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Acute Anti-Ischemic Effect of Testosterone in Men With Coronary Artery Disease

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Background—The role of testosterone on the development of coronary artery disease in men is controversial. The evidence that men have a greater incidence of coronary artery disease than women of a similar age suggests a possible causal role of testosterone. Conversely, recent studies have shown that the hormone improves endothelium-dependent relaxation of coronary arteries in men. Accordingly, the aim of the present study was to evaluate the effect of acute administration of testosterone on exercise-induced myocardial ischemia in men.

Methods and Results—After withdrawal of antianginal therapy, 14 men (mean age, 58 ± 4 years) with coronary artery disease underwent 3 exercise tests according to the modified Bruce protocol on 3 different days (baseline and either testosterone or placebo given in a random order). The exercise tests were performed 30 minutes after administration of testosterone (2.5 mg IV in 5 minutes) or placebo. All patients showed at least 1-mm ST-segment depression during the baseline exercise test and after placebo, whereas only 10 patients had a positive exercise test after testosterone. Chest pain during exercise was reported by 12 patients during baseline and placebo exercise tests and by 8 patients after testosterone. Compared with placebo, testosterone increased time to 1-mm ST-segment depression (579 ± 204 versus 471 ± 210 seconds; $P<0.01$) and total exercise time (631 ± 180 versus 541 ± 204 seconds; $P<0.01$). Testosterone significantly increased heart rate at the onset of 1-mm ST-segment depression (135 ± 12 versus 123 ± 14 bpm; $P<0.01$) and at peak exercise (140 ± 12 versus 132 ± 12 bpm; $P<0.01$) and the rate-pressure product at the onset of 1-mm ST-segment depression ($24\,213 \pm 3750$ versus $21\,619 \pm 3542$ mm Hg$\times$bpm; $P<0.05$) and at peak exercise ($26\,746 \pm 3109$ versus $22\,527 \pm 5443$ mm Hg$\times$bpm; $P<0.05$).

Conclusions—Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease. This effect may be related to a direct coronary-relaxing effect. (*Circulation*. 1999;99:1666-1670.)

Key Words: hormones ■ ischemia ■ heart diseases ■ coronary disease ■ exercise

The evidence that men have a greater incidence of coronary artery disease and myocardial infarction than women of similar age, together with the evidence that android fat distribution is associated with a greater incidence of coronary heart disease compared with gynoid distribution, helped to reinforce the belief that high testosterone levels are associated with an increased risk for coronary artery disease. Except for this indirect evidence linking testosterone and coronary heart disease, no direct evidence is available at this time to support the hypothesis that plasma testosterone levels or testosterone administration is associated with an increased risk of coronary artery disease and myocardial infarction.

The link between plasma testosterone levels and increased risk of coronary artery disease has been attributed at least in part to the unfavorable effect of the hormone on HDL cholesterol and fibrinolysis.[1–3] HDL cholesterol is higher in women than in men, and some reports suggest that testosterone substitution in men is associated with a decrease in plasma levels of HDL cholesterol.[1,2] Glueck et al[3] reported that testosterone correlates positively with the major stimulator of fibrinolysis, ie, tissue plasminogen activator activity, and inversely with plasminogen activator inhibitor activity and fibringen. Recent studies, however, have shown that 2-month therapy with testosterone undecanoate has a beneficial effect on lipoprotein profiles in older men.[4] In addition, although there may be an influence of plasma testosterone levels on prothrombotic state, there is no epidemiological evidence that links high testosterone levels with coronary artery disease.[4]

Previous reports indicate that testosterone may improve symptoms in patients suffering from angina pectoris and improves postexercise ST-segment depression in patients with angina.[5–13] In a long-term study (4 to 8 weeks), Jaffe[13] observed that intramuscular testosterone administration improved postexercise ST-segment depression compared with

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placebo in 50 men who had ST-segment depression after exercise. The mechanisms by which testosterone reduced ST-segment depression were not investigated. These early studies, although suggestive of a beneficial effect of testosterone in patients with angina were not randomized and placebo-controlled and were conducted in patients without angiographic evidence of coronary artery disease. Moreover, the study by Jaffe[13] evaluated the effect of testosterone only on postexercise ST-segment depression, with no information provided on the time course of ST-segment depression and hemodynamic parameters. Furthermore, all previous studies conducted in patients with angina pectoris have not used pure testosterone and therefore have not evaluated the effect of testosterone by itself on cardiovascular physiology.

