Myocardial infarction and the normal arteriogram – possible role of viral myocarditis

David O'Neill, John D. McArthur, John A. Kennedy and Geoffrey Clements¹

Cardiac Department, Western Infirmary, and ¹Department of Virology, University of Glasgow, Glasgow, UK.

Summary: In a prospective study we identified a group of 12 patients diagnosed as having acute myocardial infarction but with electrocardiographic features of non-transmural infarction and serological evidence of recent Coxsackie B infection favouring the possibility of myocarditis. The group included 9 females and 3 males, aged from 38–60 y. Coronary arteriography was carried out in 11 patients. Eight of the 11 patients showed no significant ($>50\%$) coronary arterial obstruction.

We suggest that coronary artery disease did not contribute to the clinical presentation in the majority of these patients and that the likely diagnosis was viral myocarditis in at least 6 of them. We conclude that viral myocarditis may simulate myocardial infarction and contribute to the uncommon but controversial syndrome of myocardial infarction with a normal coronary arteriogram.

Introduction

Following myocardial infarction, radiologically normal coronary arteries are found in a small proportion of patients – probably less than 3% (Arnett & Roberts, 1976; Betriu *et al.*, 1981). This phenomenon has attracted much interest in recent years and the explanation remains controversial (Fox, 1983). The commonly proposed theories to explain this finding are transient coronary artery occlusion with subsequent recanalization, coronary arterial spasm, and technical factors affecting interpretation of the arteriogram. The possibility that some such cases may in fact be explained by viral myocarditis has not yet been fully explored.

The suggestion that viral myocarditis may simulate infarction is by no means new (Woods *et al.*, 1975) and the Coxsackie group B viruses, which are considered to be the commonest cause of viral heart disease (Woodruff, 1980), have been shown to cause localized myocardial necrosis in both animals (Riad *et al.*, 1981) and humans (Desa'neto *et al.*, 1980). In a previous study (O'Neill *et al.*, 1983) we noted a relatively high incidence of raised neutralization titres to Coxsackie B viruses in patients diagnosed as non-transmural myocardial infarction. We suggested that, in some of these patients, myocarditis might be the true pathology and that coronary arteriography might therefore be expected to be normal.

We have identified a group of patients diagnosed as

definite or probable non-transmural myocardial infarction but with raised Coxsackie B neutralization titres. We report the results of coronary arteriography in this group which shows that in patients selected on this basis there is a high incidence of normal arteriograms.

Patients and methods

During the period January 1979 to December 1981, neutralization titres to Coxsackie B viruses were measured in all patients admitted to the Coronary Care Unit of the Western Infirmary, Glasgow, with a diagnosis of definite or probable non-transmural myocardial infarction. Patients fulfilling the following criteria were selected for inclusion in this study: diagnosis of definite or probable non-transmural myocardial infarction; no past history of proven ischaemic heart disease (since pre-existing coronary artery disease would invalidate coronary arteriography as a discriminator between infarction and myocarditis); survival to 48 h after admission; neutralization titre to any Coxsackie B virus of $>1/256$ estimated on a single venous blood sample on admission. This criterion indicates a probability of recent infection rather than proof of such an infection (Grist & Bell, 1974). Paired samples were not required since the neutralizing antibody titre is usually maximal and static by the time of clinical presentation (Grist & Bell, 1974; O'Neill *et al.*, 1983). On the basis of our sample of hospital patients with a titre of $>1/256$, 70% had a history of a recent flu-like illness and/or target organ

Correspondence: D. O'Neill, M.R.C.P., Medical Unit, Crosshouse Hospital, Crosshouse, by Kilmarnock, UK.

Accepted: 8 November 1984

Table I Features of 12 cases of suspected non-transmural myocardial infarction with raised titres to Coxsackie B virus

Case	Age	Sex	Max. Coxsackie titre	ECG site changes	Cardiac enzymes	Findings on arteriography
1	54	F	B ₂ 256	Ant.	Raised	Normal
2	43	F	B ₄ 1024	Ant. + Inf.	Normal	80% stenosis L.A.D.
3	38	M	B ₁ 1024	Ant. + Inf.	Raised	Normal
4	40	F	B ₄ 512	Ant.	Normal	Multiple stenoses L.A.D. 75% stenosis Cx
5	40	F	B ₄ 256	Ant.	Raised	Normal
6	43	M	B ₂ 256	Ant.	Raised	Normal
7	48	F	B ₂ 512	Ant. + Inf.	Normal	80% stenosis L.A.D. 80% stenosis Cx
8	60	F	B ₂ 256	Ant. + Inf.	Normal	30% stenosis RCA
9	44	F	B ₄ 256	Ant.	Normal	Normal
10	46	F	B ₃ 512	Ant.	Raised	Normal
11	53	F	B ₄ 512	Ant.	Raised	Normal
12	59	M	B ₄ 512	Ant. + Inf.	Raised	Not done

