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# Effect of testosterone cypionate on postexercise ST segment depression

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*A randomised double blind study was carried out with 50 men who had ST segment depression of 0·1 mV or more after a modified two-step exercise test. Rate and duration of exercise were the same for the last of each subject's several pretreatment tests as for his tests after 4 and 8 weeks of treatment with placebo or testosterone cypionate, 200 mg, intramuscularly weekly. The sum of ST segment depression in leads II, V4, V5, and V6 taken immediately, and 2, 4, and 6 minutes after exercise did not change significantly after 4 or 8 weeks of placebo treatment, but did decrease by 32 per cent ($P<0·0001$) and 51 per cent ($P<0·0001$) after 4 and 8 weeks, respectively, of testosterone cypionate treatment. The mechanism by which testosterone cypionate treatment results in lessened postexercise ST segment depression is not established.*

Premenopausal women have a lower incidence of myocardial infarction and death than men of similar age (Stamler, 1967). This observation has led to the notion that testosterone may predispose to, or that oestrogen may protect against, coronary artery disease. However, there has been no direct evidence linking testosterone administration to an increased incidence of myocardial infarction. On the contrary, it is oestrogen administration that has been associated with an increased incidence of myocardial infarction (Blackard *et al.*, 1970; Coronary Drug Project Research Group, 1970).

Recently, oestrogen administration has been found to increase ST segment depression in the postexercise electrocardiogram (Jaffe, 1976). Conversely, ethyloestrenol, an anabolic steroid, was found to lessen postexercise ST segment depression (Jaffe, 1973), and preliminary trials with testosterone cypionate[1] showed that this agent was particularly effective in this action. Therefore, the randomised double-blind study presented here was designed and carried out to test further the effect of testosterone cypionate therapy on the postexercise electrocardiogram.

## Patients and methods

Fifty men were selected for this study from patients who had postexercise horizontal or downsloping ST segment depression of at least 1 mm (0·1 mV) in lead II, V4, V5, or V6 which had not been present in pre-exercise tracings. Subjects with evident valvular heart disease, symptoms or signs of cerebrovascular insufficiency or congestive heart failure, or electrocardiographic evidence of left ventricular hypertrophy, intraventricular conduction defect (QRS duration $\geq$0·12 second), or atrial fibrillation, and those receiving digitalis, quinidine, procainamide, or propranolol were excluded.

A two-step exercise test was used, employing a rate and duration of exercise for each subject that would result in postexercise ST segment depression. The two-step test was used for this study rather than a graded exercise test because we had had much prior experience in evaluating other therapeutic interventions using this test. Each subject performed at least three tests (not necessarily at the same workload) before he started treatment. The tests were carried out with the objectives of selecting subjects, establishing individual test workloads, and eliminating the possibility of improvement in exercise test performance resulting from a training effect. The last test before starting treatment was considered the baseline examination for comparison with subsequent tests in which exercise was performed at the same rate and for the same time as during the baseline examination.

A standard 12-lead resting electrocardiogram was taken before each exercise test. Leads II, V4, V5, and V6 were taken immediately, 2, 4, and 6 minutes after exercise, and at additional intervals as needed to observe the electrocardiogram until its return to the pre-exercise appearance. Brachial

[1]Depotestosterone (Upjohn).

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cuff blood pressures were obtained with the subject in the supine position before exercise and immediately after exercise. Each test in a series was performed at about the same time of day and at least 4 hours postprandially. Every attempt was made to maintain exercise, work routine, food intake, and medication at a constant level throughout the study. However, because of the known effect of testosterone of causing fluid retention (Murad and Gilman, 1975), frusemide was administered to control fluid retention if, during the study, a subject gained 2·5 kg over pretreatment weight. For this reason 4 placebo treated and 9 testosterone cypionate treated subjects received frusemide for a mean duration of 2 weeks. 'Coronary vasodilator' drugs were discontinued 12 hours before each exercise test.

