7.4 Assessment and Interpretation of Atherosclerotic Coronary Plaques

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Contents

7.4.1 Clinical Background

Acute coronary events, such as unstable angina, myocardial infraction, or sudden cardiac death, are usually caused by erosion or rupture of a coronary atherosclerotic plaque. Exposure of thrombogenic material to the blood stream leads to platelet aggregation, and the resulting thrombus may partially or completely occlude the coronary artery lumen, leading to ischemia and possible myocardial necrosis. In the majority of cases, the "culprit lesion", i.e., the atherosclerotic plaque that ruptures or erodes to initiate the process outlined above, does not reduce the lumen of the coronary artery to a significant extent before the acute coronary event (Falk 1995, Little 1988, Little 1996). Most underlying lesions are non-stenotic; that is, they do not lead to significant obstruction of the blood flow prior to rupture. For this reason, many individuals are asymptomatic prior to their first coronary event and acute myocardial infarction or sudden death often occurs without previous symptoms to alert the patient to the fact that coronary atherosclerosis is present and acute ischemia is about to occur (Harper 1979).

Since targeted therapy, such as lipid-lowering medication, can substantially reduce the risk of coronary artery disease events (Sheperd 1995, Downs 1998), it is necessary to identify individuals who are at increased risk for acute coronary events in the asymptomatic stage. Traditionally, the classical cardiovascular risk factors have been used to identify individuals at risk – and most professional societies have endorsed their use to quantify an individual's risk for future coronary events. Specific algorithms have been developed that are based on atherosclerotic risk factors, such as the Framingham algorithm, which considers age, sex, total and HDL cholesterol levels, blood pressure, and smoking status [Adult Treatment Panel III 2001; in some versions also diabetes (Wilson 1998)], or the PROCAM algorithm, which incorporates age, LDL cholesterol, trigylcerides, blood pressure, diabetes, smoking, and family history of coronary disease, but is available only for men (Assmann 1993, Assmann 2002). These and other risk-prediction algorithms are established and useful in clinical practice but have limited predictive power, as the maximum relative risk that can be predicted is approximately a ten-fold increase compared to individuals without any risk factors. However, frequently, patients with acute coronary events have no "traditional" risk factors at all.

Since coronary disease events are caused by plaque rupture, it is an intriguing concept to use imaging methods that permit detection, quantification, and possibly also characterization of coronary atherosclerotic plaque to carry out individualized risk stratification. Assessment of coronary atherosclerotic plaque burden through quantification of coronary calcification has already been shown to be of high predictive value concerning the occurrence of future coronary events in asymptomatic individual and to permit better risk stratification than risk factor analysis (Raggi 2000, Shaw 2003, Vliegenhart 2002) (also see Sect. 7.2). Since, however, calcium constitutes only one component of plaque and non-calcified morphological structures, such as a large necrotic core and thin fibrous cap, are usually considered to indicate high propensity towards plaque rupture (Burke 2003), there is growing interest in the use of imaging to visualize and analyze non-calcified coronary atherosclerotic plaque components.

7.4.2 Clinical Concepts

Theoretically, plaque visualization and analysis through imaging may be useful in two related, but distinct clinical situations. First, in asymptomatic individuals with a certain constellation of risk factors, it can be difficult to make decisions about initiating, e.g., lipid-lowering therapy. Even modern guidelines leave room for individual decisions; for example, the NCEP-ATP III guidelines state that in individuals with 0 to 1 "traditional" risk factor and an LDL cholesterol level of 160–190 mg/dl, the use of lipid-lowering medication is "optional". It is currently assumed that imaging for further risk stratification is most useful in individuals who, based on analysis of traditional risk factors, seem to be at "intermediate risk" for coronary artery disease events (a risk between 5 and 20% over the next 10 years) (Taylor 2003, Greenland 2001).

Second, patients who have diffuse or localized atherosclerotic disease of the coronary arteries, as demonstrated by invasive angiography, but an absence of hemodynamically relevant coronary artery stenoses may profit from further work-up. There is justified hope that, in the future, imaging will guide certain interventions to specifically lower the risk of rupture of plaques deemed to be "vulnerable", i.e., those at high risk to cause ischemic events. However, even though fitting terms, such as "plaque sealing", have already been coined for such treatments (Meier 1997, Mercado 2003), it is a concept that still requires validation since no appropriate studies have been conducted thus far.

