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Fibrin formation and platelet activation in patients with myocardial infarction and normal coronary arteries

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Coronary spasm is the mechanism most often postulated to explain the rare combination of myocardial infarction and angiographically normal coronary arteries, although the reported evidence for its role is circumstantial rather than conclusive. Whereas the importance of thrombosis in myocardial infarction is uncontested in the presence of significant coronary artery disease, there is little in vivo evidence for thrombosis in angiographically normal coronary arteries.

Among 11 consecutive patients with acute myocardial infarction undergoing thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) 3·2±0·7 h after onset of chest pain, and angiography 10·2±4·5 days later, three young men had normal coronary arteries. Their cases are documented electrocardiographically, enzymatically and angiographically. Mean plasma levels of fibrinopeptide A (FPA) and beta-thromboglobulin (BTG) were clearly elevated before and during rtPA therapy: FPA 52±41 ng ml^{-1}, BTG 257±46 ng ml^{-1}. They did not differ significantly from corresponding mean plasma levels in the eight patients with severe coronary artery disease: FPA 67±66 ng ml^{-1}, BTG 181±75 ng ml^{-1}.

We conclude that fibrin formation and platelet activation are probably equally important in the early hours of myocardial infarction, whether or not significant coronary artery disease is present.

Introduction

Myocardial infarction with angiographically normal coronary arteries is a rare event and an enigma that has received much attention in the literature[1–6]. The prevalence of normal or nearly normal coronary arteries is high, however, in certain subsets of patients with myocardial infarction, such as in young women using oral contraceptives and smoking[7–9], in young men during or following severe physical exercise[10,11] or in very young patients[2,12,13]. Suggested mechanisms for the 'unproven combination'[1] of myocardial infarction and normal coronary arteries include: coronary spasm[14–17], coronary emboli[2], thrombosis with spontaneous lysis[18,19], regression of coronary atheromatosis[20,21], trauma[22], small vessel disease[23] and angiographically unidentifiable coronary lesions[24]. Acute myocardial ischaemia without coronary atheromatosis can also originate from an extreme imbalance between oxygen demand and supply or an abnormal haemoglobin–oxygen dissociation[25].

Fibrinopeptide A (FPA), cleaved from fibrinogen by thrombin[26], is a very sensitive marker of thrombosis in vivo[27,28]. Elevated FPA plasma levels have been reported in patients with acute myocardial infarction[29–32], unstable angina[33] and venous thromboembolism[34]. Similarly, beta-thromboglobulin (BTG) plasma levels reflecting enhanced platelet activation[35] have been shown to be elevated in patients with acute myocardial infarction[36,37] and unstable angina[37,38].

We measured plasma levels of FPA, BTG and platelet factor 4 (PF4) in 11 consecutive patients with acute myocardial infarction who underwent intravenous thrombolytic therapy with rtPA and angiography. Three patients had normal coronary arteries. Their cases are documented here and the markers of fibrin formation and platelet activation compared with those measured in patients with

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myocardial infarction and significant coronary artery disease.

Methods

PATIENTS AND MANAGEMENT

Inclusion and exclusion criteria for thrombolytic therapy were according to the European Cooperative rtPA study[39] except for the time lapse from onset of pain (< 4 h) and anticoagulation that excluded our patients. 100 mg rtPA (predominantly single chain material) provided by Boehringer-Ingelheim, Switzerland, was infused intravenously over 3 h. All patients underwent biplane left ventriculography and selective coronary arteriography between 5 and 19 (mean $10 \pm 4{\cdot}5$) days after thrombolytic therapy.

COAGULATION AND PLATELET TESTS

Blood samples were taken by careful venepuncture before starting the rtPA infusion and 90 min later during rtPA therapy, but before initiating the heparin infusion. They were collected into precooled sample tubes, containing the following anticoagulants (for 9 ml of blood): 1 ml 0·102 M citrate, 1 ml cytosin theophyllin adenosin dipyramidol (CTAD) (Boehringer–Mannheim) supplemented with 200 μg D-phenyl-prolyl-arginine-chloromethylketone (PPACK) as thrombin inhibitor[40]. The blood samples were carefully mixed, immediately cooled on ice and centrifuged at 4 °C/2500 *g* for 30 min within 1 hour of sampling. The plasma was stored at −70 °C. A record was kept of each blood sample in order to identify eventual difficulties in sampling and processing.

FPA was determined in our laboratory using a previously published radioimmunoassay (RIA)[28] with the following modifications: cross-reacting fibrinogen was eliminated by bentonite absorption before using the fibrinogen-free supernatant for the RIA. Free antigen was separated from bound antigen by use of an immobilized second goat-anti-rabbit antibody (Immunobeads, Bio Rad laboratories). Previously measured levels of FPA in 15 normal individuals were $1{\cdot}9 \pm 0{\cdot}8$ ng ml^{-1} [32].

