Serum Estrogen Levels in Men with Acute Myocardial Infarction

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Serum estradiol and serum estrone levels were assessed in 29 men with acute myocardial infarction; in 17 men with unstable angina; in 14 men in whom myocardial infarction was ruled out; in 12 men without apparent coronary heart disease but hospitalized in an intensive care unit; and in 28 men who were not hospitalized and who acted as control subjects. (The 12 men who were hospitalized but who did not have coronary heart disease were included to control for physical and emotional stress of a severe medical illness.) Ages ranged from 21 to 56 years. Age, height, and weight did not differ significantly among groups. Blood samples were obtained in the patient groups on each of the first three days of hospitalization. The serum estrone level was significantly elevated in all four patient groups when compared with that in the control group. Estrone level, then, did not differentiate patients with and without coronary heart disease. Serum estradiol levels were significantly elevated in the groups with myocardial infarction, unstable angina, and in the group in whom myocardial infarction was ruled out. However, estradiol levels were *not* significantly elevated in the group in the intensive care unit without coronary heart disease when compared to the level in the normal control group. Serum estradiol levels, then, were elevated in men with confirmed or suspected coronary heart disease but were not elevated in men without coronary heart disease even under the stressful conditions found in an intensive care unit. Serum estradiol levels were significantly and positively correlated ($p < 0.03$) with serum total creatine phosphokinase levels in the patients with myocardial infarction. The five patients with myocardial infarction who died within 10 days of admission had markedly elevated serum estradiol levels. The potential significance of these serum estradiol elevations is discussed in terms of estradiol's ability to enhance adrenergic neural activity and the resultant increase in myocardial oxygen demand.

Elevations of serum estradiol and estrone levels have been reported in men (24 to 48 years) who have recovered from myocardial infarction [1–4]. Serum levels of testosterone, androstenedione, and dihydrotestosterone, when evaluated, have not been elevated. These observations suggest that hyperestrogenemia may be a risk factor for myocardial infarction in middle-aged men.

Additional support for the possibility that estrogen may be a risk factor has come from studies in which estrogens have been administered to men. When survivors of myocardial infarction were treated with estrogens, they had a higher incidence of reinfarction compared with men of similar age who were not treated with estrogens. The rate

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of reinfarction was positively related to the dose of estrogen [5,6]. In addition, patients with carcinoma of the prostate treated with estrogens had an increased mortality rate from cardiovascular disease [7].

In women, the relationship of estrogens to myocardial infarction appears to be more complex. On the one hand, the incidence of myocardial infarction in women who are premenopausal is significantly lower than in men of similar ages [8], and both bilateral oophorectomy and early menopause are associated with an increased risk of premature ischemic heart disease [9–11]. These associations have led to the suggestion that estrogens protect against myocardial infarction in women. On the other hand, young women using estrogen-containing oral contraceptives have an increased risk of myocardial infarction [12,13], particularly when other risk factors are present [14]. The relationship of estrogen to myocardial infarction in women, then, is unclear.

Thus, if estrogen is a risk factor for myocardial infarction, its pathophysiology will have to be considered separately for each sex. The present study is concerned only with the relationship of estrogen to myocardial infarction and coronary disease in men under age 56.

The reports of serum estradiol elevations just cited [1–4] were in men in whom myocardial infarction had occurred at least two months previously. There are no published reports of studies of serum estrogen levels in men during the acute phase of myocardial infarction. The present study evaluates estrogen levels during that time period.

The present study also examines the question of whether serum estrogen elevations in men precede myocardial infarction. Therefore, estrogen levels are examined in two groups of men known to be at risk of myocardial infarction—patients admitted to the hospital with a diagnosis of unstable angina but without a history of prior myocardial infarction and men admitted to the hospital with chest pain but without electrocardiographic or enzyme evidence of either myocardial ischemia or infarction, that is, patients in whom myocardial infarction was ruled out.

The effects that stress might have on estrogen levels in patients hospitalized with acute myocardial infarction or unstable angina are unknown. However, an attempt was made to assess the role that stress might play by studying the serum estrogen levels of acutely ill male patients who were in a medical intensive care unit but who did not have evidence of coronary heart disease.

PATIENTS AND METHODS

Group 1. Patients with myocardial infarction: These 29 men (aged 31 to 56 years, mean age = 47.2, standard deviation = 7.4 years) had electrocardiographic and serum creatine phosphokinase (CPK) evidence of acute myocardial infarction and were admitted to a coronary intensive care unit.

