Circulation



ARTICLES

# Ischemia-Related Lesion Characteristics in Patients With Stable or Unstable Angina

## A Study With Intracoronary Angioscopy and Ultrasound

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## Abstract

*Background* Postmortem-derived findings support the common beliefs that lipid-rich coronary plaques with a thin, fibrous cap are prone to rupture and that rupture and superimposed thrombosis are the primary mechanisms causing acute coronary syndromes. In vivo imaging with intracoronary techniques may disclose differences in the characterization of atherosclerotic plaques in patients with stable or unstable angina and thus may provide clues to which plaques may rupture and whether rupture and thrombosis are active.

*Methods and Results* We assessed the characteristics of the ischemia-related lesions with coronary angiography and intracoronary angioscopy and determined their compositions with intracoronary ultrasound in 44 patients with unstable and 23 patients with stable angina. The angiographic images were classified as noncomplex (smooth borders) or complex (irregular borders, multiple lesions, thrombus). Angioscopic images were classified as either stable (smooth surface) or thrombotic (red thrombus). The ultrasound characteristics of the lesion were classified as poorly echo-reflective, highly echo-reflective with shadowing, or highly echo-reflective without shadowing. There was a poor correlation between clinical status and angiographic findings. An angiographic complex lesion (n=33) was concordant with unstable angina in 55% (24 of 44); a noncomplex lesion (n=34) was concordant with stable angina in 61% (14 of 23). There was a good correlation between clinical status and angioscopic findings. An angioscopic thrombotic lesion (n=34) was concordant with unstable angina in 68% (30 of 44); a stable lesion (n=33) was concordant with stable angina in 83% (19 of 23). The ultrasound-obtained composition of the plaque was similar in patients with unstable and stable angina.

*Conclusions* Angiography discriminates poorly between lesions in stable and unstable angina. Angioscopy demonstrated that plaque rupture and thrombosis were present in 17% of stable angina and 68% of unstable angina patients. Currently available ultrasound technology does not discriminate stable from unstable plaques.

angina ultrasonics angiography

The morphology of coronary atherosclerotic lesions is heterogeneous between and within individuals.[1] [2] [3] [4] [5] [6] It is now common belief that acute ischemic syndromes result from a disruption of a lipid-rich atheromatous plaque, setting into action a cascade of pathogenic mechanisms such as platelet activation, adhesion, and aggregation; increased vasoconstriction; and thrombus formation.[7] [8] [9] [10] [11] [12] Plaques prone to rupture are lipid rich and have a thin, fibrous capsule.[10] [11] [12]

In vivo characterization of atherosclerotic lesions in patients with stable or unstable angina is of importance to better understand the pathogenic mechanisms operative in an individual patient and may allow the identification of plaques that have undergone rupture.

Two recently developed intracoronary imaging tools have the potential to provide these insights. Intracoronary ultrasound imaging provides information about plaque size and composition,[13] [14] [15] and intracoronary angioscopy accurately detects the presence of plaque rupture and intracoronary thrombus.[16] [17] [18] [19]

The purpose of this study was to determine the composition and characteristics of the ischemia-related lesion with the sequential use of intracoronary angioscopy and ultrasound imaging in patients with stable and unstable angina before intracoronary intervention. These findings were correlated with coronary angiographic characteristics.

## Methods

Between September 1992 and March 1993, a nonconsecutive series of 75 patients who were scheduled for coronary intervention were studied. In 1 patient, the procedure was discontinued because of severe ischemic chest pain after introduction of the angioscope into the ischemia-related coronary artery. Immediate percutaneous transluminal coronary angioplasty was successful without adverse sequelae. The angioscope was introduced in 7 patients, but the obtained images were of insufficient quality. Thus, the study population comprised 44 patients with unstable angina and 23 patients with stable angina. Table 1⇓ lists the clinical and angiographic data of these patients.

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**Table 1.**

Baseline Patient and Angiographic Characteristics

The investigations were approved by the Institutional Review Board of the Cardiology Department of the Dijkzigt Ziekenhuis. The patients were studied after informed consent was obtained.

## Procedures

Selective coronary angiography in multiple projections was performed before and after angioplasty. All patients received aspirin (250 mg) and intracoronary nitroglycerin before the procedure. They received anticoagulation with heparin, so activated clotting time was >300 seconds.

After passage of a 0.014-in guide wire across the lesion, intracoronary angioscopy was always performed first, followed by intracoronary ultrasound imaging. In all instances, an attempt was made to cross the lesion with both devices to obtain information about the entire lesion.

Coronary angioplasty or other interventional techniques were used according to standard practice.

## Selection of Ischemia-Related Lesion

In patients with single-vessel disease, the most severe lesion within that vessel was considered the ischemia-related lesion. In patients with multivessel disease and unstable angina, the selection was determined by the combination of ECG localization indicated by transient ST-T segment changes during ischemia at rest and the closest corresponding coronary vessel containing the most severe lesion.