7.4.3 Visualization of Coronary Atherosclerotic Plaques

Invasive coronary angiography, the clinical "gold standard" for coronary artery visualization, is limited to providing a "luminogram" of the coronary arteries. The occurrence of coronary atherosclerotic plaque is usually accompanied by an outward growth of the vessel (compensatory enlargement), so that in spite of growing amounts of atherosclerotic plaque, the lumen remains unchanged. This process of usually referred to as "remodeling" (Glagov 1997). Therefore, invasive angiography is therefore unsuited to visualize coronary atherosclerotic plaque (Fig. 7.28), and, instead, intravascular ultrasound (IVUS) is considered the clinical method of choice (Mintz 2001). In IVUS, high-resolution cross-sectional images of the coronary artery wall are obtained. However, it is an extremely invasive and expensive modality and therefore unsuited for routine applications in risk stratification. Optical coherence tomography is also an invasive, cross-sectional imaging method that provides even better spatial resolution than IVUS (Brenzinski 1996, Jang 2002), but much like IVUS requires the catheter to be introduced into the coronary artery, is thus highly invasive and expensive, and not suited for routine applications.

Non-invasive imaging modalities that have been evaluated as to their ability to assess coronary atherosclerotic plaques include magnetic resonance imaging (MRI) and multi-slice CT (Fayad 2002). MRI offers the theoretical advantage of being free of potentially limiting side effects (such as radiation exposure and the need for contrast injection), but is fraught with limited spatial resolution and long examination times. Even though the ability to visualize coronary atherosclerotic plaques in-vivo has been shown (Fayad 2000, Botnar 2000, Kim 2002), these disadvantages have so far proven to severely limit clinical applications. Multi-slice CT, by contrast, is widely available, can be performed rapidly, and provides high-resolution images. The evaluation of multi-slice CT concerning its ability to visualize non-calcified coronary atherosclerotic plaques, first reported by Becker et al. (2000), has therefore been pursued by a number of research groups, With the increasingly sophisticated imaging technology, promising initial results have been obtained.

7.4.4 Visualization of Non-calcified Plaques by Multi-slice CT

While coronary calcifications, due to their high X-ray attenuation, can be assessed by CT in non-contrast-enhanced images, visualization of non-calcified plaque components requires intravenous contrast enhancement and the use of scan protocols

