Coxsackie B virus infection in coronary care unit patients

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SUMMARY It has been suggested that Coxsackie B virus infections may play a part in causing or triggering myocardial infarction. This study was designed to compare the incidence of such infections in Coronary Care Unit patients and normal controls. The choice of a suitable criterion for diagnosis of Coxsackie infection is discussed fully.

Two hundred and fifty admissions to a Coronary Care Unit and 100 control subjects had a serum sample tested by microneutralisation for Coxsackie B antibodies. The incidence of infection among 130 patients diagnosed as acute myocardial infarction was 5% compared with 4% in the control group.

In a subgroup classified as non-transmural myocardial infarction, the incidence of infection was 14%. The sex ratio of this group differed from the myocardial infarction group as a whole suggesting that the non-transmural group may not have been homogeneous. Normal coronary arteriograms were subsequently found in three patients who were diagnosed as non-transmural myocardial infarction but who had serological evidence of recent Coxsackie infection.

This study does not demonstrate an association between Coxsackie infection and myocardial infarction as a whole and does not support the view that Coxsackie infection causes or provokes myocardial infarction. It does, however, suggest that myocarditis may simulate non-transmural infarction.

Coxsackie B virus infections are known to cause chest pain as one possible component of a constellation of symptoms. It has been suggested that such infections may be associated with acute myocardial infarction (MI) and the association may either be due to simulation of the symptoms and electrocardiographic changes of MI or to triggering an actual MI. Woods et al. found evidence of recent infection in 8-6% of patients with acute transmural MI while Nicholls and Thomas reported serological evidence of recent infection using less strict criteria in 26-3% of patients with recent MI. However, Griffiths et al. who included a normal group in their study failed to demonstrate any significant association between Coxsackie B infection and acute MI.

This conflicting evidence led us to compare the incidence of raised neutralisation titres to Coxsackie B virus in Coronary Care Unit (CCU) admissions and in normal controls. We have placed special emphasis on distinguishing transmural from non-transmural MI since it is in the latter group that diagnostic confusion with myocarditis is most likely to arise.

Patients and methods

All patients admitted with chest pain to the CCU of the Western Infirmary, Glasgow, between 1st June 1980 and 31st January 1981 were included in the study with the exception of 16 patients who died before a blood sample was taken. Diagnosis of myocardial infarction was based on the demonstration of typical electrocardiographic changes and raised serum enzymes (serum AST, serum ALT, LD, total CK and CKMB). Transmural and non-transmural MI were distinguished by the presence or absence of pathological Q waves or loss of R wave force. Within 24 hours of admission each patient had a blood sample withdrawn for Coxsackie serology.

During the period of study blood samples were also drawn from a control group of outpatients with hypertension, peptic ulcer, chronic stable angina and osteoarthritis. Sera were separated and stored at −20°C. Before use they were heated at 56°C for 30 minutes.
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min. Neutralising antibodies to Coxsackie group B viruses types 1–5 were estimated by a microneutralisation test as described by Bell and Grist 1970. Sera were tested in serial twofold dilutions against approximately 100 TCD of virus (unit volume 0.025 ml) in microtitre plates. Serum-virus mixtures were incubated for one hour at room temperature before the addition of 0.1 ml of Hela cell suspension (15 000 cells in medium containing 10% fetal calf serum). Parallel plates were set up using serial dilutions of standard antisera to Coxsackie B types 1–5 (Colindale). Plates were incubated at 37°C in a humidified incubator for three days in 5% CO₂ in air. The cytopathic effect was read visually, the end point being the last dilution not to show a cytopathic effect.

Three patients were subjected to coronary arteriography as a part of this study (see below). Coronary arteriograms in right and left oblique views with added caudocranial projections were obtained both on cine and cut film at least three months after the acute admission.