Before starting treatment, the nature of the study and possible effects and side-effects of cottonseed oil and of testosterone cypionate were thoroughly discussed with each subject and written informed consent was obtained.

Vials containing 10 ml of either cottonseed oil (placebo) or testosterone cypionate (200 mg/ml in cottonseed oil) which were identical in appearance except for a code number assigned by the Pharmacy Department of Bay Medical Center, where they had been prepared, were randomly assigned to the subjects. Each subject received 1 ml of either cottonseed oil or testosterone cypionate in cottonseed oil intramuscularly each week for 8 weeks. Neither the subject nor anyone involved in his medical care or testing learned which of the two materials was administered until after the study was completed. Records were kept of each subject's haemoglobin, haematocrit, and electrocardiographic response to exercise before treatment and after 4 and 8 weeks of treatment. Subjects were weighed weekly.

In each of 3 exercise tests (baseline, after 4, and after 8 weeks of treatment) for each subject the depression of the ST segment below the isoelectric line was measured at a locus 80 ms after the onset of the ST segment. Measurements were made in leads II, V4, V5, and V6 taken immediately, and 2, 4, and 6 minutes after exercise. The sum of these 16 measurements was used for comparing each baseline test with those performed after 4 and 8 weeks of treatment. [The severity of the ischaemic response may be graded not only by the magnitude of ST segment displacement, but also by its duration after the end of exercise (Bruce and Hornsten, 1969; Detry, 1973). Therefore the sum of the 16 measurements reflects both the magnitude and the duration of the ST segment depression in 4 leads, and may be a more representative assessment of the stress-induced abnormality than if only a single lead or time interval is employed.] The measurements were made from electrocardiographic tracings that were identified only by a numerical code that was unknown to the observer.

## Results

Characteristics of the 50 men are shown in Table 1. Subjects ranged from 35 to 71 years in age, with a mean age of 58; 27 had earlier been found to have hypertension (diastolic pressure $\geq$90 mmHg); 10 had diabetes mellitus; 43 had stable, characteristic angina pectoris of at least 6 months' duration; and 20 had had a previous myocardial infarction confirmed by an abnormal Q-wave on electrocardiogram or by a clinical course (including cardiac enzyme changes) suggesting infarction. After the study was completed, the characteristics of the placebo and of the testosterone cypionate treated groups were tabulated (Table 1). There was no significant difference in any of the characteristics listed when they were analysed by the t test for the difference of means.

In the group treated with placebo for 4 weeks the sum of ST depression changed by mean $\pm$SEM values of $-0{\cdot}4 \pm 0{\cdot}5$ mm and by $0{\cdot}6 \pm 2{\cdot}4$ per cent; and after 8 weeks by $-0{\cdot}2 \pm 0{\cdot}3$ mm and by $1{\cdot}6 \pm 2{\cdot}4$ per cent. None of these changes was significant when analysed by the paired t test (Table 2).

After 4 weeks of testosterone cypionate treatment the sum of ST depression decreased by mean $\pm$SEM values of $3{\cdot}9 \pm 0{\cdot}9$ mm and by $31{\cdot}7 \pm 6{\cdot}5$ per cent; and after 8 weeks by $6{\cdot}0 \pm 1{\cdot}0$ mm and by $51{\cdot}2 \pm 7{\cdot}0$ per cent. All of these decreases were highly significant ($P < 0{\cdot}0001$) (Table 2).

Neither the mean haemoglobin level nor the mean haematocrit level changed significantly with 4 or 8 weeks of placebo treatment (Table 3). After 4 and 8 weeks of testosterone cypionate treatment, mean haemoglobin levels increased 0·7 and 1·4 g/100 ml, and mean haematocrit levels increased 3

Table 1 *Characteristics of the subjects*

| | *All subjects* | *Placebo-treated subjects* | *Testosterone cypionate-treated subjects* |
|---|---|---|---|
| Number of subjects | 50 | 25 | 25 |
| Age range (y) | 35–71 | 46–71 | 35–70 |
| Mean age (y) | 58 | 61 | 57 |
| Hypertension | 27 | 14 | 13 |
| Diabetes mellitus | 10 | 5 | 5 |
| Angina pectoris | 43 | 21 | 22 |
| Previous myocardial infarction | 20 | 10 | 10 |

and 5 ml/100 ml, respectively, all significant ($P < 0.001$) increases.

