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Angina with normal coronary arteriograms
Value of coronary sinus lactate estimation in diagnosis and treatment

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SUMMARY Thirty-five patients with chest pain of sufficient severity to warrant coronary arteriography had normal coronary arteriograms. In each of them coronary sinus lactate was measured before and during atrial pacing. In 16 the lactate metabolism was normal as shown by a change between resting and peak pacing arteriovenous lactate difference of less than 0·09 mmol/l (0·8 mg/100 ml). Nineteen patients had abnormal lactate metabolism, the change being greater than 0·09 mmol/l (0·8 mg/100 ml). Sixteen (84%) of the group with abnormal lactate metabolism responded symptomatically to oral beta-blockade in contrast to only one patient in the normal group ($P < 0·001$). After 1 year all 16 patients with abnormal lactate metabolism who had responded to beta-blockade worsened when placebo was substituted. Fifteen of the 16 patients with normal lactate metabolism had become free of symptoms on no specific drug therapy; it is thus unlikely that their original pain was of cardiac origin.

By estimating the coronary sinus lactate, it is, therefore, possible to divide patients with chest pain and normal coronary arteriograms into two groups. Those with pain of non-cardiac origin have normal lactate metabolism, are unlikely to respond to beta-blockade, and improve spontaneously. The group with abnormal lactate metabolism have genuine angina, usually respond to beta-blockade, and deteriorate when treatment is discontinued. Further observation is required to determine the prognosis of the two groups and to estimate the frequency of development of coronary artery disease.

Up to 10 per cent of patients with suspected angina pectoris have normal coronary arteriograms (Kemp *et al.*, 1973). Even when coronary arteries are normal, abnormal electrocardiograms at rest or on exercise and abnormal myocardial lactate metabolism after atrial pacing suggest myocardial ischaemia (Boudoulas *et al.*, 1974; Richardson *et al.*, 1974).

We report here a series of 35 patients with chest pain who had normal coronary arteriograms. All had coronary sinus lactate estimations after atrial pacing to identify the development of anaerobic myocardial metabolism. Their response to treatment was also assessed.

Patients and methods

PATIENTS

Thirty-five patients, 16 men aged 26 to 58 years (mean 46 years) and 19 women aged 21 to 54 years (mean 44 years), were investigated. In each case we considered that the severity of the patient's chest pain warranted invasive investigation and graded the pain as 'definite' or 'uncertain' angina pectoris on our interpretation of the symptoms. No patient had evidence of anaemia, thyroid disease, diabetes mellitus, valvar heart disease, hypertension, or autoimmune disease. Before the investigations beta-blocking drugs had been discontinued for 1 week and digoxin for 2 weeks.

ELECTROCARDIOGRAPHY

A resting 12-lead electrocardiogram was recorded immediately before the radiotelemetric exercise electrocardiogram which was performed under standard conditions (Jackson *et al.*, 1975). ST segment depression in lead V5 was measured before and after exercise. Ischaemia was considered present when there was ST segment depression of at least 1 mm for 0·08 s or more in at least 5 consecutive beats.

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Table 1 *Summary of results*

		Abnormal lactate metabolism (n=19)	*Normal lactate metabolism (n=16)*	*P*
Clinical diagnosis	'Definite'	16	3	<0·001
	'Uncertain'	3	13	<0·001
Pacing induced angina		17	8	<0·02
Abnormal electrocardiogram	Resting	5	2	NS
	Exercise	8	2	NS
	After pacing	13	4	<0·02

NS, not significant; n, number of patients.

CORONARY SINUS LACTATE PACING STUDY

This was performed as described in the preceding paper (Jackson *et al.*, 1978).

CORONARY ARTERIOGRAPHY

This was performed as described in the preceding paper (Jackson *et al.*, 1978).

Results

These are summarised in Table 1. Statistical analysis employed Student's t test and Fisher's exact test.

CORONARY SINUS LACTATE

Nineteen patients had a change in resting and peak pacing arteriovenous lactate difference greater than 0·09 mmol/l (0·8 mg/100 ml) which we consider is indicative of ischaemia (Jackson *et al.*, 1978). Sixteen patients had normal myocardial lactate metabolism.

CLINICAL DIAGNOSIS

'Definite' angina was present in 19 patients (54%), of whom 16 had abnormal lactate metabolism and 3 normal lactate metabolism ($P < 0·001$).

ELECTROCARDIOGRAPHY

In 5 of the 19 patients with abnormal lactate metabolism the resting electrocardiogram was abnormal, but is was also abnormal in 2 of the 16 patients with normal lactate metabolism, a total incidence of 20 per cent. Of the 35 patients (30%), 10 had an abnormal exercise electrocardiogram (Fig.), 8 coming from the abnormal lactate group. Of the 35 patients, 17 had abnormal electrocardiograms after pacing (50%) (Parker *et al.*, 1969), 13 of these were in the abnormal lactate group ($P < 0·02$). Pacing induced angina in a total of 25 (71%) and 17 of these had abnormal lactate metabolism ($P < 0·02$).

