Intracoronary Thrombus and Complex Morphology in Unstable Angina
Relation to Timing of Angiography and In-Hospital Cardiac Events

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In 78 consecutive patients with unstable angina, we performed coronary angiography randomized to either the first day of presentation or later during the hospital admission to assess the frequency of intracoronary thrombus and complex coronary morphology relative to the time of symptomatic presentation and the impact of these angiographic features on outcome. Early angiography (17±6 hours) was performed in 42 patients and late angiography in 36 patients (5.7±2.1 days). Twelve patients randomized to late angiography required urgent cardiac catheterization 3.9±2.2 days after admission. Coronary thrombi were present in 43% (18 of 42) of early angiography patients and in 38% (14 of 36) of late angiography patients (p=NS). Only 21% (five of 24) late elective angiography patients had coronary thrombi, but 75% (nine of 12) of late urgent angiography patients had thrombi (p<0.05 vs. both early and late elective angiography patients). There was no difference in the frequency of complex coronary morphology among patients randomized to early angiography (42%, or 15 of 36), late urgent angiography (42%, or five of 12), and late elective angiography (38%, or nine of 24). Cardiac events (death, myocardial infarction, and urgent revascularization) were more frequent in the patients with coronary thrombus (73%, or 23 of 32), complex coronary morphology (55%, or 16 of 29), and multiple-vessel disease (58%, or 29 of 50) than in the patients without these angiographic features (17%, or eight of 46; 31%, or 15 of 49; and 7%, or two of 28, respectively; all p<0.05). Multiple regression analysis demonstrated that coronary thrombus was the best angiographic predictor of cardiac events. Thus, angiographic detection of intracoronary thrombi varies according to the temporal relation between angiography and chest pain at rest. Coronary thrombi are also strongly predictive of cardiac events. (Circulation 1989;80:17–23)

Controversy exists with respect to the pathogenesis of unstable angina. Maseri et al observed that coronary artery spasm may precipitate crescendo angina, whereas Moise et al subsequently suggested that unstable angina was due to progression in the extent and severity of coronary atherosclerosis. Several investigators have suggested that coronary artery thrombus formation, most likely secondary to plaque rupture, may precipitate unstable angina. However, the frequency of coronary thrombus identification by coronary angiography in unstable angina is diverse and possibly related to the fact that the data arise from retrospective studies of selected patients where the timing of coronary angiography relative to symptomatic presentation varied widely. In patients studied up to 6 months after presentation, Ambrose et al also reported an increase in frequency of complex coronary morphology in unstable angina but did not relate these findings to identification of intracoronary thrombus or outcome.

We performed a randomized prospective study of coronary angiography in patients with unstable angina to assess the effect of timing of angiography on the frequency of coronary thrombus and complex coronary morphology and to determine the significance of angiographic extent of disease, com-
plex coronary morphology, and coronary thrombus on in-hospital outcome.

**Methods**

**Patient Population**

We prospectively studied 78 consecutive patients with unstable angina who presented to St. Michael’s Hospital between November 1985 and April 1987. All patients were admitted to the coronary care unit within 24 hours of the qualifying resting chest pain with a diagnosis of unstable angina defined as rapid acceleration of previously established anginal syndrome to include rest pain of less than 20 minutes duration (crescendo angina: \( n = 34 \)) or prolonged ischemic chest pain of more than 20 minutes duration without electrocardiographic (ECG) or enzymatic evidence of myocardial infarction (acute coronary insufficiency: \( n = 44 \)). All patients, therefore, had rest pain considered to be ischemic in nature. The presence of ST shift on the ECG was not required for admission to the study. Patients with left bundle branch block or previous bypass surgery and patients more than 75 years old were excluded. All patients gave informed consent for the investigation. The protocol was accepted by an ethics review committee of the University of Toronto.

**Study Protocol**

Patients were admitted to the coronary care unit and received standardized medical therapy. Antianginal medications previously administered on a chronic basis were continued. For each patient, we examined all ECG information from the time of qualifying chest pain to coronary care unit admission and selected the tracing with the most significant ST shift. One of the investigators measured ST shift in millivolts 80 msec after the S wave, and a shift of 1 mV or more was considered significant. All patients received topical nitroglycerin administration, and additional medical therapy was initiated if the patient had recurrent chest pain. Therapy with calcium antagonists, \( \beta \)-blockers, or both was left to the discretion of the referring cardiologist. Intravenous heparin and aspirin were not initiated as therapy in this study population before angiography. Sixteen patients were taking aspirin at the time of admission.