Yue et al[14] showed that testosterone induces endothelium-independent relaxation of isolated rabbit coronary artery and aorta. The authors suggested that this may depend on an effect of testosterone on potassium conductance and potassium channels but not on ATP-sensitive potassium channels, and they showed that this effect is not sex-dependent or mediated by a classic hormonal receptor.[14] Thus, experimental evidence suggests that testosterone plays a role in the regulation of coronary artery tone and may have a potential beneficial effect on myocardial ischemia.

The purpose of the present study was to assess the effect of acute intravenous administration of testosterone on exercise-induced myocardial ischemia in men with proven coronary heart disease.

Methods

Patient Population

The study population included 18 patients (mean age, 58 ± 4 years; range, 45 to 66 years). All patients had proven coronary artery disease assessed by selective coronary angiography, 5 had suffered a previous myocardial infarction, and all were on antianginal medications. Coronary artery disease was defined as a stenosis >70% in one of the major epicardial coronary arteries as assessed by quantitative angiography. Before inclusion into the study, patients performed, off therapy, 1 positive exercise test using the modified Bruce protocol.

Patients with severe organic insufficiency, left ventricular hypertrophy, conduction disturbances that could prejudice the interpretation of the ST segment, uncorrected hypokalemia, unstable angina, or recent (<3 months) acute myocardial infarction, as well as those with primary valvular disease, congenital heart disease, myocardial or pericardial disease, or congestive heart failure, were excluded from the study. Patients receiving digitalis or antidepressant drugs were not included as well.

Study Protocol

Patients entered the study after a baseline exercise test performed in complete pharmacological washout showing at least 1-mm ST-segment depression. After withdrawal of antianginal and cardioactive therapy, patients underwent 2 exercise tests performed 2 days apart (Wednesday and Friday) at the same hour (±1 hour) of the day. The exercise tests were performed 30 minutes after administration of testosterone (2.5 mg IV in 5 minutes) or placebo (intravenously). Patient treatment was allocated according to a computer-generated random list prepared before the beginning of the study.

Exercise Testing

While off therapy, all patients underwent repeated symptom-limited exercise tests on different days at the same hour of the day (±1 hour) according to the modified Bruce protocol. Nitrates other than sublingual nitroglycerin were withdrawn 1 day before each exercise

test. Calcium channel blocking and β-adrenergic blocking agents were withdrawn 4 and 5 days before the study, respectively. Sublingual nitrates were allowed for the control of anginal episodes up to 6 hours before each exercise test.

A 12-lead ECG was obtained at rest, every minute during the test, at the onset of 1 mm of ST-segment depression, at peak exercise, and every minute during recovery. Leads V_2, V_5, and II were continuously monitored, and a complete 12-lead ECG was obtained at the end of each stage, at the onset of 1 mm of planar ST-segment depression, and at peak exercise. Systolic and diastolic blood pressures were measured at rest and monitored every 3 minutes during exercise and recovery.

A positive response in the ECG was defined as a horizontal or downsloping ST-segment depression >1 mm at 60 ms after the J point occurring in ≥6 consecutive complexes. The exercise test was concluded at the point of physical exhaustion, or in the presence of ST-segment depression >3 mm, severe angina, severe dyspnea, complex ventricular arrhythmia, or a decline in systolic blood pressure >20 mm Hg. Total exercise time, time to myocardial ischemia, duration of ECG ischemic changes, heart rate, blood pressure at the onset of 1-mm ST-segment depression, maximal ST-segment depression, and the time to development of angina during exercise were recorded. The ST segment 60 ms after the J point was evaluated after signal averaging by a computer-assisted system in all 12 leads. The lead showing the greatest ST-segment depression in the pretreatment exercise test was selected for analysis. The supervision and analysis of the exercise tests were performed by experienced investigators (G.R., F.P., and B.B.) unaware of treatment and its sequence.

Blood samples for the evaluation of plasma testosterone, 17β-estradiol, estrone, follicle stimulating hormone, luteinizing hormone, and sex hormone binding globulin were obtained before and after each exercise test.

