Neurohormonal response to orthostatic stress during the menstrual cycle

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Abstract

Cardiovascular morbidity and mortality are lower in menstruating and in postmenopausal women receiving estrogen. In this investigation, we have studied the sympathetic response to standing during the follicular and luteal phases of the menstrual cycle. In 16 normal women, the baseline plasma norepinephrine levels in the follicular phase were 82.3±7.4 pg/ml and increased to 113.0±6.3 pg/ml ($p<0.0001$), during the luteal phase of the menstrual cycle. Estradiol levels were also higher in the luteal phase (118.1±7.6 pg/ml) compared to the follicular phase (46.8±5.0 pg/ml; $p<0.0001$). In the standing position, the percentage increase in norepinephrine levels was significantly lower in the luteal phase and correlated inversely ($r=-0.7031$; $p>0.001$) with the baseline estradiol values. Therefore, the sympathetic response to a physiological stress is attenuated, during the luteal phase of the menstrual cycle in normal women.

Introduction

Cardiovascular morbidity and mortality are significantly lower in premenopausal women than in age-matched men. This difference is no longer apparent following the onset of menopause (Colditz et al, 1987; Wolf et al, 1991). Premenopausal women appear to be protected from cardiovascular disease. Therefore, it is possible that female sex hormones may influence the pathophysiological processes leading to cardiovascular disease (Barrett-Connor, Bush 1991; Colditz et al, 1991; Lobo, Stampfer 1990). This protective effect was first believed to be mediated by changes in lipid metabolism, but direct estrogen effects on vessel wall physiology seemed to be more important (Mendoza et al, 1981; Phillips 1993; Gilligan et al, 1994; Williams et al, 1990). Recent studies suggest on the contrary, that cardiovascular protection may be mediated, in part, by estrogen influence on the autonomic nervous system function (Del Rio et al, 1993; Du et al, 1995).

The cardiovascular system is under constant control by the sympathetic and parasympathetic divisions of the autonomic nervous system. Abnormal autonomic activity

increases the risk of cardiovascular disease (Du et al, 1995; Maliani et al, 1991). Indirect evidence from several clinical studies suggest that estrogen modulate sympathetic neurotransmission. Under similar stressful conditions, men show a higher increase in circulating norepinephrine that women (Del Rio et al, 1993; Lenders et al, 1987). Lindheim et al (1992) have found that postmenopausal women have higher basal plasma level of norepinephrine than premenopausal women. Moreover, when exposed to psychological stress a further and marked increase in plasma norepinephrine is observed. This exaggerated neurohormonal response is partially blunted after treatment with estrogen. Finally, black women have a greater norepinephrine response to stress during the follicular compared to the luteal phase of the menstrual cycle (Mills et al, 1996). Thus, sympathetic responses to mental stress are favorably influenced by estrogen and this influence is particularly obvious during the luteal phase of the menstrual cycle. Hence, in this investigation, we have compared the sympathetic response, to orthostatic stress, of the follicular with the luteal phase of the menstrual cycle of normal women.

Material / Methods

Subjects:

Sixteen normal female volunteers, between 21 and 34 years old, participated in the study. All women were normotensive, not taking contraceptives or any other medication and had no history of cardiovascular disease.

Protocol:

Daily basal body temperature and menstrual flow pattern were recorder before the study period. During the following menstrual cycle, blood samples were obtained on follicular phase (5-7 day) and on luteal phase (20-22 day) of the menstrual cycle. Analysis of the serum estradiol and progesterone were used to verify the correct phase of the menstrual cycle.

Sample handling and hormonal assays:

Blood samples were drawn in the morning (9:00-11:00 a.m.). An intravenous fluid-filled plastic catheter, was inserted into an antecubital vein. Baseline blood samples were taken after 30 min., in the supine position. A second sample was drawn after 5 min., in the standing position (Cryer et al, 1974). For analysis of norepinephrine 5 ml of blood were placed into prechilled tubes containing 100 μl of an 8% solution of ethylenediamine tetracetic acid and 6% glutathione. The tubes were inverted several times and centrifuged within 2 h at 4° C and 3.000 r.p.m. Plasma was stored at -70° C. Norepinephrine levels were measured by high pressure liquid chromatography and electrochemical detection (Eheretrom, Johasson 1985). Plasma estradiol and progesterone concentrations were assessed by radioimmunoassay (Diagnostic Products Inc. Los Angeles, CA, USA). The within and between days coefficients of variation for these radioimmunoassay were 4% to 6% and 8% to 10% respectively.

