

## Effect of oestrogens on postexercise electrocardiogram

Martin D. Jaffe

From 2110 Sixteenth Street, Bay City, Michigan 48706, U.S.A.

*The effect of three oestrogens (including an oestrogen-progestogen combination) on the postexercise electrocardiogram was studied in 33 men and 18 women who earlier had shown ST segment abnormalities after exercise. When pretreatment exercise tests were compared with tests after two weeks of treatment, the post-exercise ST segments which were abnormal before treatment became even more abnormal in 18 (90%) of 20 subjects treated with conjugated oestrogens 10 mg daily, in 16 (89%) of 18 subjects treated with stilboestrol 5 mg daily, and in 12 (92%) of 13 subjects treated with norethynodrel (9.85 mg) and mestranol (0.15 mg)<sup>1</sup> daily. The ST segment abnormalities reverted to pretreatment appearance within 6 weeks of stopping oestrogens. When 10 subjects with normal near-maximal exercise tests were treated for 2 weeks with conjugated oestrogens 10 mg daily, the tests remained unchanged in 9.*

*The hypothesis favoured to explain these findings is that of an oestrogen-induced increase in coronary artery smooth muscle tone. An increase in arterial tone would also account for the increased incidence of myocardial (and cerebral) infarction that has been reported among individuals treated with oestrogen, either alone or in combination with progestogen.*

The reason premenopausal women have a lower incidence of death from myocardial infarction than men of similar age is not understood (Stamler, 1967). That oestrogen alone affords this protection against myocardial infarction seems unlikely in view of the fact that oestrogen administration has been shown to be associated with an increased incidence of myocardial infarction (Robinson, Higano, and Cohen, 1963; McDowell, Louis, and McDevitt, 1967; Blackard *et al.*, 1970; Coronary Drug Project Research Group, 1970) and also of stroke (Robinson *et al.*, 1963; McDowell *et al.*, 1967; Blackard *et al.*, 1970). Administration of oestrogens with progestogens in the form of oral contraceptive agents has also been associated with myocardial infarction (Waxler *et al.*, 1971; Dear and Jones, 1971; Maleki and Lange, 1973; Radford and Oliver, 1973; Ciraulo, 1975) and stroke (Masi and Dugdale, 1970; Dalessio, 1972; Collaborative Group for the Study of Stroke in Young Women, 1973; Horenstein, 1975). There has been no generally acceptable explanation for these findings. If oestrogens induce changes in the circulation

even before infarction, recognition of these changes might offer new insights into the little understood relation between sex hormones and coronary heart disease. It was reasoned that the postexercise electrocardiogram reflects the capability of the coronary arteries (including collaterals) to deliver blood to meet myocardial oxygen needs for any given exercise load. An effect of oestrogen on the coronary circulation might, therefore, be shown by changes in the postexercise electrocardiogram. In this study, the effect of three oestrogens (including an oestrogen-progestogen combination) was assessed by this technique.

### Patients and methods

The effect of oestrogens on the postexercise electrocardiogram was studied in 33 men and 18 women who had previously been shown to have an abnormal electrocardiographic response to exercise. Their ages ranged from 40 to 70 years (mean 57). Eighteen subjects had had a previous myocardial infarction confirmed by an abnormal Q wave on the electrocardiogram or by a clinical course (including cardiac enzyme changes) suggesting infarction; 38 had stable, characteristic, but not in-

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<sup>1</sup>Enovid (Searle).

capacitating angina pectoris; 30 were receiving treatment for hypertension (diastolic pressure  $\geq 90$  mmHg) and 19 for diabetes mellitus. Subjects with incapacitating angina pectoris, the 'intermediate coronary syndrome', or cerebrovascular insufficiency were excluded because of the concern that myocardial infarction or stroke might be precipitated by oestrogen administration. Subjects with an organic heart murmur, overt congestive heart failure, or electrocardiographic evidence of left ventricular hypertrophy, intraventricular conduction defect (QRS duration  $\geq 0.12$  s), or atrial fibrillation, and those receiving digitalis, quinidine, procainamide, or propranolol were also excluded.