ECHOCARDIOGRAPHY

This was normal in all patients.

Table 2 *Response to treatment*

	Abnormal lactate metabolism (n=19)	*Normal lactate metabolism (n=16)*	*P*
Relief of pain by glyceryl trinitrate	15	3	<0·001
Improvement on treatment with propranolol	16	1	<0·001
Symptoms after stopping propranolol	16	1	<0·001

RESPONSE TO TREATMENT

All patients were treated with sublingual glyceryl trinitrate and oral propranolol. The dose of propranolol was increased until optimum beta-blockade was achieved, as defined by reduction of peak exercise heart rate (Jackson *et al.*, 1975). Sixteen patients (84%) within the abnormal lactate group responded to propranolol (Table 2) in contrast to only 1 patient with normal lactate metabolism ($P < 0·001$). All patients in the abnormal lactate group who responded to oral propranolol had an increase in the frequency of angina when placebo was substituted one year later, whereas 15 of the 16 patients with normal lactate metabolism had become pain free on no specific treatment. The withdrawal of beta-blockade was not associated with any rebound angina. Fourteen

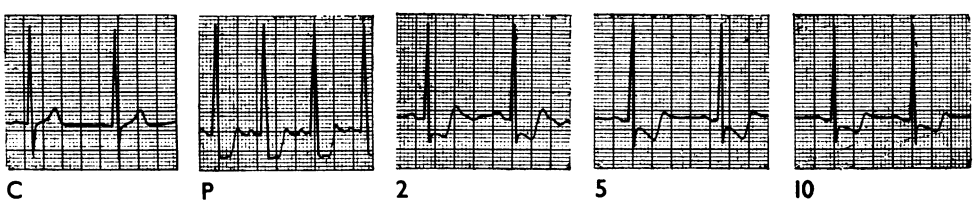

Fig. *Depression of ST segment by exercise in patient with normal coronary arteries. Control (C), maximum ST segment depression during exercise (P), and 2, 5, and 10 minutes after exercise.*

patients (74%) with abnormal lactate metabolism responded to glyceryl trinitrate while only 3 (19%) with normal lactate metabolism did so ($P < 0.001$).

Discussion

Typical angina pectoris can occur in patients shown to have normal major coronary arteries on selective coronary arteriography (Kemp *et al.*, 1973; Richardson *et al.*, 1974). Previous studies have identified patients with normal coronary arteries with both abnormal electrocardiograms at rest or on exercise and abnormal lactate metabolism after atrial pacing (Boudoulas *et al.*, 1974; Richardson *et al.*, 1974). We have previously shown that patients with coronary artery disease have a change in resting and peak pacing arteriovenous lactate difference greater than 0·09 mmol/l (0·8 mg/100 ml) and we believe that this indicates the development of anaerobic metabolism (Jackson *et al.*, 1978). By this definition, atrial pacing induced abnormal lactate metabolism in 19 patients.

It has also been shown in patients with coronary artery disease that myocardial lactate metabolism improves, and the time from atrial pacing to pain increases after glyceryl trinitrate (Chiong *et al.*, 1972). We have recently shown that beta-blockers have a similar beneficial effect (Jackson *et al.*, 1977). Of 19 patients with abnormal lactate metabolism, 15 responded to glyceryl trinitrate and 16 to propranolol. In contrast, of 16 patients with normal lactate metabolism only 1 responded to propranolol and 3 to glyceryl trinitrate. Measurement of coronary sinus lactate is thus the most reliable objective means of predicting response to either glyceryl trinitrate or propranolol. It was noteworthy that the patients with abnormal lactate metabolism all worsened when propranolol was withdrawn after 12 months of therapy, whereas all but 1 patient with normal lactate metabolism were free from pain on no specific treatment 12 months after investigation. As most of the patients with normal lactate metabolism had chest pain which had been labelled clinically 'uncertain' angina, it is likely that their pain was not of cardiac origin. We believe that there is now sufficient evidence for us to advocate the routine estimation of coronary sinus lactate before and during atrial pacing in patients with chest pain and normal coronary arteriograms, as there appear to be two distinct groups of patients who differ in their prognosis and response to treatment. While the outlook for patients with genuine angina and normal coronary arteriograms is good (Kemp *et al.*, 1973), further follow-up is still required. It remains to be shown whether patients with angina and normal coronary arteriograms, but with abnormal lactate metabolism, are at risk of developing coronary artery disease.

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