Group 2. Patients with unstable angina: These 17 men (aged 35 to 55 years, mean age = 45.6, standard deviation = 6.8 years) were admitted to the coronary intensive care unit with chest pain typical of angina. All had electrocardiographic evidence of myocardial ischemia. However no electrocardiographic or blood enzyme evidence of myocardial infarction was present. These patients were studied to see if serum estradiol levels were elevated in patients with evidence of myocardial ischemia but without infarction. They did not have a history of prior myocardial infarction but are known to have an increased risk of myocardial infarction [15].

Group 3: Patients in whom myocardial infarction was ruled out: These 14 men (aged 26 to 54 years, mean age = 44.3, standard deviation = 8.5 years) were admitted to the coronary intensive care unit with chest pain but were found not to have enzyme or electrocardiographic evidence of myocardial infarction. Electrocardiographic evidence of myocardial ischemia was not studied. Previous studies [16,17] have shown that some patients in this category do have coronary heart disease and therefore are at increased risk of myocardial infarction.

Group 4. Patients in the intensive care unit without coronary artery disease: These 12 men (aged 30 to 52 years, mean age = 46.1; standard deviation = 8.7 years) were admitted to the intensive care unit with a variety of medical illnesses but had no electrocardiographic evidence or history suggesting coronary heart disease. These patients were observed to control for the physical and emotional stress of severe medical illness that resulted in admission to an intensive care unit.

Group 5. Volunteer control subjects with no known pathology: The 28 control subjects (all men) (aged 21 to 51 years, mean age = 40.5, standard deviation = 8.4 years) volunteered to donate blood specimens and had no known illnesses.

Men with illnesses known to affect blood estradiol levels, for example, liver disease, were excluded from all groups.

Blood Samples. Blood samples for serum estradiol and estrone were obtained at approximately 9:00 A.M. When possible, blood samples were obtained in each of the four groups of patients on the first, second, and third days after admission. Single blood samples were obtained from the control subjects.

Assay Methods. Serum estradiol and estrone levels were assayed by radioimmunoassay. The method used was that described by Longcope et al. [18] after celite column purification with ethyl acetate-iso-octane as eluent. The intra-assay and the interassay coefficients of variation are respectively ±5.6 and ±6.5 for estradiol and ±6.7 and ±7.3 for estrone.

Blood samples from each of the five study groups were collected and run concurrently throughout the duration of the study. Individual assay runs included blood samples from the control subjects and the various groups of patients. Quality-control serum samples were analyzed with each assay, and good agreement was obtained in all runs.

TABLE I Serum Estradiol and Estrone Levels in Group 1 (Myocardial Infarction)

Patient Number	Estradiol (pg/ml)			Estrone (pg/ml)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	27.5	42.2	29.2	54.9	78.4	60.2
2	26.5	24.7	30.6	60.5	66.2	73.3
3	20.5	28.4	36.2	44.1	82.7	87.3
4*	79.5	. . .	. . .	158.1	. . .	. . .
5*	290.0	. . .	. . .	857.1	. . .	. . .
6	47.2	39.4	93.9	46.7	44.6	80.9
7	206.2	76.5	23.3	204.2	167.9	128.4
8	27.5	66.2	27.1	166.2	147.6	156.1
9	34.6	35.5	49.4	63.2	67.3	85.4
10	39.8	60.1	248.0	99.6	111.7	135.0
11	261.8	383.2	67.2	96.7	185.5	45.3
12	79.3	219.5	203.6	67.3	199.4	192.1
13	13.2	36.3	70.4	57.4	18.3	51.6
14*	113.6	90.0	98.0	432.3	285.0	310.4
15	60.0	36.6	58.6	86.5	123.2	78.2
16	46.5	34.5	. . .	41.2	57.6	. . .
17	31.8	37.4	14.4	63.2	92.6	43.5
18	44.5	71.3	44.2	107.0	142.7	45.9
19	27.9	64.2	30.8	99.0	185.1	98.1
20	109.1	31.1	64.6	156.5	21.1	61.2
21	96.4	48.6	87.0	91.3	49.9	61.6
22	62.0	75.3	. . .	113.1	104.6	. . .
23*	94.6	102.3	243.7	199.2	269.3	333.5
24	67.5	36.8	52.9	61.2	71.9	105.2
25	121.5	. . .	. . .	161.1	. . .	. . .
26	42.4	. . .	. . .	34.3	. . .	. . .
27	. . .	25.3	31.6	117.2	36.5	33.2
28	52.7	64.6	. . .	36.7	23.8	267.9
29*	141.7	. . .	. . .	769.3	. . .	. . .
Mean	80.9	72.1	76.4	156.7	109.7	115.2
SD	70.1	77.6	69.4	198.5	74.7	86.7

* Died within 10 days of admission.