Testosterone Analysis

Ten milliliters of blood was collected in plain tubes. Whole blood was spun at 3500 rpm for 9 minutes. The serum obtained was then stored at $-80°C$ for a maximum of 4 weeks. Plasma levels of testosterone were assessed with a chemiluminescence analysis. The lower limit of normal testosterone levels in men by this method is 9 mg/dL.

Statistics

Data are expressed as mean$\pm$1SD or percentages where appropriate. Two-tailed paired nonparametric test (Wilcoxon) was performed to test statistical significance. A value of $P<0.05$ was considered significant. Spearman's correlation test was performed to evaluate statistical correlation between baseline and peak testosterone plasma levels and time to 1-mm ST-segment depression.

Results

Fourteen patients met the inclusion criteria and entered the study; their clinical characteristics are given in Table 1. Four patients were excluded from the study: 2 were unable to exercise, 1 because of severe claudication and the other because he suffered a knee injury between the baseline and first study drug exercise tests, and 2 were excluded because they did not interrupt antianginal therapy before one of the exercise tests.

All patients showed at least 1 mm of ST-segment depression during baseline exercise test and on exercise after placebo, and 4 patients had a negative test (<1-mm ST-segment depression) after testosterone ($P=0.06$, Table 2). Chest pain or discomfort was reported by 12 patients during baseline and placebo exercise tests and by 8 patients after testosterone. The exercise test was discontinued because of worsening chest pain in 10 patients after placebo and in 6 patients after testosterone and because of fatigue in 4 patients after placebo and in 8 after testosterone. Baseline plasma levels of testosterone are shown in Table 3. Six

TABLE 1. Clinical and Angiographic Characteristics of the Patients Included in the Study

Mean age, y	58±4
Previous MI, n	5
Cholesterol >210 mg/dL, n	7
Diabetes, n	1
Cigarette smoking, n	4
Family history, n	6
Coronary artery disease, n	14
1 Vessel	4
2 Vessels	7
3 Vessels	3

patients had baseline plasma levels below the lower limits of normal. However, none of the patients had clinical features suggestive of hypogonadism. Plasma testosterone levels increased significantly (by 2 orders of magnitude) after intravenous testosterone administration (Table 3), and no difference in the hormonal plasma levels was observed between samples obtained before and after exercise (527±342 versus 518±337 mg/dL, P=NS). Compared with placebo, testosterone significantly prolonged time to 1-mm ST-segment depression (579±204 versus 471±210 seconds; $P<0.01$) and total exercise time (631±180 versus 541±204 seconds; $P<0.01$) (Table 4, Figure 1). Testosterone significantly increased heart rate at the onset of 1-mm ST-segment depression (135±12 versus 123±14 bpm; $P<0.01$) and at peak exercise (140±12 versus 132±12 bpm; $P<0.01$) and the rate-pressure product at the onset of 1-mm ST-segment depression (24 213±3750 versus 21 619±3542 mm Hg×bpm; $P<0.05$) and at peak exercise (26746±3109 versus 22527±5443 mm Hg×bpm; $P<0.05$). Maximum ST-segment depression and recovery time of ST-

TABLE 2. Effect of Testosterone and Placebo on Exercise Time and Time to 1-mm ST-Segment Depression in 14 Patients With Coronary Artery Disease

Patient	Treatment Sequence	Time to 1-mm ST, s		Exercise Time, s	
		Testosterone	Placebo	Testosterone	Placebo
1	P/T	780	640	810	720
2	P/T	890	758	910	808
3	T/P	−VE	670	773	760
4	P/T	−VE	628	795	729
5	T/P	720	600	730	660
6	T/P	720	680	750	770
7	P/T	−VE	149	596	266
8	T/P	237	150	290	170
9	T/P	360	350	420	390
10	P/T	−VE	335	524	345
11	T/P	383	271	422	329
12	P/T	530	350	550	527
13	P/T	720	652	726	682
14	T/P	450	360	540	480
Mean±SD		579±204	471±210	631±180	541±204

P indicates placebo; T, testosterone; and −VE, negative exercise test.