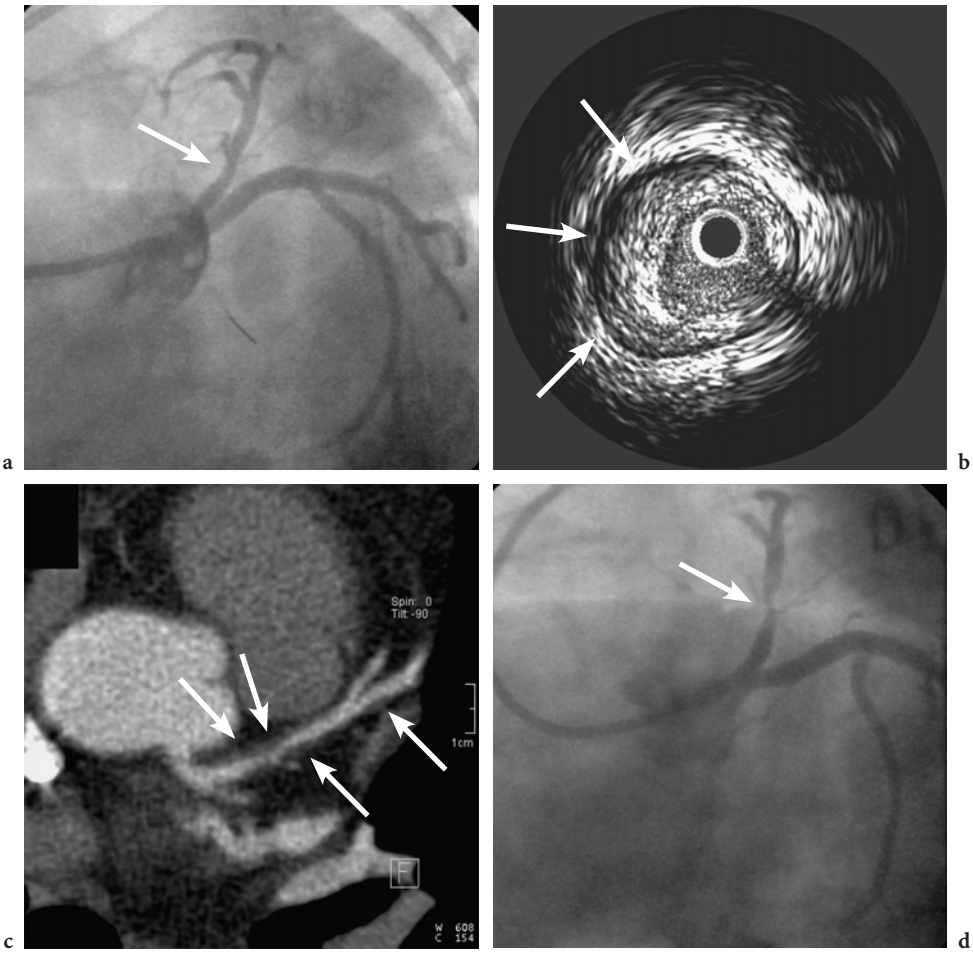


Fig. 7.28a–d. Case report: A 63-year-old female patient was admitted to the hospital because of chest pain at rest (unstable angina). Coronary angiography showed only non-significant stenosis of the proximal LAD (**a**). The patient was examined using intravascular ultrasound (IVUS) (**b**) and 16-slice CT (**c**). Both showed substantial amounts of non-calcified atherosclerotic plaque in the proximal LAD (*arrows*). The patient was discharged on aspirin and lipid-lowering medication. Two months after the first admission, she was admitted to the hospital again with an acute non-ST-elevation myocardial infarction. Immediate coronary angiography showed a tight stenosis in the proximal LAD (**d**, *arrow*). Plaque rupture had occurred at a site that had been free of significant stenosis but with substantial plaque burden, undetected by invasive angiography, at initial presentation.

with higher spatial resolution – and, consequently, substantially higher radiation exposure (Hunold 2003). Such scan protocols were initially used to visualize coronary artery stenoses (Nieman 2002, Ropers 2003); however, the observation that non-calcified coronary atherosclerotic plaque could frequently be visualized in these high-resolution CT scans of the coronary arteries (Becker 2000) sparked rapidly growing interest in using this imaging modality for the non-invasive detection, quantification, and characterization of coronary plaque in the context of risk assessment (Fayad 2002, Naghavi 2003). Several studies using 4-, 16-, and recently also 64-slice CT scanners have confirmed the ability of multi-slice cardiac CT to visualize non-calcified or partly calcified coronary atherosclerotic plaques (Fig. 7.29), but clinical applications will require thorough assessment and validation of the ability of CT to detect, quantify, and perhaps characterize the composition of coronary athero-