BTG and PF4 were determined by specific ELISA, both obtained from Boehringer–Mannheim, F.R.G. Normal values for BTG are 10–40 ng ml^{-1}. These values are comparable to BTG levels obtained by RIA[41]. PF4 plasma levels were measured in order to exclude in vitro platelet activation by venepuncture artefact (normal range: < 10 ng ml^{-1}, a BTG/PF4 ratio < 3 indicating in vitro platelet activation[42].

In addition, blood samples for plasma creatine kinase/MB levels were taken 8, 12, 16, 24 and 48 h after the onset of thrombolytic therapy.

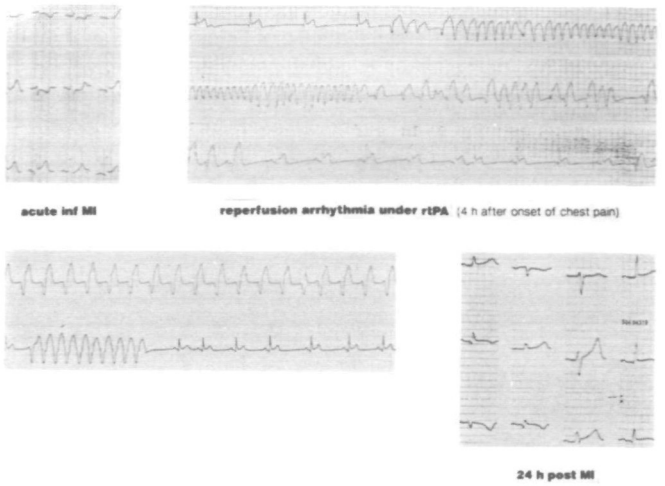
Results

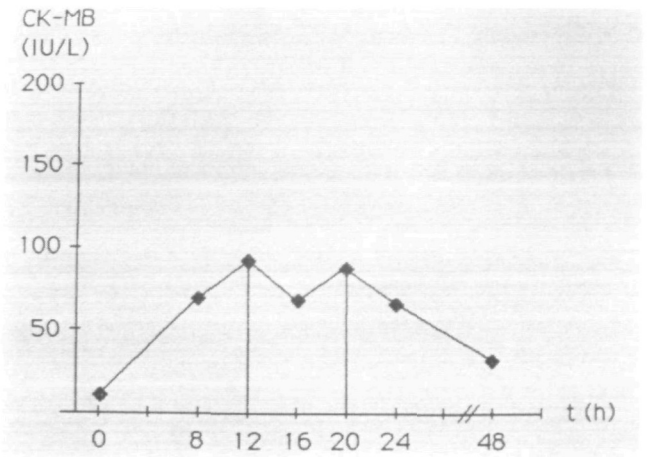
PATIENTS WITH NORMAL CORONARY ARTERIES (GROUP A)

The three cases (numbers 5, 9 and 10) with angiographically normal coronary arteries after myocardial infarction are documented separately in Figs 1–3. All blood samples for FPA and BTG measurements were taken without difficulty.

Case 5 (Fig. 1)

A young sportsman, 27 years of age and a regular smoker, had a 4-month history of transient precordial discomfort at rest, but a normal maximal treadmill test, suggesting the possibility of spastic angina. He was admitted with severe nitroglycerin-resistant chest pain that had begun during an ice-hockey match. The electrocardiogram showed an acute inferolateral myocardial infarction. Intravenous thrombolytic therapy with rtPA was initiated 3 h 15 min after the onset of chest pain. A bradycardiac nodal rhythm followed by self-limited ventricular tachycardia/flutter and a sudden relief of chest pain suggested reperfusion 1 h later. Another short episode of ventricular tachycardia 2 h after the end of thrombolytic therapy and a double peaked curve of creatine kinase/MB plasma levels suggested a reocclusion and secondary reperfusion. No further complication occurred. An inferior Q-wave infarction evolved subsequently. However, no regional wall motion abnormality indicative of transmural myocardial infarction was noted angiographically 5 days after the acute event. The coronary arteries were normal, except for systolic narrowing of the left anterior descending artery by myocardial bridging. This abnormality, however, could not be responsible for the acute ischaemic event in the inferior myocardial region, nor probably for the history of transient precordial discomfort at rest, since the diastolic diameter of the left anterior descending artery was also normal. FPA plasma levels were elevated (6·3 ng ml^{-1} and 39·4 ng ml^{-1}), indicating thrombosis before and 90 min after initiation of thrombolytic therapy. The corresponding high BTG plasma levels (172 and 256 ng ml^{-1}) and normal PF4 levels (10 and 29 ng ml^{-1}) documented markedly enhanced platelet activation in vitro without activation.





