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Antilipolytic therapy in angina pectoris
Reduction of exercise-induced ST segment depression

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A double-blind cross-over study was performed on 12 men with stable angina pectoris in order to determine the effect of antilipolytic treatment on exercise tolerance and exercise-induced electrocardiographic changes. The men were exercised to the onset of anginal pain using a reproducible and standardized ergometric load.

A nicotinic acid analogue was used to reduce plasma free fatty acids and free glycerol before and during exercise testing and to eliminate their post-exercise rise. This was associated with significant reduction of exercise-induced ST segment depression ($P<0.005$), though there was no significant difference in the duration of exercise before the onset of pain.

A change in the proportions of lipid and carbohydrate for oxidation by the ischaemic myocardium, making relatively more glucose available, is a likely explanation.

The availability of free fatty acids (FFA) to the myocardium is increased during physical activity because of augmented intramyocardial lipolysis (Kaijser *et al.*, 1972) and also because of a rapid rise in plasma concentration caused by continued mobilization from adipose tissue (Friedberg *et al.*, 1960; Carlson, 1967). These changes are likely to be more pronounced in patients with ischaemic heart disease than in healthy subjects, since the former have an excessive accumulation of intramyocardial lipid (Wartman *et al.*, 1956) and frequently show an exaggerated lipolytic response to adrenergic stimulation (Kershbaum *et al.*, 1961; Penick, 1962). Such observations have suggested that control of the metabolic response to exercise may be of value to patients with angina pectoris, since there is biochemical (Kurien and Oliver, 1970; Shug and Shrago, 1973; de Leiris, Bricknell, and Opie, 1974), experimental (Kurien, Yates, and Oliver, 1971; Kjekshus and Mjøs, 1972; 1973), and clinical (Oliver, Kurien, and Greenwood, 1968; Rowe, Neilson, and Oliver, 1975) evidence that excess FFA can be harmful during myocardial ischaemia.

This might be achieved either by antilipolytic treatment or by increasing glucose availability (Oliver, 1972; Opie, 1972). Lipolysis in adipose tissue and in the heart is inhibited by nicotinic acid (Carlson and Orö, 1962; Christian *et al.*, 1969; Lassers *et al.*, 1972), but it can have a distinct hypotensive effect. A nicotinic acid analogue (NAA), 5-fluoro-3-hydroxy-methylpyridine hydrochloride, produces few haemodynamic effects but retains a potent antilipolytic action (Rowe *et al.*, 1973). This report describes the effects of this drug on exercise tolerance and exercise-induced electrocardiographic changes in patients with stable angina.

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Patients and methods

Patients

Twelve men aged 49 to 65 years (average 56 years) were studied. All had angina pectoris for a minimum of 6 months before the study: the average duration from onset of symptoms was 70 months (range 9 months to 10 years). Three of these men had an inferior myocardial infarct more than 6 months before and had residual electrocardiographic abnormalities at rest; 8 developed horizontal or downsloping ST segment depression of 1 mm in response to exercise; and 1 patient without electrocardiographic evidence of myocardial ischaemia had severe three-vessel disease shown by coronary angiography.

Eight patients had been taking a beta-adrenergic blocking drug: the dosage was halved 10 days

before and stopped 72 hours before the study. All lipid lowering agents were discontinued 4 weeks before entering hospital. No patient was taking a digitalis preparation or diuretic and all were free of clinical evidence of left ventricular failure. Four patients were cigarette smokers but this was not allowed while they were in hospital. Body weight averaged 75 kg (range 65 to 90 kg).

Clinical and laboratory procedures

The patients were admitted to hospital for 3 days. Preliminary studies were performed on the first day, when exercise tests were done to establish a 'pain work load' (i.e. the work load necessary to induce pain in each individual), to familiarize the patient with the equipment, and to minimize the problem of improvement in exercise tolerance with successive tests. The exercise was performed using a constant load, upright bicycle ergometer (Elema Ergometer System 380). Continuous electrocardiographic monitoring was performed from bipolar chest leads CR2, CR4, and CR5 during exercise, and standard leads I, II, III and orthodox chest leads V2, V4, and V5 after exercise. The electrocardiogram was recorded with an Elema Mingograf 34 ink-writing machine at standard calibration (10 mm = 1 mV) and measurement made with paper speed 25 mm/s.