Other Indexes. Total serum creatine phosphokinase levels were obtained, when possible, on three successive days after admission. These levels were determined using the method of Rosalki et al. [19].

Clinical-hemodynamic subset classifications based on clinical examination, chest x-ray, and blood pressure status on admission and during the first 24 hours of hospitalization were established for each patient [20].

RESULTS

The data for each patient for estradiol and estrone values are presented in **Tables I to V.**

Statistical Analyses. The tests of statistical significance employed were t tests between independent groups, or t tests for repeated measurements, when appropriate. Because significant differences in variance occurred between some groups, which violates an assumption of the parametric t test, nonparametric chi-squares were also calculated where appropriate. No major differences in statistical outcomes occurred between the two techniques.

No significant differences in either serum estradiol or serum estrone mean levels occurred among the three days within any group. Therefore, averages of the three days for estradiol levels, and the three days for estrone levels were computed for each patient. These means are portrayed in **Figures 1 and 2,** and are the data utilized for all subsequent statistical analyses, including the means and standard deviations of the groups presented in **Table VI.**

Estradiol Results. The means of serum estradiol levels of the group with myocardial infarction, the group with unstable angina, and the group in whom myocardial infarction was ruled out were all significantly elevated over the comparable mean of the control group. Significance levels ranged from $p < 0.005$ to $p < 0.001$ (Table II and Figure 1).

The mean serum estradiol level of the group in intensive care who did not have coronary heart disease was not significantly different from the mean of the control group.

The means of estradiol values of the group with myocardial infarction and the group with unstable angina were not significantly different. However, these two groups of patients, who all had confirmed coronary heart disease, had mean estradiol levels that were significantly higher than the mean estradiol level of the pa-

TABLE II Serum Estradiol and Estrone Levels in Group 2 (Unstable Angina)

Patient Number	Estradiol (pg/ml)			Estrone (pg/ml)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	54.5	53.6	49.0	32.4	46.8	39.1
2	59.1	61.2	78.6	51.2	46.2	67.9
3	57.5	63.9	52.3	50.6	56.1	41.4
4	37.5	55.6	58.4	109.8	96.3	108.5
5	42.1	156.7	96.5	65.2	308.6	153.6
6	63.7	102.4	65.5	65.9	108.3	57.4
7	97.5	44.4	42.7	41.4	42.1	59.3
8	32.9	...	...	74.2	...	...
9	48.6	18.5	20.9	50.1	50.4	46.5
10	86.7	87.1	79.0	93.5	100.2	79.7
11	71.1	...	...	48.6	...	...
12	58.0	...	...	41.8	...	...
13	99.6	31.2	49.3	107.1	35.5	49.9
14	81.3	71.0	83.7	65.4	49.2	25.3
15	31.2	28.2	35.7	73.4	75.4	71.4
16	143.7	249.7	75.1	104.6	277.0	122.6
17	36.2	51.1	56.7	38.4	72.6	102.2
Mean	64.8	76.8	60.2	65.5	97.5	73.2
SD	29.6	60.8	20.7	25.1	86.1	36.4

TABLE III Serum Estradiol and Estrone Levels in Group 3 (Myocardial Infarction Ruled Out)

Patient Number	Estradiol (pg/ml)			Estrone (pg/ml)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	24.9	17.6	...	37.3	36.1	...
2	62.2	72.1	...	78.0	67.5	...
3	30.1	...	...	79.3	...	...
4	10.0	25.4	28.2	24.5	31.4	22.4
5	23.3	25.8	34.4	105.3	66.8	43.4
6	51.7	43.5	111.0	60.5	67.3	42.8
7	56.4	69.0	...	92.9	79.0	...
8	67.0	59.9	96.3	53.5	67.2	68.6
9	82.6	143.6	94.7	69.4	80.1	62.6
10	17.2	...	...	26.0	...	...
11	97.7	55.3	42.2	72.1	49.3	50.5
12	44.9	31.5	40.0	44.5	33.7	40.3
13	65.2	51.4	...	38.4	32.7	...
14	57.4	63.0	116.9	61.0	80.8	83.9
Mean	49.3	54.8	70.5	60.2	57.6	51.8
SD	25.6	33.4	37.5	24.4	19.7	19.2