Patients were randomized to cardiac catheterization within the first 24 hours (17±6 hours) of admission (\( n = 42 \)) or to angiography to be performed later during the hospital admission (5.7±2.1 days, \( n = 36 \)). The patients were followed in hospital, and myocardial infarction (creatinine kinase more than twice normal), revascularization, and death were identified. Revascularization and late cardiac catheterization were classified as urgent if performed because of continued chest pain at rest despite maximal medical therapy including intravenous nitroglycerin. Of the 36 patients randomized to late angiography, 12 underwent urgent cardiac catheterization 3.9±2.2 days postadmission. The remaining 24 patients randomized to late angiography settled on medical therapy and had elective cardiac catheterization 6.6±1.5 days postadmission. Urgent revascularization, myocardial infarction, and death were considered in-hospital cardiac events.

**Coronary Angiography**

Coronary arteriograms were analyzed visually by two teams of two observers experienced in angiographic interpretation but unaware of the clinical data and timing of angiography. Differences were mediated by consensus. A stenosis of 50% or more was considered significant. The morphology of all coronary stenoses in the “worst” view was described according to the following criteria: 1) complex coronary morphology as a stenosis with irregularity, overhang, or both; and 2) coronary artery thrombus as a filling defect surrounded by contrast medium at the site of a high-grade stenosis, or luminal staining at the site of a high-grade stenosis or total occlusion, or upward convexity or irregularity without vessel tapering at the site of an abrupt occlusion. Each vessel could have complex morphology, thrombus, or both. Significant diagonal stenoses were considered as left anterior descending coronary artery disease and significant obtuse marginal stenoses as left circumflex disease. These detailed coronary angiographic interpretations were performed after hospital discharge and were not available to the clinician. For each patient, the most complex stenosis type present was taken as describing the patient’s coronary morphology.

**Statistical Analysis**

The differences in frequency of coronary morphology between groups was assessed by Fisher’s exact test. All data is expressed as mean±SD, and continuous variables were compared with one-way analysis of variance or unpaired Student’s \( t \) test where appropriate. A \( p \) value of less than 0.05 was considered significant. Multiple regression analysis (SAS statistical package) of coronary thrombus, multiple vessel disease, and complex coronary morphology was performed to determine the best predictor of cardiac events.

**Results**

The demographic, coronary anatomic, and cardiac event data are shown in Table 1 according to randomization to early or late angiography. The early and late angiographic groups were similar in age, sex distribution, previous infarction, cardiac events, and extent of disease.

The late angiography group was further subdivided into the patients who had elective or urgent cardiac catheterization. Cardiac events occurred more frequently in patients with early angiography or urgent late angiography than in patients with late elective angiography. In assessing the distribution of coronary artery disease, there were fewer patients with no stenoses of 50% or more and more patients
with two-vessel disease in the patients randomized to early angiography as compared with the patients with late elective angiography.

In Figure 1, the distribution of coronary anatomic findings (i.e., no complicated stenoses, complex morphology, or coronary thrombus, based on timing of angiography) is shown. The incidence of coronary thrombus in the patients randomized to early angiography of 43% (18 of 42) was similar to the 38% (14 of 36) in those with late angiography. We then divided the patients randomized to late angiography into those with and without urgent angiography. The frequency of coronary thrombus in the late angiography patients who required urgent investigation was 75% (nine of 12), which was significantly greater than the frequency of coronary thrombus in both those undergoing late elective angiography (21%, or five of 24, \( p < 0.01 \)) and those randomized to early angiography (43%, or 18 of 42; \( p < 0.05 \)). The frequency of coronary thrombus in the late elective angiography patients (21%, or five of 24) was less than that of early angiography patients (43%, or 18 of 42), but this difference did not reach statistical significance (\( p = 0.07 \)). There was no significant difference in the frequency of complex morphology in the patients randomized to early (42%, or 15 of 36) or late angiography (39%, or 14 of 36). Similarly, there was no difference in complex morphology frequency in the patients with late urgent angiography (42%, or five of 12) and late elective angiography (38%, or nine of 24).