When subjects were grouped as placebo or testosterone cypionate treated, there was no significant change in weight, pre-exercise blood pressure, or immediate postexercise systolic pressure or heart rate after either 4 or 8 weeks of treatment (Table 3). However, when the testosterone cypionate treated subjects were subgrouped so that the first subgroup consisted of those whose change in ST segment

Table 2 *Comparison of sum of ST segment depression in leads II, V4, V5, and V6 before treatment (baseline) with values after 4 and 8 weeks of treatment with placebo or testosterone cypionate*

| *Subject No.* | *Sum of ST depression* | | | *Change in sum of ST depression* | | | |
|---|---|---|---|---|---|---|---|
| | *Baseline (mm)* | *4 weeks (mm)* | *8 weeks (mm)* | *4 weeks (mm)* | *(%)* | *8 weeks (mm)* | *(%)* |
| *Placebo treated* | | | | | | | |
| 1 | 14·7 | 14·2 | 12·4 | −0·5 | −3·4 | −2·3 | −15·6 |
| 2 | 40·2 | 30·1 | 34·3 | −10·1 | −25·1 | −5·9 | −14·7 |
| 3 | 10·2 | 10·5 | 8·9 | 0·3 | 2·9 | −1·3 | −12·7 |
| 4 | 12·3 | 14·1 | 10·9 | 1·8 | 14·6 | −1·4 | −11·4 |
| 5 | 29·0 | 23·2 | 25·8 | −5·8 | −20·0 | −3·2 | −11·0 |
| 6 | 14·2 | 13·8 | 13·1 | −0·4 | −2·8 | −1·1 | −7·7 |
| 7 | 10·9 | 9·8 | 10·2 | −1·1 | −10·1 | −0·7 | −6·4 |
| 8 | 3·5 | 3·6 | 3·3 | 0·1 | 2·9 | −0·2 | −6·1 |
| 9 | 5·2 | 4·8 | 4·9 | −0·4 | −7·7 | −0·3 | −5·8 |
| 10 | 11·0 | 11·3 | 10·5 | 0·3 | 2·7 | −0·5 | −4·5 |
| 11 | 9·0 | 8·2 | 9·0 | −0·8 | −8·9 | 0·0 | 0·0 |
| 12 | 6·8 | 6·7 | 6·8 | −0·1 | −1·5 | 0·0 | 0·0 |
| 13 | 14·9 | 16·1 | 15·2 | 1·2 | 8·0 | 0·3 | 2·0 |
| 14 | 10·8 | 10·3 | 11·2 | −0·5 | −4·6 | 0·4 | 3·7 |
| 15 | 15·4 | 15·9 | 16·0 | 0·5 | 3·2 | 0·6 | 3·9 |
| 16 | 7·4 | 7·5 | 8·0 | 0·1 | 1·3 | 0·6 | 8·1 |
| 17 | 9·8 | 9·4 | 10·7 | −0·4 | −4·1 | 0·9 | 9·2 |
| 18 | 6·3 | 6·2 | 7·0 | −0·1 | −1·6 | 0·7 | 11·1 |
| 19 | 12·6 | 13·4 | 14·0 | 0·8 | 6·3 | 1·4 | 11·1 |
| 20 | 7·0 | 7·9 | 7·8 | 0·9 | 12·9 | 0·8 | 11·4 |
| 21 | 7·3 | 9·4 | 8·2 | 2·1 | 28·8 | 0·9 | 12·3 |
