Unstable Coronary Plaque and Its Relation to Coronary Calcium

Axel Schmermund, MD; Raimund Erbel, MD

Abstract—Coronary calcium is intimately associated with coronary atherosclerotic plaque development. The use of electron-beam computed tomography (EBCT) for accurate quantitative measurements has led to an increased interest in understanding the clinical importance of coronary calcium, particularly in terms of the ability to identify unstable coronary plaques that underlie the clinical acute coronary syndromes. Histopathologic studies have demonstrated that calcium is a frequent feature of ruptured plaques, but the presence or absence of calcium does not allow for reliable distinction between unstable versus stable plaques. This issue is complicated by the lack of a prospective definition for “unstable.” Plaque rupture is sometimes found in apparently healthy subjects and in patients with clinically stable disease. Coronary atherosclerosis is a coronary systemic disease process. Imaging of coronary calcium, although unable to identify a localized unstable plaque, potentially can identify the more clinically pertinent “unstable patient.” Almost all patients with a recent acute coronary syndrome have measurable coronary calcium because moderate-to-advanced coronary plaque disease is already present, although obstructive disease frequently is not. Prospective studies have demonstrated that extensive coronary calcium detected by EBCT is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization, and coronary death. The incremental prognostic value of coronary calcium compared with that of risk factor assessment remains to be fully defined. The occurrence of an acute coronary syndrome is determined by many factors apart from the extent of atherosclerotic plaque disease. Large prospective trials in the general population are needed to define the subgroups that will benefit most from quantitative assessment of coronary calcium. (Circulation. 2001;104:1682-1687.)

Key Words: calcium ■ plaque ■ coronary disease ■ risk factors ■ prognosis

Coronary calcium is a specific expression of coronary atherosclerotic plaque disease.1 The ability to obtain an accurate quantitative measure of coronary calcium using electron-beam computed tomography (EBCT) has led to an increased interest in understanding its clinical importance.1,2 Figure 1 shows a 3-dimensional representation of calcium in the coronary tree and aorta. EBCT scanning in 1 breath-hold and standardized image analysis, partly on the basis of volumetric representations (Figure 1), allow for reproducible measurements of coronary calcium.3 However, the prognostic value of such measurements remains elusive.2,4-10 Specifically, it has been argued that calcium is characteristic of stable coronary artery disease (CAD) and that acute coronary syndromes frequently occur in the absence of coronary calcium.4-6 On the other hand, because calcium is a common component of histologically defined “unstable” plaques, it may be that a marker for the unstable process, rather than a marker for a specific site of the unstable process, provides significant clinical information.

The core question is: Can we expect to predict acute coronary syndromes on the basis of coronary calcium assessment? To answer this question, we need to examine the relationship between coronary calcium and the unstable coronary plaques that underlie the acute coronary syndromes.

Unstable Plaques: Definitions

In clinical terms, unstable plaques are defined by the occurrence of acute coronary syndromes. Unstable angina, non-Q-wave myocardial infarction, and Q-wave myocardial infarction or sudden coronary death (SCD) can be viewed as points on a continuum of clinical presentations with the same underlying cellular mechanisms and pathological features.11,12 A useful histopathologic definition of unstable plaques has been provided by the American Heart Association (AHA) on the basis of work by Herbert Stary (Figure 2).13-15 This classification describes the natural history of plaque initiation and development designated by lesion types I (earliest lesion) through VI (complicated lesion). Early lesions up to type III lesions are potentially reversible. Lesion types IV and Va are called atheroma and fibro-atheroma, respectively. They can progress to vessel occlusion or to type VI lesions, that is, plaques with rupture, erosion, hematoma or hemorrhage, and thrombus formation. The difference between type IV and V plaques lies in the composition of the layer covering the lipid
lipid core exposes tissue factor and thrombogenic material to more important than others.\textsuperscript{16} indicate plaque vulnerability, or if some characteristics or a combination of them is required to\textsuperscript{1} any one of these characteristics to indicate plaque vulnera-

From a prospective viewpoint, lesion types IV and V can be called vulnerable plaques. In these plaques, an intact tissue layer is covering the lipid core ("cap"). Unfortunately, the nature of necropsy studies does not allow for true prospective studies. Various morphological and cellular characteristics have been associated with the propensity of type IV and V lesions to rupture or cause clinical events.\textsuperscript{11,12,15,16} Among these characteristics are a large lipid core size, a thin fibrous cap or layer above the lipid core, the loss of smooth muscle cells, the presence of inflammatory cells, and proteolytic activity in this layer. Perhaps with the exception of thickness of the fibrous cap <65 \textmu m,\textsuperscript{16} however, threshold values for any one of these characteristics to indicate plaque vulnerability are unknown. Also, it is unclear if one of these characteristics or a combination of them is required to indicate plaque vulnerability, or if some characteristics are more important than others.\textsuperscript{16}