TABLE IV Serum Estradiol and Estrone Levels in Group 4 (Intensive Care Unit, No Coronary Heart Disease)

Patient Number	Estradiol (pg/ml)			Estrone (pg/ml)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	35.2	44.9	16.5	21.1	96.9	25.1
2	26.5	22.5	26.5	69.0	59.1	59.5
3	15.7	17.6	15.3	91.4	77.6	81.2
4	17.9	35.1	23.2	20.4	12.5	32.2
5	28.1	45.1	19.9	108.1	116.0	126.1
6	36.6	22.8	52.3	188.5	120.5	168.6
7	51.7	73.2	...	47.3	34.7	...
8	48.4	28.5	...	34.8	11.2	...
9	56.2	60.0	...	27.4	34.2	...
10	86.7	76.0	60.5	122.9	115.8	115.0
11	35.2	31.3	...	58.6	55.4	...
12	27.3	40.7	39.9	32.5	47.8	45.9
Mean	38.8	41.5	30.8	68.5	65.1	81.7
SD	19.7	19.4	16.3	51.1	39.7	50.8

TABLE V Serum Estradiol and Estrone Levels in Group 5 (Control)

Volunteer Number	Estradiol (pg/ml)	Estrone (pg/ml)
1	31.7	54.7
2	42.6	49.3
3	23.3	24.7
4	24.3	32.5
5	19.8	35.8
6	44.4	36.8
7	47.3	42.7
8	27.9	19.0
9	16.3	14.1
10	36.4	33.9
11	22.9	40.8
12	49.7	20.5
13	40.5	30.8
14	31.2	37.3
15	42.1	57.3
16	28.6	33.4
17	30.2	47.1
18	25.6	40.2
19	32.3	42.1
20	32.8	46.6
21	30.3	52.0
22	32.1	43.4
23	37.4	57.1
24	16.3	39.6
25	24.1	47.8
26	16.9	41.2
27	23.6	32.1
28	24.8	41.1
Mean	30.6	39.1
SD	9.3	10.9

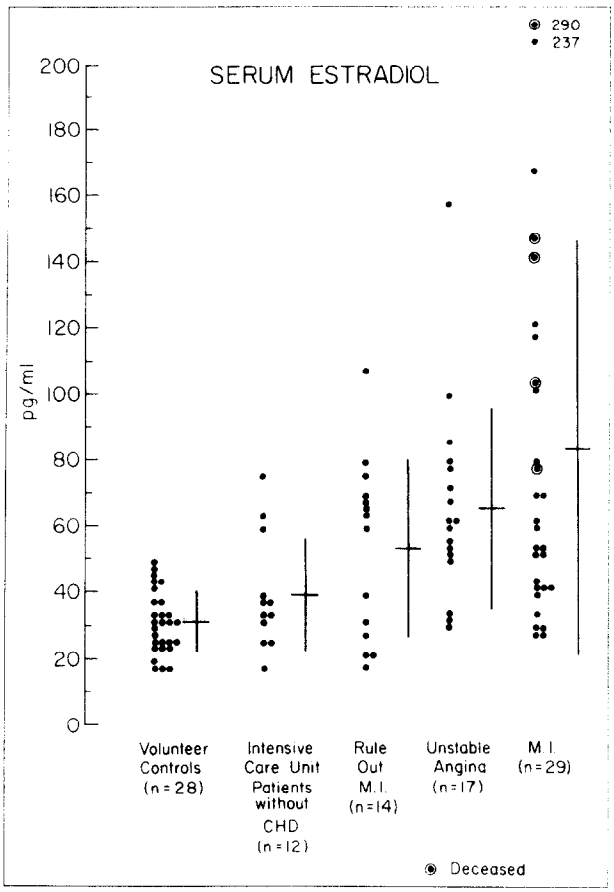

Figure 1. *Distributions of serum estradiol levels.*

tients in the intensive care unit who did not have coronary heart disease.