| 22 | 10·3 | 9·2 | 11·6 | −1·1 | −10·7 | 1·3 | 12·6 |
| 23 | 10·1 | 10·3 | 11·5 | 0·2 | 2·0 | 1·4 | 13·9 |
| 24 | 9·5 | 10·3 | 10·9 | 0·8 | 8·4 | 1·4 | 14·7 |
| 25 | 11·3 | 13·8 | 13·7 | 2·5 | 22·1 | 2·4 | 21·2 |
| Mean ±SEM | 12·0 ±1·5 | 11·6 ±1·1 | 11·8 ±1·3 | −0·4 ±0·5<br>P > 0·4 | 0·6 ±2·4<br>P > 0·7 | −0·2 ±0·3<br>P > 0·5 | 1·6 ±2·4<br>P > 0·5 |
| *Testosterone cypionate treated* | | | | | | | |
| 1 | 7·0 | 0·0 | 0·0 | −7·0 | −100·0 | −7·0 | −100·0 |
| 2 | 4·9 | 1·2 | 0·0 | −3·7 | −75·5 | −4·9 | −100·0 |
| 3 | 13·8 | 0·8 | 0·7 | −13·0 | −94·2 | −13·1 | −94·9 |
| 4 | 3·3 | 3·4 | 0·2 | 0·1 | 3·0 | −3·1 | −93·9 |
| 5 | 5·0 | 3·2 | 0·8 | −1·8 | −36·0 | −4·2 | −84·0 |
| 6 | 15·9 | 9·0 | 3·7 | −6·9 | −43·4 | −12·2 | −76·7 |
| 7 | 8·3 | 3·6 | 2·0 | −4·7 | −56·6 | −6·3 | −75·9 |
| 8 | 10·1 | 4·9 | 2·5 | −5·2 | −51·5 | −7·6 | −75·2 |
| 9 | 8·2 | 5·5 | 2·1 | −2·7 | −32·9 | −6·1 | −74·4 |
| 10 | 10·0 | 3·4 | 3·2 | −6·6 | −66·0 | −6·8 | −68·0 |
| 11 | 20·9 | 10·6 | 6·9 | −10·3 | −49·3 | −14·0 | −67·0 |
| 12 | 10·1 | 9·8 | 3·5 | −0·3 | −3·0 | −6·6 | −65·3 |
| 13 | 8·2 | 2·8 | 3·7 | −5·4 | −65·8 | −4·5 | −54·9 |
| 14 | 44·9 | 28·6 | 21·8 | −16·3 | −36·3 | −23·1 | −51·4 |
| 15 | 11·8 | 8·3 | 6·3 | −3·5 | −29·7 | −5·5 | −50·8 |
| 16 | 9·0 | 6·6 | 5·6 | −2·4 | −26·7 | −3·4 | −37·8 |
| 17 | 20·3 | 17·6 | 13·7 | −2·7 | −13·3 | −6·6 | −32·5 |
| 18 | 29·7 | 23·3 | 22·8 | −6·4 | −21·5 | −6·9 | −23·2 |
| 19 | 15·4 | 13·9 | 12·3 | −1·5 | −9·7 | −3·1 | −20·1 |
| 20 | 12·6 | 12·8 | 10·2 | 0·2 | 1·6 | −2·4 | −18·0 |
| 21 | 11·3 | 11·0 | 9·9 | −0·3 | −2·6 | −1·4 | −12·4 |
| 22 | 12·1 | 13·3 | 11·2 | 1·2 | 9·9 | −0·9 | −7·4 |
| 23 | 10·5 | 9·8 | 9·9 | −0·7 | −6·7 | −0·6 | −5·7 |
| 24 | 7·0 | 7·3 | 6·7 | 0·3 | 4·3 | −0·3 | −4·3 |
| 25 | 10·5 | 11·3 | 12·0 | 0·8 | 7·6 | 1·5 | 14·3 |
| Mean ±SEM | 12·8 ±1·8 | 8·9 ±1·4 | 6·9 ±1·3 | −3·9 ±0·9<br>P < 0·0001 | −31·7 ±6·5<br>P < 0·0001 | −6·0 ±1·0<br>P < 0·0001 | −51·2 ±7·0<br>P < 0·0001 |