TABLE 3. Plasma Hormone Levels After Testosterone and Placebo

	Placebo	Testosterone
Testosterone, mg/dL	4.75±1.76	527±342*
Estrone, pg/mL	20±15	20±18
FSH, mIU/mL	5.2±2.7	5.3±3
LH, mIU/mL	2.6±1.2	2.5±1.1
17β-Estradiol, pmol/L	121±24	120±25
Estradiol/testosterone, ×10^{-3}	8.1±0.5	4.2±1.4*
SHBG, nmol/L	42±10	42±12

FSH indicates follicle-stimulating hormone; LH, luteinizing hormone; and SHBG, sex hormone–binding globulin.
*$P<0.01$.

segment changes were significantly improved by testosterone administration (2.1±0.4 versus 1.7±0.3 mm, $P<0.05$; and 215±34 versus 168±48 seconds, $P<0.01$, respectively). After testosterone administration, an increase in exercise time was noted in 12 of the 14 patients, and no significant changes were observed in 2 patients (Table 2). A significant inverse correlation was found between baseline plasma levels of testosterone and the improvement in time to 1-mm ST-segment depression, whereas no correlation was found between the latter variable and peak testosterone levels (Figure 2).

Discussion

The present study shows that acute administration of testosterone improves exercise-induced myocardial ischemia in male patients with coronary artery disease. Although testosterone has an anti-ischemic effect in patients with normal plasma testosterone levels, this effect seems to be more evident in those patients with lower plasma levels of the hormone. The anti-ischemic effect is not dependent on the peak plasma levels achieved, thus suggesting that possibly lower doses of testosterone may be also effective.

Previous studies have evaluated the effect of testosterone administration, usually given intramuscularly, on cardiovascular function and symptoms in men. However, these early studies have not evaluated homogeneous populations of patients with coronary heart disease, not all studies were placebo-controlled, and in all studies the evaluation of myocardial ischemia was indirect, based on the frequency of anginal episodes or postexercise ST-segment depression.

Lesser[15] reported a significant reduction of symptomatic episodes of angina in 91 of 100 patients with angina pectoris after treatment with testosterone given at a dosage of 25 mg IM. The authors also reported no effect of sesame oil injections in 5 patients who were used as control subjects. Jaffe showed that after several weeks of treatment, intramuscular testosterone administration reduced postexercise ST-segment depression in patients with angina pectoris. In all these studies, however, there is no documentation of coronary artery disease.[13] Mechanisms suggested for the effects of testosterone were vasodilation of epicardial coronary arteries or their collaterals and improvement of oxygen-carrying capacity of blood as a consequence of an increase in blood hemoglobin levels. However, the vasoactive properties of the hormone have not been shown until recently.

TABLE 4.   Effect of Testosterone and Placebo on Heart Rate and Blood Pressure During Exercise

	Baseline				1-mm ST-Segment Depression				Peak Exercise			
	Heart Rate, bpm		Blood Pressure, mm Hg		Heart Rate, bpm		Blood Pressure, mm Hg		Heart Rate, bpm		Blood Pressure, mm Hg	
Patient	T	P	T	P	T	P	T	P	T	P	T	P
1	64	73	140	150	135	120	190	180	139	128	190	180
2	74	79	120	130	155	144	175	190	158	144	175	190
3	103	86	125	150	NA	140	NA	180	145	140	185	180
4	81	74	140	145	NA	118	NA	155	138	125	180	165
5	76	68	160	160	148	125	185	200	156	130	185	200
6	90	78	120	115	123	128	160	170	143	143	170	180
7	90	88	135	135	NA	100	NA	160	120	106	160	150
8	90	98	150	150	135	130	180	160	140	138	190	170
9	84	84	130	130	131	127	170	175	138	138	200	200
10	74	64	150	130	NA	105	NA	150	118	110	220	150
11	90	80	120	130	143	135	180	160	150	140	200	160
12	67	54	130	120	136	108	210	190	140	135	220	200
13	93	84	150	150	136	145	190	200	149	146	200	200
14	74	76	130	130	130	118	180	175	135	128	180	175
Mean±SD	82±9	77±12	137±13	135±13	135±12	123±14	181±14	173±18	140±12	132±12	191±18	177±20

Yue et al[14] showed that testosterone induces relaxation of isolated precontracted rabbit coronary artery and aorta. The vasorelaxing effect of testosterone seems to be endothelium-independent, at least in vitro, because Yue et al did not find any significant difference between the relaxation effect of the hormone on isolated rings with or without endothelium. Furthermore, inhibition of nitric oxide synthase, prostaglandin synthase, aromatase, and guanylate cyclase did not affect the vasorelaxing effect of testosterone, which also was not affected by blockade of testosterone receptors. The fact that the relaxing effect of testosterone was significantly attenuated by potassium channel inhibitors led the authors to suggest that potassium conductance and potassium channels that were not ATP-sensitive may be involved in the relaxing mechanism of testosterone.[14]

