Coronary artery thrombosis in patients with unstable angina

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SUMMARY This report describes the clinical course, coronary artery anatomy, and ventricular function of 16 patients in whom coronary artery thrombosis was detected at the time of cardiac catheterisation. All patients had an unstable clinical course in which accelerated angina occurred a mean of four weeks (range four days to 12 weeks) before catheterisation, and four patients had recent subendocardial myocardial infarction. In all patients severe coronary artery disease was documented at catheterisation. Fifteen patients had segmental wall motion abnormalities involving the left ventricular wall that was supplied by the coronary artery in which there was thrombus. Three patterns of coronary artery thrombus were noted: (1) thrombus proximal to high-grade coronary artery stenosis; (2) thrombus distal to high-grade coronary artery stenosis; and (3) thrombus in segments of the arterial tree in which there was no high-grade coronary artery stenosis. Though the precise cause of the coronary artery thrombosis in our patients is unknown, it may have been a result of stasis, a ruptured atherosclerotic plaque, or coronary spasm. The common clinical course with unstable angina of acute onset suggests the possibility that the thrombus may have been responsible for the abrupt change in clinical condition or may have been a contributing factor in the patients' course.

The significance of coronary artery thrombosis in the pathophysiology of ischaemic heart disease remains controversial. Various authors have reported on the incidence of intracoronary thrombus in patients with transmural myocardial infarction,¹⁻¹¹ subendocardial myocardial infarction,^{5,10} and sudden coronary death,^{5,9,12-14} but the cause or effect relation remains uncertain. In the past, detection of coronary thrombus has been difficult and patients have been identified mainly at the time of necropsy. There is little information available concerning the clinical setting and significance of coronary thrombus detected during life. This report describes the clinical course of 16 patients who were deemed to have coronary thrombus which was detected at the time of cardiac catheterisation.

Subjects and methods

During a three year period 1976 to 1979, 16 of a total of 3553 patients undergoing cardiac catheterisation for suspected coronary artery disease were found to have a radiolucent central filling defect that was consistent with coronary artery thrombus. The angiographic recognition of intra-

coronary thrombus is subjective. Certain features however, exist which allow differentiation from atheromatous disease and strongly suggest the presence of intraluminal thrombus. These features include: (1) the presence of a smooth central filling defect surrounded by contrast material (Renografin) seen in multiple projections; and (2) the absence of calcification within the defect. Limited pathological confirmation (see Results) in these patients supports these criteria. The clinical course, location of thrombus, coronary anatomy, and left ventricular function in these 16 patients were analysed.

Catheterisation was performed with the use of the Sones or the Judkins technique. No patient had coronary thromboembolism related to the catheterisation as judged by (1) lack of other emboli; (2) absence of prolonged angina during the study; and (3) lack of electrocardiographic evidence of myocardial infarction occurring during the catheterisation.

Results

As can be seen from Table 1, there were 13 men and three women with a mean age of 61.3 years. The indication for cardiac catheterisation in all patients

Table 1 Clinical characteristics

Case no.	Sex	Age (y)	Associated cardiovascular disease	Previous angina or infarction	Onset of symptoms before catheterisation
1	F	61	None	None	3 wk
2	F	67	History of constrictive pericarditis	None	6 wk
3	M	59	None	Interior infarct 11 y before cath	4 d
4	M	63	None	None	6 wk
5	M	61	None	None	8 wk
6	M	63	Aortic stenosis	None	8 wk
7	M	65	None	None	2 wk
8	F	73	ASO	Interior infarct 4 y before cath	4 wk
9	M	56	None	Inferior infarct 10 y before cath	12 wk
10	M	50	None	None	2½ wk
11	M	65	None	None	2 wk
12	M	61	None	Stable angina for 5 mth	2 wk
13	M	58	None	Anteroseptal infarction 4 y before cath	1 wk
14	M	58	None	None	2½ wk
15	M	65	None	None	3 wk
16	M	57	None	ASHD S/P SVBPG to LAD 4 y before cath	3 wk

ASO, arteriosclerosis obliterans; ASHD, arteriosclerotic heart disease; SVBPG, saphenous vein bypass graft; LAD, left anterior descending coronary artery; S/P, status post.

was the onset of increasingly frequent and severe angina despite conventional medical treatment. Fifteen of the 16 patients had the onset of acute symptoms within two months of catheterisation and fulfilled the *Coronary Artery Surgery Study* definition of unstable angina.* The remaining patient had the onset of increasingly frequent and severe angina beginning three months before the catheterisation. Five patients had known ischaemic heart disease before the onset of acute symptoms, while in the remaining patients the angina was of new onset. Thirteen patients had angina at rest; none of these, however, had the clinical features of Prinzmetal's angina. Despite conventional medical treatment in hospital, 12 patients continued to have angina before catheterisation. Four patients had sustained recent subendocardial myocardial infarction, but no patient had uncontrolled congestive heart failure or rhythm disturbance.