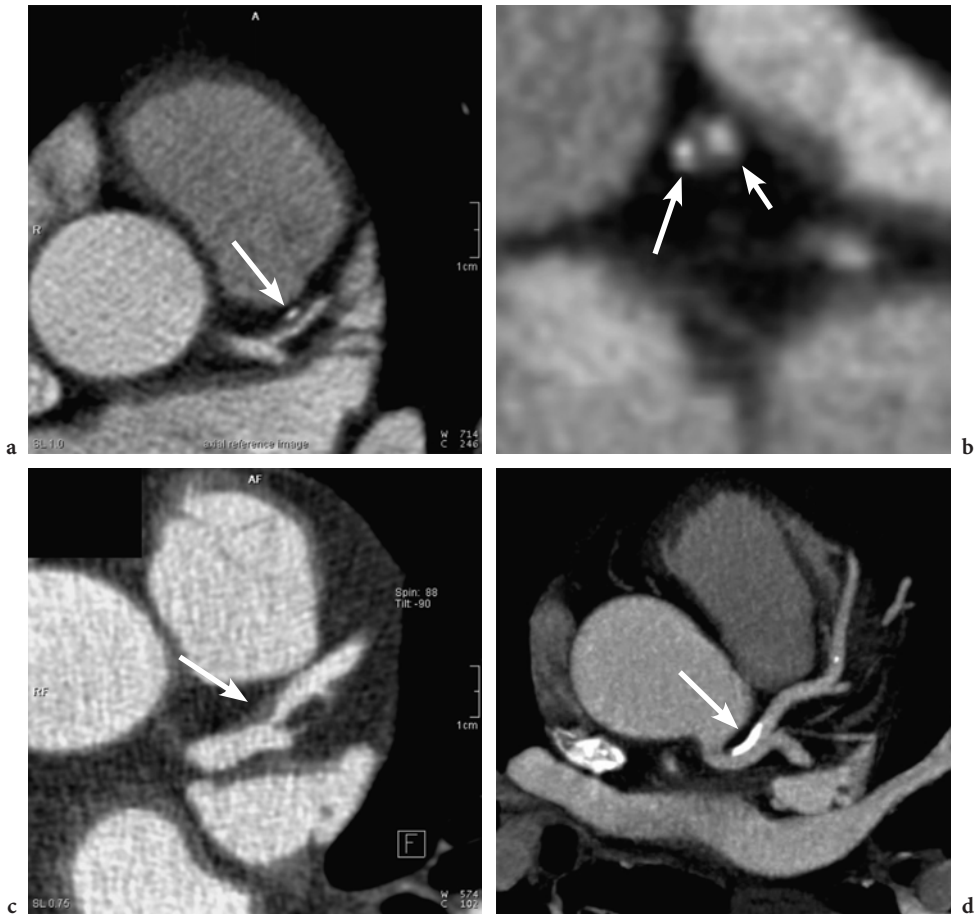


Fig. 7.29a–d. Coronary atherosclerotic plaque visualization with 16-slice CT. **a** A partly calcified plaque in the proximal LAD is depicted on an axial cross-sectional image with 1-mm slice thickness. **b** The cross-section of the LAD lesion shows the partly calcified plaque (*large arrow* calcified plaque, *small arrow* contrast-enhanced coronary artery lumen). **c** Non-calcified plaque (*arrow*) at the proximal LAD visualized with MPR. **d** Completely calcified plaque (*arrow*) in the LM in MIP

sclerotic plaques. Such evaluations are currently in an early stage and firm conclusions as to clinical applicability would be premature.

7.4.4.1 Detection of Non-calcified Plaques

Becker et al. (2003) reported a sensitivity of 66% for the ability of 4-slice CT to detect single coronary atherosclerotic plaques in ex-vivo heart specimens. In a recent in-vivo study done with 16-slice CT, Achenbach et al. (2004) analyzed 22 patients (83 coronary artery segments) by IVUS and multi-slice CT. A sensitivity of 78% and specificity of 87% for the detection of coronary artery segments with non-calcified plaque was reported. In a study of 37 patients, Leber et al. (2004) compared 16-slice CT to IVUS in 875 coronary artery segments, each 3 mm in length. Similar to the previous study, the authors also found a sensitivity of 78% for the detection of non-calcified plaque (specificity 92% for any plaque). Schoenhagen et al. (2003) provided area under the receiver operating characteristics curve values for plaque detection by 16-slice CT and IVUS in 46 coronary segments (14 patients). Values of 0.87–0.97 indicated the high accuracy of 16-slice CT for plaque detection com-

pared to IVUS (Schoenhagen 2003). Leber et al. (2005) compared the performance of new 64-slice CT technology, with enhanced spatial and temporal resolution, with those of IVUS in the detection of atherosclerotic plaques in 18 patients and 32 coronary branches that showed 55 lesions (Leber 2005). The authors found a sensitivity of 84% and a specificity of 91% in the detection of lesions compared to IVUS and a significantly increased accuracy compared to 16-slice CT. They concluded that contrast-enhanced 64-slice CT allows for the identification of proximal coronary lesions with excellent accuracy and that measurements of plaque and lumen areas correlated well with the results obtained with IVUS.