## Angiography

A modified classification of angiographic morphology proposed by Ambrose et al[20] was used to categorize each target lesion as noncomplex (concentric or eccentric with smooth borders) or complex (eccentric with irregular borders or overhanging edges, multiple irregularities, or intraluminal filling defects).

Quantitative coronary angiography was performed with the CAAS-2 system (PIE Data) with the non–contrast-filled catheter as calibration.[21]

## Imaging Devices

The percutaneous coronary angioscopic device was a 4.5F monorail-type polyethylene catheter device accommodated by an 8F guiding catheter (Baxter-Edwards).

Ultrasound imaging was performed with a commercially available intracoronary 4.3F, 30-MHz ultrasound catheter (Cardiovascular Imaging Systems Inc).

To facilitate the review process, a real-time fluoroscopy or cineangiography was combined with real-time angioscopy and ultrasound imaging by use of split-screen videotaping. This provided a better orientation of the place from which the angioscopic and ultrasound images were derived within the coronary tree.

## Analysis of Angioscopic and Ultrasound Images

Qualitative analyses of both angioscopic and ultrasound images were performed by the consensus of three observers with no access to clinical records or cinefilm during assessment. Thrombi were defined as a red, intraluminal mass adherent to the intima. Thrombi were categorized as nonmobile and mural

(closely adherent to the vessel wall), mobile (protruding into the lumen), or totally occlusive. Yellow plaques were defined as areas of homogeneous yellow clearly identifiable from the normal white wall.

Wall surface was classified as ulcerated when a major disruption of the plaque was found. When ulceration was absent but wall irregularities were noted, the surface was classified as irregular. Finally, when none of these alterations was present and the wall presented the characteristic pattern noted in normal nonstenotic segments, the surface was classified as smooth.

Angioscopic images of lesions were classified as thrombotic lesions if they had an irregular, ulcerated raised surface with the presence of thrombus or as stable lesions if the raised surface was regular and smooth without thrombus (Fig 1⇓).

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**Figure 1.**

Angioscopic images of a stable lesion (left) with smooth, white surface and thrombotic lesion (right) with disrupted surface and red thrombus.

The composition of the ischemia-related lesion was classified as poorly echo-reflective or highly echo-reflective intimal thickening (Fig 2⇓). The last group was further subdivided according to the presence or absence of acoustic shadowing. An intimal thickening was considered poorly echo-reflective if the echo

density was less than that seen for the adventitia and highly echo-reflective if the echo density was equal to or greater than that of the adventitia.

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**Figure 2.**

Angioscopic images of the types of ultrasound-derived lesions: (A) plaque with poorly echo-reflective tissue between 4 and 9 o'clock, (B) plaque with highly echo-reflective tissue with eccentric location between 1 and 4 o'clock, (C) plaque with highly echo-reflective tissue with shadowing, and (D) mixed plaque composed of poorly echo-reflective tissue at 6 to 11 o'clock and highly echo-reflective with shadowing at 1 to 5 o'clock.

The results of previous comparisons between histology and ultrasound showed that poorly echo-reflective intimal thickening corresponds to loose fibrous tissue, lipid, and thrombus; highly echo-reflective intimal thickening without shadowing represents dense fibrous tissue; and highly echo-reflective intimal thickening with acoustic shadowing indicates calcium deposition.[14 22 23] The concentricity versus the eccentricity of the plaque was determined by the ratio between the thinnest and thickest parts of the intimal thickening. Eccentricity was defined by a ratio <0.7.

A lesion was considered homogeneous if the plaque consisted of >75% of one type of echo-reflectivity induced by the lesion determined from an integrated pullback image of the entire lesion. A lesion was considered predominantly calcific if calcium occupied >180° of the vessel circumference. A lesion was

defined as mixed if it contained both highly and poorly echo-reflective areas occupying >25% of the plaque surface or if calcium deposits occupying >30° and <180° of the vessel circumference were present. The intergroup observer variability performed in a random sample of 30 patients for angioscopic image classification yielded κ values of 1.0 for the presence of thrombus, 0.78 for a protruding or mural thrombus, 0.8 for the surface of a lesion, 0.93 for yellow plaque, and 0.94 for a thrombotic lesion. The κ values for ultrasound classification of echo-reflectivity of lesions ranged from 0.85 (calcium present) to 1.0 (homogeneous versus mixed type).