L.A.D.: left anterior descending artery; Cx: circumflex artery; Ant.: anterior; Inf.: inferior; ECG: electrocardiogram.

involvement typical of Coxsackie B virus infection such as acute pericarditis or Bornholm disease (O'Neill *et al.*, 1983).

A diagnosis of definite non-transmural myocardial infarction was based on: (a) chest pain compatible with myocardial infarction of greater than 30 min duration; (b) electrocardiographic criteria (persistent, 48 h, new T wave inversion and/or ST segment shift, absence of pathological Q waves, and no significant loss of R force); (c) elevation of serum cardiac enzymes measured daily for 3 d after admission.

A diagnosis of probable non-transmural myocardial infarction was based on identical criteria but with no elevation of cardiac enzymes.

Coronary and left ventricular angiography was carried out non-urgently with full patient consent. One patient was examined early (at 4 weeks) because of recurrent chest pain suggesting unstable angina. In two patients angiography was delayed pending weight reduction. Coronary arteriography was carried out by the Judkins technique using both cine and cut film. Standard views were 60°LAO and 30°RAO with the additional use of a caudo-cranial view for the left coronary artery. Arteriograms were reported by two independent observers. A fasting venous blood sample was taken within the first 24 h after admission for blood lipid analysis. Exercise testing was carried out routinely at three months after the acute episode. Other investigations were carried out where appropriate. Neutralizing antibodies to Coxsackie group B viruses types 1–5 were estimated by micro-neutralization as described by Bell & Grist (1970).

Results

During the period of study, 108 patients admitted to the Coronary Care Unit were diagnosed as definite or probable non-transmural myocardial infarction. Of these patients, twelve (11%) fulfilled the criteria for inclusion in the study. This group included nine females and three males and ages ranged from 38–60 (mean 47 years). Although no patient had a history of documented coronary disease, three patients (cases 6, 9 and 11 in Table I and II) had a past history of undiagnosed chest pains.

At presentation, none of the group had clinical features, such as pericardial friction or chest wall tenderness, which were suggestive of Coxsackie B infection. Three patients however admitted to 'flu-like' illnesses within the preceding 6 weeks.

Neutralizing antibody titres are shown in Table I. Seven patients had paired samples taken 2 weeks after the initial sample. In six instances the paired sample showed no change in titre. One patient (case 12) showed a fourfold increase in titre from 1/128 to 1/512.

Electrocardiographic changes

All patients showed T wave inversion usually with associated ST segment shift. No patient had isolated ST segment depression. The site of changes was limited to the anterior zone in seven cases and involved both anterior and inferior zones in five (Table I). None of the patients had electrocardiographic changes restricted to the inferior zone.

Table II Investigations and risk factors of 12 cases of suspected non-transmural myocardial infarction with raised titres to Coxsackie B virus

Case	Exercise test	Ergometrine test	Cigarettes smoked daily	Hypertension	Cholesterol (mmol/l)	Triglycerides (mmol/l)
1	Negative	Chest pain ECG normal	25	No	4.7	1.1
2	Positive	—	25	No	5.2	1.4
3	Negative	—	7	No	5.4	0.9
4	Positive	—	15	Yes	6.8	0.7
5	Negative	—	0	Yes	4.5	0.8
6	Equivocal (LBBB)	Negative	0	No	5.8	1.5
7	Negative	—	15	Yes	6.1	0.9
8	Negative	—	20	No	6.6	1.0
9	Negative	—	15	No	4.9	1.3
10	Negative	Negative	15	No	8.0	2.0
11	Negative	Negative	20	Yes	5.3	2.7
12	—	—	30	No	5.4	0.7

—: not done.

Coronary arteriography

This was carried out in 11 patients (one patient died soon after discharge from hospital before further investigation could be initiated). The results are shown in Table I. The delay from the acute event to angiography was 1–22 months (mean 8 months). Significant obstructive coronary artery disease (stenosis > 50%) was found in three patients. Single vessel disease was found in one of these cases, two-vessel disease in one and three vessel disease in one. In those three cases (cases 2, 4 and 7) the angiographic findings were thought likely to explain the acute episode. No significant coronary obstructive artery disease was found in eight patients. Five of these had completely normal arteriograms, two had trivial atheroma of the right coronary artery, and one had a 30% stenosis of the right coronary artery.

