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Angiographic progression in patients with angina pectoris and normal or near normal coronary angiograms who are restudied due to unstable symptoms

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Background Syndrome X patients commonly remain symptomatic during follow-up and may be readmitted with unstable anginal symptoms. Angiographic disease progression must be considered as a possible mechanism for instability, particularly where multiple coronary risk factors are present and an interval of several years has elapsed since previous angiography.

Methods and Results We reviewed data from 139 consecutive patients with chest pain and normal or near normal coronary angiograms (101 patients with completely normal angiograms and 38 patients with minimal lumenal irregularities). During a 5-year period, 24 patients (19 women, median age 56 years) underwent repeat angiography due to primary unstable angina (median interval between angiograms 58 months (range 8–130 months)). This group included three patients with minimal lumenal irregularities and four patients with left bundle branch block. Only two patients had progression to significant angiographic stenosis (>30% diameter reduction); both were male patients with minimal irregularities at baseline angiography, left bundle branch block and multiple coronary risk factors. However, overall only two of 18 (11%) patients with one or more conventional coronary risk factors had angiographic progression.

Conclusions Unstable symptoms in patients with chest pain and previously normal or near normal coronary arteriograms are rarely due to angiographic disease progression. However, the presence of minimal lumenal irregularities at baseline angiography and LBBB may identify a sub-group at increased risk.
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Key Words: Angiographic progression, chest pain with normal coronaries, unstable angina.

Introduction

Patients with chest pain and normal coronary angiograms have a favourable long-term prognosis with an incidence of myocardial infarction and cardiovascular death similar to the general population[1–6]. However, despite the reassurance of normal angiography, such patients often remain symptomatic during follow-up and may be subject to hospital readmission with symptoms and electrocardiographic changes suggestive of unstable angina. Equally, patients with no significant angiographic stenoses may account for up to 19% of unstable angina patients in large studies[7]. Thus, prospective identification of unstable angina patients without significant angiographic disease, particularly where previous angiography has been normal, represents an important challenge in current cardiological practice. In this study, we investigated angiographic disease progression in a consecutive cohort of patients with previously normal or near normal angiograms who developed unstable anginal symptoms during follow-up.

Patients and methods

Patient selection

The study population included 139 consecutive patients with typical exertional chest pain and normal or near normal coronary arteriograms (no stenoses >20% diameter reduction) who were referred to our clinic in a five

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year period between January 1991 and January 1996. All patients had undergone systematic clinical characterization including a treadmill stress electrocardiogram, two-dimensional echocardiography and coronary spasm provocation testing (hyperventilation and/or ergonovine challenge). Patients with left ventricular hypertrophy, cardiomyopathy, valvular heart disease or documented coronary artery spasm were excluded. In addition, patients with known extracardiac causes for chest pain (e.g. painful upper gastrointestinal or musculoskeletal disorders) were also excluded. The patients were divided into two groups according to the results of their baseline angiogram: Group 1 (n=101) with completely normal coronary angiograms; and Group 2 (n=38) patients with minimal lumenal irregularities (<20% diameter reduction).

During the study period, 24 patients (17%) developed unstable angina leading to hospital readmission and subsequently underwent repeat angiography to exclude significant angiographic progression. All had symptoms satisfying Braunwald's criteria for class B (primary) unstable angina[8]. Twenty-one patients (87%) had Braunwald class III symptoms (one or more episodes of angina at rest within the preceding 48 hours) and the remaining 3 patients (13%) had Braunwald class I symptoms (patients with accelerated angina without rest pain). No patients suffered death or acute myocardial infarction during the follow up period. Two patients had a history of previous non-Q wave myocardial infarction but both had completely normal baseline angiograms.

Risk factor scoring

The presence of coronary risk factors was scored on a scale of 0 to 5. Specifically, one point was scored according to the presence of each of the following risk factors: hypercholesterolemia, hypertension, cigarette smoking, diabetes or a family history of premature coronary artery disease. Serum cholesterol levels were measured during initial characterization of patients in the out patient clinic and repeated during admissions for unstable angina. Patients with levels of greater than $5{\cdot}4\ \mathrm{mmol}\,.\,\mathrm{l}^{-1}$ on either occasion were considered to have hypercholesterolemia. Hypertension was defined by any history of hypertension resulting in the initiation of antihypertensive therapy. Patients were classified as non-smokers only if they had never smoked or had given up cigarettes more than 5 years prior to referral. A positive family history was defined as a documented history of coronary disease in a first degree relative occurring before 60 years of age.