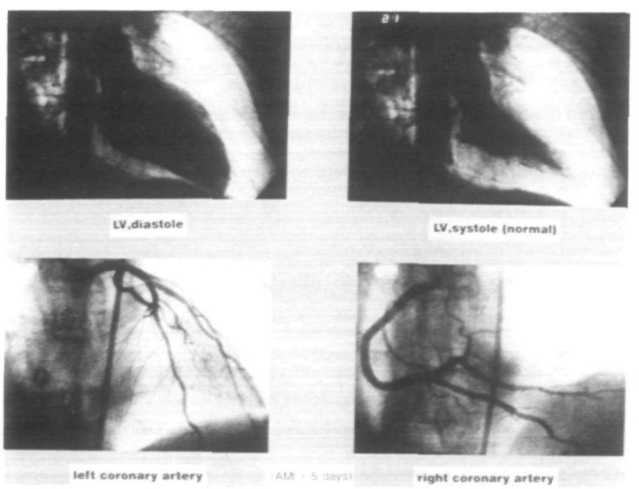
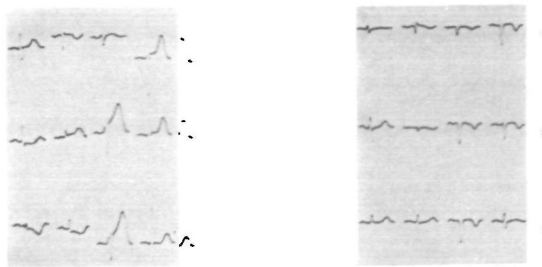
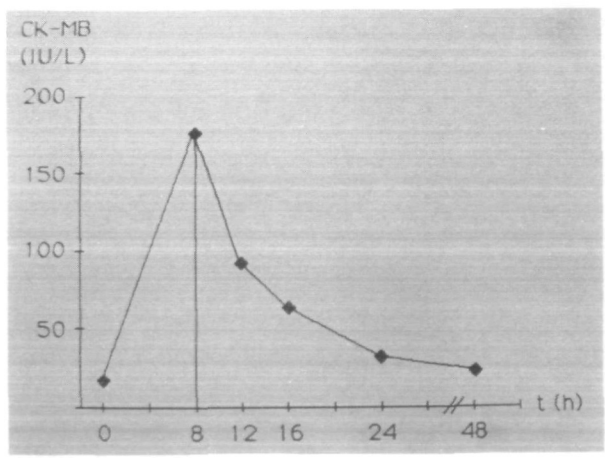


Figure 1 27-year-old man with acute inferior myocardial infarction undergoing thrombolytic therapy with rtPA 3·3 h after onset of chest pain. See text for details.



(rtPA within 3 h 30)



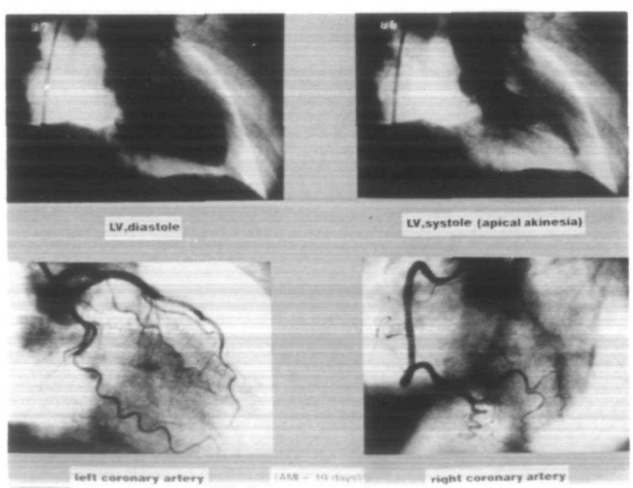
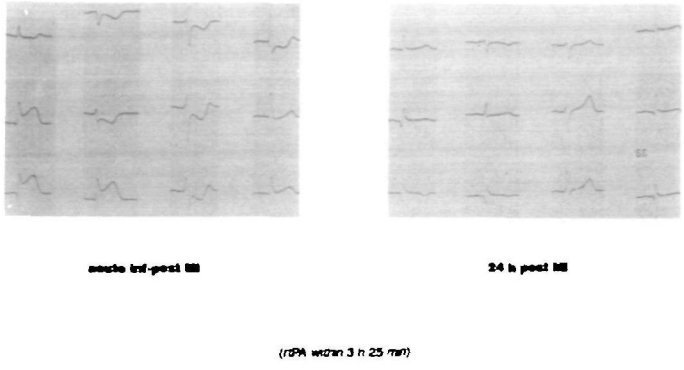


Figure 2 43-year-old man with acute anterior myocardial infarction undergoing intravenous thrombolytic therapy with rtPA 3·5 h after onset of chest pain. See text for details.