A well-tried exercise procedure was followed (Redwood *et al.*, 1971): on day 1 the work load was started at 200 kilopond metres per minute (kpm/min) and increased by 100 kpm/min each minute until pain occurred (i.e. 'pain work load'). The subject was rested for 20 minutes and the study repeated starting at the 'pain work load' minus 100 kpm/min, with an increase by 100 kpm/min each 3 minutes. This was designed to produce pain within the second 3-minute period, which is the optimum time for assessment of antianginal agents (Reichek *et al.*, 1974).

On days 2 and 3, the exercise study was performed in the morning after an overnight fast. A cannula was inserted into an antecubital vein under local anaesthesia 75 minutes before starting exercise and the patients remained supine. After 15 minutes either 100 mg NAA or 10 ml normal saline were administered intravenously over 5 minutes. The administration of drug or placebo on days 2 or 3 was randomly determined and the study was conducted double blind. Exercise was begun at the 'pain work load' minus 100 kpm/min. This was increased by 100 kpm/min every 3 minutes, and the time from establishing the first constant work load to the onset of pain was measured to the nearest second by a stopwatch. After exercise the patient rested for 20 minutes. Blood, 20 ml, was drawn for serum FFA (Trout, Estes, and Friedberg, 1960) and glycerol (Chernick, 1969) concentrations at –75 min, –60 min (before injection), –30 min, and immediately before exercise; at the onset of pain; and 20 minutes later. Plasma glucose (Nimmo, Kirby, and Lassers, 1973) was estimated at –60 min before exercise and at the onset of pain.

Systolic and diastolic pressures were measured at each of the above intervals by a mercury manometer and cuff using phase 4 of Korotkov for the diastolic pressure. Heart rate was measured from electrocardiograms at the same time, and also at 1-minute intervals for 8 minutes after the onset of pain.

Exercise-induced ST segment depression was measured 'blind' by the same observer at intervals of 1 minute after the onset of pain. It was recorded to the nearest 0·5 mm at the point of maximum depression in horizontal or downsloping segments, or at the point of the minimum depression in upsloping segments. The sum of the ST depression from leads I, II, III and V2, V4, and V5 at each minute was used as the index of ST change for each patient.

Changes in ST segments at each interval were compared using the Wilcoxon test for non-parametric data. The combined results, over all the time periods, were analysed using Friedman's method of analysis of variance of ranked data (Colquhoun, 1971). Other statistical analyses were by Student's t-test (two-tailed).

Results

Metabolic changes

The changes in plasma FFA and plasma glycerol are summarized in Fig. 1. There was no significant difference between FFA and glycerol concentrations before the injection of NAA or placebo on the 2 successive days of the study. The downward trend with time was related to the period of rest (Carlson, 1967).

The changes in response to exercise on the placebo day were similar to those previously reported in healthy subjects (Carlson, 1967; Friedberg *et al.*, 1960). After administration of the NAA, the plasma FFA and glycerol levels were at all times significantly below those recorded on the placebo day. In particular, plasma FFA and glycerol were below the initial levels immediately after stopping exercise and the normal post-exercise rebound rise in FFA was almost completely abolished by the NAA.

The mean plasma glucose at the time of pain on the placebo day was 5·2 ±0·3 mm/l (93 ±6 mg/100 ml) (±SEM) and on the NAA day 5·5 ±0·3 mm/l (99 ±5 mg/100 ml) (NS).

Exercise tolerance

The period for which patients exercised before the onset of pain on the 2 days (NAA and placebo) was not significantly different (Fig. 2). The mean duration of exercise over the placebo day was 4 min, 32 s ±47 s (±SEM) and on the NAA day was 4 min, 14 s ±40 s (NS).