Analysis of the timing of in-hospital cardiac events revealed that all but three occurred after coronary angiography. These three patients had myocardial infarction and coronary thrombus; in two patients, infarction occurred in the 24 hours before late but urgent angiography. Thus, only two of the nine patients with thrombus at late urgent angiography had myocardial infarction before the procedure. The frequency of coronary thrombus was the same in those receiving aspirin (44%, or seven of 16) as in those not receiving aspirin (40%, or 25 of 62).

In Table 2, the in-hospital cardiac event rate is depicted according to the coronary morphology and extent of coronary disease. Cardiac events, which include myocardial infarction \( (n=6) \), death \( (n=4) \), and urgent revascularization \( (n=21) \); i.e., 17 patients who had aortic coronary bypass surgery and four who had percutaneous transluminal coronary angioplasty occurred more frequently in the patients with coronary thrombus (73%, or 23 of 32), complex morphology (55%, or 16 of 29), and multiple vessel disease (58%, or 29 of 50) than in the patients without these angiographic features (17%, or eight of 46; \( p < 0.0001 \)), or 31%, or 15 of 49; \( p < 0.03 \); 7%, or two of 28; \( p < 0.0001 \), respectively). The frequency of not urgent revascularization was similar in patients with or without these angiographic features.

The frequency of cardiac events in patients with coronary thrombus was similar in the three subgroups of patients (i.e., 67%, or 12 of 18 in patients with early angiography, 89%, or eight of nine in patients with late urgent angiography, and 60%, or three of five in patients with late nonurgent angiography).

We performed multiple regression analysis to assess the relative significance of coronary thrombus, multiple-vessel disease, and complex morphology in determining in-hospital cardiac events. Thrombus was the most significant angiographic variable \( (F=12.1, p=0.001) \). Multiple-vessel disease was also predictive of in-hospital cardiac events \( (F=10.0, p=0.002) \). However, complex morphology alone was not predictive \( (F=2.0, p=0.16) \).

There were 10 patients with complex morphology who had no evidence of coronary thrombus. Of these 10 patients, seven had no cardiac events (three of these seven had nonurgent revascularization) and three patients had urgent revascularization. All but one patient had multiple-vessel coronary artery disease. Of the 19 patients with coronary

### Table 1. Demography, Coronary Anatomy, and Cardiac Events

<table>
<thead>
<tr>
<th></th>
<th>Early angiography ( n=42 )</th>
<th>Late angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yr)</td>
<td>All ( n=36 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elective ( n=24 )</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56±10</td>
<td>59±9</td>
</tr>
<tr>
<td>Male</td>
<td>35 (83)</td>
<td>28 (78)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>20 (48)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>17 (40)*†</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Time of angiography</td>
<td>17±6 hr</td>
<td>5.7±2.1 days</td>
</tr>
<tr>
<td>Vessels diseased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5*</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>10*</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Mean</td>
<td>1.9±1.1</td>
<td>1.8±1.3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*p < 0.05 vs. late elective; †p < 0.05 vs. late urgent.

Numbers in parentheses are percentages.
coronary thrombi, whereas six of the seven with late urgent angiography and crescendo angina had coronary thrombi.

To assess the predictive value of the admission ECG for determining coronary morphology, we analyzed patients based on the presence or absence of ST shift; this relation is shown in Table 3. Of the 39 patients with ST shift, 31 (or 79%) had complex morphology, coronary thrombus, or both at angiography. However, of the 39 patients without ST shift, only 11 (or 28%) had these angiographic features ($p<0.001$ versus ST shift).

**Discussion**

The hypothesis that thrombus occurs more frequently in patients with early angiography within 24 hours of admission rather than later during hospital admission is not substantiated by our data. This finding notwithstanding, we found that the presence of coronary thrombus has an important temporal link to the presence of chest pain at rest when assessing our total study group. The frequency of coronary thrombus was 50% (27 of 54) in patients who had angiography within 24 hours of rest pain (i.e., combining patients with early angiography and late but urgent angiography) as compared with 21% (five of 24) in those with late elective angiography. We also show that the presence of ST shift on the admission ECG predicts an increased frequency of coronary thrombus and complex morphology.

