Identification of Coronary Thrombus After Myocardial Infarction by Intracoronary Ultrasound Compared With Histology of Tissues Sampled by Atherectomy

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This study compares the ability of intracoronary ultrasound (ICUS) to identify thrombus by means of actual criteria, with the histologic studies of tissues removed by directional atherectomy in patients treated previously with thrombolytic therapy. Coronary angiography and intravascular ultrasound imaging were performed before atherectomy in 34 patients who had received intravenous thrombolytic therapy for acute myocardial infarction a mean of 6 days before. The lesion morphology and the percentage of stenosis were defined on the angiogram. The ultrasound characteristics of the narrowing were described as intraluminal thrombus, mural thrombus, mixed plaque, and dense plaque. Thirty patients were studied. Thrombus was suspected in 8 patients on angiography. By ICUS, the presence of thrombus was predicted in 21 patients. Histologic studies of excised tissues found thrombus in 20 of the 30 patients. When ICUS was compared with histology, the true-positive rate was 80% and the false-positive rate was 50%; the true-negative rate was 50% and the false-negative rate was 20%. The correlation between observers was high. These observations suggest that ICUS may be useful in identifying fresh thrombus. The findings of this study help to confirm the criteria for diagnosing intraluminal thrombus by ICUS imaging.

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After thrombolytic treatment for myocardial infarction, angiography often demonstrates a severe residual stenosis that may partially regress with time.[1] This spontaneous improvement suggests that a portion of the stenosis may be caused by residual thrombus. The significance of residual thrombus and the time course of its resorption are unclear, but previous studies have shown that the presence of thrombus during mechanical intervention may increase the incidence of abrupt closure.[2,3] The angiographic criteria used to identify thrombus are not as sensitive as angioscopy.[4,5] Identification of thrombus by intracoronary ultrasound (ICUS) imaging was performed during in vitro and animal studies, but the criteria for ultrasound identification of thrombus in human coronary arteries in vivo is not well defined.[5,6] The purpose of this study was to compare the observations of ICUS before and after directed atherectomy in patients who had been treated with thrombolytic therapy after an acute myocardial infarction. The hypothesis of this study is that the correlation between histology and ICUS images would provide a more accurate means of establishing criteria for the identification of thrombus by ICUS imaging.

METHODS

Patient group: The study group comprised 34 patients (30 men and 4 women, aged 54 ± 15 years [range 28 to 72]). Each patient had an admitting diagnosis of acute myocardial infarction and had had prior intravenous thrombolytic therapy <5 hours after the onset of symptoms. Aspirin 250 mg/day and intravenous heparin were given at the time of treatment with thrombolytic therapy. Patients were maintained on subcutaneous calcium heparinate with the dose adjusted to maintain the partial thromboplastin time at 2 to 3 times the control level and aspirin at 250 mg/day. Other medical treatment varied per patient.

Angiographic studies: Selective coronary angiography was performed a mean of 6 days (range 4 to 11) after admission. At least 6 views of the left coronary system and 4 views of the right coronary system were filmed and analyzed using a quantitative angiographic system (DCI System, Philips, Inc.). The coronary angiogram was examined by 2 independent observers. The culprit lesion was defined as the stenosis related to the electrocardiographically documented infarction site. Lesion morphology was defined according to the classification of Ambrose et al[6]: concentric, type I eccentric, type II eccentric, or lesions with multiple irregularities. Thrombus was assessed angiographically using the grading system adapted from the Thrombolysis In Myocardial Infarction (TIMI) IIIA study as a small, moderate, or large thrombus responsible for an intraluminal filling defect (TIMI grade 2, 3, or 4), or as a possible thrombus, suspected because of a reduced contrast and hazy appearance in the lumen of the responsible artery (TIMI grade 1).

