Relationship Between Sex Hormones, Myocardial Infarction, and Occlusive Coronary Disease

Myron H. Luria, MD; Mark W. Johnson, PhD; Richard Pego, MD; Carlos A. Seuc, MD; Sergio J. Manubens, MD; Mark R. Wieland, MS; Ralph G. Wieland, MD

• **An alteration in sex hormones has been considered a risk factor for myocardial infarction. In this study, estradiol (E_2) and testosterone (T) levels were evaluated in healthy firefighters, patients with myocardial infarction acutely and during their convalescence, patients with no evidence of occlusive coronary artery disease on arteriography, and patients with chronic angina pectoris in whom there was at least one vessel that indicated 50% occlusive coronary artery disease. Although T levels were similar in all groups, E_2 levels were substantially higher in patients with myocardial infarction and in patients with chronic angina pectoris. These results support the hypothesis that elevated estrogen levels may be a risk factor for myocardial infarction and coronary artery disease, possibly by promoting clotting or coronary spasm.**

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An alteration in sex hormones has been suggested as a major predisposing factor for myocardial infarction.[1-4] Studies indicate that estradiol (E_2) and estrone levels, when compared with the levels of control subjects, are higher in young survivors of myocardial infarction, whereas serum testosterone (T) concentrations are not notably different. Moreover, the ratio of serum concentrations of E_2 to T has been correlated with the degree of glucose-insulin-lipid defect in young patients with a history of myocardial infarction. In this study, we have attempted to expand on this hypothesis by studying patients in a wider age group and at different periods during the clinical course of coronary artery disease. Persons were evaluated within the first 24 hours and also during the postacute convalescent phase after acute myocardial infarction. To study whether these hormonal alterations may be a prospective factor for myocardial infarction and a possible factor in the development of atherosclerosis or simply a result of myocardial infarction, we also evaluated the conditions of a group of patients who were hospitalized and were undergoing coronary artery catheterization. We compared patients without any evidence of occlusive coronary disease with those who had 50% or more occlusive disease in at least one major coronary artery.

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From the Department of Medicine, St Luke's Hospital and Case Western Reserve University School of Medicine, Cleveland.

Reprint requests to the Department of Medicine, St Luke's Hospital, 11311 Shaker Blvd, Cleveland, OH 44104 (Dr Luria).

PATIENTS AND METHODS

Four separate groups of patients were studied. No patient in any group was receiving digitalis, estrogen preparations, β-receptor blocking agents, or other antihypertensive agents. None had feminizing attributes, eg, a slow rate of beard growth, unusually smooth skin, or gynecomastia. None had small testes, and none was hypertensive at the time of examination, being treated for hypertension, or gave a history suggesting hypertensive disease. The protocol for this study was approved by the St Luke's Hospital Human Research Committee, Cleveland. Group 1 consisted of 12 active firefighters, aged 37 to 57 years, whose conditions were evaluated before entering an exercise fitness program. None had a history of atherosclerotic heart disease, and all exercised on a bicycle ergometer to a maximum level without the development of ECG alterations consistent with acute coronary insufficiency or chest discomfort.

Group 2 consisted of 11 nonobese men, aged 37 to 58 years, consecutively admitted to the cardiac care unit of St Luke's Hospital with acute transmural myocardial infarction as determined by a typical history, ECG findings, and abnormal creatine phosphokinase and lactic dehydrogenase cardiac enzyme alterations. Serum samples were obtained during the acute phase (group 2A) within 24 hours of admission to the hospital and after the postacute convalescent phase (group 2B) just before discharge from the hospital. For groups 3 and 4, blood samples from patients undergoing cardiac catheterization were drawn and assigned to this study.

Group 3 consisted of six consecutive men, aged 34 to 64 years, undergoing coronary arteriography for evaluation of chest pain who were found to have no evidence of occlusive coronary artery disease. Group 4 consisted of 21 consecutive men, aged 34 to 60 years, undergoing coronary arteriography for evaluation of chest pain who were found to have 50% or more stenosis of a major coronary vessel. The arteriographic procedure and analysis have been described previously.[5] Serum E_2 and T levels were measured by modified antibody-specific radioimmunoassays.[6,7] Differential statistical significance was estimated by the Student's *t* test. Analysis of covariance also was employed.