Angiographic analysis

All angiograms were reviewed independently by two experienced investigators blinded to the identity of the patients. Progression to significant angiographic stenosis was considered to be present if a significant lumenal stenosis (>30% diameter reduction) was present in any angiographic projection. Angiographic data were acquired on a digital system (Philips Integris HM3000) incorporating a validated software package for quantitative angiography.

Results

The 24 patients who underwent repeat angiography due to unstable angina consisted of 19 women and 5 men; median age 56 years old (range 42 to 74 years). The median interval between the baseline and repeat angiography was 58 months (range 8–130 months). All 24 restudied patients had a history of typical exertional angina and all had experienced chest pain during treadmill exercise testing. Left bundle branch block was present on the resting ECG of four patients. A positive electrocardiographic response to exercise (horizontal or down-sloping ST segment depression >1 mm at 60 ms after the J point) was documented in all 20 patients without left bundle branch block. Ten (50%) patients without left bundle branch block also had transient electrocardiographic changes on Holter monitoring indicating ischaemia during unstable chest pain. 16 patients (67%) were receiving multiple drug therapy prior to the episode of instability with six patients receiving triple therapy (nitrates, beta-blockers and calcium antagonists) and 10 receiving double therapy with nitrate and a beta-blocker or calcium antagonist. At least one coronary risk factor was present in 18 patients (75%) and 16 patients (67%) had more than one risk factor (Table 1).

The unstable group included 21 patients from Group 1 (21%) and three patients from Group 2 (8%) (Fig. 1). At repeat angiography, three patients from Group 1 (14%) had developed minimal lumenal irregularities (<20% lumen diameter reduction) but none had developed significant angiographic stenoses. The remaining 18 Group 1 patients (86%) had completely normal repeat angiograms. In contrast, two patients from Group 2 (67%) showed evidence of angiographic disease progression with new lesions of >30% lumen diameter reduction. In one case (patient 16), a 69% left circumflex artery stenosis developed in a patient who had previously had minor irregularities in the left anterior descending artery and its first diagonal branch (Fig. 2). In the other case (patient 17), an 83% mid left anterior descending artery stenosis developed in a patient who had previously had minor irregularities in the same vessel and the right coronary artery. The new angiographic stenoses were eccentric with irregular lumenal borders in both cases. Both patients with significant angiographic disease progression were males with left bundle branch block on the baseline ECG and more than one risk factor for coronary artery disease (Table 1). However, overall only two of 18 (11%)

Table 1 Clinical and angiographic characteristics of 24 patients with chest pain and normal coronary angiograms restudied due to unstable symptoms

Patient number	Age (years)/ gender*	Result of 1st angiogram (A1)†	Results of 2nd angiogram (A2)†	A1–A2 interval (years)	Risk factor score	Plasma cholesterol ($mmol \cdot l^{-1}$)	Other risk factors‡	Reversible ST segment changes during pain	Tl-201 perfusion abnormalities¶
1	50/F	N	N	10·2	0	5·3	–	+	–
2	63/F	N	N	4·0	2	7·9	H	§	o
3	64/F	N	N	2·5	2	5·6	H	+	+
4	52/F	N	N	3·2	2	6·0	H	o	+
5	61/M	N	IR	9·2	0	5·0	–	+	–
6	51/F	IR	IR	7·2	4	6·3	H, FH, C	+	+
7	59/F	N	N	7·3	3	7·2	H, C	o	+
8	73/M	N	IR	5·1	3	5·8	H, C	§	+
9	60/F	N	N	3·1	2	7·4	H	+	+
10	44/F	N	N	1·3	2	5·5	H	+	+
11	50/F	N	N	5·6	3	6·9	H, FH	+	+
12	49/F	N	IR	0·6	2	7·7	FH	o	–
13	73/F	N	N	9·0	0	5·1	–	o	+
14	53/F	N	N	5·9	0	4·9	–	+	o
15	52/F	N	N	6·9	3	6·6	H, D	o	–
16	56/M	IR	S#	3·1	2	7·0	FH	§	+
17	49/M	IR	S**	5·4	3	7·2	H, C	§	+
18	55/F	N	N	4·6	2	4·9	H, C	+	–
19	62/M	N	N	1·7	1	5·3	FH	o	+
20	43/F	N	N	2·0	2	7·1	H	o	–
21	60/F	N	N	10·9	0	4·7	–	o	–
22	60/F	N	N	3·8	1	7·0	FH	+	+
23	78/F	N	N	1·4	2	6·7	H	o	–
24	61/F	N	N	5·8	0	5·0	–	o	o

*Age at time of second angiogram/F = female; M = male.
†N = completely normal angiogram; IR = minor irregularities (<20% lumen diameter reduction); S = stenosis (>30% lumen diameter reduction).
‡H = hypertension; FH = positive family history of premature coronary disease; C = history of cigarette smoking; D = diabetes.
§Presence of left bundle branch block on electrocardiogram excluding ST segment analysis.
¶+ = perfusion abnormality; o = no perfusion abnormality; – = perfusion study not performed.
#69% proximal left circumflex artery stenosis. **83% mid left anterior descending artery stenosis.