The increase in time to 1-mm ST-segment depression shown after intravenous administration of testosterone suggests an acute anti-ischemic effect of the hormone. The increase in heart rate and rate-pressure product observed either at 1-mm ST-segment depression or at peak exercise

may support a direct vasodilator effect of testosterone on coronary circulation. The fact that blood pressure and heart rate at rest were similar before and after testosterone administration may indicate that a peripheral effect of the hormone, although possible, may not be a determinant of the anti-ischemic effect of testosterone. The increase in time to 1-mm ST-segment depression shown in this study is similar to that observed in women after acute administration of 17β-estradiol, showing a similar effect of sex-related sex hormones in men and women.[16] Collins et al[17] have in fact shown that intracoronary administration of 17β-estradiol restores endothelium dependent relaxation in women but not in men, suggesting a specific role of sex-related sex hormones on the cardiovascular system.

The anti-ischemic effect of testosterone shown in this study may explain the cardioprotective effect of testosterone supplementation in men with hypotestosteronemia. Indeed, in the present study, the patients who benefited most from testosterone administration were those with lower testosterone
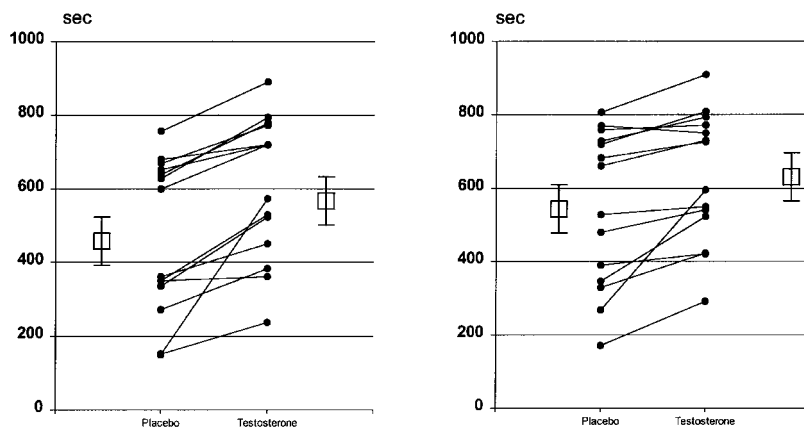

Figure 1. Time to 1-mm ST-segment depression and total exercise time after either placebo or testosterone in patients with coronary artery disease. Intravenous administration of testosterone significantly improved both parameters.
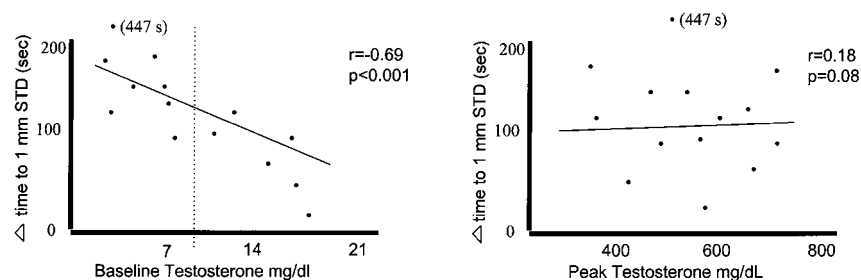
Figure 2. Correlation between baseline plasma testosterone levels and improvement in time to 1-mm ST-segment depression and total exercise time after intravenous testosterone administration. A significant inverse correlation was found between baseline plasma levels of testosterone and improvement in time to 1-mm ST-segment depression, whereas no correlation was found with improvement in total exercise time. Dotted line represents lower limit of normal testosterone values in men.