Intracoronary ultrasound studies: ICUS imaging was performed before and after atherectomy. The intravascular imaging system consisted of a disposable imaging catheter (Intertherapy by CVIS, Inc., Sunnyvale, California), catheter drive module, and real-time video display. The 2-piece catheter included a polyethylene sheath and a 3.9Fr cable with a 25 MHz transducer on the dis-

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tal end with a mirror at 45°. An 8Fr guiding catheter was placed in the ostium of the coronary artery and the ICUS transducer was advanced into the distal segment of the target vessel over a 0.014-inch guidewire. The target lesion and the corresponding reference segments were imaged. The time gain control settings were adjusted to deemphasize the blood backscatter. Fluoroscopic guidance and contrast injections were used to ensure proper positioning of the catheter. Ultrasound images were updated with fluoroscopic images and audio annotations to ensure correct location during off-line analysis. All studies were recorded on high-resolution 0.5-inch S-VHS videotape.

Atherectomy protocol: Heparin at a dose of 10,000 U was given intravenously before the procedure. Directional atherectomy was performed from the femoral approach through an 11Fr guiding catheter using Simpson's atherectomy catheter (DVI, Inc., Redwood City, California) as previously described.[7] The atherectomy catheter was advanced over a 0.014-inch high-torque floppy guidewire under fluoroscopic guidance. The size of the catheter was selected according to angiographic measurements of the arterial diameter. The number of cuts varied between 4 and 16 (mean 9 ± 6/procedure). Angiographic guidance during the procedure was used to determine if an adequate result was achieved (residual stenosis <30% of vessel diameter). After the atherectomy was completed, ICUS was performed to evaluate the result. The qualitative or quantitative ultrasound results were not used to perform futher atherectomy or change therapy.

Ultrasound image analysis: Ultrasound images were reviewed independently by 2 observers who were unaware of the angiographic results or clinical status. Vessel morphology was described according to previous studies by Gussenhoven,[8] Tobis,[9] Potkin,[10] and their coworkers. The ultrasound characteristics of the tissue at the culprit lesion site were classified as: (1) mixed plaque = fibrous or atheromatous tissue producing a heterogeneous density of echoreflectance; (2) dense plaque = intense echoreflectance with a compact area of echogenicity often associated with distal shadowing consistent with calcium; (3) intraluminal thrombus = granular or finely speckled intense echoreflections that scintillate during real-time imaging (the structure appears mobile with blood flow); and (4) mural thrombus = linear echogenic density along the wall of the plaque which is not as dense or compact as fibrous tissue and may still move with blood flow or expand during arterial pulsations. Definition of ultrasound tissue characteristics did not differ among the observers. Independent classifica-

TABLE I Statistical Analysis*

	Ultrasound	Histology
True positive	+	+
True negative	–	–
False positive	+	–
False negative	–	+

*Sensitivity, specificity, and predictive value were calculated as follows: sensitivity = number of true positives divided by number of true positives and number of false negatives; specificity = number of true negatives divided by number of false positives + number of true negatives; predictive value = number of true positives divided by number of true positives + number of false positives; + = positive; – = negative.

TABLE II Plaque Composition in 30 Patients

Composition	Ultrasound (no. of specimens)	Histology (no. of specimens)	Composition
Speckled scintillations mobile or layered in wall	21	20	Thrombus
Mildly echogenic	20	23	Fibrous atheroma
Densely echogenic	7	6	Dense fibrosis
Intense echoes with shadowing	6	2	Calcium