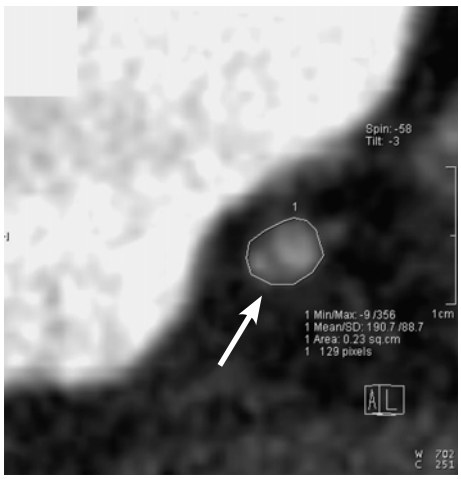
The drawback to all of these studies is that they were small. Thus, so far, information about the accuracy and reproducibility of multi-slice CT for plaque detection is limited, and both systematic validation of the methodology and further studies on a larger scale are advisable.

7.4.4.2 Quantification of Coronary Atherosclerotic Plaques

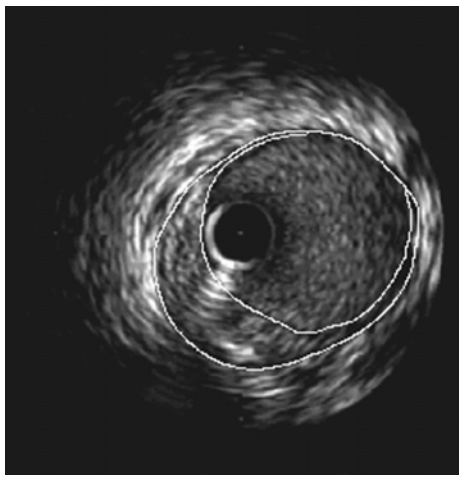
Currently, knowledge about the ability of CT techniques to quantify the amount of non-calcified coronary atherosclerotic plaque is extremely limited. In a phantom study, it was observed that under the prerequisite of using thin slice collimation, multi-slice CT may permit assessment of plaque volumes, but systematic overestimation of plaque volumes may occur (Schroeder 2001). Achenbach et al. described a close correlation (r = 0.8) but systematic underestimation of the mean plaque volume per coronary segment in multi-slice CT (24 ± 35 mm^3) compared to IVUS (43 ± 60 mm^3) (Achenbach 2004). The reason for this may have been the fact that limited image quality prevented plaque visualization by multi-slice CT in some segments, thus leading to a global underestimation of plaque volume.

7.4.4.3 Characterization of Coronary Atherosclerotic Plaques

Under the assumption that lipid-rich plaques have a higher risk of rupture with consequent thrombosis than fibrotic plaques, researchers have tried to use measurements of CT attenuation values to differentiate plaque types (Kopp 2001). Reports in which multi-slice CT and IVUS were compared demonstrated that CT could detect a variety of densities in coronary atherosclerotic plaques in vivo. In a study



a



b

Fig. 7.30a,b. Quantification of atheroslcerotic plaque dimensions with 16-slice CT. **a** Cross-section of the proximal LAD, with an eccentric atherosclerotic plaque (arrow), reveals a vessel area of 0.23 cm^2. **b** The corresponding IVUS cross-section determines a vessel area of 0.21 cm^2

of 12 patients, Schroeder et al. (2001) found that plaques characterized as "hypo-echoic" or "soft" on IVUS – and thus usually assumed to be more likely to rupture – had a lower mean CT attenuation (14 ± 26 HU) than plaques characterized as "fibrotic" (91 ± 21 HU) or "calcified" (419 ± 194 HU). In the study mentioned above, Leber et al. (2004) found a mean density of 49 ± 22 HU for "soft", 91 ± 22 HU for "fibrous", and 391 ± 156 HU for calcified plaques. Similar observations were made ex vivo: In 21 specimens of carotid arteries, lipid-rich plaques could be distinguished from fibrous plaques by their mean CT attenuation (39 ± 12 HU vs. 90 ± 24 HU) (Estes 1997), and in ex-vivo heart specimens, densities of 47 ± 9 and 104±28 HU, respectively, were found for 33 lipid-rich and fibrous plaques (Becker 2003). Animal models have also confirmed the in-vivo and ex-vivo findings in human arteries. Viles-Gonzalez et al. (2004) reported lipid-rich plaques with a density of 51 ± 25 HU and fibrous-rich plaques with a density of 116 ± 27 HU based on 16-slice CT scans of rabbit aortas (Viles-Gonzalez 2004), (Table 7.9). It should be noted that a potential pitfall is that CT attenuation values of thrombus overlap with those measured by CT density for "soft" coronary atherosclerotic plaques. Here, the morphology of the lesion in relation to the vessel wall may give further distinguishing information.