On angiography, left ventricular contractility appeared normal in six patients. Three patients showed diffusely impaired contractility (cases 4, 8 and 11). Two patients (cases 2 and 10) showed regional hypokinesia.

Other investigations

Maximal treadmill exercise testing was carried out in 11 patients. Two had tests positive for myocardial ischaemia (cases 2 and 7). One patient (case 6) developed left bundle branch block during exercise. Ergometrine testing during angiography using incremental doses from 0.05 to 0.3 mg was carried out in

case 10 with negative results. Bedside ergometrine testing was carried out in three patients. Two had negative tests and one (case 1) developed chest pain but no electrocardiographic changes.

Two patients (cases 7 and 11) had treated hypertension and two (cases 4 and 5) had a past history of hypertension although normotensive without treatment during the period of study. Three patients (see Table II) had mild lipid abnormalities and one (case 11) was grossly obese. Ten patients were regular cigarette smokers. The mean consumption of the group with obstructive coronary arterial disease was 18.8 cigarettes daily compared to 11.7 cigarettes daily for the group without obstructive coronary artery disease. This difference was not statistically significant.

Further observations

The survivors have been followed up for 14–40 months (mean 28 months). Five patients have had subsequent episodes of chest pain sufficiently severe to warrant admission. Two of these patients (cases 2 and 4) had obstructive coronary artery disease and three (cases 1, 3 and 6) had normal arteriograms. Case 7 had had chronic mild chest pain of typical anginal type.

Discussion

The absence of obstructive coronary artery disease on arteriography is uncommon in patients who have had

myocardial infarction even where infarction is non-transmural (Madigan *et al.*, 1976). Five of the patients in this study had no rise in cardiac enzymes during hospital admission and thus might be classified as belonging to the group of intermediate coronary syndrome. However, only 10% of patients with this syndrome might be expected to show normal coronary arteriograms (Scanlon, 1981).

We suggest therefore that the surprising finding of normal coronary arteriograms in eight of the eleven patients studied is related to the selection of this group for the likelihood of recent Coxsackie B infection and that Coxsackie myocarditis was the actual diagnosis in at least six of these cases. One patient (case 1) developed chest pain during ergometrine infusion and the possibility of coronary artery spasm must be considered. Another patient (case 6) has subsequently shown features suggestive of hypertrophic obstructive cardiomyopathy.

The mechanism by which Coxsackie infection may cause myocardial damage is uncertain. Apart from the obvious possibility that infection may cause localized or widespread myocarditis, it has been suggested that infection may produce coronary arteritis and subsequent infarction or alternatively precipitate infarction in vulnerable patients such as those with pre-existing coronary disease or hypertension (Woods *et al.*, 1975). We suggest that myocarditis is the likeliest explanation of myocardial injury in those patients with normal coronary arteriograms.

The group of patients under study is small and analysis of clinical and investigative data from the study of patients did not show that it was possible to

predict with confidence which patients had significant coronary disease. The group was predominantly young and female. Exercise testing was negative in two patients with coronary disease and coronary risk factors were common in those patients with and those without obstructive coronary disease. Recurrent chest pain was a common sequel, regardless of arteriographic findings.

Surprisingly, viral myocarditis has received little attention as a cause of 'myocardial infarction' in subjects with normal arteriograms (Rosenblatt & Selzer, 1977; Fox, 1983). A major problem is the difficulty in establishing a firm diagnosis of viral myocarditis. Patients with Coxsackie virus infection rarely demonstrate a diagnostic rise in neutralization antibody titre and high static titres merely indicate a probability of recent infection (Grist & Bell, 1974). Endomyocardial biopsy is becoming widely used and shows considerable promise as a diagnostic tool in viral heart disease. Problems exist however in the representativity of biopsies and in the interpretation of histological features. Although safe in experienced hands, this technique is invasive and may not be acceptable in patients in whom the disease is likely to be relatively mild or self-limiting (Baandrup & Mortensen, 1984).

We conclude that Coxsackie myocarditis may explain the finding of patent coronary arteries in some patients who have been labelled as non-transmural myocardial infarction. Following non-transmural infarction, particularly in younger and female patients, coronary arteriography may be useful, not only in delineating coronary disease, but also in excluding it.

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