It is of interest that the mean estradiol level of the five patients with myocardial infarction who died within 10 days of admission was 151.7 pg/ml, compared with a mean level of 67.1 pg/ml in the 24 patients who survived (Figure 1).

It is also of interest that a number of the blood estradiol levels in the group with myocardial infarction were grossly elevated, and in the high female range, for example, 383, 290, 248, and 243 pg/ml. Our laboratory values for blood estradiol levels in women normally range from 50 to 500 pg/ml, depending on the phase of the menstrual cycle. Estradiol values above 100 pg/ml have not been seen in normal men in our laboratory. It should be noted, however, that the elevated means of estradiol in the group with myocardial infarction were not due solely to these five grossly elevated values. Ten of the 29 patients with myocardial infarction had elevations of 100 pg/ml or more, on at least one of the three days that blood specimens were obtained. Moreover, 19 of these patients who did not have blood levels above 100 pg/ml had a mean plasma estradiol level of 47.3 ± 16.2 pg/ml which is significantly ($p < 0.001$) higher than the mean of 30.6 ± 9.3 pg/ml of the control subjects. Only six of the 29 patients with myocardial infarction had peak serum estradiol levels that were less than one standard deviation of the control group above the mean of the control group.

Finally, the serum estradiol levels in the three groups of men with confirmed or suspected coronary heart disease showed marked intra-individual variation among the three days. Those with marked elevations of estradiol tended not to have these elevations on all occasions, as may be seen in Tables I to III.

Estrone Results. The mean serum estrone levels of all the groups of patients with confirmed or suspected coronary heart disease were significantly higher than the mean serum estrone level of the control group. Unlike estradiol, estrone was also significantly elevated in the patients with acute severe illnesses and without coronary heart disease (Table VI). Estrone, then, did not differentiate patients with coronary heart disease from patients in the intensive care unit who did not have coronary heart disease.

Correlations. The following product-moment correlations were computed in the group with myocardial infarction.

A significant correlation was obtained between the peak serum creatine phosphokinase levels and peak serum estradiol levels ($r = 0.41$, $n = 29$, $p < 0.03$). The correlation of peak serum creatine phosphokinase levels with peak serum estrone levels, conversely, did not approach statistical significance ($r = 0.07$).

No significant correlations were found between the clinical-hemodynamic subset classification [20] and either estrogen.

No significant correlations were observed in our data between age, height, or weight and either estrogen in the group with myocardial infarction. The combined data from all five groups also failed to yield significant correlations between age, height, or weight and either estrogen.

The correlations between estradiol and estrone levels in each group were also examined. These correlations were highly statistically significant ($p < 0.001$) in the group with myocardial infarction ($r = 0.602$) and in the group with unstable angina ($r = 0.719$), moderately significant ($p < 0.05$) in the group in whom myocardial infarction was ruled out ($r = 0.535$), and nonsignificant in patients in the intensive care unit without coronary heart disease ($r = 0.064$) and in the control subjects ($r = 0.172$).

Standard drugs, for example, nasal oxygen and morphine for pain, were administered as required. Nitrate, propranolol, parenteral lidocaine, and other anti-arrhythmic drugs were utilized in selected patients. No apparent relationships between these drugs and blood estrogen levels were observed.

Follow-up Estradiol Levels in Patients with Myocardial Infarction. In 12 patients with myocardial infarction, a single blood sample was drawn during the recovery phase, three to nine months after infarction. These blood samples did not have the markedly elevated estradiol levels found in these same patients when they were acutely ill. The absence of these elevated values was reflected in a lower mean and smaller standard deviation during the recovery phase. The mean estradiol level of these patients in the acute phase was 90.5 ±