Even though these findings are intriguing and certainly indicate an opportunity to detect and analyze coronary atherosclerotic plaques non-invasively by CT, it again needs to be pointed out that the current knowledge is preliminary and that the clinical implications of these initial findings are still unclear.

7.4.4.4 Clinical Results

Several smaller studies have investigated the visualization and detection of non-calcified coronary atherosclerotic plaques in defined patient subgroups without further validation. Fischbach et al. (2003) used 4-slice CT in a study of 100 subjects at high risk according to the PROCAM score. In more than 80% of cases, the coronary arteries of these patients showed calcified or non-calcified lesions (Fischbach 2003). The authors suggested classifying these high-risk individuals as pre-symptomatic patients with subclinical atherosclerosis. Leber et al. (2003) carried out contrast-enhanced 16-slice CT in 21 patients with acute myocardial infarction and 19 patients with stable angina. While 96% of plaques were calcified in patients with stable angina, only 76% of all plaques were calcified in patients after acute myocardial infarction. Ten percent of patients with acute myocardial infarction (2 out of 21) had no detectable calcium, but did have detectable non-calcified plaques (Leber et al. 2003). Similarly, Schroeder et al. (2003) reported that, out of 68 patients with risk factors for coronary artery disease, three out of 29 patients without calcified plaque had detectable non-calcified plaque (Schroeder 2003). Nikolaou et al. (2003) reported that seven of 48 (15%) patients investigated in another series had detectable non-calcified plaque in the absence of coronary calcification. All of these studies were limited by the lack of a validation method, such as IVUS, but the results seem to indicate that, in some cases, the presence of coronary atherosclerotic plaque may be possible without detectable calcium. Since no follow-up was performed in either study, the prognostic significance of this observation is unknown and it remains to be clarified whether the additional effort to detect non-calcified plaque (investigation time, contrast agent, and radiation) as compared to coronary calcium imaging alone is justified, especially since false-positive findings are well possible.

7.4.5 Perspective

Experience collected with coronary calcium detection by CT over many years provides clear evidence that the assessment of coronary atherosclerotic plaque burden by CT can be a useful prognostic marker. Initial data concerning imaging of non-calcified plaque by CT demonstrated that multi-slice CT may indeed be able to detect and quantify the presence and amount of non-calcified plaque with impressive accuracy and that limited conclusions concerning the characterization of plaque can be drawn from measurements of CT attenuation within