Statistical analysis:

Neurohormonal responses to orthostatic stress were assessed by Student's t test for paired

data. The relations between the norepinephrine and estradiol plasma levels were determined using the Pearson correlation coefficient. Data are expressed as means* SEM.

Results

Baseline plasma levels of norepinephrine and estrogen during the follicular and luteal phases of the menstrual cycle.

Supine plasma norepinephrine levels, during the follicular phase, were 82.3±7.4 pg/ml and increased significantly to 113.0±6.3 pg/ml ($p<0.0001$) during the luteal phase (Fig. 1). Baseline plasma estradiol levels were also higher in the luteal phase 118.1±7.6 pg/ml compared to the follicular phase (46.8±5.0 pg/ml; $p<0.0001$). No correlation was found between norepinephrine levels and estradiol concentration, during the two phases of the menstrual cycle.

Neurohormonal responses to orthostatic stress.

In the standing position, norepinephrine levels rose to 192.4±20.0 pg/ml during the follicular phase and to 169.9±9.0 pg/ml during the luteal phase. The neurohormonal response to standing was similar in both phases of the menstrual cycle (Fig. 1). However, when these neurohormonal responses were expressed as a percentage change, to correct for the higher baseline levels of the luteal phase, a significant difference ($p<0.001$) was found (Fig. 2). Furthermore, in the supine position there was no correlation between baseline plasma norepinephrine and estradiol concentrations in both phases of the menstrual cycle, where as, the percentage increase of plasma norepinephrine during standing was significantly and inversely correlated with the estradiol levels ($r=0.7031$ $p<0.001$). In other words, during the luteal phase of the menstrual cycle, the sympathetic response to orthostatic stress, as expressed by the norepinephrine plasma levels, appears to be influenced by estrogen.

Discussion

Sympathetic nervous system activity varies as a function of the phase of the menstrual cycle. Plasma norepinephrine levels are lowest in the follicular phase, begin to increase just before the luteinizing hormone (LH) surge and reach the highest values during the luteal phase (Blum et al, 1992; Goldstein et al, 1983; Tollan et al, 1983). This cyclic variation, in the activity of the sympathetic nervous system, is very likely due to a modulating effect of estrogen on the autonomic nervous system (DeVries 1990; Du et al, 1995).

Clinical and experimental studies indicate that estrogen influence sympathetic neurotransmission. These modulating effects appear to be inhibitory and they are active at the presynaptic and peripheral sites (Du et al, 1991; Scisio, Dicarlo 1994). These inhibitory effects are also apparent during stressful conditions. Most studies have used mental and pharmacological stresses to study the modulating effects of estrogen under experimental conditions (Manhem et al, 1991; Mills et al, 1996; Tollan et al, 1993). In this investigation we have used a physiological stress to compare the sympathetic response to standing, the percentage increase of plasma norepinephrine was significantly smaller during the luteal phase of the menstrual cycle. Moreover, this percentage increase in norepinephrine was significantly

and inversely related to the baseline levels of estrogen. Thus, the sympathetic response to a physiological stress appears to be attenuated by estrogen.

Cardiac autonomic imbalance, with the predominance of sympathetic activity, is present in the majority of patients with acute coronary syndromes (Maliani et al, 1991) and is also the underlying pathophysiological substrate of sudden cardiac death (Bigger et al, 1993). A sex difference in the hemodynamic response to coronary artery occlusion and in the risk for sudden cardiac death have been reported (Colditz et al, 1987). Therefore, it is possible that estrogen favorably modulate the exaggerated sympathetic response observed under pathological circumstances.

In summary, the results of this investigation suggest that the sympathetic response to a physiological stress is attenuated by estrogen. This favorable modulating effect could, in part, explain the lower cardiovascular morbidity and mortality of menstruating women.