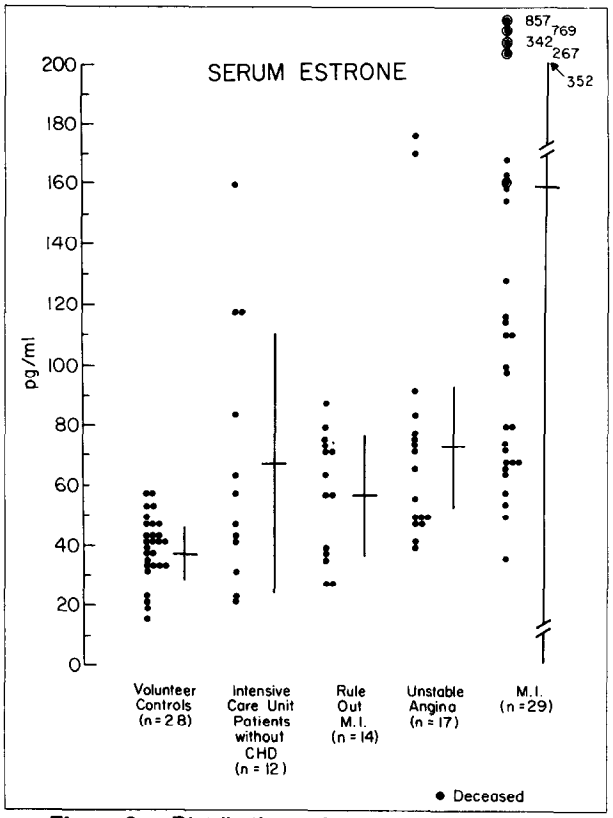

Figure 2. *Distributions of serum estrone levels.*

TABLE VI **Means and Significance Levels of Differences between Means of Estradiol and Estrone Levels in Groups 1 to 5***

	Estradiol (pg/ml)			Estrone (pg/ml)		
	Mean	SD	p	Mean	SD	p
Means of Group 1	82.5	63.7		159.0	193.0	
1 versus 2			NS			<0.03
3			<0.04			<0.01
4			<0.002			<0.03
5			<0.001			<0.002
Means of Group 2	65.3	30.0		73.8	40.0	
2 versus 3			NS			NS
4			<0.01			NS
5			<0.001			<0.01
Means of Group 3	52.7	26.9		56.9	20.5	
3 versus 4			NS			NS
5			<0.005			<0.01
Means of Group 4	39.2	17.1		66.9	43.6	
4 versus 5			NS			<0.05
Means of Group 5	30.6	9.3		39.1	10.9	

* Group 1, myocardial infarction (n = 29); Group 2, unstable angina (n = 17); Group 3, myocardial infarction ruled out (n = 14); Group 4, intensive care unit, no coronary heart disease (n = 12); Group 5, control (n = 28).

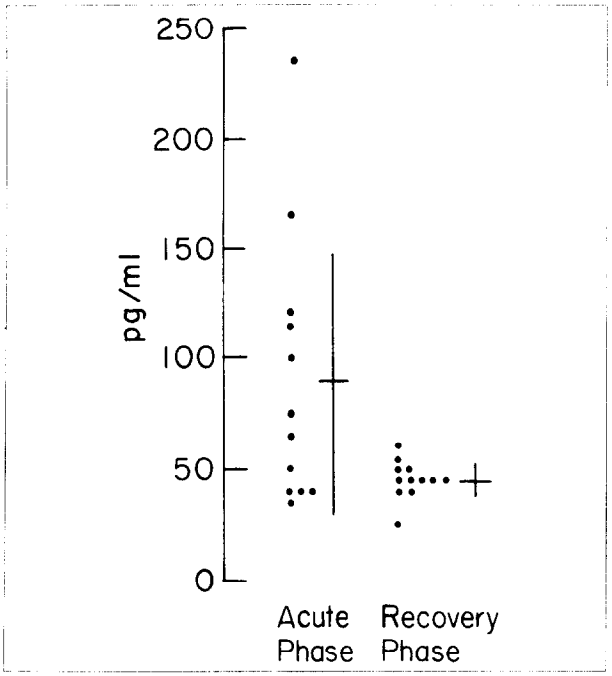

Figure 3. *Distributions of serum estradiol levels in the acute and recovery phases in 12 patients with myocardial infarction.*

59.4 pg/ml; in the recovery phase, 47.5 ± 8.0 pg/ml (**Figure 3**).

The standard deviation of the estradiol level in the acute phase was significantly greater than the standard deviation of the estradiol level in the recovery phase. Hence, a parametric t test cannot be employed to evaluate the difference between the means of the acute and recovery phases. Therefore, the nonparametric Wilcoxon matched-pairs signed-ranks test [21] was used. This test indicates that a significant difference ($p < 0.05$) does exist between the estradiol levels in the acute and recovery periods.

The mean estradiol level in the recovery phase was significantly higher than the mean estradiol level of the control subjects ($p < 0.001$).