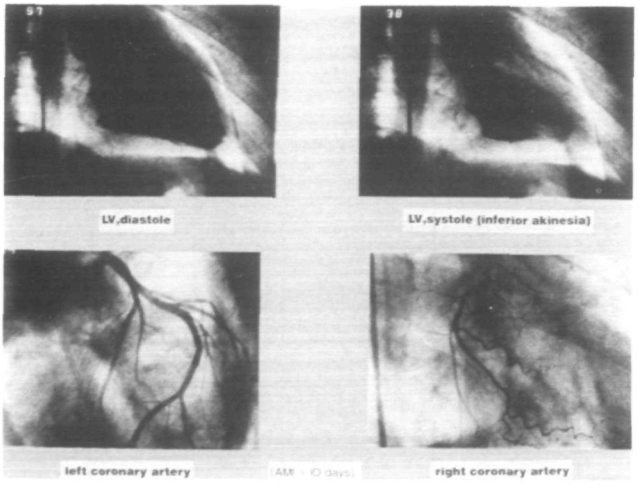


Figure 3 38-year-old man with acute infero-posterior myocardial infarction undergoing intravenous thrombolytic therapy with rtPA 3·4 h after onset of chest pain. See text for details.

Table 1 Pertinent data on 11 patients with acute myocardial infarction and angiographically normal (group A) or significantly diseased (group B) coronary arteries after thrombolysis

Case	Sex	Age (yr)	Time onset pain to TL (h)	ECG signs of MI	CK/MB-peak (hours from onset TL)	Days since TL	Angiography CAD	Patency IRA	Res. Sten. IRA	Wall motion in jeopard. region	FPA before TL (ng mg^{-1})	FPA during TL (ng mg^{-1})	BTG before TL (ng ml^{-1})	BTG during TL (ng ml^{-1})	PF4 before TL (ng ml^{-1})	PF4 during TL (ng ml^{-1})
group A (normal coronary arteries)																
5	m	27	3·3	inf-lat	1680/91 (12 h) 1652/87 (20 h)	5	0	+(RCA)	0%	normal LV	6·3	39·4	172	256	10	29
9	m	43	3·5	ant	2230/175 (8 h)	19	0	+(LAD)	0%	(a) ap	15·3	56·4	284	304	199	215
10	m	38	3·4	inf-post	2868/169 (6 h)	10	0	+(CX)	0%	a inf	73·4	119·2	253	275	111	153
Mean		36	3·4		2259/145	11·3						51·7		257		
±SD		8 2	0 1		594/47	7						41·4		46		
group B (significant coronary artery disease)																
1	m	50	4	inf-lat	3255/500 (8 h)	5	1VD	+(RCA)	55%	a inf-post	17·9	—*	159	—*	44	—*
2	m	35	2	inf-post	744/87 (8 h)	9	1VD	+(RCA)	90%	(h) inf	235·8	63·6	287	188	183	103
3	m	62	3·6	inf-post	2193/145 (12 h)	16	3VD	+(RCA)	90%	h inf	—*	—*	—*	—*	—*	—*
4	m	55	2·9	inf-post	771/83 (16 h)	8	2VD	+(RCA)	65%	normal LV	16·8	102·1	43	131	3	40
6	m	49	4	inf-post	1705/175 (12 h)	8	2VD	+(RCA)	90%	h-a inf	30·7	155·2	100	193	12	42
7	f	64	2·7	ant-lat	1371/183 (8 h)	11	1VD	+(LAD)	99%	d ap	68·9	70·0	198	263	67	139
8	m	40	3·7	ant-lat	5250/442 (8 h)	14	1VD	+(LAD)	80%	a-d ant-ap	51·4	41·0	167	102	43	10
11	m	49	2·2	ant	639/93 (8 h)	7	1VD	+(LAD)	99%	normal LV	1·6**	13·0	233	289	143	190
Mean		50·5	3·1		1991/213	9·8			83%			66·8		181		
±SD		9·9	0·8		1585/164	3·7			16%			65·7		75		

*data eliminated because of spurious elevation by blood sampling difficulty; **heparin pretreatment; a = akinesia, ant = anterior, ap = apical, BTG = beta-thromboglobulin, CAD = coronary artery disease, CK/MB = creatine kinase/MB-fraction, CX = circumflex artery, d = dyskinesia, ECG = electrocardiogram, FPA = fibrinopeptide A, h = hypokinesia, inf = inferior, IRA = infarct-related artery, LAD = left anterior descending artery, lat = lateral, MI = myocardial infarction, PF4 = platelet factor 4, post = posterior, RCA = right coronary artery, Res. Sten. = residual stenosis, TL = thrombolysis, 1,2,3-VD = 1,2,3-vessel disease.

Case 9 (Fig. 2)

A 43-year-old man, a heavy smoker without history of angina, was admitted with severe nitroglycerin-resistant chest pain and electrocardiographic signs of an acute anterior myocardial infarction. Intravenous thrombolytic therapy with rtPA was initiated 3 h 30 min after onset of pain. Ventricular extrasystoles in salvos 50 min later were interpreted as a reperfusion arrhythmia, since chest pain abruptly disappeared. No complication occurred. Peaking in creatine kinase/MB plasma levels was early. An anterior Q-wave infarction, with loss of R-potentials from V1 to V4, developed. Angiography, 19 days after the acute event, showed a localized but distinct apical akinesia, attributable to a long left anterior descending artery. Coronary arteries, however, were normal. FPA plasma levels were elevated (15·3 and 56·4 ng ml^{-1}) before and during thrombolytic therapy, as were BTG plasma levels (284 and 304 ng ml^{-1} respectively), indicating thrombosis and platelet activation. Since PF4 levels (199 and 215 ng ml^{-1}) were also elevated, however, additional platelet activation in vitro had to be presumed in this case.