Quantitative measurements were obtained from a cross-sectional image taken at the narrowest part of the lesion. Total vessel area was defined as the area central to the ultrasound-defined boundary between adventitia and media-intima thickening. Lumen area was defined as the area central to lumen-intimal boundary. Plaque area was calculated as the difference between total vessel area and lumen area. The mean difference of the measurements of 30 lesion lumen areas and 30 plaque areas and interobserver variability obtained by two independent investigators was 0.02±0.37 and 0.03±0.62 $mm^2$ ($r$=.97 and $r$=.99), respectively.

### Statistical Analysis

All measured values are presented as mean±SD. The unpaired $t$ test, the $\chi^2$ test with Yates' correction, and Fisher's exact test were used when appropriate. A value of $P$<.05 was considered statistically significant. The interobserver variations were assessed with the use of unweighted κ coefficients.[24]

## Results

### Procedures

Passage of the imaging catheters through the ischemia-related lesion was obstructive to blood flow and associated with chest pain and ECG ST-T segment changes in almost all patients. These changes were quickly reversible after withdrawal of the catheter except in 2 patients in whom abrupt occlusion occurred at the site of the ischemia-related lesion. This was treated effectively with balloon angioplasty. The angioscope caused a small, nonocclusive dissection in 1 patient. Subsequent balloon angioplasty resulted in an occlusive dissection that was managed effectively by stent implantation.

In 4 patients, the culprit lesion was too tight to allow crossing with the angioscope, and the observations were restricted to the proximal aspect of the stenosis. In the 2 patients in whom the lesion could not be crossed with the ultrasound probe, the plaque composition was taken from postangioplasty examination.

### Lesion Characteristics

Tables 1 through 3⇑⇓⇓ give the angiographic and intracoronary angioscopy findings and ultrasound characteristics of the ischemia-related lesions. An angiographically complex lesion was present in 39% of the stable angina patients and in 55% of the unstable angina patients. An angioscopically thrombotic lesion was present more often in patients with unstable angina than in patients with stable angina (68% versus 17%, $P$<.01). The presence of a yellow plaque (containing lipids) was similar in both groups. The presence of wall disruption or ulceration of complex lesions was not detectable with ultrasound. The composition, presence and distribution of calcium, and eccentricity and extent of the plaque were similar in unstable and stable angina patients.

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**Table 2.**

Angioscopic Characteristics of Ischemia-Related Lesions

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**Table 3.**

Intracoronary Ultrasound Characteristics of Ischemia-Related Lesions

## Correlations Among Clinical, Angiographic, Angioscopic, and Ultrasonic Lesion Characteristics

Tables 4⇓ and 5⇓ list the correlations among the findings of angiography, angioscopy, and ultrasound of the ischemia-related lesions in patients with stable and unstable angina. It appears that the clinical syndrome and angiographic findings were poorly correlated. An angiographic complex lesion (n=33) or noncomplex lesion (n=34) was concordant with unstable angina (n=44) or stable angina (n=23) in 55% (24 of 44) and 61% (14 of 23), respectively (Table 4⇓).

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**Table 4.**

Correlation Between Angiographic, Angioscopic, and Ultrasound Findings of Lesions in Patients With Stable and Unstable Angina

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**Table 5.**

Correlation Between Angioscopic and Ultrasound Lesion Characteristics in Patients With Stable or Unstable Angina

An angioscopic thrombotic lesion (n=34) or stable lesion (n=33) was concordant with unstable or stable angina in 68% (30 of 44) and 83% (19 of 23), respectively (Table 4⇑).

There were no significant correlations among the lesion characteristics obtained with angiography, angioscopy, and ultrasound (Tables 4⇑ and 5⇑). An angiographic complex lesion (n=33) or noncomplex lesion (n=34) was concordant with an angioscopic thrombotic lesion (n=34) or stable lesion (n=33) in 58% (19 of 33) and 56% (19 of 34), respectively (Table 4⇑).

Ultrasonic-defined lesion characteristics were almost equally represented between angiographically complex and noncomplex lesions (Table 4⇑) and between angioscopic thrombotic and stable lesions (Table 5⇑).

## Discussion

Individual atherosclerotic lesions have a striking heterogeneity in both their composition and appearance. Much evidence has accumulated, primarily from postmortem studies, to show that acute ischemic syndromes are associated with plaque fissuring and superimposed thrombosis.[7 8 9 10 11 12] Clinical angioscopic studies confirmed the presence of an intracoronary thrombus.[16 17 18 19] Recently, Davies et al[12] performed an elegant postmortem study of aortic plaques from men who had died suddenly. They emphasized the importance of the volume of a central lipid pool in plaques that had undergone thrombosis. The size of the extracellular lipid pool exceeded 40% of the cross-sectional area in 91% of thrombosed plaques but in only 3.2% of nonthrombosed plaques. Ample evidence indicates that lipid-rich atheromatous plaques that have a thin, fibrous capsule are prone to plaque fissuring.[1 2 3 4 5 6 7 8 9 10 11 12] Clearly, it would be of great importance if we could identify, in vivo, plaques prone to fissuring. In vitro pathological studies showed that intravascular ultrasound imaging can allow us to visualize the fibrous cap and provides acoustic characterization of the composition of a coronary plaque, including calcium, dense fibrous tissue, loose fibrous tissue, intimal hyperplasia, and extracellular lipid.[14 22 23]