A two-step exercise test was used employing a rate and duration (usually between 3 and 6 minutes) of exercise for each subject, which would result in an abnormal postexercise ST segment response. The two-step test rather than a graded exercise test was used for this study because of our previous experience in evaluating other therapeutic interventions using this test. Horizontal or downsloping ST segment depression of 0.1 mV (1 mm) or more not present on the pre-exercise tracing was the single criterion by which the electrocardiographic response to exercise was termed abnormal: this occurred in 48 subjects. Horizontal or downsloping ST segment depression of at least 0.5 mm but less than 1 mm was termed possibly abnormal: this occurred in 3 subjects.

At least three exercise tests were obtained before starting treatment. The tests were carried out with the object of selecting subjects, establishing individual test workloads, and eliminating the possibility of improvement in exercise test performance resulting from a training effect. The last postexercise electrocardiogram before treatment (baseline) was compared with that recorded at the completion of two weeks of oestrogen treatment, when exercise was performed at the same rate and for the same time as during the baseline test. In addition, in 24 of the 51 subjects similar testing was performed 4 to 6 weeks after treatment was completed, and this postexercise electrocardiogram was compared with the baseline recording and that obtained after two weeks of oestrogen treatment.

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

others, and at least four hours after a meal. Exercise and work routines, food intake, and drug treatment were maintained at a constant level between tests. No short or long acting 'coronary vasodilators' were taken by the subjects during the 12 hours before exercise testing.

Before starting treatment and after the nature of the study and possible effects of the drugs had been thoroughly discussed, written informed consent was obtained from each subject.

At the time the postexercise ST segment of the baseline and post-treatment recordings were compared and the differences between them recorded, the recordings were identified only by a code which was unknown to the observer. The code was then broken in order to determine which recordings were baseline and which were post-treatment. Grading was as follows:

*Grade 0:* No change in ST segment slope or depression as compared with the corresponding baseline recording after exercise.

*Grade 1:* Decrease of the ST segment slope. To be so classified, an upsloping ST segment must have become horizontal or downsloping, or a horizontal ST segment must have become downsloping.

*Grade 2:* ST segment depression up to 1 mm greater than in the corresponding baseline tracing.

*Grade 3:* ST segment depression of 1 mm or more greater than in the corresponding baseline tracing.

Each of the 51 subjects was treated for two weeks with either conjugated oestrogens<sup>1</sup> 10 mg daily, stilboestrol 5 mg daily, or norethynodrel 9.85 mg with mestranol 0.15 mg (Enovid) daily.

Ten additional subjects (5 men; 5 women), selected from patients found to be free of evident disease on routine history and physical examination, who had a normal resting and postexercise electrocardiogram were treated with conjugated oestrogens 10 mg daily for 2 weeks and then retested.

## Results

The effect of conjugated oestrogens, 10 mg daily, on the electrocardiographic response to exercise was evaluated in 20 subjects of whom 17 had an abnormal and 3 a possibly abnormal exercise test before treatment. Eighteen (90%), including the 3 subjects with a possibly abnormal exercise test before treatment, showed an increase in post-exercise ST segment changes after two weeks of treatment (Table).

Eighteen other subjects who had an abnormal exercise test before treatment were given stilboestrol, 5 mg daily (Table). Sixteen (89%)

<sup>1</sup>USP

TABLE Distribution of subjects according to degree of increase of postexercise ST segment abnormality after two weeks of hormone treatment

	Increase of ST segment abnormality				Total cases (%)
	Grade 0	1	2	3	
Conjugated oestrogens, 10 mg daily	2 (10)	11 (55)	6 (30)	1 (5)	20
Stilboestrol, 5 mg daily	2 (11)	6 (33)	6 (33)	4 (22)	18
Norethynodrel 9.85 mg + mestranol* 0.15 mg, 10 mg daily	1 (8)	3 (23)	5 (38)	4 (31)	13
All oestrogen-treated subjects	5 (10)	20 (39)	17 (33)	9 (18)	51

\*Enovid (Searle).

showed an increase in postexercise ST segment changes after 2 weeks of treatment.