Severe coronary artery disease, with more than 50 per cent reduction in lumen diameter of at least

*The definition of unstable angina is found in the *Manual of Operations of Coronary Artery Surgery Study*. "Unstable angina or a substantially new pattern of chest pain which began in the past two months. The last episode of chest pain should have occurred within the week prior to the initial study hospitalization and without the patient having had electrocardiographic changes or elevated cardiac enzymes reflecting a recent myocardial infarction."

one coronary artery, was present at the time of cardiac catheterisation in all 16 patients (Table 2). Six had triple-vessel disease, eight had involvement of two vessels, and two had single-vessel disease. Normal left ventricular wall motion was seen in one patient. The remaining 15 patients had segmental wall motion abnormalities involving the left ventricular wall that was supplied by the coronary artery in which there was thrombus. Fourteen of these 15 patients had additional segmental wall motion abnormalities in areas not supplied by the coronary artery involved with thrombus.

Thrombi (Table 2) were found in the right coronary artery in six patients (Fig. 1), in the left anterior descending coronary artery in five patients (Fig. 2), and in the circumflex system in five patients (Fig. 3 and 4). There was no evidence of distal embolisation in the distribution of the coronary artery involved. No thrombus resulted in complete occlusion of the coronary artery, but all resulted in 50 per cent or greater obstruction at the site. Three patterns of thrombus were noted: (1) thrombus proximal to high-grade coronary artery stenosis, four patients; (2) thrombus distal to high-grade stenosis, seven patients, and (3) thrombus occurring in a coronary artery segment in which there was no associated coronary artery stenosis of 50 per cent or more, five patients.

Pathological confirmation of the coronary artery thrombus was obtained in three patients. Of these, angiographically documented right coronary artery thrombi were removed at the time of operation in two patients (Fig. 5). Histological examination was

Fig. 1 Left anterior oblique view showing thrombus in right coronary artery proximal to occlusion.

Fig. 2 Left anterior oblique view showing thrombus in left anterior descending coronary artery distal to high-grade stenosis. There is also high-grade stenosis distal to thrombus.

consistent with a recent thrombus in both. The third patient died suddenly, presumably from an arrhythmic event, 24 hours after catheterisation. Angiography had documented a proximal right

Fig. 3 Left anterior oblique view showing thrombus in proximal circumflex system.

Table 2 Coronary artery anatomy

Case no.	Vessels involved with significant* coronary artery disease	Location of thrombus	Luminal narrowing by thrombus (%)	Relation of thrombus to coronary artery disease
1	RCA	Proximal LAD	90	No significant atherosclerotic narrowing near area of thrombus
2	RCA, circ	Proximal circ	90	Proximal to 60% stenosis
3	RCA, circ, LAD	Proximal circ	≥95	Distal to ≥95% stenosis
4	LAD, circ	Proximal LAD	80	Distal to ≥95% stenosis
5	RCA, LAD, circ	Proximal LAD	50	Distal to ≥95% stenosis
6	LAD, circ	Proximal RCA	≥95	No significant atherosclerotic narrowing near area of thrombus
7	RCA, LAD, circ	Proximal RCA	90	Proximal to occlusion of RCA
8	LAD, circ	Proximal and mid-RCA	≥95	No significant atherosclerotic narrowing near area of thrombus
9	LAD, circ, RCA	Proximal RCA	95	Distal to ≥95% stenosis
10	LAD, diag	Proximal RCA	≥95	No significant atherosclerotic narrowing near area of thrombus
11	RCA, circ, LAD	Proximal circ	90	Proximal to 70% stenosis
12	LAD, RCA, circ	Proximal obtuse marginal	80	Distal to ≥95% stenosis
13	RCA	Proximal LAD	≥95	No significant atherosclerotic narrowing near area of the thrombus
14	Circ, LAD	Middle LAD	70	Distal to ≥95% stenosis
15	LAD, RCA	Distal RCA	70	Distal to ≥95% stenosis
16	LAD, circ	Distal circ	≥95	Proximal to ≥95% stenosis

* ≥50% stenosis.
LAD, left anterior descending coronary artery; RCA, right coronary artery; circ, circumflex coronary artery.

coronary artery thrombus, which was confirmed at the time of necropsy.

Twelve patients underwent saphenous vein bypass graft surgery with a mean of 2.4 grafts per patient. In all patients a graft was placed distally in the vessel in which there was thrombus. One of the surgically treated patients underwent early postoperative (two weeks) catheterisation as part of a procedure to evaluate graft patency. At the time of the early postoperative study, the coronary artery thrombus was still present. Three patients were treated medically.