Currently, experience with using intracoronary ultrasound to characterize the composition of coronary lesions in patient studies is limited. Hodgson et al[15] performed a morphological analysis of the ultrasound images obtained from ischemia-related lesions in patients with unstable or stable angina. They found that patients with unstable angina had more poorly echo-reflective lesions and fewer severe calcific lesions or intraluminal calcium deposits than patients with stable angina. We could not confirm these findings, and we found that the compositions of stable and unstable plaques were nearly identical. The discrepancy between the findings of these two studies may be explained by differences in image quality. The mechanical system used in this study has a higher dynamic range and resolution than that used by Hodgson et al. However, the ultrasonic findings should be interpreted with caution because, although poorly echo-reflective lesions are thought to represent lipid-containing lesions, ultrasound imaging systems at present cannot distinguish between loose fibrous tissue, lipid-rich lesions, and thrombus.

Our angioscopic findings are in agreement with previous angioscopic studies[16 17 18 19] and demonstrate that thrombus and ulcerated plaques are present in two thirds of the cases. An interesting question arises as to why we did not observe the presence of a thrombus in the other one third of the unstable patients. This question has several possible answers. The intensive premedication with heparin and aspirin and the time interval between the last symptoms and examination may have induced dissolution of thrombus and wall repair. Plaque disruption may have been small and associated with only a small thrombus that was difficult to see with angioscopy or was located in a segment not completely explored with angioscopy. The thrombus may have been dislodged by the catheter or may have been flushed away into the distal part of the vessel. Another interesting possibility is that our angioscopic observations were correct and that alternative mechanisms other than rupture and thrombosis, such as vasospasm or the recently suggested possibility of smooth muscle cell proliferation with plaque expansion, cause luminal narrowing.[25] It is also of note that rupture and thrombosis were observed in 17% of the patients with stable angina. This observation has not been made by other investigators in patients with stable

angina.[16] [17] [18] These findings suggest that rupture and thrombosis do not always lead to the clinical manifestation of an acute coronary syndrome. Unfortunately, the resolution of ultrasound imaging is insufficient to reliably visualize a rupture of the plaque, possibly because plaque ruptures are much smaller than larger dissections after coronary angioplasty that are reliably detected with ultrasound.

We found that approximately two thirds of the lesions in patients with stable and unstable angina were yellow. This yellow color of a plaque is caused by lipid that contains carotene. A white plaque may also contain lipid because cholesterol is white and does not always contain carotene.

## Study Limitations

The study group consists of a nonconsecutive series of patients, which may have introduced a bias. This study was performed in a subset of unstable patients having angina at rest or early postinfarction angina selected for balloon angioplasty and thus precludes generalization of the findings to all patients with unstable angina.

Unstable angina pectoris is a dynamic process with different pathophysiological mechanisms that wax and wane over time. Therefore, any study will represent a snapshot, and certain processes may have been missed. Only monitoring during a longer period would resolve this problem.

Currently available imaging devices are still bulky and stiff. In a few cases, the ischemia-related lesions could not be crossed or could not be completely imaged because of the curvature of the vessels, so interrogation of the entire lesion was not possible and certain lesion characteristics may have been missed.

Even after the lesions were crossed, certain aspects may have escaped detection because the current angioscopic design does not include a flexible, steerable tip, so the entire surface area cannot always be inspected. Structures lying behind calcific lesions cannot be detected with ultrasound because the plaque prevents penetration of the ultrasonic beam. Also, the wire and strut artifact present with the 4.3F ultrasound catheter may introduce incomplete visualization of the plaque.

## Conclusions

Sequential imaging of the ischemia-related lesion with intracoronary angioscopy and ultrasound is feasible and relatively safe in patients undergoing coronary intervention. Additional imaging can be associated with ischemic complications, which could be successfully managed with subsequent coronary interventions. The information obtained with angioscopy is complementary to coronary angiography with regard to the distinction between stable and unstable features of the coronary lesion. Ultrasound does not discriminate between stable and unstable plaques.

Both intracoronary imaging techniques do not allow identification of a lipid-rich plaque with a thin fibrous cap known to be prone at rupture.

Ultrasonic imaging (30-MHz) does not yield enough resolution to accurately detect plaque composition. Improvement of the quality of intracoronary ultrasound images is necessary to provide accurate information on the size of the volume of the extracellular lipid pool, thickness of the fibrous cap, or location and depth of a fissure of the cap.[26]

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