Necropsy studies take a retrospective view. Type VI lesions have been established as representing unstable, complicated plaques. They are characterized by injury to the tissue layer covering the lipid core. The most common type VI lesion is plaque rupture.\textsuperscript{12,16} Rupture of the layer above the lipid core exposes tissue factor and thrombogenic material to blood components, initiating a cascade of thrombotic changes that can result in sudden occlusion of the vessel lumen. Up to 30\% of sudden coronary deaths may be caused by plaque rupture.\textsuperscript{16,17} The endothelium is absent, exposing the intima and predominantly smooth muscle cells and proteoglycans. Plaque erosion can be diagnosed only in the presence of an overlying thrombus and if serial sectioning fails to detect plaque rupture. Plaque hemorrhage may originate from the luminal surface and, in such cases, represents a subtype of plaque rupture.\textsuperscript{18} A pivotal complication of the aforementioned lesions is arterial thrombus deposition, which can potentially result in occlusion of the vessel and abrupt reduction of blood flow.

To provide for a clear definition in the setting of this article, we will use the term vulnerable plaque to describe Stary type IV and V lesions that have the potential to develop into type VI (complicated) lesions. To describe type VI lesions, we will use the term complicated plaque. Most complicated plaques are disrupted, but some also show plaque erosion or other pathology as described above. The overall term describing both vulnerable and complicated plaques is unstable plaque.

In Vivo Studies Using Intravascular Ultrasound

Intravascular ultrasound (IVUS), unlike coronary angiography, allows for visualization of changes of the vessel wall, the site of development of atherosclerotic plaques. The above-mentioned classification of coronary lesions suggested by the AHA can be reproduced using IVUS (Figure 3).\textsuperscript{19} Indeed, clinical symptoms—stable or unstable angina—are related to plaque morphology described by IVUS in analogy to the AHA classification rather than to angiographic stenosis severity.\textsuperscript{19} In particular, IVUS enables the detection of plaque rupture.\textsuperscript{19–21} The changes in plaque morphology can be examined over time.\textsuperscript{21} Unfortunately, such studies are limited to symptomatic patients undergoing coronary angiography. Acute coronary syndromes often are not preceded by typical symptoms of CAD.\textsuperscript{22}

Complicated Plaques in Symptomatic and Asymptomatic Subjects

Histopathologic studies have established plaque rupture (AHA lesion type Vla) as the most common cause of acute coronary syndromes\textsuperscript{11,12,16–18} and this has been confirmed by in vivo studies using IVUS.\textsuperscript{20} However, a number of observations indicate that the detection of plaque rupture is neither sensitive nor specific for distinguishing patients with acute coronary syndromes from those without. An obvious explanation is provided by plaque erosion, which frequently causes intraluminal thrombus deposition (AHA lesion type V1c).\textsuperscript{16,17} Plaque rupture, however, is also observed in \textless 25\% of patients with stable angina pectoris.\textsuperscript{11,20} It is detected in \textless 20\% of patients dying of noncardiac, but atherosclerosis-related, causes.\textsuperscript{23} Furthermore, and perhaps most surprisingly, \textless 10\% of apparently healthy individuals with traumatic death show plaque rupture.\textsuperscript{23,24} Also, \textgreater 1 plaque rupture often is observed in individuals with SCD.\textsuperscript{11,25} Such individuals frequently show evidence of previous healed plaque ruptures which are calcified. Conversely, SCD and other acute coro-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Extensive calcium in the coronary arteries of a 51-year-old man who had sustained an inferior myocardial infarction 2 weeks earlier. LAD indicates left anterior descending coronary artery; RCA, right coronary artery.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Schematic representation of the histopathologic classification of coronary lesions proposed by the AHA. Adapted from Stary et al.\textsuperscript{16}}
\end{figure}
nary syndromes can be the consequence of coronary athero-
sclerotic plaques without rupture or overlying thrombus
deposition during life, particularly in young individuals.26
The observations noted above illustrate the problems en-
countered in attempting to predict acute coronary syndromes
on the basis of histopathology of atherosclerotic plaques.
Furthermore, the pathology of acute coronary syndromes
cannot be reduced to the analysis of a localized unstable
plaque. In any given subject with coronary atherosclerosis,
there is a spectrum of plaques at various stages of develop-
ment. Although discrete vulnerable and complicated plaques
can be localized, the process of destabilization involves the
complete coronary system.11,25

Coronary Calcium in Complicated Plaques
In a series of 50 patients with a mean age of 49 years, Farb et
al17 reported that calcium is a frequent feature (in ≈70% of
subjects) of plaque rupture. Calcium was associated less
frequently with plaque erosion.17 Burke et al27 classified
culprit plaques in 108 victims of SCD with a mean age of 50
years as “stable” (n = 20), “erosion” (n = 33), “acute rupture”
(n = 37), and “healed rupture” (n = 18). The most frequently
calcified plaques were acute ruptures (80%). The most
extensively calcified plaques were healed ruptures. Eroded
plaques displayed the lowest frequency and extent of calcium.
Taylor et al28 reported similar results. Figure 4 illustrates
these findings schematically.