Table 3 *Results of treatment with placebo or with testosterone cypionate 200 mg/week (mean ±SEM)*

| | *Placebo treated N=25* | | | *Testosterone cypionate treated N=25* | | | *Testosterone cypionate treated* | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *ST decreased > 50% N=15* | | *ST decreased < 50% N=10* | |
| | *Baseline* | *4 weeks* | *8 weeks* | *Baseline* | *4 weeks* | *8 weeks* | *Baseline* | *8 weeks* | *Baseline* | *8 weeks* |
| Haemoglobin (g/dl) | 15·3 ±0·2 | 15·2 ±0·2 | 15·3 ±0·2 | 15·5 ±0·2 | 16·2 ±0·2* | 16·9 ±0·2* | 15·4 ±0·2 | 16·9 ±0·3* | 15·7 ±0·2 | 16·8 ±0·3* |
| Haematocrit (ml/dl) | 45 ±0·5 | 45 ±0·5 | 46 ±0·5 | 46 ±0·5 | 49 ±0·5* | 51 ±0·5* | 45 ±0·5 | 51 ±1·0* | 47 ±0·5 | 51 ±1·0† |
| Weight (kg) | 83 ±2·5 | 84 ±2·5 | 84 ±2·5 | 79 ±2·0 | 81 ±2·0 | 81 ±2·0 | 79 ±2·5 | 82 ±2·5 | 81 ±3·5 | 81 ±3·5 |
| Pre-exercise BP (mmHg) | 134 ±4 / 80 ±2 | 132 ±4 / 76 ±2 | 133 ±4 / 77 ±2 | 135 ±4 / 81 ±2 | 133 ±4 / 80 ±4 | 135 ±4 / 80 ±6 | 130 ±4 / 79 ±2 | 132 ±4 / 78 ±2 | 142 ±7 / 84 ±7 | 139 ±6 / 84 ±3 |
| Postexercise systolic BP (mmHg) | 166 ±4 | 168 ±6 | 166 ±6 | 172 ±5 | 168 ±5 | 167 ±6 | 174 ±6 | 166 ±8 | 169 ±9 | 168 ±11 |
| Postexercise heart rate (beats/min) | 132 ±4 | 134 ±4 | 134 ±4 | 138 ±4 | 135 ±4 | 134 ±4 | 135 ±6 | 129 ±6‡ | 142 ±5 | 141 ±4 |

Significantly different from baseline as determined by Student's t test.
*P < 001.
†P < 0·01.
‡ < 0·05.

depression at 8 weeks of treatment was greater than 50 per cent (i.e. the first 15 testosterone cypionate treated subjects listed in Table 2), and the second subgroup consisted of those whose ST segment depression was less than 50 per cent (i.e. the last 10 testosterone cypionate treated subjects listed in Table 2), then the subjects in the first subgroup experienced a significant ($P < 0·05$) decrease in postexercise heart rate. This was not found in the second subgroup (Table 3).

During the first 4-week treatment period 3 testosterone cypionate treated subjects received frusemide to control water retention. They showed a mean decrease in ST segment depression of 24·3 per cent as compared with a mean decrease of 32·3 per cent for the 22 testosterone cypionate treated subjects who received no frusemide during that time. Nine testosterone cypionate treated subjects who received frusemide during the second 4-week treatment period showed a mean decrease in ST segment depression of 53 per cent, whereas, the 16 testosterone cypionate treated subjects who received no frusemide during that time had a mean decrease of 50·2 per cent. This suggests that the effect of testosterone cypionate on postexercise ST segment depression was not significantly altered by adding frusemide.

## Discussion

Although the placebo effect can have a strong and favourable influence on the symptoms of patients with angina pectoris (Dimond *et al.*, 1960), it has not been shown to affect electrocardiographic abnormalities after exercise. The lack of effect of placebo on the results of exercise testing is confirmed here by the lack of significant ($P > 0·7$ and $P > 0·5$) change in postexercise ST segment depression after 4 and 8 weeks of placebo treatment (Table 2).