Previous pathologic studies suggest that patients who die of unstable angina have a high prevalence of intracoronary thrombi. Our study in a broad spectrum of patients with unstable angina extends these findings by demonstrating an association of intracoronary thrombi identified by coronary angiography with a higher frequency of in-hospital cardiac events, including death, myocardial infarction, and urgent revascularization after an episode of unstable angina. Because the acquisition of coronary angiographic data in our study was randomized according to time from presentation, the determination of our secondary objective (i.e., the relation between coronary anatomic findings and in-hospital outcome) could have been influenced by our study design. However, this seems unlikely given that the frequency of coronary thrombus and in-hospital events was similar in both early and late angiographic groups, and, irrespective of whether coronary thrombi occurred within early, late elective, or late urgent groups, the propensity to develop in-hospital events in association with thrombi was the same.

Vetrovec et al. and Bresnahan et al. retrospectively analyzed coronary angiograms in patients with unstable angina and found coronary thrombi in 6–35% of patients studied up to 2 months after presentation. Capone et al. studied patients with recent onset of unstable angina and found the frequency of coronary thrombi was 52% if angiography was performed within 24 hours of symptoms.
and 28% in patients with angiography performed 1–14 days after rest pain. Our findings are very similar in that coronary thrombi were present in 43% of patients with angiography in the first day and in only 21% of patients after resolution of their rest pain. However, we randomly assigned our patients to early and late catheterization and therefore eliminated the possibility of selection bias of sicker patients for early angiography that may have occurred in the study of Capone et al.² Capone et al did not state how the patients were selected for early angiography and did not assess in detail the extent of coronary disease or coronary morphology.

Ambrose et al⁵ initially described the angiographic features of complex coronary lesions in unstable angina. The presence of coronary thrombus, complex morphology, or both occurred in 57% of our patients undergoing early angiography as opposed to the frequency of 72% reported by Ambrose et al. This discrepancy is likely explained by the fact that patients with stenoses of less than 50% were excluded from this study² but were included in our study. We found that the frequency of complex coronary morphology was not altered by the timing of coronary angiography or the presence of recurrent unstable angina. Based on these data, it seems reasonable to speculate that the presence of complex lesions is a precursor for the presence of identifiable intracoronary thrombi. Because patients with complex coronary morphology without intracoronary thrombi had cardiac events infrequently and multiple regression analysis revealed that complex coronary morphology was not independently predictive of cardiac events, it seems likely that the development of intracoronary thrombi modulates the cardiac events associated with unstable angina and also may account for recurrent symptoms or failure to stabilize with medical therapy.

Because the complications of unstable angina are related, at least in part, to coronary thrombus, they may be potentially preventable by appropriate therapy. Telford and Wilson¹⁰ suggested that intravenous heparin prevents infarction and death in unstable angina, but this study was associated with a high frequency of patient withdrawal. A larger study by Theroux et al¹¹ recently concluded that both aspirin and heparin reduce in-hospital cardiac events in unstable angina. Data from ISIS-2¹² also suggest that aspirin early in the course of acute ischemic syndromes may improve outcome. Long-term therapy with aspirin after unstable angina improves 3-month¹³ and 2-year¹⁴ outcome. It is interesting to note that previous administration of aspirin had no effect on the frequency of coronary thrombi at angiography in this population of unstable angina patients. Recent preliminary studies also suggest that tissue-type plasminogen activator (t-PA) may be useful in the treatment of unstable angina.⁵,¹⁶ Because these studies did not show a reduction in cardiac events, a prospective study is necessary to define the role of thrombolytic therapy in unstable angina, particularly because aortocoronary bypass surgery¹⁷,¹⁸ and standard medical therapy¹⁹,²⁰ do not appear to significantly alter the frequency of in-hospital cardiac events.