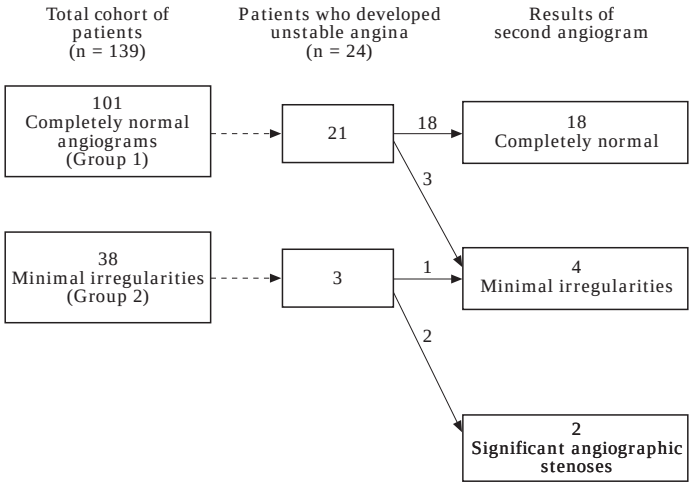


Figure 1 **Diagram summarizing the classification of patients according to the presence of minimal angiographic irregularities (<20% diameter stenosis) at baseline and subsequent incidence of progression to significant angiographic stenosis (>30% diameter stenosis) at repeat angiography during instability.**

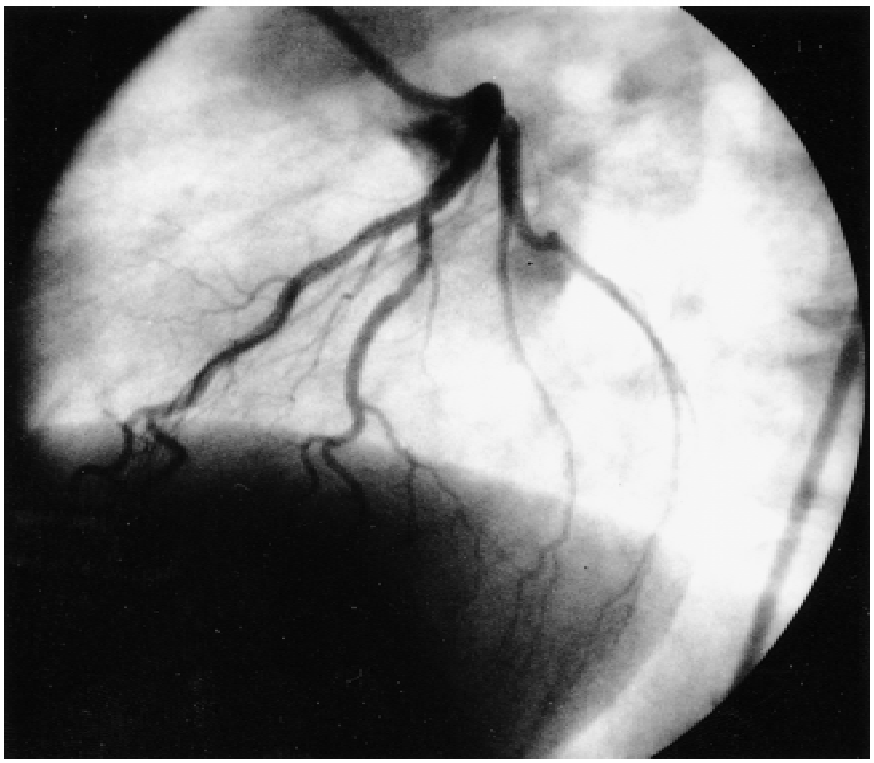
patients with one or more conventional coronary risk factors had angiographic progression. Significant angiographic progression was not present in any of six patients with no coronary risk factors. Two of four unstable patients with left bundle branch block (patients 8 and 17) also had evidence of global deterioration in left ventricular function at repeat cardiac catheterisation, although this was associated with the evolution of significant epicardial stenosis in only one patient (patient 17).