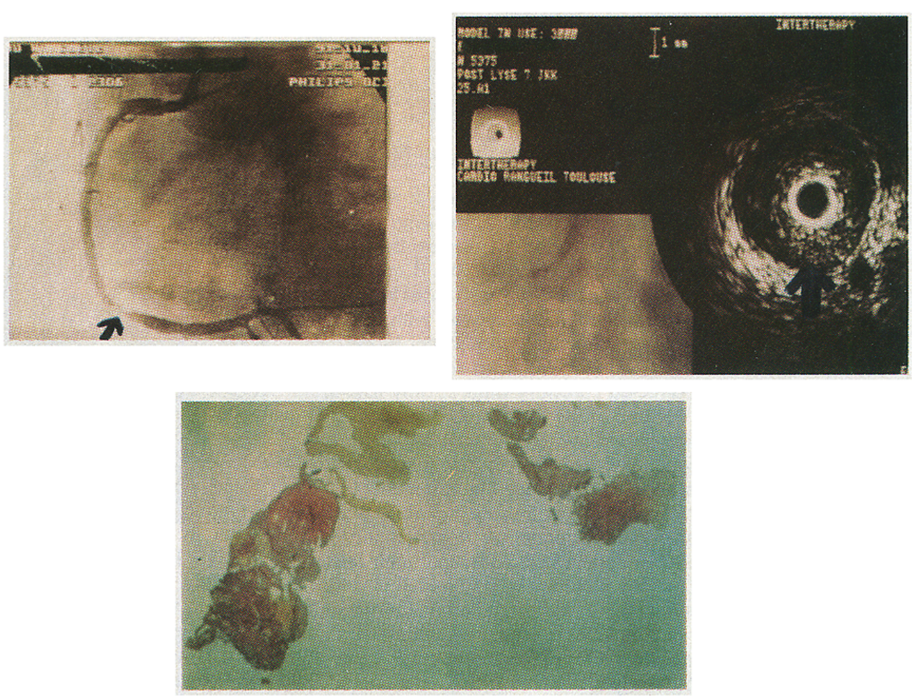

FIGURE 1. Angiogram of right coronary artery in the left anterior oblique projection showing severe stenosis *(arrow)* 6 days after a myocardial infarction treated with streptokinase. Intravascular ultrasound image before atherectomy demonstrates a speckled echo density *(arrow)* which was mobile with blood flow. Histology of tissue sample removed by directed atherectomy demonstrates thrombus associated with a small amount of fibrous tissue.

tion yielded complete agreement in >85% of images. Cases of disagreement always involved the differentiation between mixed plaque and mural thrombus.

Tissue analysis: The specimens obtained by directional atherectomy were placed in 10% buffered formalin. After fixation, the tissue was prepared (4 μm sections) for histology and stained with hematoxylineosin, Masson's trichrome, and elastic Verhoeff stains. Light microscopy was performed by an independent histopathologist who was unaware of the clinical, angiographic or ICUS findings. Each specimen was evaluated for the presence of atherosclerotic plaque, fresh or consolidated thrombus, fatty atheroma, fibrous hyalinous plaque, or calcium. Thrombus and intraplaque hemorrhage were defined as amorphous material, with a characteristic collection of red cells interlaced with fibrin strands in close apposition to atheromatous material. The presence of intimal hyperplasia, media, or adventitia was noted.

Statistical analysis: After the narrowing had been classified as belonging to a category (or after thrombus was identified) by imaging and by histology, the sensitivity, specificity, accuracy, and predictive values were calculated as shown in Table I. We analyzed the contingency table to test the relationships between histology and ultrasound. Because of fewer patients, concordance between ultrasound and histologic studies was tested by applying the chi-square test to the theoretical distribution of half and half (50% probability of finding concordant cases by pure chance). Statistical significance was set at the 5% level ($p < 0.05$).

RESULTS

Patients studied: The study was performed in 30 patients; 4 of the 34 patients treated with directional atherectomy after thrombolytic therapy were excluded because the ultrasound catheter was unable to cross the lesion before atherectomy in 2 patients and the ultrasound images were inadequate for evaluation in 2 patients. The only complication (14 of 30 patients [47%]) was transient spasm, which occurred when the transducer was advanced into severe stenoses or small distal segments of vessel. All 30 patients were evaluated before and after directional atherectomy by intravascular ultrasound imaging; angiographic and histologic data were available for all patients.

Angiographic results: There were 16 lesions in the left anterior descending artery, 12 in the right coronary artery, and 2 in the circumflex artery. The mean percent stenosis after thrombolytic therapy was 78 ± 9%. Thrombus grade 2, 3, or 4 was noted on the angiogram in 5 patients and thrombus grade 1 in 3 patients, with an artery that otherwise appeared angiographically normal. The other 22 patients (73%) had no evidence of thrombus on angiography. The target lesion was concentric in 17 patients (57%) and eccentric type I or II in 10 patients (33%). The correlation with ultrasound was poor: ultrasound showed 11 concentric (37%) and 19 excentric (63%) lesions.