Discussion

Although evidence for the role of coronary artery thrombosis in the pathophysiology of arteriosclerotic heart disease has been gained from several sources including necropsy series and animal models, there is very little information on coronary artery thrombosis shown by angiography. Several reports¹⁵⁻¹⁶ have documented the clinical course of patients with coronary artery thrombosis as a result of thromboembolic complications related to cardiac catheterisation, but this situation probably has little relevance to spontaneously occurring coronary artery thrombosis.

The significance of coronary artery thrombosis appears to depend on the clinical setting. In fatal infarction, the incidence of coronary artery thrombosis varies. Some authors have found that the majority of patients dying with myocardial infarction have coronary artery thrombosis. The high

incidence of thrombosis, the intimal erosion at the site of thrombus, and the location of the thrombus in the coronary artery supplying the area of necrosis have been the basis for the argument that there is a cause-and-effect relation.¹⁻⁴ In addition, Fulton and Sumner,¹⁷ using radiofibrinogen, have shown central radionegative cores in occlusive thrombi in coronary arteries supplying areas of acute infarction, and this finding suggests that the thrombi were formed early and may have preceded the infarction. Other authors have disputed this causal relation and have maintained that the thrombus occurs as a result of the infarction.⁵⁻⁹ Support for this argument rests on the finding of a low incidence of coronary artery thrombosis not only in fatal subendocardial infarction but also in transmural infarction⁵⁻⁸ and the increase in frequency of thrombosis with increasing time between the onset of acute ischaemic symptoms and death.⁹ In patients with sudden cardiac death, the incidence of coronary artery thrombosis is considerably lower, occurring in less than one-third of the cases.⁵⁻¹²⁻¹⁴ In other subsets, for example patients with myocardial infarction and angiographically normal coronary arteries, thrombosis with subsequent lysis or recanalisation is postulated but remains unproven.¹⁸⁻¹⁹ We have found no published observations on the possible role of coronary artery thrombosis in unstable angina.

The cause of coronary artery thrombosis is con-

Fig. 4 Left anterior oblique view showing thrombus in the proximal circumflex.

Fig. 5 Left anterior oblique view showing thrombus in right coronary artery. Thrombus was removed at time of operation.

trovascular. The pathological association between thrombus and a ruptured atheromatous plaque has led to the postulate that rupture of the plaque may cause platelet adhesion, platelet aggregation, release of tissue thromboplastin, and subsequent thrombosis.^{20,21} It has been suggested that coronary artery spasm may either cause the rupture of the plaque^{20,22} or result in stasis that eventually leads to thrombus formation.²³ In our patients there are several possibilities. The location of thrombus distal to a high-grade stenosis may imply stasis as a cause. It is possible that in these patients the stenosis itself was part of a thrombotic process that had occurred at an earlier time, producing the change in symptoms, but that had become adherent, organised, and indistinguishable angiographically from atherosclerotic narrowing. In those patients in whom thrombus was seen in a segment of the arterial tree without severe coronary artery disease, a ruptured plaque or coronary spasm with subsequent stasis may have been the cause of the thrombus.

The frequency with which coronary artery thrombus occurs is unknown. During the period in which these patients were identified, 1202 patients underwent angiography for evaluation of an unstable clinical course defined as progressive escalation in the frequency and severity of angina pectoris in a three-month period before catheterisation despite conventional medical treatment. The 16 patients identified here represent 1.3 per cent of these 1202 patients. This incidence of 1.3 per cent may be artificially low because of the inherent insensitivity of angiography in detecting thrombus. Our criteria for the diagnosis of coronary thrombus include an intraluminal filling defect that is separate from the arterial wall. Thrombi that are adherent or moulded to the wall may not be distinguishable from an atherosclerotic plaque. Moreover, the incidence of coronary artery thrombosis in all patients with an unstable clinical course is uncertain because not all patients with this problem undergo angiography.

In the patients presented here, the treatment regimen was based on the clinical course, coronary artery anatomy, and ventricular function rather than on the basis of thrombus. All 13 patients who underwent surgery had grafts placed in the vessel involved with thrombus. The importance of anticoagulant or thrombolytic treatment in either the medically or the surgically treated groups remains to be determined.

The precise significance of coronary artery thrombosis in the cases described here is unknown. In four patients the thrombus was visualised between six and 12 weeks after the onset of the clinical syndrome. It could be argued that if the thrombus was responsible for the clinical syndrome

it might have undergone resolution or organisation and have become difficult to distinguish angiographically from an atherosclerotic plaque. The time required for this, however, is unknown. The common course with the abrupt and recent onset of increasingly frequent and severe angina leads us to believe that the thrombus may have been responsible for the abrupt change in clinical condition or may have been a contributing factor in the patients' course.

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Addendum

After this article was submitted, DeWood *et al.*¹ published their data on the high incidence (69.8%) of coronary thrombosis in patients undergoing angiography during the early hours of transmural myocardial infarction. Their data suggest that spasm or thrombosis with recanalisation or both may play a significant role in patients during the early course of a transmural myocardial infarction.

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