In contrast, postexercise ST segment depression decreased by 31·7 per cent after 4 weeks of treatment with testosterone cypionate and by 51·2 per cent after 8 weeks of treatment, both decreases being highly significant ($P < 0·0001$).

There are many possible mechanisms by which testosterone cypionate treatment might result in decreased postexercise ST segment changes. For example, it might lessen postexercise ST segment abnormality by decreasing myocardial oxygen requirements. The immediate postexercise systolic blood pressure and the immediate postexercise heart rate reflect myocardial oxygen consumption. Neither was significantly decreased after testosterone cypionate treatment when statistical analysis dealt with the 25 testosterone cypionate treated subjects grouped together (Table 3). However, the subgroup consisting of the 15 testosterone cypionate treated subjects who developed a decrease in ST segment depression of greater than 50 per cent after 8 weeks of treatment experienced a mean postexercise heart rate which was significantly ($P < 0·05$) slower after treatment than before treatment (Table 3). This slower heart rate might be the cause of lessened ischaemia (consequent to decreased myocardial oxygen need) or it might be the result of lessened ischaemia. That is, myocardial ischaemia produces many changes in cardiac haemodynamics which might lead to an increased heart rate (Schlant, 1974). Therefore, lessened postexercise ischaemia might result in a slower postexercise heart rate. However, it is doubtful that a

decrease in postexercise heart rate accounts for the decrease in postexercise ST segment depression after testosterone cypionate treatment because the change in the postexercise heart rate did not correlate with the change in the postexercise ST segment depression in these subjects ($r=0{\cdot}156$; $P=0{\cdot}6$).

Androgens increase red cell 2,3 diphosphoglycerate (Parker *et al.*, 1972) which may make oxygen more available to myocardial cells and which may inhibit platelet aggregation (Iatridis *et al.*, 1975) and may alter blood volume (Besa *et al.*, 1974). Testosterone produces a sense of increased physical vigour, increases skeletal muscle mass and strength, and causes retention of sodium, potassium, chloride, protein, and water (Murad and Gilman, 1975). These effects were not investigated in this study (except for recording subjects' weight).

An increased oxygen carrying capacity resulting from an increase in the blood haemoglobin level induced by testosterone cypionate treatment is another possible mechanism leading to lessening of postexercise ST segment abnormality. It is recognised (Shahidi, 1973) that haemoglobin levels rise in response to testosterone or anabolic steroid administration. In the present study mean haemoglobin values increased significantly ($P<0{\cdot}001$) after both 4 and 8 weeks of treatment with testosterone cypionate (Table 3). However, there was no significant correlation ($r=-0{\cdot}021$; $P>0{\cdot}9$) between changes in haemoglobin and postexercise ST segment depression in subjects treated with testosterone cypionate. This suggests that the decrease in mean postexercise ST segment depression after testosterone cypionate treatment probably results from a mechanism other than that of an increase in haemoglobin level.

Testosterone and anabolic steroids have been shown (Grunt and Higgins, 1960; Háva and Helfert, 1967; Greenberg *et al.*, 1973) to mediate a decrease in smooth muscle tone. An increase in coronary arterial smooth muscle mass secondary to sex hormone administration has been suggested (Jaffe and Rowe, 1972) as a mechanism for increasing coronary collateral development. Therefore, effects of testosterone on coronary arterial smooth muscle tone and/or mass may lead to dilatation of coronary arteries or their collaterals, and thereby decrease postexercise ST segment depression.

Testosterone might alter cell membrane properties or the distribution of ions to cause a change in the electrophysiology of the heart resulting in a lessening of postexercise ST segment depression. In the present study angina pectoris was not evaluated. However, in preliminary longer term studies the frequency and severity of angina pectoris decreased with testosterone cypionate treatment, suggesting that the decrease in ST segment depression may be related to lessened ischaemia rather than to altered electrophysiology.

This study shows that testosterone cypionate treatment results in lessened postexercise ST segment depression. The mechanism or mechanisms underlying this finding are unknown.

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