COMMENTS

The results of this study indicate that estradiol levels are significantly elevated in men with confirmed or suspected coronary heart disease, but not in hospitalized men without clinical evidence of coronary heart disease. Elevations of estrone, however, occurred in hospitalized men with and without evidence of coronary heart disease. Therefore, estradiol did, and estrone did not, differentiate the men with confirmed or suspected coronary heart disease from the men with other illnesses in this study. Further, the estradiol level, but not the estrone level, was significantly correlated with total serum creatine phosphokinase elevations in the patients with myocardial infarction. Although the mean levels of estrone were consistently higher than those of estradiol in all groups, and approached a twofold difference in the group with myocardial infarction, estradiol is more than three times as biologically active as estrone [22]. Therefore, it appears that estradiol is the more important of the two hormones with respect to coronary heart disease in men. Accordingly, the possible biologic bases for relationships between estradiol and coronary heart disease should be considered. The reported roles of estradiol in enhancing adrenergic activity may be such a biologic basis.

The critical role of adrenergic stimulation in a variety of cardiac diseases is now well recognized [23]. Estrogens have been reported to have a number of physiologic effects, each of which could increase adrenergic activity. Specifically, estradiol has been reported to have effects that could: (1) increase the synthesis of adrenergic neurotransmitters [24,25]; (2) inhibit the enzymatic degradation of adrenergic neurotransmitters [26–30]; and (3) potentiate the synaptic activity of adrenergic neurotransmitters [31,32].

In clinical studies, estrogen administration has been reported to produce an effect on the electroencephalographic results similar to that produced by adrenergic stimulants such as norepinephrine and amphetamine [33–35].

Conventional antidepressant medications, for example, monoamine oxidase inhibitors and tricyclics, are generally considered to achieve their effects by augmenting the adrenergic activity of the central nervous system [36]. It is of interest that estrogens have also been used successfully as antidepressants [37].

These observations suggest that estrogens act as adrenergic stimulants and are significant in the context of the numerous reports of the beneficial effects of adrenergic blocking agents in the treatment of angina [38] and ventricular arrhythmias [39,40]. Adrenergic blocking agents have also been reported to reduce the rates of reinfarction and sudden death in survivors of myocardial infarction [41,42]. Conversely, amitriptyline, a drug believed to increase adrenergic neural activity, has been reported to produce a significant increase in the incidence of sudden cardiac death in patients with diagnosed coronary heart disease [43].

The mechanisms involved in these effects are complex. However, it is known that cardiac sympathetic stimulation increases myocardial oxygen demand [44] and lowers the threshold for ventricular fibrillation in the presence of experimental coronary occlusion [45]. It is now recognized that sudden cardiac death is usually due to ventricular fibrillation [46]. If estradiol increases adrenergic stimulation, then patients with coronary heart

disease who have elevated estradiol levels would be expected to have a high level of cardiac adrenergic stimulation and thereby could be predisposed to ventricular fibrillation and sudden cardiac death.

The significant correlation of estradiol levels with total serum creatine phosphokinase levels in our group with myocardial infarction is interpretable in the context of estradiol's increase of adrenergic stimulation. Peak serum creatine phosphokinase levels have been positively correlated with infarct size [47]. An increased myocardial oxygen demand secondary to increased adrenergic stimulation in the presence of coronary occlusion would be expected to increase the size of the infarct, with a corresponding elevation in total serum creatine phosphokinase levels. Conversely, the administration of an adrenergic blocking agent (propranolol) has been reported to reduce the serum creatine phosphokinase levels in patients with myocardial infarction [48].

These findings suggest that marked elevations in estradiol may predispose men with coronary heart disease to ventricular fibrillation and/or massive myocardial infarction. Of the five patients in the group with myocardial infarction who died, two died of ventricular fibrillation and three died of pump failure secondary to massive myocardial infarction. As noted earlier, these patients had markedly elevated estradiol levels.

The estradiol elevations observed in the group with unstable angina and in the group in whom myocardial infarction was ruled out may account, in part, for their symptoms of chest pain. An increased adrenergic stimulation of the heart secondary to elevated estrogen levels would increase myocardial oxygen demands and, in men with coronary heart disease, produce pain due to myocardial ischemia.

The question of whether or not marked estradiol elevations precede acute myocardial infarction cannot be answered directly from our data. However, the fact that estradiol elevations similar to those seen in men immediately after acute myocardial infarction were also observed in the two groups of men whose diagnoses are associated with a high risk of subsequent myocardial infarction, that is, those with unstable angina and those in whom myocardial infarction was ruled out, suggests that the estradiol elevations may precede the occurrence of the infarction.