Electrocardiographic changes

There was no significant difference in ST segment depression in each patient's electrocardiogram before the administration of drug or placebo on the 2 days of the study. The NAA produced significantly less ST segment depression during the 8 minutes immediately following the completion of exercise (Table). The overall difference between drug and placebo was highly significant ($P < 0.005$).

No patients developed arrhythmias on either day of the study except for single ventricular premature beats. Seven patients had one or more ventricular premature beats during exercise and the 8 minutes after pain. The mean number of ventricular premature beats recorded during the exercise and post-exercise period of the placebo day was 1·8 (range 0 to 15) and on the NAA day 3·0 (range 0 to 26) (NS).

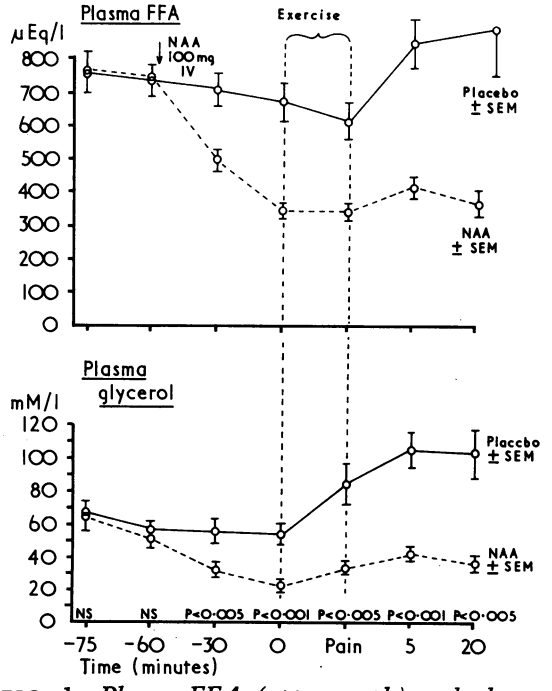

FIG. 1 *Plasma FFA (upper graph) and plasma glycerol (lower graph) in 12 men with angina when receiving placebo or the nicotinic acid analogue (NAA).*

Haemodynamic changes

There was no significant difference in each patient's heart rate or systolic and diastolic blood pressure in the period before exercise on either day. The average heart rate for the 12 patients on the NAA day was slightly lower at all times from the onset of pain and this reached statistical significance at the onset of pain (placebo 120 ±7 beats per min: NAA 112 ±6 beats per min: $P < 0.03$) and at 3

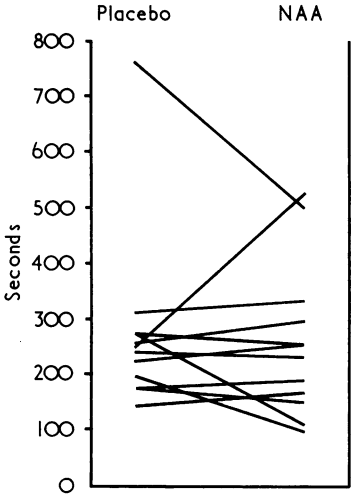

FIG. 2 *Duration of exercise before the onset of pain when receiving a placebo (to the left of the figure) and the nicotinic acid analogue (to the right of the figure) in 12 men with angina. The results for each man are connected.*

TABLE *Effect of nicotinic acid analogue on ST segment depression after exercise in 12 men with angina pectoris, who acted as their own controls*

Minutes after exercise	*ST segment depression mean ±SEM (mm)* *Placebo*	*Nicotinic acid analogue*	*P (analysis of paired data n=12)*
1	1·8 ±0·5	0·9 ±0·4	<0·025
2	2·0 ±0·8	1·2 ±0·6	<0·025
3	1·8 ±0·7	1·5 ±0·6	NS
4	1·7 ±0·7	1·2 ±0·5	NS
5	1·4 ±0·5	0·9 ±0·4	<0·025
6	1·2 ±0·8	0·6 ±0·4	<0·025
7	1·1 ±0·5	0·5 ±0·3	NS
8	0·8 ±0·5	0·4 ±0·3	NS
Combined difference			<0·005
Pre-exercise	0·3 ±0·2	0·3 ±0·1	NS