Criteria for diagnosis of recent infection

Diagnosis of recent Coxsackie virus infection is based, in practice, on measurement of antibody titres. An acceptable criterion for recent infection remains controversial. Lerner and Wilson7 have suggested criteria for the association of a virus infection with acute or chronic myocardiopathy but in practice high-order associations are difficult to establish in the case of Coxsackie virus infections.8 A fourfold or greater rise in titre is taken to provide good evidence of recent infection.1 Unfortunately, peak antibody titres have usually been reached by the time the first sample is taken1 and Wood et al9 found only one instance of a fourfold rise in their study of 104 chest pain patients. Grist and Bell1 found that titres of 1/512 and over were strongly associated with a diagnosis of acute myocarditis suggesting recent infection.

We considered it important to validate our own criteria before embarking on this study. One observer (D O’N) examined retrospectively clinical data from 291 unselected cases in the Western Infirmary over a period of three years which showed neutralisation titres to Coxsackie B virus to a level of 1/256 or above. The data were examined without access to the Coxsackie titres and each case allocated solely on clinical grounds to one of three groups.

1 Recent infection by Coxsackie virus—141 patients.
2 No evidence of recent infection (incidentally raised titres)—60 patients.
3 The remaining 90 patients were classified as “doubtful” and will not be considered further in the context of validation of criteria for diagnosis of recent infection.

Serological data from groups 1 and 2 were compared with a view to distinguish recent infection from incidentally raised titres.

Seventy-one patients in group 1 and 22 patients in group 2 had paired samples of serum available. A fourfold rise in titre was found in four patients in group 1 and one patient in group 2 (the latter patient was admitted with acute generalised lymph node enlargement and was subsequently diagnosed as having Hodgkin’s disease). A fourfold rise in titre was uncommon in this study even in patients with clinical evidence of a recent Coxsackie infection and was therefore not by itself regarded as a suitably sensitive criterion for the diagnosis of a recent infection. In only five instances was there a raised titre in the second sample following a normal first sample and only two of these cases were in group 1. This confirms that the titres are usually raised by the time of clinical presentation.

A single serotype rise was found to be equally common in both groups 1 and 2 and therefore did not correlate with recent infection as suggested by Nicholls and Thomas.4 We examined also the correlation of the titre height (on presentation) with the clinical diagnosis. The results are shown in the Figure. A presenting titre of ≥1/256 correlated poorly with recent infection (30% of patients belonged to group 2). A presenting titre of ≥1/1024 correlated extremely well with recent infection (only 3%
belonged to group 2) but excluded 74% of group 1 patients.

A presenting titre of 1/512 or greater correlated well with recent infection including 72% of patients in group 1 and includes 26% of the group 2. This titre was regarded as being highly suggestive of recent infection in agreement with the work of Grist and Bell. We therefore chose a titre of 1/512 or greater as our criterion for recent infection.

**Results**

Serum samples were obtained from 250 admissions to the CCU (182 men and 68 women). A diagnosis of acute MI was made in 130 patients of whom 108 were classified as transmural infarction and 22 as non-transmural infarction. The transmural MI group comprised 82 men and 26 women. The non-transmural group comprised 11 men and 11 women, a sex ratio significantly different from that in the transmural MI group (p < 0.05). The mean age of the MI group was 58.1 yr and was similar in both the transmural and non-transmural groups. MI was sited anteriorly in 55 patients and inferiorly in 65 patients. In 10 patients the site was indeterminate or involved both anterior and inferior zones. One hundred and twenty patients were classified as chest pain without myocardial infarction (89 men and 31 women). The mean age of this group was 54.6 yr. Ischaemic cardiac pain was the clinical diagnosis in 67 of these 120 patients.

Only 11 patients had a clinical diagnosis of acute viral myopericarditis. The remaining 42 patients had miscellaneous causes of chest pain such as hiatus hernia, biliary disease and pain of unknown origin. Serum was tested from 100 control patients (52 men and 48 women). The mean age in this group was 58.8 yr.