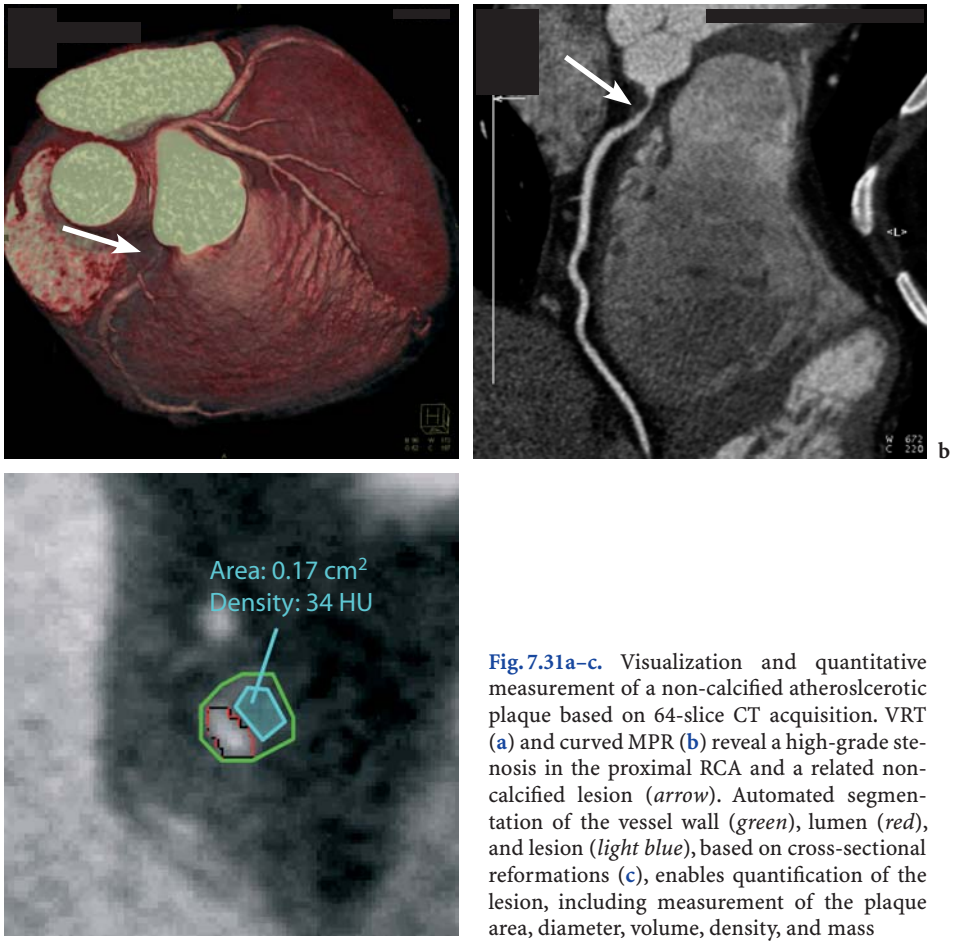


Fig. 7.31a–c. Visualization and quantitative measurement of a non-calcified atheroslcerotic plaque based on 64-slice CT acquisition. VRT (**a**) and curved MPR (**b**) reveal a high-grade stenosis in the proximal RCA and a related non-calcified lesion (*arrow*). Automated segmentation of the vessel wall (*green*), lumen (*red*), and lesion (*light blue*), based on cross-sectional reformations (**c**), enables quantification of the lesion, including measurement of the plaque area, diameter, volume, density, and mass

Table 7.9. CT attenuation measured in various types of atherosclerotic plaques by multi-slice CT

Author	Material, scanner	Lipid-rich plaque	Fibrous plaque	Calcific plaque
Estes 1998	Carotid endatherectomy (ex-vivo), 1-slice	39 ± 12 HU	90 ± 24 HU	–
Schroeder 2001	Coronary plaque (in vivo), 4-slice	14 ± 26 HU	91 ± 21 HU	419 ± 159 HU
Leber 2003	Coronary plaque (in vivo), 16-slice	49 ± 22 HU	91 ± 22 HU	391 ± 156 HU
Becker 2003	Coronary plaque (ex vivo), 4-slice	47 ± 9 HU	104 ± 28 HU	–
Viles-Gonzalez 2004	Aortic plaque in rabbit (in vivo), 16-slice	51 ± 25 HU	116 ± 27 HU	–

the atherosclerotic lesion. Future developments will be two-fold: First, steady improvements of scanner technology has occurred during the past several years and will continue to occur. It is thus reasonable to expect that the accuracy for plaque detection and the ability to provide some sort of plaque characterization will also continue to improve. Second, there is currently a paucity of clinical data concerning the prognostic significance of the observations that have been made so far. Appropriately conducted clinical trials will need to deliver evidence that multi-slice CT plaque imaging can provide useful data – either

in primary risk assessment of asymptomatic individuals or, more likely, in the assessment of the propensity of non-stenotic lesions discovered in invasive coronary angiography to rupture and cause acute coronary events at a later time. The recently introduced 64-slice CT scanners with high spatial and temporal resolution in conjunction with semi-automated measurement tools will serve as a robust basis for further clinical evaluation (Fig. 7.33).

These developments will have to be accompanied by the design and verification of appropriate treatment methods. The combination of non-invasive imaging for risk assessment and effective interventions to lower the risk of coronary events will only then offer a life-saving approach for thousands and thousands of patients.

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