Norethynodrel (9.85 mg) with mestranol (0.15 mg) (Enovid) was given daily to 13 additional subjects who had abnormal exercise tests before treatment (Table). Twelve (92%) showed increased postexercise ST segment changes after 2 weeks of treatment.

In 46 (90%) of the 51 subjects oestrogen treatment resulted in an increase in the postexercise ST segment abnormalities; in 5 (10%) of the 51 subjects there was no change; and in no instance did the ST segment abnormality lessen with treatment (Table). When 24 of the 51 subjects were tested again 4 to 6 weeks after oestrogens were stopped, it was found that the postexercise ST segment abnormalities had reverted to a pretreatment appearance in all.

The immediate postexercise heart rate of subjects in the three treatment groups before treatment was  $131 \pm 5$  (mean  $\pm$  SEM) beats per minute and after treatment was essentially unchanged ( $132 \pm 4$  beats per minute). The immediate postexercise systolic pressure before treatment was  $162 \pm 6$  mmHg and after treatment was  $157 \pm 4$  mmHg. This difference was not significant. The subjects averaged 0.5 kg weight gain with treatment. No myocardial infarction or stroke occurred with treatment.

Three subjects had previously had coronary arteriography. In two this showed the presence of obstructive coronary artery disease. The other, a 48-year-old man with angina pectoris and a possibly abnormal electrocardiographic response to exercise, had a normal coronary arteriogram. He was treated with conjugated oestrogens, 10 mg daily, which were discontinued after 5 days because of greatly increased frequency and severity of chest pain. An exercise test two days later showed an increase (grade 2) in ST segment abnormality after exercise.

Of the normal subjects who were treated for 2 weeks with conjugated oestrogens, 10 mg daily, 9 showed no change in the postexercise electrocardiogram after treatment and 1 developed a more horizontal ST segment (without ST segment depression) than before treatment.

### Discussion

Exercise-induced ST segment depression is usually considered evidence of myocardial ischaemia (Detry, 1973), though factors other than ischaemia may also produce these changes (Bruce, 1974; Lary and Goldschlager, 1974). Since most of the subjects in this study had clinically evident coronary heart disease as manifested by angina pectoris or a previous myocardial infarction, the postexercise ST segment changes in this group were probably the result of ischaemia in most instances.

That the increase in postexercise ST segment abnormality represents an incidental oestrogen-induced electrocardiographic abnormality is unlikely because none of the 10 subjects with normal stress tests developed postexercise ST segment depression when treated with oestrogen. Furthermore, the fact that oestrogen did not produce postexercise ST segment abnormalities in these normal subjects suggests that the reserve capacity of their coronary arteries was such that the adverse effect of oestrogens was insufficient to result in ischaemic electrocardiographic abnormalities after exercise. Oestrogen administration did, however, increase postexercise ST segment changes in subjects who earlier had an abnormal or a possibly abnormal electrocardiographic response to exercise. This is compatible with the view that oestrogen treatment further reduced an already diminished coronary blood flow.

This study shows that the postexercise ST segment abnormalities that are present before oestrogen treatment become even more pronounced

immediately after treatment, and then revert to pre-treatment appearance within the subsequent 6 weeks. Any hypothesis that is proposed to explain the mechanism of action of oestrogen on the circulation must be able to explain these findings and also explain the manner by which oestrogen predisposes to myocardial or cerebral infarction. The finding that the adverse effect of oestrogen on the circulation is reversible as long as infarction has not occurred tends to exclude a process that is essentially irreversible (e.g. accelerated atherogenesis or thrombus formation) as a mechanism of oestrogen action.