The incidence of serological evidence of Coxsackie infections in the CCU patients and controls is shown in Table 1. Of the MI group seven of 130 patients (5%) had evidence of infection compared with four of 100 (4%) of the control group. If the non-transmural MI group is considered separately, the incidence of infection was considerably higher (14%) than in the control group, but the number of patients in this sample (22) is small and thus this difference is not statistically significant. The non-MI chest pain group included six from 120 patients with serological evidence of Coxsackie infection (5%). There was therefore no increased incidence of Coxsackie infections among MI patients or non-MI chest pain patients. As expected the subgroup of CCU patients with a clinical diagnosis of viral myopericarditis showed an increased incidence of Coxsackie infection—four from 11 patients (36%)

**Discussion**

Of the 250 admissions to the CCU in this study an initial clinical diagnosis of viral myopericarditis was attached to only 11 patients (4%). Four of these 11 patients (36%) subsequently proved to have serological evidence of Coxsackie infection. The remaining seven patients presumably had infection due either to other viruses (although screening for common respiratory viruses was negative in all cases) or to infection with Coxsackie B virus associated with titres lower than our criterion demanded (three patients in this group had Coxsackie titres of 1/256). Clearly defined Coxsackie illnesses were therefore relatively uncommon in our CCU occurring in only 2% of admissions. It has, however, been suggested by Woods et al., that covert Coxsackie infection may cause, provoke or simulate MI in some instances. Their study based on a fourfold rise
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in neutralisation titre was however uncontrolled. Nicholls and Thomas, also in an uncontrolled study, found a fourfold rise in titre in 7/38 MI patients. Our own study however failed to demonstrate an increased incidence of Coxsackie infections in MI patients and is in line with the conclusions of Griffiths et al. There was, in addition, no evidence that Coxsackie infection contributes significantly to the problem of non-MI chest pain in the CCU.

Our finding of an excess of anterior MI patients among those with serological evidence of Coxsackie infection supports the observation of Wood et al., although Woods et al found no significant excess in their 20 patients with transmural MI.

The subgroup classified as non-transmural MI has several interesting features: (i) the sex ratio of 1:1 differs significantly from that of the total MI group, suggesting that this subgroup contains patients with pathology other than coronary artery disease. It is of interest that Pohjola et al. noted a similar difference in sex ratio between transmural and non-transmural infarction in a large study involving 728 MI patients; (ii) three patients from this subgroup, who had evidence of recent Coxsackie infection, were subsequently demonstrated to have normal coronary arteriograms—a finding quite unexpected in non-transmural MI; (iii) the incidence of infection in this subgroup was 14% compared with 4% in the control group. Although this difference lacks statistical significance, such significance would be difficult to obtain in the presence of such small numbers satisfying the criteria for infection.

These findings suggest that the group classified as non-transmural MI may have contained patients who, in fact, suffered from viral myocarditis. The electrocardiographic changes of myocarditis are usually most prominent in anterior leads. Of these patients 14% (3/22) had evidence of recent Coxsackie infection using our criteria and none showed significant titres by complement fixation to the following antigens: psittacosis-LGV, Mycoplasma pneumoniae, influenza A and B, adenovirus, parainfluenza, herpes simplex, respiratory syncytial virus, cytomegalovirus, varicella zoster and measles. An agent affecting 19/22 (86%) of patients in this group with findings compatible with acute viral myocarditis has not been defined in this study. A similar situation exists in the group of patients presenting with a clinical picture of acute viral myopericarditis: a minority, 36% (4/11), had evidence of a recent infection with Coxsackie B by our criteria. It is possible that viruses not routinely tested for—for example, Coxsackie A—may play a role in contributing to undiagnosed viral infections in the groups studied.

We have therefore failed to demonstrate an association between Coxsackie infection and MI as a whole but suggest that viral myocarditis may be wrongly diagnosed as non-transmural MI in a number of patients (small in relation to all MI patients).

Further scrutiny of patients diagnosed as non-transmural MI is indicated, for prognostic reasons, to exclude cases of myocarditis (which may explain some cases of "MI" with normal coronary arteriograms). We are currently engaged in an angiographic study designed to investigate this question. The availability of a reliable method of detecting IgM specific for Coxsackie B virus would also help to clarify the situation.

References


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