RESULTS

Data obtained on patients in each of the four groups are given in the Table. Comparison of the control population

Age, Height, Weight, and Plasma Sex Hormone Levels in Four Study Groups*

	Group 1† Firefighters (N = 12)	Group 2A† Acute Infarction (N = 11)	Group 2B† Convalescence (N = 11)	Group 3† No CAD (N = 6)	Group 4† CAD (N = 21)
Age, yr	46.2 ± 6.3	51.6 ± 6.1	...	47.7 ± 11.7	49.4 ± 7.1
Height, cm	180 ± 2	176 ± 4	...	175 ± 4	176 ± 8‡
Weight, kg	88 ± 7	79 ± 10	...	76 ± 6	78 ± 10‡
E_2, pg/mL	38 ± 9	52 ± 9	51 ± 14	30 ± 9	46 ± 11
T, ng/dL	471 ± 56§	506 ± 268	509 ± 132	567 ± 183	557 ± 167
$E_2/T \times 10^3$	8 ± 1§	13 ± 8	10 ± 3	5 ± 1	9 ± 2

*E_2 indicates estradiol; T, testosterone; and CAD, coronary artery disease.
†Mean ± SD.
‡N = 20.
§N = 10.

and patients with acute myocardial infarction (groups 1 and 2A) disclosed statistically significant differences for E_2 ($P < .01$), E_2/T ($P < .05$), height ($P < .01$), and weight ($P < .05$). When the data of persons without notable occlusive coronary artery disease were compared with the data of those with evidence of at least 50% occlusive coronary artery disease (groups 3 and 4), significant differences were found only for E_2 ($P < .01$) and E_2/T ($P < .01$). When the control populations were grouped together (groups 1 and 3) and compared with patients with acute myocardial infarction and occlusive coronary artery disease (groups 2A and 4), significant differences were found only for E_2 ($P < .001$), E_2/T ($P < .05$), and weight ($P < .05$). No differences of statistical significance were found for E_2, T, or E_2/T levels measured during the acute stage of myocardial infarction and during convalescence.

Weights and E_2 levels were significantly higher in the firefighters compared with the weights and E_2 levels in patients without occlusive coronary artery disease demonstrated on coronary arteriograms (groups 1 and 3) ($P < .01$). Since estrogen production is increased in obese men[8] and since both estrogen and T levels may be related to age, we performed an analysis of covariance.[9] To adjust the comparison of estrogen and T levels between groups for age and obesity, we used age and either weight itself or an obesity index as the covariants. The ponderal index (PI)[10] and the body mass index (BMI)[11] were employed as obesity indices. For groups 1, 2A, 3, and 4, respectively, the PI in inches per cube root of weight in pounds was 12.3 ± 0.3, 12.5 ± 0.6, 12.5 ± 0.4, and 12.5 ± 0.5. The BMI in kilograms per height in meters squared was 27.1 ± 1.9, 25.4 ± 3.2, 24.9 ± 1.9, and 25.4 ± 2.8, respectively. There was no statistically significant difference for these indices between groups 1 and 2A or between groups 3 and 4. There was similarly no statistically significant difference for the PI between groups 1 and 3. The BMI, however, was significantly different between groups 1 and 3 ($P < .025$).

Analysis of covariance using age and either PI or BMI as covariants disclosed statistically significant differences for E_2 between groups 1 and 2A ($P < .005$), groups 3 and 4 ($P < .001$), and the combined groups 1 plus 3 vs groups 2A plus 4 ($P < .001$). The respective significance levels for differences in E_2 levels when age and weight were the covariants were $P < .025$, $P < .001$, and $P < .001$.

There was no statistically significant difference between the groups for T levels when adjusted for age and either an obesity index or weight.

A statistically significant difference for E_2/T was not found between groups 1 and 2A when these groups were adjusted for either PI, BMI, or weight. Using the same covariants, however, a statistically significant difference for E_2/T was found between groups 3 and 4 ($P < .005$) and also between the combined groups 1 plus 3 vs groups 2A plus 4 ($P < .025$).