It is interesting in the light of our study to speculate on the mode of resolution of unstable angina. Multiple factors are likely operative and include spontaneous thrombolysis, healing and resorption of plaque hemorrhage and rupture, a decline in determinants of oxygen consumption

### Table 2. Relation of Coronary Anatomy and Hospital Events in Unstable Angina

<table>
<thead>
<tr>
<th></th>
<th>Myocardial infarction</th>
<th>Death</th>
<th>Urgent revascularization</th>
<th>Not urgent revascularization</th>
<th>No events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=32)</td>
<td>6 (19)*</td>
<td>4 (13)</td>
<td>13 (41)*</td>
<td>3 (9)</td>
<td>6 (19)*</td>
</tr>
<tr>
<td>No (n=46)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (17)</td>
<td>9 (20)</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Complex morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=29)</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>12 (41)*</td>
<td>5 (17)</td>
<td>8 (28)*</td>
</tr>
<tr>
<td>No (n=49)</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>9 (18)</td>
<td>7 (14)</td>
<td>27 (55)</td>
</tr>
<tr>
<td>Multiple-vessel disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=50)</td>
<td>6 (12)</td>
<td>4 (8)</td>
<td>19 (38)*</td>
<td>9 (18)</td>
<td>12 (24)*</td>
</tr>
<tr>
<td>No (n=28)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>3 (11)</td>
<td>23 (82)</td>
</tr>
</tbody>
</table>

* *p*<0.05 vs. no.

Numbers in parentheses are percentages.

### Table 3. Frequency of ST Shift on the Admission Electrocardiogram According to Coronary Morphology

<table>
<thead>
<tr>
<th>Coronary morphology</th>
<th>Frequency of ST shift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early catheterization (n=42)</td>
</tr>
<tr>
<td>No complexity</td>
<td>5/18 (28)</td>
</tr>
<tr>
<td>Complex morphology</td>
<td></td>
</tr>
<tr>
<td>without thrombus</td>
<td>3/6 (50)</td>
</tr>
<tr>
<td>Coronary thrombus</td>
<td>15/18 (83)*</td>
</tr>
</tbody>
</table>

* *p*<0.05, †*p*<0.002 vs. no complexity.

Numbers in parentheses are percentages.
with rest and medical therapy and the recruitment of coronary collaterals. Our data support the hypothesis proposed by Willerson et al\(^2\) that in many patients unstable angina is caused by intracoronary thrombi secondary to atherosclerotic plaque rupture. Wilson et al\(^2\) and Ambrose et al\(^3\) have suggested that the coronary lesion after thrombolytic therapy in acute myocardial infarction was similar to that described in unstable angina (i.e., high ulceration index\(^2\) or complex coronary morphology\(^3\)). It is likely that there is a continuum of acute coronary syndromes with myocardial infarction being precipitated by an occlusive thrombus on an ulcerated plaque, whereas in unstable angina, myocardial infarction is averted because of protective coronary collaterals, subocclusive thrombus, or spontaneous thrombolysis. Gottho et al\(^4\) have recently demonstrated the importance of alterations in oxygen demand as a cause of myocardial ischemia in unstable angina patients who have plaque rupture without apparent thrombus.

The ability of visual assessment of coronary angiograms to detect coronary thrombus is unknown. Levin and Fallon,\(^5\) using postmortem coronary angiography, suggested that stenoses with irregular borders or intraluminal lucencies were predictive of intracoronary thrombus or plaque rupture. Ambrose et al\(^6\) found an increased frequency of complex angiographic morphology in patients with unstable angina. These authors, however, did not assess the presence of angiographic coronary thrombus in their patient population and used angiographic data gathered up to 6 months after the episode of unstable angina. Our data suggest that complex morphology as defined by Ambrose et al\(^7\) is frequent in unstable angina, but we extend their findings by demonstrating that the in-hospital cardiac events in unstable angina are related to coronary thrombi and not to complex morphology alone. Sherman et al\(^8\) found in a small selected patient population that coronary angiography was inaccurate in identifying coronary thrombus because coronary thrombus formation was identified at coronary angioscopy during bypass surgery in all patients with unstable angina but much less commonly at angiography. Thus, the frequency of intracoronary thrombi in unstable angina is likely more than what we detected by angiography. We conclude from our study that intracoronary thrombi identified at coronary angiography are not only frequent in patients with unstable angina but that they also may mediate the cardiac events associated with this syndrome.

**Acknowledgments**

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**References**


**KEY WORDS** • unstable angina • complex coronary morphology • coronary thrombi • cardiac events
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