Ultrasound analysis of plaque morphology: Figures 1, 2, and 3 are representative images of intracoronary thrombus identified by ICUS. By ultrasound, 20 lesions (67% of patients) were classified as having mildly echogenic atheroma suggesting mixed plaque, 7 lesions (23% of patients) were classified as having densely echogenic atheroma suggesting dense plaque, with identification of calcium in 6 lesions. The presence of thrombus was predicted in 21 patients (70%). The correlation

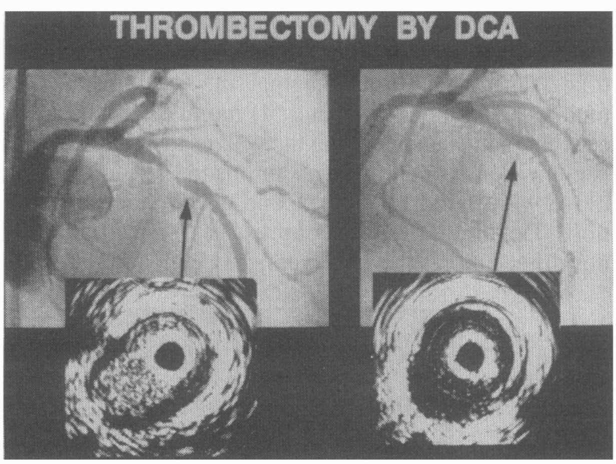

FIGURE 2. *Left,* angiogram 6 days after thrombolytic therapy for acute anterior wall myocardial infarction, showing severe residual stenosis in the mid–left anterior descending artery. The corresponding ultrasound image *(below left)* from 3 mm distal to the area of greatest stenosis *(arrow)* shows a speckled echodense ovoid structure that scintillated and moved with blood flow, consistent with intraluminal thrombus adjacent to the plastic sheath of the ultrasound catheter from *6 to 9 o'clock. Right,* angiogram after directed coronary atherectomy (DCA), showing 50% residual stenosis at the level of the tightest lesion. The ultrasound image *(below right)* taken at the same level as the image shown *below left* reveals that the speckled intraluminal structure is no longer present. The ultrasound catheter in the center is surrounded by the echogenic white plastic sheath and then by the echolucent lumen. At the periphery is a semicircle of a thin echo-dense structure, consistent with internal elastic membrane *(11 to 5 o'clock),* behind which is a thin echolucent layer, consistent with arterial media. This structure is not present between *6 and 9 o'clock,* consistent with removal of intima. Media may not be visualized as a separate layer because of its low echogenicity.

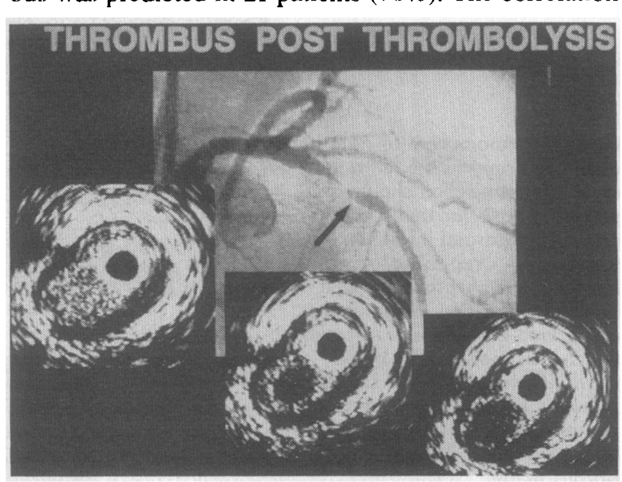

FIGURE 3. The mobile action of the echogenic structure shown in Figure 2 is demonstrated in this series of 3 different frames taken at the same position of the ultrasound catheter. The central echogenic stucture moves in and out of the plane of the ultrasound cross section, consistent with a more mobile or liquid core and a more organized peripheral structure.

