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## **Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women.**

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#### **Abstract**

**OBJECTIVES:** We sought to compare the effects of estrogen/transvaginal progesterone gel with estrogen/medroxyprogesterone acetate (MPA) on exercise-induced myocardial ischemia in postmenopausal women with coronary artery disease or previous myocardial infarction, or both.

**BACKGROUND:** Estrogen therapy beneficially affects exercise-induced myocardial ischemia in postmenopausal women; however, women with an intact uterus also take progestin to protect against uterine malignancies. The effects of combination estrogen/progestin therapy on myocardial ischemia are unknown.

**METHODS:** Eighteen postmenopausal women (mean +/- SD age 59+/-7 years) were given 17-beta-estradiol in single-blinded manner for four weeks (1 mg/day for three weeks then 2 mg/day for one week). Estradiol (2 mg/day) was then continued, and the patients were randomized (double-blind) for 12 days to either transvaginal progesterone gel (90 mg on alternate days) and oral MPA placebo (10 mg/day), or vice versa. After another two weeks on estradiol alone, the patients crossed over to progestin treatment and repeated the protocol on the opposite treatment. Patients underwent treadmill exercise testing after each estradiol phase and at day 10 of each progestin phase.

**RESULTS:** Exercise time to myocardial ischemia increased after the first estrogen phase as compared with baseline (mean difference with 95% confidence interval [CI]: 72 s [34 to 110],  $p = 0.001$ ), and was increased by combination estradiol/progesterone therapy as compared with estradiol/MPA therapy (92 s [35 to 149],  $p = 0.001$ ). Two patients (11%) were withdrawn while taking estradiol/MPA owing to unstable angina.

**CONCLUSIONS:** Combination estrogen/transvaginal progesterone gel increases exercise time to myocardial ischemia, as compared with estrogen/MPA. These results imply that the choice of progestin in women at higher cardiovascular risk requires careful consideration.

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