There are also histopathologic reports suggesting that
ruptured plaques are less likely to be calcified.29,30 Gertz and
Roberts,29 in a series of 17 patients with plaque rupture and
fatal acute myocardial infarction (AMI), observed less exten-
sive calcium in ruptured than in nonruptured coronary seg-
ments. Cheng et al,30 comparing 12 lesions that presumably
causcd fatal AMI with 12 stable lesions, also observed less
extensive calcium in the former lesions. Although these
studies included relatively few patients, IVUS studies in
much larger patient populations also found unstable clinical
symptoms associated with less calcium.31,32
The disparate results of the above-named studies can be
explained in part by differences in methodology and patient
age and selection, as well as methods of preservation. The
observation remains that calcium is frequently present in
complicated plaques and that it can be quite extensive in these
plaques. Because there is considerable overlap between all
types of plaques, calcium is a marker for neither unstable nor
stable plaques.

Coronary Calcium in Acute Coronary Syndromes
We performed EBCT in 118 consecutive patients (mean age,
57 ± 11 years) with previous AMI (n = 101) or unstable angina
(n = 17) as the first manifestation of CAD.33 The vast majority
of patients with at least moderate angiographic disease (105
of 110; 96%) had measurable calcium by EBCT. Those
patients with a negative EBCT had minimal or no atheroscle-
rotic plaque formation (confirmed by IVUS). They were
younger and tended to be active cigarette smokers.
Raggi et al8 recently confirmed these findings in 172
patients with a first AMI (mean age, 53 ± 8 years). The
angiographic status of these patients was not reported. Over-
all, 165 (96%) patients showed coronary calcium by EBCT.
In 87% of the 172 patients, the extent of calcium was greater
than would have been expected with regard to their age and
sex. These data suggest that even in patients with an acute
coronary syndrome as the first manifestation of CAD, coro-
nary calcium is almost always present and usually exceeds
the amount observed in asymptomatic subjects or patients
with atypical symptoms.
Acute coronary syndromes generally result from extensive
coronary atherosclerosis.34 This explains why extensive cal-
cium is frequently observed in patients with acute coronary
syndromes, although calcium cannot be used to identify
unstable plaques. The extent of coronary calcium is closely
related to the extent of coronary atherosclerosis (Figure
5).35–38 Patients with a negative EBCT rarely have angi-
ographic CAD, and multivessel CAD is almost never ob-
served.1,2 More importantly, nonobstructive plaques are re-
vealed by EBCT.35,38 These plaques often show advanced stages of development in terms of the Stary classification and are important determinants of the clinical course of the disease, especially regarding AMI.39

The mechanisms that influence atherosclerotic plaque development—and progression of calcification40—at least in part affect the coronary tree in a systemic fashion. In a clinical study, the term “multifocal plaque instability” has been coined.41 Thus, the importance of identifying localized vulnerable or complicated plaques needs to be weighed against assessing the extent of atherosclerotic plaque disease as the underlying substrate of instability.

The concern remains that it may be impossible to separate patients who will develop an acute coronary syndrome from patients who will develop stable angina pectoris on the basis of coronary calcium.42 This may not necessarily be problematic because stable angina can be identified and treated. The challenge is to determine who with the same atherosclerotic plaque burden will have a clinical acute coronary syndrome and who will have no clinical manifestation of the disease. In individual subjects, comparable amounts of atherosclerotic plaque disease can have vastly different functional consequences, which are determined by numerous factors that are only partly understood. On the basis of EBCT, how important is the extent of coronary atherosclerosis as a prognostic factor in its own right?

Short- and Long-Term Prospective Studies

In patients presenting to the emergency room with chest pain and no initial objective signs of myocardial ischemia, a negative EBCT indicated an excellent prognosis with regard to major cardiac events over the subsequent 1 to 4 months.43,44 EBCT yielded negative predictive values in the range of 98% to 100%. In symptomatic patients undergoing coronary angiography, increased amounts of coronary calcium detected by EBCT were highly predictive of subsequent events over 30 months.45 In direct comparison, EBCT performed better than coronary angiography (that is, number of stenotic major coronary arteries) in this respect.