between observers was 83.3%. Thrombus was easily identified by the 2 observers in 17 patients: speckled scintillations were pedunculated in 10 patients and were mural without any other abnormalities in 7 patients. All these cases showed speckled scintillations mobile with blood flow. Thrombus was suspected and discussedby the 2 observers in 4 patients because the speckled scintillations were included in a mildly linear echogenic aspect or in a dense echogenic aspect, and the mobility with blood flow was not found. The distribution of thrombus according to the ultrasound tissue characteristics are shown in Figure 4. The ultrasound identification of thrombus alone, not associated with a significant amount of plaque, was observed in 3 patients (10%). Thrombus was identified in 14 of 20 patients (70%) who had mildly echogenic plaque consistent with fibroatheromatous disease. Thrombus was identified by ultrasound in 4 of 7 patients (57%) who had a dense echogenic pattern of plaque consistent with fibrocalcific disease.

Histologic studies: The results of the histologic analysis for the distribution of thrombus is shown in Figure 5. There was histologic evidence of thrombus retrieved from the directional atherectomy biopsy in 20 of the 30 patients (67%). One of the excised tissue samples had thrombus alone without any atherosclerotic plaque. Atheroma or loose fibrous tissue was present in 23 specimens and densely fibrotic atherosclerotic plaque was present in 6. Thrombus was associated with 17 of the 23 fibrous atheroma specimens and with 2 of the 6 densely fibrotic specimens.

Comparison of ultrasound and histologic studies: The ultrasound description of plaque composition compared with the findings on histology is presented in Table II. Mildly echogenic plaque identified by ICUS or histologic fibroatheromatous tissue was more frequently associated with thrombus than dense echogenic plaque or histologic fibrocalcific tissue ($p < 0.02$). The correlation between ICUS and atherectomy sample sites showed that ultrasound was capable of qualitative imaging that showed very significant agreement with the results obtained from histology (ultrasound vs histology: chi-square = 4.80, $p < 0.05$).By comparing ICUS image features and histologic detection of thrombus (Table III), the true-positive rate was 80% and the false-positive rate was 50%; the true-negative rate was 50% and the false-negative rate was 20%. There were 16 ultrasound intravascular thrombi that were found by histology. The sensitivity of ultrasound for identifying thrombus was high (80%), with a specificity and predictive value <80% (50% and 76.6%, respectively). Sensitivity and specificity of ultrasound for identifying thrombus were ˇF380% because of the false-negative or false-positive data (n = 9). These calculations assume that atherectomy successfully retrieved thrombus in all lesions in which it was present, and that no thrombus was formed or dislodged during the atherectomy procedure itself. ICUS performed after atherectomy allows study of the principal features of these false-positive (n = 5) and negative (n = 4) data. With regard to the 5 false-positive data, ICUS was positive after atherectomy in 2 patients, showing a thrombus not retrieved by the atherectomy device: the Dotter effect was predominant. Thrombus was certainly dislodged by the atherectomy device in 1 patient and found distal to the target lesion. In 1 patient, ICUS probably misinterpreted artifacts as thrombus. For the 4 false-negative data, the possibility of thrombus formation by atherectomy exists in 1 patient because ultrasound was negative before and positive after atherectomy. In 3 patients, we can presume that we misinterpreted thrombus as mixed plaque. In these 3 patients, the study was performed >5 days after myocardial infarction, and the histologic specimens revealed a fibrin matrix with old red cells embedded. If we consider that 4 false-positive and 1 false-negative data were due to atherectomy procedure itself, the sensitivity of ICUS to detect thrombus was 84%, the specificity 71%, and the predictive value 89% (Table IV).

TABLE III ICUS/Histology Correlations (ICUS images before DCA)

		Histologic Thrombus	
		Yes	No
ICUS Thrombus	Yes	16	5
	No	4	5

Sensitivity = 80%; specificity = 50%; positive predictive value = 76.6%; negative predictive value = 55.6%.
DCA = direct coronary atherectomy; ICUS = intracoronary ultrasound.

TABLE IV ICUS/Histology Correlations (after correction by ICUS after DCA)

		Histologic Thrombus	
		Yes	No
ICUS Thrombus	Yes	16	2
	No	3	5

Sensitivity = 84.2%; specificity = 71.4%; positive predictive value = 88.8%; negative predictive value = 62.5%.
Abbreviations as in Table III.