Exercise electrocardiography was repeated in six patients following the unstable episode of which only one patient showed a substantially increased ECG changes. Coronary spasm provocation testing (hyperventilation and/or ergonovine testing) was repeated in seven patients after symptom stabilisation but was negative in all cases. None of the patients exhibited ST segment elevation suggestive of typical Prinzmetal's vasospastic angina during the acute admission and ambulatory electrocardiographic monitoring performed in seven patients after stabilisation did not reveal ST segment elevation in any case. Reversible defects consistent with ischaemia were present in all nine patients who had undergone Thallium-201 dipyridamole myocardial perfusion imaging prior to the episode of instability. Thallium scanning was not repeated after the unstable episode in these patients as it was felt to be unlikely to affect management after a normal repeat angiography. However, seven patients who had not undergone previous testing underwent thallium scanning following the unstable episode and four of these patients had reversible perfusion abnormalities. Dobutamine stress echocardiography was performed in both patients with significant angiographic progression. In one case (patient 17), the stress echocardiogram was performed within one month of repeat angiography and clearly showed stress induced left ventricular systolic dysfunction. Interestingly, this was not clearly regional and was interpreted as being related to a combined effect of the left anterior descending epicardial stenosis and microvascular dysfunction. In the other case (patient 16), stress echocardiogram was negative but was not performed until after the new circumflex lesion had been dilated by balloon angioplasty.

Discussion

The results of this study confirm and expand those of previous studies[4,5] which have shown that, despite the prognostic reassurance provided by normal or near coronary angiography, syndrome X patients frequently remain symptomatic with episodes of unstable chest pain. Such unstable episodes commonly possess all the clinical features which are characteristic of unstable angina in patients with angiographic coronary disease and consequently, acute admission to coronary care often results[5,6]. All the patients in this study satisfied Braunwald's criteria for primary unstable angina[8] and the majority (87%) fell into class IIIB, previously identified as a high risk group[9,10]. Following admission of such patients, the attending cardiologist needs to exclude the possibility that destabilization is due to significant angiographic progression. This possibility is of particular concern in patients with conventional coronary risk factors and where an interval of several years has elapsed since the previous angiogram. Such circumstances were commonly the case in our patients with one or more coronary risk factors being present in 18 of 24 (75%) patients and a median interval between angiograms of 58 months (maximum 130 months). Both patients with significant angiographic progression had more than one coronary risk factor (Table 1) but overall only 2 of 18 (11%) patients with one or more risk factors

(a)



(b)