There are currently 3 published studies reporting on EBCT-derived prospective prediction of hard events (ie, AMI and cardiac death) in asymptomatic subjects (Table).6,8,9 Arad et al9 observed a tendency for higher scores in subjects with hard events than in subjects who underwent revascularization. The prespecified calcium score cut points of 80 and 160 both were associated with odds ratios of approximately 22 for suffering coronary death or AMI, with wide confidence intervals (95% CI, 5.1 to 97.4 and 6.4 to 77.4, respectively). The status of established risk factors was determined by questionnaire. In a multivariate analysis in a subgroup of patients with all information available (n=787), the calcium score cut points were associated with odds ratios for suffering any event in the range of 14 to 20 and the risk factors, including age, with odds ratios in the range of 3 to 6.

Raggi et al8 (Table) found that subjects with calcium scores in the highest quartile had an odds ratio of 21.5 (95% CI, 2.8 to 162.4) for suffering AMI or cardiac death. Risk factor data were obtained by questionnaire. Subjects in the highest quartile had a significantly higher number of risk factors than those in other quartiles. The median calcium score of 444 (95% CI, 201 to 787) was a strong predictor of cardiac death or AMI, with an odds ratio of 20.4 (95% CI, 4.9 to 85.5). The status of established risk factors was determined by questionnaire. In a multivariate analysis in a subgroup of patients with all information available (n=787), the calcium score cut points were associated with odds ratios for suffering any event in the range of 14 to 20 and the risk factors, including age, with odds ratios in the range of 3 to 6.

Demographic and Design Characteristics of the Published Reports on the Predictive Value of EBCT for Myocardial Infarction and Cardiac Death in Subjects With No Clinical CAD

<table>
<thead>
<tr>
<th>Arad et al9</th>
<th>Raggi et al8</th>
<th>Detrano et al8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n</td>
<td>1177</td>
<td>672</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>53±11</td>
<td>52±8</td>
</tr>
<tr>
<td>Scanning protocol</td>
<td>3-mm slices lesion ≥0.93 mm²</td>
<td>3-mm slices lesion ≥1.37 mm²</td>
</tr>
<tr>
<td>Median calcium score</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Mean follow-up, y</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Follow-up completed, %</td>
<td>99.6</td>
<td>100</td>
</tr>
<tr>
<td>Hard events, n</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Comment</td>
<td>Standard EBCT scanning protocol Participants self-referred or referred by physicians in response to newspaper information and commercial mailings</td>
<td>Standard EBCT scanning protocol Participants referred by primary care physicians for assessment of cardiovascular risk</td>
</tr>
</tbody>
</table>

Unusual EBCT scanning protocol with low sensitivity for detecting calcium Participants selected on the basis of high-risk status according to Framingham equations
Summary and Outlook

Imaging of coronary calcium does not allow for reliable identification of unstable coronary plaques. Indeed, on the basis of the difficulties inherent in the histopathologic definitions, it is doubtful if any of the currently available noninvasive imaging techniques can prospectively identify vulnerable or complicated coronary plaques with some degree of accuracy.

Even in young age groups, subjects sustaining acute coronary syndromes have much more extensive and severe coronary atherosclerosis than age- and sex-matched controls. 5,6 By virtue of the ability to determine overall plaque burden, direct visualization and quantification of coronary calcium appears to be very helpful for identification of subjects at increased risk. The available data suggest that even though we cannot at present define the unstable plaque, there is the potential to identify the “unstable patient.”

The only way to reach definitive conclusions at this point is to obtain more data from large prospective clinical trials that adhere to the principles of good clinical and epidemiological practice. Such trials are now in the planning process or already underway. Two trials will examine the predictive value of EBCT-derived coronary calcium in the general population, one in the United States (Multi-Ethnic Study of Atherosclerosis [MESA]) and one in Germany (Heinz Nixdorf Recall Study). The latter study has begun recruitment of 4200 subjects who are being contacted through mandatory citizen registries. During an observation period of 5 years, there will be a direct comparison of the ability of EBCT and competing techniques, such as ultrasound measures of carotid intima-media thickness and the ankle-brachial index, to predict AMI and cardiac death. It is hoped that these studies will not only further elucidate the prognostic value of imaging coronary calcium but also will place this test in the public health and health-economic context.

References


11. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of...


Unstable Coronary Plaque and Its Relation to Coronary Calcium
Axel Schmermund and Raimund Erbel

Circulation. 2001;104:1682-1687
doi: 10.1161/hc3901.093339
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/14/1682

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/