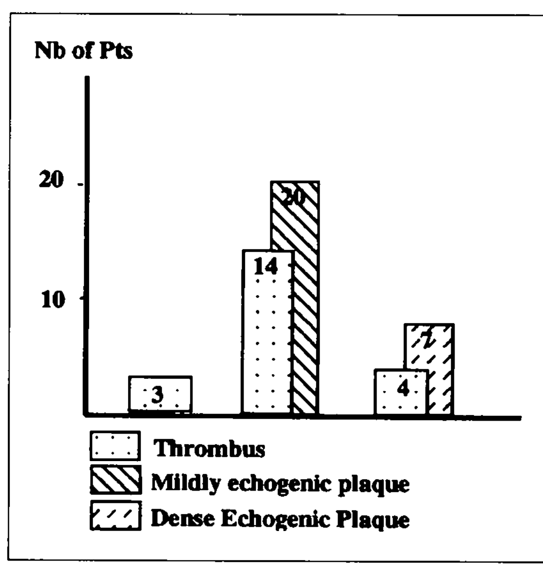

FIGURE 4. Predominant characteristics on intravascular ultrasound. Thrombus was predicted in 70% of patients; 70% of patients had thrombus with mild plaque, and 57% with dense plaque. Nb = number.

DISCUSSION

Until now, identification of thrombus by intravascular ultrasound has been controversial. Jain et al[11] reported a patient whose intraluminal thrombus was suspected by ICUS, but not confirmed by histology after directional atherectomy. He concluded that ICUS was unable to distinguish soft plaque from thrombus on the basis of its echogenic appearance. Keren and Leon[12] described the ultrasound characteristic of intraluminal thrombus as speckled echogenicity that was less dense than fibrous plaque, but difficult to differentiate from the ultrasound pattern of loose connective tissue or fibromuscular tissue. To define the appearance of thrombi of varying composition, this author explored the determinants of a clot echogenic pattern by intravascular ultrasound in in vitro study[13]: Identification of thrombus was possible if aggregated red blood cells were present and if the frequency of the transducer was >20 MHz, but ICUS could not detect platelet thrombus and had a limited role in detecting the initial thrombus in acute events.

Our study was performed >1 day after the initial event, and for this reason, thrombus originated from aggregated red blood cells and not from fibrin and platelets, as confirmed by histology.

Angioscopy has been shown to be more accurate than ICUS in identifying thrombus. Pandian,[14] Weintraub,[15] and their co-workers, in an experimental study, compared angioscopy and ICUS and found a sensitivity of 100% for angioscopy and 80% for ICUS in vitro and in animals in vivo when a thrombus was artificially placed in normal vessels. Siegel et al[4] found the specificity of ICUS in identifying thrombus to be 95% and the sensitivity 57% because of false-negative interpretation of laminar clots in normal vessels and the inability to distinguish disrupted atheroma from intraluminal thrombus. All these studies were performed either with normal vessels or with atheromatous arterial segments, but not in in vivo human atheromatous arteries.

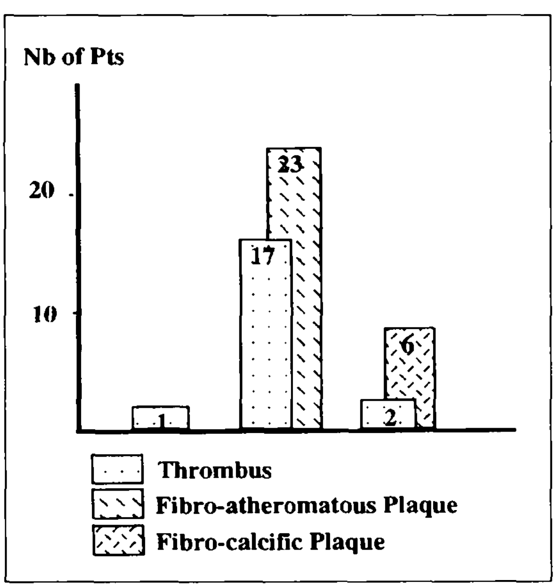

FIGURE 5. Predominant characteristics on histologic examination. These results confirm the finding shown in Figure 4. Thrombus was present in 67% of patients. It was seen with fiberatheromatous plaque in 74% of patients, and with fibrocalcific plaque in 33% of patients. NB = number.