Case 10 (Fig. 3)

A 38-year-old man with no history of angina was admitted with nitroglycerin-resistant chest pain that had begun during a soccer game. With typical electrocardiographic signs of acute inferoposterior myocardial infarction, intravenous thrombolytic therapy with rtPA was started 3 h 25 min after the onset of chest pain. The pain diminished gradually during therapy. No reperfusion arrhythmia was noted. Creatine-kinase MB plasma levels peaked very early. An inferior Q-wave infarction evolved within 24 h. No complication occurred. Angiography 10 days later confirmed an inferior akinesia corresponding to the posterior descending branch of a dominant circumflex artery. However, except for minor wall irregularities, the coronary arteries were normal. FPA (73·4 and 119·2 ng ml^{-1}) and BTG (172 and 256 ng ml^{-1}) plasma levels were markedly elevated, documenting fibrin formation and platelet activation in vivo with some platelet activation in vitro (PF4 levels 111 and 153 ng ml^{-1}).

PATIENTS WITH SIGNIFICANT CORONARY ARTERY DISEASE (GROUP B)

The pertinent data and results of patients with significant coronary artery disease after a first myocardial infarction are compared with those of patients with normal coronary arteries in Table 1. The mean age was higher (50·5 ± 10 vs 36 ± 8 years). All patients were admitted with typical clinical and electrocardiographic signs of acute myocardial infarction (five inferoposterior, three anterolateral). Intravenous thrombolytic therapy with rtPA was initiated between 2 and 4 h (mean 3·1 ± 0·8 h vs 3·4 ± 0·1 h in group A) after the onset of chest pain, which disappeared in all but one case, while arrhythmias suggesting reperfusion were noted in 4 out of 8 cases. Peaking of creatine kinase plasma levels occurred within 12 h in 7 out of 8 patients. Q-wave infarction developed in all patients. Angiography 9·7 ± 3·7 days after the acute event revealed a normal left ventricle in two cases treated very early, only small hypokinetic zones in two cases, and akinetic or dyskinetic regions corresponding with the electrocardiographic infarct site in four cases. The infarct-related artery was patent in all patients, with a mean residual stenosis of 84 ± 15%. FPA (mean 66·8 ± 65·7 ng ml^{-1}) and BTG (mean 181 ± 75 ng ml^{-1}) plasma levels were elevated before and during thrombolytic therapy in all patients but one (case 11) whose first FPA value was low because of spurious heparin. Three out of 16 FPA values were not taken into account because of sampling difficulties. In 5 out of 13 blood samples a BTG/PF4 ratio <3 indicated some platelet activation in vitro[42].

Discussion

PREVALENCE OF NORMAL ANGIOGRAPHY AFTER MYOCARDIAL INFARCTION

The prevalence of angiographically normal coronary arteries after myocardial infarction is 1–4% according to bigger series[13,43]. No significant coronary stenosis or zero vessel disease is found in 7–19% of postinfarction patients[4,13,20]. Very young patients[13], however, especially women taking oral contraceptives and smoking[7–9,19] and young men who sustain myocardial infarction during or immediately following severe physical exercise[10,11] have high prevalence (30–45%) of angiographically normal or insignificantly diseased coronary arteries.

CORONARY SPASM

Spasm is the mechanism most often postulated to explain the combination of myocardial infarction and angiographically normal coronary arteries[14–17,43], although the reported evidence for its

role is circumstantial rather than causal. Among 679 young survivors of myocardial infarction undergoing angiography, Gohlke *et al.*[13] found 25 patients with normal coronary arteries, 32 with non-significant (< 50%) lesions and 112 with unifocal disease; none of these patients had a history of repeated angina at rest of the Prinzmetal type prior to myocardial infarction. Oliva *et al.* demonstrated coronary spasm angiographically in six patients early after acute myocardial infarction[14], but the spasm consistently occurred at the site of a severe coronary lesion, whereas no spasm was demonstrated in two cases of myocardial infarction and normal coronary arteries[3]. Vasospasm has been incriminated in myocardial infarction during or immediately following vigorous excercise[10].

The success of early thrombolytic therapy has established the great importance of thrombosis compared with spasm in myocardial infarction. Rentrop *et al.* demonstrated the negligible effect of intracoronary nitroglycerin very early after the onset of chest pain[44]. Vasoconstriction, however, might play a role in reocclusion during thrombolytic therapy[45].