minutes after pain (placebo 76 ±5 beats per min: NAA 68 ±4 beats per min : $P < 0.02$). On the day of the NAA, there was a trend for the systolic blood pressure to be higher when pain occurred (placebo 160 ±6 mmHg (21·3 ±0·8 kPa) : NAA 177 ±8 mmHg (23·5 ±1·1kPa) : $P = 0.10$) and for the diastolic blood pressure to be higher at 5 minutes after pain (placebo 91 ±2 mmHg (12·1 ± 0·3kPa) : NAA 96 ± 2 mmHg (12·8 ±0·3kPa) : $P < 0.025$). The product of systolic blood pressure and heart rate was not significantly different for all patients either before exercise, at the point of pain, or 5 minutes after pain.

Discussion

Depression of the ST segment induced by standardized exercise in patients with angina was less when they were given a nicotinic acid analogue (NAA). A metabolic explanation is likely, since this NAA decreased plasma FFA before exercise and reduced the expected postexercise rise, presumably leading to decreased FFA extraction by the myocardium (Carlson *et al.*, 1972). As the NAA has an antilipolytic effect similar to nicotinic acid, reduction in any exercise-induced increase in myocardial lipolysis (Lassers *et al.*, 1972) may also have occurred. Reduction of FFA extraction will change the proportion of lipid and carbohydrate making relatively more glucose available for oxidation by the myocardium. Similar findings have been reported recently during infusion of glucose-insulin-potassium in atrial-pacing-induced angina (Chiong, West, and Parker, 1976). Reduction of intracellular FFA could lead to an increase in available ATP (Shug and Shrago, 1973), stabilize membrane function (Pande and Mead, 1968), and decrease myocardial oxygen consumption (Mjøs, 1971) and all these would reduce the effects of myocardial ischaemia at a given work load. A metabolic explanation is also supported by the positive correlation between the degree of ST segment depression and coronary sinus lactate levels, measured during atrial pacing in patients with ischaemic heart disease (Parker *et al.*, 1969): this correlation persisted into the recovery phase after the cessation of pain, unlike changes in haemodynamic parameters of myocardial oxygen consumption which correlate poorly with ST changes after exercise (Detry, Piette, and Brasseur, 1970). The possibility also arises that this nicotinic acid analogue has a direct effect on intracellular potentials, independent of its antilipolytic action, but nicotinic acid itself has recently been shown not to have any such effect on mammalian ventricular muscle fibres (Beresewicz and Wojtczak, 1976).

The haemodynamic changes at the time of pain could be explained by increased myocardial contractility with a rise in blood pressure and reflex decrease in heart rate. An increase in contractility produced by a reduction in FFA levels has been shown in ischaemic dog hearts (Kjekshus and Mjøs, 1972). The oxygen requirements might, therefore, be determined by a complex interaction between increased metabolic efficiency and increased contractility, which results in unchanged exercise tolerance. A test of this hypothesis would require measurement of the ejection time, dP/dt, ventricular volumes, and measurement of coronary sinus indices of ischaemic metabolism, such as lactate, potassium, and creatine phosphokinase.

There was no significant difference in the time during which patients could exercise before the onset of pain. The disparity of effect of the NAA on ST segment depression and pain threshold is not explained, though it has already been recognized that the correlation of ST changes with pain is poor (Borer *et al.*, 1975). The product of systolic pressure and heart rate has been shown to correlate positively with myocardial oxygen requirements and, in a given individual, has a constant value at the onset of ischaemic chest pain (Robinson, 1967). It has also been shown that there is a close positive correlation between the degree of ST segment depression during exercise and this product. This correlation holds even if the same product reflects an increased heart rate and lower blood pressure on different occasions (Detry *et al.*, 1970). But there was no difference in this product when pain occurred on each of the 2 days of this study, despite a significant decrease in heart rate with the NAA as this was compensated by a trend towards higher blood pressure.

This is the first demonstration that reduction of plasma FFA concentration can alter ST segment changes associated with myocardial ischaemia. Though pain tolerance was unchanged, further studies of the effects of metabolic intervention in patients with angina are indicated.

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Notes