Possible sources of the marked elevations of estrone and estradiol observed in our data should be considered. Either an increase in the production rate or a decrease in the metabolic clearance rate of these two hormones could produce the reported results. Our data do not allow direct assessments of these measures. However, the major shifts in hormone levels observed among 24-hour periods in our data are suggestive of changes in production rate. Comparable abrupt changes in the production of estradiol and estrone occur at mid-cycle in women. Changes in metabolic clearance rate are not known to produce such major rapid shifts in blood hormone levels.

A major source of estradiol production in normal men is conversion of testosterone to estradiol via aromatization in muscle and adipose tissue [49]; lesser sources are direct secretion by the testicle [50] and conversion of estrone to estradiol [51]. Major sources of estrone include conversion of androstenedione to estrone via aromatization [51] and direct secretion by the adrenal [52]. Finally, small amounts of estrone result from conversion of estradiol to estrone [51] and from direct secretion of estrone by the testes [50].

Our results showed positive significant correlations of serum estradiol levels and serum estrone levels in men with confirmed or suspected coronary heart disease, but no significant correlations of these two hormones occurred in men without coronary heart disease in this study. Any explanation of the biologic bases for the increased estradiol levels in men with confirmed or suspected coronary heart disease must be able to account for the high significant correlations of estradiol with estrone in these patients.

Stress-induced stimulation of adrenal cortical hormone production does not appear to be a likely source of the observed elevated and correlated levels of estradiol and estrone. Although adrenal cortical stimulation via adrenocorticotropic hormone does increase serum estrone levels [53], neither adrenocorticotropic hormone [53] nor surgical stress [54] increases serum estradiol levels. The observed elevations of estrone in our patients who were hospitalized without evidence of coronary heart disease, then, may reflect the stress of hospitalization and acute physical illness. However, this type of stress does not explain the estradiol elevations seen in our patients with confirmed or suspected coronary heart disease, and it would not produce the observed significant correlations of estradiol and estrone in these patients.

Obese men have been reported to have elevations of serum estradiol and serum estrone [55]. However, the levels of estradiol observed in the obese men were much lower, and the degree of obesity much greater, than that observed in our patients with coronary heart disease. Our patients were only 14 percent above ideal body weight, whereas the obese men studied by Stanik et al. [55] were 54 percent above ideal body weight. Further, in our data, serum estradiol levels were not correlated with body weight expressed as a percentage of ideal body weight. Obesity, therefore, is not an adequate explanation of the results of our study of hormone levels.

The most reasonable source of the elevated serum estradiol and estrone levels observed in our patients

with coronary disease, extrapolating from the normal state, would seem to be a heightened aromatization in adipose and muscle tissues of androstenedione and testosterone to estrone and estradiol, respectively. This mechanism is the most reasonable because, in normal men, it is the only mechanism that might increase both estrogens proportionately—the adrenal cortex secretes estrone but not estradiol [53], whereas the testicle secretes estradiol but relatively little estrone [50]. Only increased peripheral aromatization would produce both hormones proportionately.

The reason for a possible increased level of aromatization in our patients is unknown. However, an in vitro study [56] suggests a possible mechanism. The addition of norepinephrine to Sertoli cell-enriched cultures induced an increase in aromatization of testosterone to estradiol. This report brings into question the role that adrenergic stimulation may play in aromatization and estradiol production. Significantly elevated serum norepinephrine levels have been reported in patients with acute myocardial infarction [57], as well as in patients with angina pectoris under mild stress [58], when the levels were compared with those of control subjects. The heightened levels of norepinephrine could, conceivably, be stimulating aromatization, with resulting elevations of estradiol and estrone in these categories of patients.

In the in vitro Sertoli cell culture study [56], the addition of the adrenergic blocking agent propranolol to the cell culture also tended to block the norepinephrine-induced increase in aromatization of testosterone to estradiol. This observation suggests the possibility of a previously unsuspected means by which adrenergic blocking agents may be exerting therapeutic effects in patients with coronary heart disease.

ACKNOWLEDGMENT

We wish to thank Mary Ellen Johnson and Kenneth Pickering for their expert technical assistance and Anna Hooten for her invaluable secretarial assistance.

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