levels. Nevertheless, we have shown that testosterone administration also has an effect in men with normal plasma testosterone levels. The peak plasma levels achieved after testosterone administration in this study are supraphysiological but similar to those obtained after injection of 25 mg IM of the hormone, usually administered to hypogonadal men. Although we cannot exclude aromatization of the hormone at tissue level, the effects of the acute administration of testosterone are attributable to a direct effect of the hormone and not to its metabolites or to its conversion into estrogens. The fact that plasma levels of estrone, 17β-estradiol, and androstenedione remained unchanged after testosterone administration may be related to the kinetics of testosterone metabolism. Therefore, it seems that the anti-ischemic effect of testosterone is dependent on a direct effect of the hormone on the coronary circulation. This effect is not mediated by a receptor, because there is no evidence that testosterone receptors exist in vascular and cardiac tissues. It is unlikely that the effects of testosterone are dependent on its conversion to estradiol via the aromatase pathway, because the plasma 17β-estradiol levels remained unchanged. Furthermore, testosterone in men is primarily metabolized to estrone, whereas 17β-estradiol is produced by androstenedione metabolism. The assumption that the effect of testosterone on the cardiovascular system is not dependent on its metabolism into estrogens is also supported by the fact that the vasorelaxing effect of the hormone in vitro is not affected by aminoglutethimide, which is a competitive nonsteroidal aromatase inhibitor that blocks the conversion of androgenic prohormones to estrogens.

The detrimental effect of androgens on cardiovascular disease shown in women has not been demonstrated in men, whereas estrogens have vasoactive properties in women but not in men, in whom they may have detrimental cardiovascular consequences. Therefore, extrapolating the effect of sex hormones by their effects in different sexes may be misleading. Sex hormones have differential sexual effects in both sexes, and it is reasonable to believe that the vascular effect of sex hormones is different in the 2 sexes.

Conclusions

We have demonstrated that acute administration of testosterone improves exercise-induced myocardial ischemia in men with coronary artery disease. This beneficial effect of testosterone may be related to direct coronary vasodilation and does not seem to be dependent on its conversion into estrogens. This effect of testosterone may explain why the

hormone has been shown to improve angina pectoris in patients who received hormone replacement. Further work is required to evaluate whether this anti-ischemic effect of the hormone has any potential therapeutic implication in men with coronary artery disease.

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Correction

In the article by Rosano et al that appeared in a previous issue of the journal (*Circulation.* 1999;99:1666–1670), the units of measurement reported for testosterone levels were incorrect. These units should be ng/mL, not mg/dL. This requires changes in the text, Table 3, and Figure 2.

Under Methods: Testosterone Analysis, the last sentence should read: "The lower limit of normal testosterone levels in men by this method is 9 ng/mL."

The seventh sentence of the second paragraph of Results should read: "Plasma testosterone levels increased significantly (by 2 orders of magnitude) after intravenous testosterone administration (Table 3), and no difference in the hormonal plasma levels was observed between samples obtained before and after exercise (527 ± 342 versus 518 ± 337 ng/mL, P=NS)."

The correct versions of Table 3 and Figure 2 appear below.

TABLE 3. Plasma Hormone Levels After Testosterone and Placebo

	Placebo	Testosterone
Testosterone, ng/mL	9.75 ± 1.76	527 ± 342*
Estrone, pg/mL	20 ± 15	20 ± 18
FSH, mUl/mL	5.2 ± 2.7	5.3 ± 3
LH, mUl/mL	2.6 ± 1.2	2.5 ± 1.1
17β-Estradiol, pmol/L	121 ± 24	120 ± 25
Estradiol/testosterone, $\times 10^{-3}$	8.1 ± 0.5	4.2 ± 1.4*
SHBG, nmol/L	42 ± 10	42 ± 12

FSH indicates follicule-stimulating hormone; LH, luteinizing hormone; and SHBG, sex hormone–binding globulin.
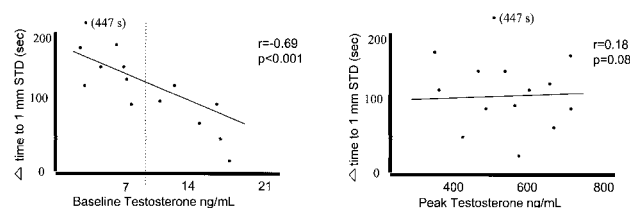

Figure 2. Correlation between baseline plasma testosterone levels and improvement in time to 1-mm ST-segment depression and total exercise time after intravenous testosterone administration. A significant inverse correlation was found between baseline plasma levels of testosterone and improvement in time to 1-mm ST-segment depression, whereas no correlation was found with improvement in total exercise time. Dotted line represents lower limit of normal testosterone values in men.