrow in image A. D: Same plaque in axial view using multi-planar reformatted MDCT data.

References

1. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation.* Oct 14 2003;108(15):1772-1778.

2. Schoenhagen P, White RD, Nissen SE, et al. Coronary imaging: angiography shows the stenosis, but IVUS, CT, and MRI show the plaque. *Cleve Clin J Med.* Aug 2003;70(8):713-719.

3. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* Mar 15 1990;15(4):827-832.

4. Arad Y, Spadaro LA, Goodman K, et al. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol.* Oct 2000;36(4):1253-1260.

5. Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology.* Sep 2003;228(3):826-833.

6. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* May 28 1987;316(22):1371-1375.

7. Virmani R, Burke AP, Farb A, et al. Pathology of the unstable plaque. *Prog Cardiovasc Dis.* Mar-Apr 2002;44(5):349-356.

8. Yamagishi M, Terashima M, Awano K, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol.* Jan 2000;35(1):106-111.

9. Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. *Circulation.* Aug 13 2002;106(7):804-808.

10. Asakura Y, Furukawa Y, Ishikawa S, et al. Successful predilation of a resistant, heavily calcified lesion with cutting balloon for coronary stenting: a case report. *Cathet Cardiovasc Diagn.* Aug 1998;44(4):420-422.

11. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med.* Sep 28 2000;343(13):915-922.

12. Leber AW, Knez A, White CW, et al. Composition of coronary atherosclerotic plaques in patients with acute myocardial infarction and stable angina pectoris determined by contrast-enhanced multislice computed tomography. *Am J Cardiol.* Mar 15 2003;91(6):714-718.

13. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. *J Am Coll Cardiol.* Apr 7 2004;43(7):1241-1247.

14. Becker CR, Nikolaou K, Muders M, et al. Ex vivo coronary atherosclerotic plaque characterization with multi-detector-row CT. *Eur Radiol.* Sep 2003;13(9):2094-2098.

15. Schroeder S, Flohr T, Kopp AF, et al. Accuracy of density measurements within plaques located in artificial coronary arteries by X-ray multislice CT: results of a phantom study. *J Comput Assist Tomogr.* Nov-Dec 2001;25(6):900-906.

16. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. *Circulation.* Jan 6 2004;109(1):14-17.

17. Schoenhagen P, Tuzcu EM, Stillman AE, et al. Non-invasive assessment of plaque morphology and remodeling in mildly stenotic coronary segments: comparison of 16-slice computed tomography and intravascular ultrasound. *Coron Artery Dis*. Sep 2003;14(6):459-462.

18. Achenbach S, Ropers D, Hoffmann U, et al. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. *J Am Coll Cardiol*. Mar 3 2004;43(5):842-847.

19. Schroeder S, Kuettner A, Leitritz M, Janzen J, Kopp AF, Herdeg C, Heuschmid M, Burgstahler C, Baumbach A, Wehrmann M, Claussen CD. Reliability of differentiating human coronary plaque morphology using contrast-enhanced multislice spiral computed tomography: a comparison with histology. *J Comput Assist Tomogr*. Jul-Aug 2004;28(4):449-454.

20. Leber AW, Knez A, von Ziegler F, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol*. Jul 5 2005;46(1):147-154.