COMMENT

Our findings confirm the correlation of increased E_2 concentrations and coronary artery disease in a variety of clinical situations.[3] Higher levels of E_2 compared with levels in control subjects were found in men during the acute stage of myocardial infarction. These levels were maintained for at least two weeks in the same patients. Higher levels also were found in patients with angina pectoris and significant occlusive coronary disease demonstrated by angiography. Thus, E_2 levels were increased compared with levels in control subjects over a wide spectrum of clinical manifestations of coronary artery disease—acute myocardial infarction, convalescence, and chronic angina.

Previous studies have indicated higher plasma E_2 levels in young 24- to 48-year-old survivors of myocardial infarction.[1,2,4] This study further extends these findings to a higher age group and also to the acute phase of myocardial infarction. In a previous study of anterior pituitary function,[12] we did not find alterations in gonadotropin levels during the stress of acute myocardial infarction. There were no notable changes in follicle-stimulating hormone and luteinizing hormone values during the first five days after infarction or during convalescence. This study indicates that the sex steroid hormones E_2 and T are similarly unaltered during the stress of acute myocardial infarction and the postacute convalescent state. Although E_2 values were significantly ($P < .01$) higher than the control values during this period (groups 1 and 2A), they were not significantly ($P > .05$) different from those of patients with chronic coronary disease (groups 2A and 4).

Phillips[3] has hypothesized that an alteration in sex hormones exists in patients with coronary artery disease. He has related the abnormal glucose tolerance associated with increased insulin response in many patients with coronary artery disease to alterations in cholesterol and triglyceride levels. This glucose-insulin-lipid defect may then be correlated with the ratio E_2/T. We have not found the relationship between E_2/T and coronary artery disease to be consistent. After adjustment for age and obesity in this study, a statistically significant difference for E_2/T was not found between control subjects and patients with acute myocardial infarction. However, a statistically significant difference for E_2/T ($P < .005$) between control subjects and patients with angiographically demonstrated coronary occlusive disease was demonstrated.

For now, it is certainly a less complicated maneuver to consider a causative role for estrogen itself rather than

E_2/T in coronary artery disease and myocardial infarction. Two lines of evidence support this hypothesis. One is clotting. Men receiving estrogens in the Coronary Drug Project[13] had an increased incidence of myocardial infarction. Since a higher incidence of thrombophlebitis and pulmonary embolism also was seen in the estrogen-treated group, a propensity toward clot production in men receiving estrogens is likely. The other is coronary spasm. The heart has been termed "a target organ" for E_2 since autoradiographic studies[14] indicate that tritiated E_2 concentrates in the atria. Additional autoradiographic studies have demonstrated estrogen receptors in the coronary arteries.[15,16] Rather than mediating a protective action on the heart, Jaffe[17] has suggested that estrogen may induce an increase in coronary artery smooth-muscle tone. When pretreatment exercise test results were compared with test results after two weeks of estrogen treatment, greater ST-segment abnormalities were noted. A role for coronary spasm[18,19] in angina pectoris and also in the development of acute myocardial infarction has now been defined. Estrogens may be important for the initiation of coronary spasm[20] in some patients with these conditions. A similar situation involving vascular spasm could include the association of estrogen treatment with exacerbation of migraine headache and other cerebrovascular diseases.[21] Recently, coronary artery spasm has been implicated as a factor in the pathogenesis of atherosclerosis.[22] This latter hypothesis could greatly expand the causative role for estrogen in coronary artery disease.

In men, T is secreted essentially by the testes. Estrogens also are secreted by the testes but approximately 65% to 75% of circulating E_2 is produced by peripheral conversion from T.[23] From approximately age 60 years, estrogen levels increase, whereas T levels diminish.[24] An increase in the efficiency of peripheral conversion of circulating T to estrogen may be responsible for these changes. The resulting hyperestrogenemia then may be associated with the increasing clinical manifestations of coronary artery disease with age. The changes demonstrated in this study, a higher level of E_2 in patients with either myocardial infarction or angiographically demonstrated occlusive coronary artery disease, might then be related to alterations occurring in the peripheral conversion process of T to estrogen at an earlier than usual age.

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