Markers of platelet activation do not specifically indicate vasospasm, since aggregating platelets may exert their effect by mechanical obstruction, enhancement of thrombosis or thromboxane A2-mediated vasoconstriction. Our measured BTG levels document platelet activation in patients with acute MI whether significant coronary artery disease is present or not. Compared with plasma levels measured between 6 and 32 h after the onset of infarction (64 ± 21 ng ml^{-1} [32]), the levels of BTG measured between 2 and 4 h after onset of chest pain were substantially higher. This might reflect a higher platelet activity in the early hours of myocardial infarction. Patients with normal coronary arteries had higher BTG levels than patients with significant coronary disease (257 ± 45 vs 181 ± 75 ng ml^{-1}). Whether this corresponds to more spastic activity in agreement with Ogasawara *et al.*[46] remains speculative in view of the small group size in our study.

CORONARY THROMBOSIS

The causal role of thrombosis in acute myocardial infarction and unstable angina with underlying significant coronary artery disease is hardly contested today. In vivo evidence is based on angiography[47,48], angioscopy[49], elevated plasma levels of fibrinopeptide A[29–33] and cross-linked fibrin degradation products[50,51], and the success of early thrombolytic therapy.

To our knowledge, evidence of a direct connection between angiographically normal coronary arteries and in vivo markers of thrombosis has not been provided so far. Elevated plasma levels of fibrinopeptide A measured as early as $3{\cdot}2 \pm 0{\cdot}7$ h after the onset of chest pain in patients with enzymatically and electrocardiographically evolving myocardial infarction suggest a causal role of thrombosis. Since FPA levels in patients with normal coronary arteries after thrombolytic therapy are not different from levels in patients with significant residual coronary disease, it might be assumed that thrombosis was the mechanism of coronary occlusion in both groups. The success of thrombolytic therapy and the failure of previously given nitroglycerin in all patients support this assumption.

On the other hand, one cannot exclude the possibility that myocardial ischaemia or necrosis per se, by mechanisms so far not elucidated, such as endothelial damage in the ischaemic territory, may be responsible for the activation of both coagulation and platelets[38]. A small intracoronary thrombus may not be the sole explanation for the high FPA plasma levels measured. Ischaemia would then be not only the consequence but also a possible cause of further fibrin formation. Elevated FPA levels in unstable angina[33,38] in contrast to stable angina[37,38] may either favour the hypothesis that intracoronary thrombosis also plays a major role in transient ischaemic episodes at rest, commonly interpreted as coronary spasm, or indicate that severe ischaemia per se activates coagulation and platelets.

Plasma levels of FPA measured between 2 and 4 h after the onset of chest pain were significantly higher than our previously published levels[30,32], which were measured between 6 and 32 h after the onset of infarction in non-heparinized patients. This might reflect a time-dependent decrease of thrombotic activity in acute myocardial infarction.

Absence of angiographically detectable coronary lesions does not imply a 'normal' coronary artery. Early endothelial cell damage without visible obstruction might have important sequelae, which have been called 'rapid progression of coronary artery disease'[6]. Platelet deposition on such an endothelial lesion, leading to intense coronary spasm of sufficient duration to provoke stasis and

finally, thrombosis, is a sequence of events postulated to explain myocardial infarction with angiographically normal coronary arteries[6,52,53]. A reduced activity and enhanced inhibition of endogenous tissue plasminogen activator in patients with myocardial infarction without visible coronary artery disease[54] might, however, lead to thrombosis without preceding spasm.

Finally, FPA is not a specific marker of coronary thrombosis, but could also reflect left ventricular, venous or extravascular fibrin generation. However, none of our three young patients with normal coronary arteries had a left ventricular aneurysm, atrial enlargement or fibrillation, signs of venous stasis or a central catheter. The venepuncture was done with extreme caution and blood samples obtained without difficulty. Extracoronary fibrin formation therefore seems improbable.

Conclusion

Myocardial infarction occurs in spite of angiographically normal coronary arteries. Fibrin formation and platelet activation are of crucial importance whether a significantly diseased or an apparently normal coronary artery occludes, as shown by equally elevated plasma levels of fibrinopeptide A very early after the onset of chest pain, the ineffectiveness of nitroglycerin and the efficacy of thrombolytic therapy.

While coronary spasm alone has not been shown conclusively to be responsible for myocardial infarction, an adjunctive role cannot be excluded. High beta-thromboglobulin plasma levels indicate a marked enhancement of platelet activity in the early hours of myocardial infarction, whether significant coronary disease is present or not.

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References

[1] Arnett EN, Roberts WC. Myocardial infarction and angiographically normal coronary arteries, an unproven combination (editorial). Circulation 1976; 53: 395–400.

[2] Rosenblatt A, Selzer A. The nature and clinical features of myocardial infarction with normal coronary angiogram. Circulation 1977; 55: 578–80.

[3] Oliva PB, Breckenridge K. Acute myocardial infarction with normal or near normal coronary arteries. Am J Cardiol 1977; 40: 1000–7.