The results of this study demonstrate that ICUS is capable of identifying in vivo thrombus associated with a recent presentation of infarction. The unique aspect of this study is that a tissue biopsy provided by directional atherectomy was used to confirm the predictions of thrombus and plaque composition based on ultrasound imaging. Rosenschein et al[16] studied histopathologic coronary lesions obtained from atherectomy in acute coronary syndromes and found that acute coronary syndromes were associated with large fresh thrombi. Our study in vivo in humans confirms the in vitro observations of previous investigators by comparing ICUS and histology, and allows criteria to be established by which the diagnosis of thrombus can be made with a high degree of certainty during clinical studies.

All 12 patients who were studied <5 days after thrombolytic therapy had ultrasound evidence for intraluminal thrombus, frequently with the echogenic structure protuding into the central lumen. In patients who underwent angiographic and ultrasound studies >5 days after thrombolytic therapy, an echogenic thrombus protuding into the lumen was rarely found. The thrombus appeared more linear and was adjacent to the wall. Its echogenic structure was more closely related to loose fibrous tissue, which was consistent with the resorption process of thrombus as it evolves into a fibrous structure. This process of resolution makes it more difficult to be certain of thrombus identification with ICUS imaging. However, the histologic confirmation of thrombus in the more acute cases suggests that thrombus can be identified with high sensitivity when the ultrasound image has a bright, speckled, echogenic appearance that scintillates with movement of the echostructure. The identification of thrombus is easier if the structure is mobile within the lumen. Identification of older thrombus is more difficult because the speckled appearance is often replaced by a more linear, mildly echogenic pattern; however, these reflections may remain mobile with blood flow if the mural thrombus protudes slightly into the arterial lumen. Histologic specimens in these cases revealed red cells embedded in a fibrin matrix similar to the observations of Fitzgerald et al.[17] This mixture of fibrin and red blood cells is consistent with the histopathologic diagnosis of an older thrombus. The variability of the echo density could predict the fibrin content and the degree of organization of the plaque.[18–20] In the present study, we found that the distribution of thrombus was more frequently associated with less dense fibroatheromatous lesions than with fibrocalcific disease. These observations are consistent with the angioscopic findings of De Feyter et al[21] in patients with unstable angina who presented with a higher incidence of thrombus associated with yellow plaque (suggesting lipid deposits) than with fibrous white plaque. These ICUS and angioscopic observations suggest that the mechanism of the development of acute myocardial infarction is a rupture of the atheroma that initiates thrombosis. Kawagoe et al[22] found a loosely speckled echogenic structure with ICUS, suggesting mural thrombus adherent to the surface of intimal plaque in 10 of 12 patients during acute myocardial infarction. The results of the present ICUS study clearly reveal the ICUS evidence of a fractured fibrous plaque with thrombus extending from the center of the plaque into the lumen in 5 of 12 patients studied <5 days after infarction.

ICUS imaging appears more competitive than angiography in detecting intracoronary thrombus and ruptured plaque. The improvement in angiographic stenoses with time is consistent with the ultrasound findings of a high incidence of residual thrombus despite successful thrombolytic therapy.

Study limitations: Excised atherectomy specimens indicate atheroma composition but may introduce a bias. The procedure samples a portion of atheroma, and certain tissue elements may not be excised, especially superficial thrombus that may be pushed downstream when the device crosses the lesion. ICUS cannot detect old thrombus, and future improvements in image resolution and gray level discrimination are necessary to improve the differentiation between atheromatous plaque and thrombus.

Conclusions: The findings of this study are significant insofar as they help to confirm the criteria for diagnosing intraluminal thrombus by ICUS imaging. The ability of ICUS imaging to identify intraluminal thrombus and to differentiate between thrombus and atherosclerotic plaque is important in evaluating coronary artery disease before interventional procedures. This study confirms that angiography is an insensitive tool for identifying the presence of thrombus and that ICUS permits better assessment of infarct-related artery.

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