That oestrogen might act to increase myocardial oxygen requirements and thereby increase post-exercise electrocardiographic abnormalities also seems unlikely because immediate postexercise systolic pressure and heart rate (which reflect oxygen need) were not higher after oestrogen treatment. The lack of significant weight gain after oestrogen treatment is evidence against a haemodilution effect or congestive heart failure as mechanisms underlying increased ST segment abnormalities.

Recently vascular spasm has been recognized as a possible mechanism leading to myocardial infarction (Cheng *et al.*, 1972; Carleton and Johnson, 1974; Sasse, Wagner, and Murray, 1975; Hellstrom, 1975; Ciraulo, 1975). Coronary arteriographic studies or necropsy of several women who experienced a myocardial infarction while receiving oral contraceptive agents did not show coronary atherosclerosis (Maleki and Lange, 1973; Radford and Oliver, 1973; Ciraulo, 1975). Spasm (constriction caused by a large increase in vascular tone) has been suggested (Ciraulo, 1975) to be the mechanism underlying these infarctions and also underlying myocardial infarction during pregnancy in women with normal coronary arteriograms (Sasse *et al.*, 1975). If oestrogen acts to increase coronary arterial tone, spasm may result if this effect is sufficiently intense. In subjects with advanced coronary obstructive disease even a modest increase in tone might result in increased postexercise electrocardiographic abnormality and a further increase in tone might result in myocardial infarction.

Coronary artery spasm may produce angina pectoris (Demany, Tambe, and Zimmerman, 1968; Oliva, Potts, and Pluss, 1973; MacAlpin, 1973; Carleton and Johnson, 1974; Donsky *et al.*, 1975). Any increase in vascular tone narrows the arterial lumen and thereby decreases arterial blood flow capacity. In the present study oestrogen treatment increased the postexercise ST segment abnormalities in a subject with normal coronary arteries (shown by arteriography) as well as in subjects with

obstructive coronary artery disease. If oestrogen results in an increase in coronary arterial (or arteriolar) tone, this mechanism would account for these findings as well as the finding that the oestrogen-induced abnormalities were lost within 6 weeks after oestrogen was stopped. An oestrogen-induced increase in coronary artery tone would also account for the occurrence of myocardial infarction in women on oral contraceptive agents (Waxler *et al.*, 1971; Dear and Jones, 1971; Maleki and Lange, 1973; Radford and Oliver, 1973; Ciraulo, 1975), and for the increased incidence of myocardial infarction in men receiving conjugated oestrogens, 5 mg daily (Coronary Drug Project Research Group, 1970), or stilboestrol, 5 mg daily (Blackard *et al.*, 1970).

When arterial smooth muscle contracts because of an increase in its tone, the degree of arterial constriction that results may be enhanced if the quantity of arterial smooth muscle is increased. Danforth, Manalo-Estrella, and Buckingham (1964) have shown that arterial smooth muscle mass increases in response to female hormones, for example during pregnancy or treatment with norethynodrel and mestranol. In this way, oestrogen treatment might further contribute to arterial constriction.

These considerations also apply to the cerebral circulation. Oestrogen treatment has been associated with an increased incidence of stroke (Robinson *et al.*, 1963; McDowell *et al.*, 1967; Blackard *et al.*, 1970). Oral contraceptive agents may exacerbate migraine headache which in some women has been followed by a stroke (Masi and Dugdale, 1970; Dalessio, 1972). Neurological symptoms in a migraine attack may be associated with spasm of the internal carotid artery or its branches and relieved by nitroglycerin (Adams and Griffith, 1970).

Oestrogen has been shown to increase contractility in the smooth muscle of the uterus (Pinto *et al.*, 1964) and to increase the responsiveness of smooth muscle in mesenteric arterioles to vasoactive hormones (Altura, 1973). However, an increase in smooth muscle tone of coronary or cerebral arteries in response to oestrogen treatment has not been studied directly. Nevertheless, an oestrogen-mediated increase in vascular smooth muscle tone accounts for the results of this study better than any other mechanism that has been considered.

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- Requests for reprints to Dr. Martin D. Jaffe, 2110 Sixteenth Street, Bay City, Michigan 48706, U.S.A.