[4] Sheldon WC, Razavi M, Lim YJ. Coronary arteriographic findings in younger survivors of acute myocardial infarction including those with normal coronary arteries. In: Roskamm H, ed. Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 47–55.

[5] Lindsay J Jr, Pichard AD. Acute myocardial infarction with normal coronary arteries (editorial). Am J Cardiol 1984; 54: 902–4.

[6] Gersh BJ, Chesebro JH, Bove AA. Myocardial infarction with angiographically 'normal' coronary arteries: is this rapid progression of early coronary artery disease? (editorial). Chest 1983; 84: 654–6.

[7] Mann JI, Inman WH. Oral contraceptives and death from myocardial infarction. Br Med J 1975; II: 245–8.

[8] Shapiro S. Oral contraceptives and myocardial infarction (editorial). N Eng J Med 1975; 293: 195–6.

[9] Jick H, Dinan B, Rothman KJ. Oral contraceptives and nonfatal myocardial infarction. JAMA 1978; 239: 1403–7.

[10] Delaye J, Beaune J, Delchaye JP. Myocardial infarction at young age during high physical exercise. In: Roskamm H, ed. Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 115–21.

[11] Pic A, Broustet JP, Saliou B, Gosse P, Guern P. Coexistence of vigorous exercise and heavy smoking in triggering acute myocardial infarction in men under 35 years — fact or fiction? In: Roskamm H, ed. Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 108–14.

[12] Thompson SI, Vieweg, WV, Alpret JS, Hagan AD. Incidence and age distribution of patients with myocardial infarction and normal coronary arteriograms. Cath Cardiovasc Diag 1977; 3: 1–9.

[13] Gohlke H, Stürzenhofecker P, Thilo A, Droste C, Görnandt L, Roskamm H. Coronary angiographic findings and risk factors in postinfarction patients under the age of 40. In Roskamm H, ed. Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 61–77.

[14] Oliva PB, Breckenridge JC. Arteriographic evidence of coronary arterial spasm in acute myocardial infarction. Circulation 1977; 56: 366–74.

[15] Johnson AD, Detwiler JH. Coronary spasm, variant angina and recurrent myocardial infarctions. Circulation 1977; 55: 947–50.

[16] Maseri A, L'Abbate A, Baroldi G *et al.* Coronary vasospasm as a possible cause of myocardial infarction. N Engl J Med 1978; 299: 1271–7.

[17] L'Abbate A, Biagini A, Mazzei MG *et al.* Major role of coronary spasm in the pathogenesis of myocardial infarction at young age. In: Roskamm H, ed. Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 129–36.

[18] Henderson RR, Hansing CE, Razavi M, Rowe GG. Resolution of an obstructive coronary lesion as demonstrated by selective angiography in a patient with transmural myocardial infarction. J Cardiol 1973; 31: 785–8.

[19] Engel HJ, Engel E, Lichtlen PR. Acute myocardial infarction in young women: evidence for spontaneous lysis of a coronary thrombus. In: Roskamm H, ed.

Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 122–8.

[20] Roskamm H. Stürzenhofecker P, Görnandt *et al.* Progression and regression of coronary artery disease in postinfarction patient less than 40 years of age. Cleve Clin Q 1980; 47: 192–4.

[21] Roberts WC, Virmani R. Formation of new coronary arteries within a previously obstructed epicardial coronary artery (intraarterial arteries): a mechanism for occurrence of angiographically normal coronary arteries after healing of acute myocardial infarction. Am J Cardiol 1984; 54: 1361–2.

[22] Harthorn JW, Kantrowitz PA, Dinsmore RE, Sanders CA. Traumatic myocardial infarction. Report of a case with normal coronary angiogram. Ann Int Med 1967; 66: 341–4.

[23] Mason JW, Strefling A. Small vessel disease of the heart resulting in myocardial necrosis and death despite angiographically normal coronary arteries. Am J Cardiol 1979; 44: 171–6.

[24] Arnett EN, Isher JN, Redwood DR *et al.* Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. Ann Intern Med 1979; 91: 350–6.

[25] Eliot RS, Bratt G. The paradox of myocardial ischemia in young women with normal coronary arteriograms. Relation to abnormal haemoglobin–oxygen dissociation. Am J Cardiol 1969; 23: 633–7.

[26] Bettelheim FR. The clotting of fibrinogen. II. Fractionation of peptide material liberated. Biochim Biophys Acta 1956; 19: 121–9.

[27] Nossel HL, Yudelman I, Canfield RE *et al.* Measurement of fibrinopeptide A in human blood. J Clin Invest 1974; 54: 43–53.

[28] Hoffmann V, Straub PW. A radioimmunoassay for rapid measurement of human fibrinopeptide A. Thromb Res 1977; 11: 171–81.

[29] Johnsson H, Orinius E, Paul C. Fibrinopeptide A in patients with acute myocardial infarction. Thromb Res 1979; 16: 255–60.