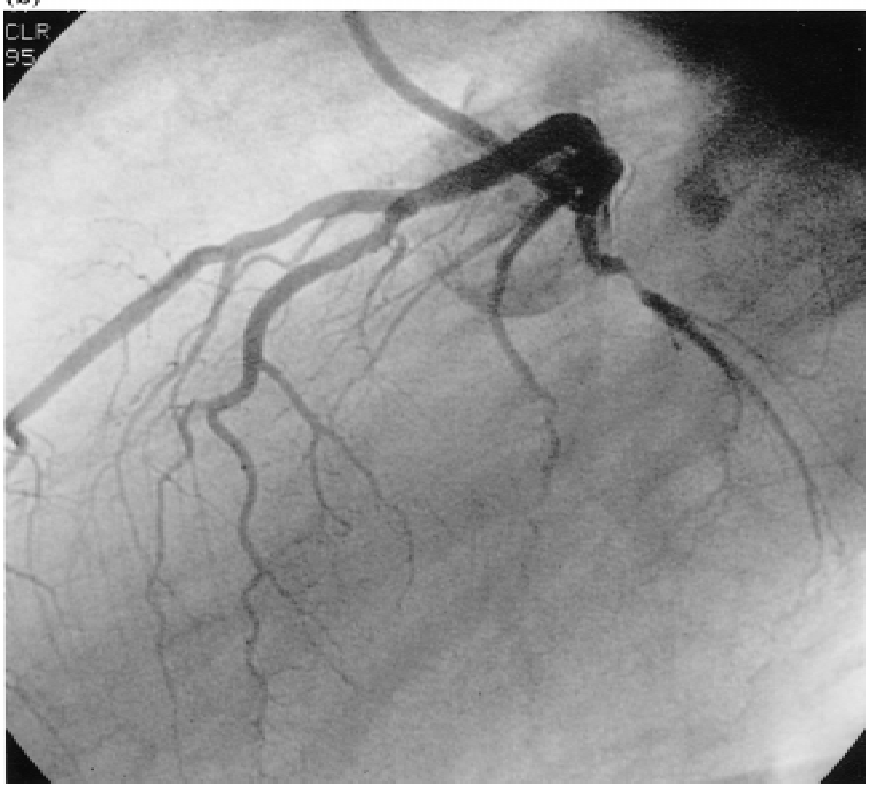


Figure 2 **Angiographic images of patient 16 showing the left coronary system in the left anterior oblique projection. (a) Minimal irregularities were evident in the left anterior descending artery and its first diagonal branch on this and other views in the baseline angiogram. However, there were no lesions of >20% lumen diameter reduction. (b) At follow-up angiography 3 years later, a significant stenosis (69%) had evolved in the left circumflex artery.**

had angiographic progression, indicating a low positive predictive accuracy. Therefore, although the importance of conventional risk factors in the evolution of coronary atherosclerosis is well established, the presence of such factors are not reliable predictors of angiographic progression in patients with previously normal or near normal angiograms who develop unstable symptoms. However, significant angiographic progression was not present in any of 6 patients with no coronary risk factors and consequently, the absence of any risk factors may have significant negative predictive value.

None of the unstable patients with completely normal baseline angiograms had significant angiographic progression but two of three patients with lumenal irregularities at baseline did develop significant stenoses. The new angiographic stenoses were eccentric with irregular lumenal borders in both cases and in this respect, exhibited angiographic features commonly associated with acute coronary syndromes[11]. Thus, minor lumenal irregularities at baseline angiography appear to identify a group of syndrome X patients at increased risk of angiographic progression. Previous studies have also indicated that lumenal irregularities are an important risk factor in relation to angiographic progression[12] and adverse clinical prognosis[1,2]. Our findings are also consistent with studies which have shown that minor angiographic lesions are frequently the site of rapid disease progression in patients with overt coronary angiographic disease[13]. However, as illustrated in Fig. 2, progression need not necessarily occur at the site of the most obvious lumenal irregularities. Therefore, lumenal irregularities may identify a vulnerable patient rather than the most vulnerable angiographic site. It is also established that significant atheromatous changes may be present in the absence of angiographic lumenal irregularity[14] and such subangiographic disease may have been present in some of our patients with completely normal angiograms; the fact that three of the patients with completely normal baseline angiograms had developed minimal lumenal irregularities at restudy is consistent with this possibility. Similarly, the incidence of subangiographic atheromatous progression cannot be excluded even in those with a completely normal angiogram at restudy.

Transient electrocardiographic changes were documented in 10 of 20 patients without left bundle branch block in relation to unstable anginal pain. However, none of the patients without left bundle branch block had angiographic progression and so transient ECG changes did not identify a group at increased risk of angiographic progression. In contrast, significant angiographic progression was present in two of four patients with left bundle branch block and one other patient with left bundle branch block developed new minimal lumenal irregularities. In a previous study of 40 patients with syndrome X, Opherk *et al.*[15] used echocardiography (n = 21) and gated blood pool scintigraphy (n = 19) to investigate changes in left ventricular function over a mean followup period of 48 ± 12 months. They demonstrated that the presence of either constant or rate dependent left bundle branch block was an adverse prognostic indicator associated with deterioration in left ventricular function. Only six patients underwent repeat angiography in Opherk's study; all six had left bundle branch block but none had significant angiographic progression. However, unlike our left bundle branch block patients with angiographic progression, all had completely normal angiograms and they were not reported to have unstable symptoms. Our data suggest that the presence of left bundle branch block may be associated with angiographic disease progression in patients with chest pain and normal coronaries who develop unstable symptoms. The findings of Opherk *et al.*[15] and Haft and Bachik[12] may indicate that the presence of lumenal irregularities on previous angiography is the more significant factor.

Study limitations

The interval between initial angiography and restudy was determined by clinical events and, therefore, varied from patient to patient. However, these are the circumstances which normally confront the attending physician and are, therefore, clinically relevant. The limitations of angiography in the assessment of low grade coronary disease and its progression have been discussed above. A larger sample size would enable more detailed statistical analysis of the influence of risk factors on angiographic progression in this patient group but would probably necessitate a multicentre study.

Conclusions

Unstable symptoms in patients with chest pain and previously normal or near normal coronary arteriograms are rarely due to angiographic disease progression. However, the presence of minimal lumenal irregularities at baseline angiography and left bundle branch block may identify a sub-group at increased risk.

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