[30] Mombelli G, Imhof V, Häberli A, Straub PW. Effect of heparin on plasma fibrinopeptide A in patients with acute myocardial infarction. Circulation 1984; 69: 684–9.

[31] Eisenberg PR, Sherman LA, Schectmann K, Peres J, Sobel BE, Jaffe AS. Fibrinopeptide A: a marker of acute coronary thrombosis. Circulation 1985; 71: 912–8.

[32] Gallino A, Häberli A, Hess T, Mombelli G, Straub PW. Fibrin formation and platelet aggregation in patients with acute myocardial infarction: effects of intravenous and subcutaneous low-dose heparin. Am Heart J 1986; 112: 285–90.

[33] Théroux P, Latour JG, Légier-Gauthier C, DeLara J. Fibrinopeptide A and platelet factor levels in unstable angina pectoris. Circulation 1987; 75: 156-62.

[34] Von Hulsteijn, Briet E, Koch C. Diagnostic value of fibrinopeptide A and beta-thromboglobulin in acute deep venous thrombosis and pulmonary embolism. Acta Med Scand 1982; 211: 323.

[35] Bolton AE, Ludlam CA, Moore S, Pepper DS, Cash JD. Three approaches to radioimmunoassay of beta-thromboglobulin. Br J Hematol 1976; 33: 323–8.

[36] Rasi V, Ikkala E, Torstila I. Plasma betathromboglobulin in acute myocardial infarction. Thromb Res 1982; 25: 203–12.

[37] Van Hulsteijn H, Kolff J, Briet E, van der Laarse A, Bertino R. Fibrinopeptide A and beta-thromboglobulin in patients with angina pectoris and acute myocardial infarction. Am Heart J 1984; 107: 39–45.

[38] Gallino A, Häberli A, Baur HR, Straub PW. Fibrin formation and platelet aggregation in patients with severe coronary artery disease: relationship with the degree of myocardial ischemia. Circulation 1985; 72: 27–30.

[39] Verstraete and the group of the European Cooperative study for rtPA. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Lancet i: 842–7, 1985.

[40] Kettner C, Shaw E. D-Phe-Pro-ArgCH2CL. A selective affinity label for thrombin. Thromb Res 1979; 14: 969–73.

[41] Bolton AE, Ludlam CA, Pepper DS, Moore S, Cash JD. Three approaches to the radioimmunoassay of beta-thromboglobulin. Br J Hematol 1976; 33: 223–8.

[42] Kaplan KL, Owen J. Plasma levels of betathromboglobulin and platelet factor 4 as indices of platelet activation in vivo. Blood 1981; 57: 199–204.

[43] Balcon R, Blümchen G, Catell M, Scharf-Bornhofen E. Myocardial infarction and normal coronary arteries: possible role of spasm. In: Roskamm H. ed. Myocardial infarction at young age. Berlin Heidelberg New York: Springer, 1981: 137–43.

[44] Rentrop P, Feit F and Reperfusion Study Group. The second Mount Sinai reperfusion trial: main endpoints. J Am Coll Cardiol 1987; 9/2: 239A (abstr.).

[45] Hackett D, Davies G, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction. Value of combined thrombolytic and vasodilator therapy. N Engl J Med 1987; 317: 1055–9.

[46] Ogasawara K, Aizawa T, Nishimura K *et al.* Beta-thromboglobulin release within coronary circulation — a potential role of platelets in ergonovine induced coronary vasospasm. Int J Cardiol 1986; 10: 15–22.

[47] Brown BG, Gallery CA, Rodney SB *et al.* Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. Circulation 1986; 73: 653–61.

[48] Ambrose JA, Winters SL, Stern A *et al.* Angiographic morphology and the pathogenesis of unstable angina pectoris. J Am Coll Cardiol 1985; 5: 609–16.

[49] Sherman CT, Litvack F, Grundfest W *et al.* Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med 1986; 315: 913–9.

[50] Francis CW, Connaghan DG, Scot WL, Marder VJ. Increased plasma concentration of crosslinked fibrin polymers in acute myocardial infarction. Circulation 1987; 75: 1170–7.

[51] Kurskal JB, Commerford PJ, Franks JJ, Kirsch RE. Fibrin and fibrinogen-related antigens in patients with stable and unstable coronary artery disease. N Engl J Med 1987; 317: 1361–5.

[52] Gertz SP, Uretsky G, Wajnberg AS, Novat N, Gotsman MS. Endothelial cell damage and thrombus formation after partial arterial constriction: relevance to the role of coronary artery spasm in the pathogenesis of myocardial infarction. Circulation 1981; 63: 476–86.

[53] Vincent GM, Anderson JL, Marshall HW. Coronary spasm producing coronary thrombosis associated with myocardial infarction. N Engl J Med 1983, 309: 220–3.

[54] Verheugt FW, Tencate JW, Sturk A *et al.* Tissue plasminogen activator activity and inhibition in acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol 1987; 59: 1075–9.