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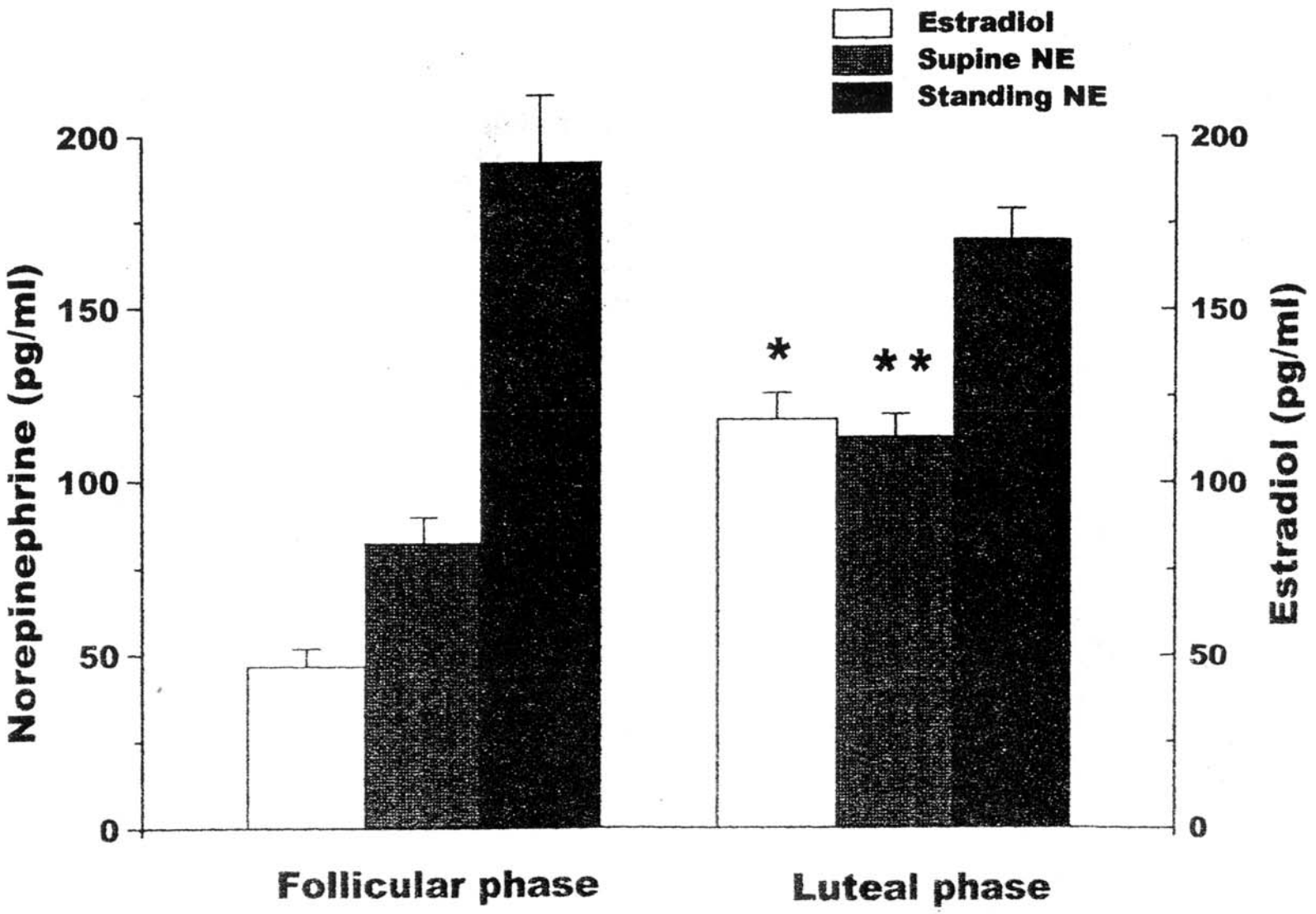

Figure 1: Estrogen and norepinephrine (NE) basal plasma levels during the follicular and luteal phase of the menstrual cycle. Both hormones, estradiol (*$p < 0.0001$) and NE (**$p < 0.0001$), were significantly higher in the luteal phase. In response to standing, the NE plasma levels reached higher, although not significantly different values.

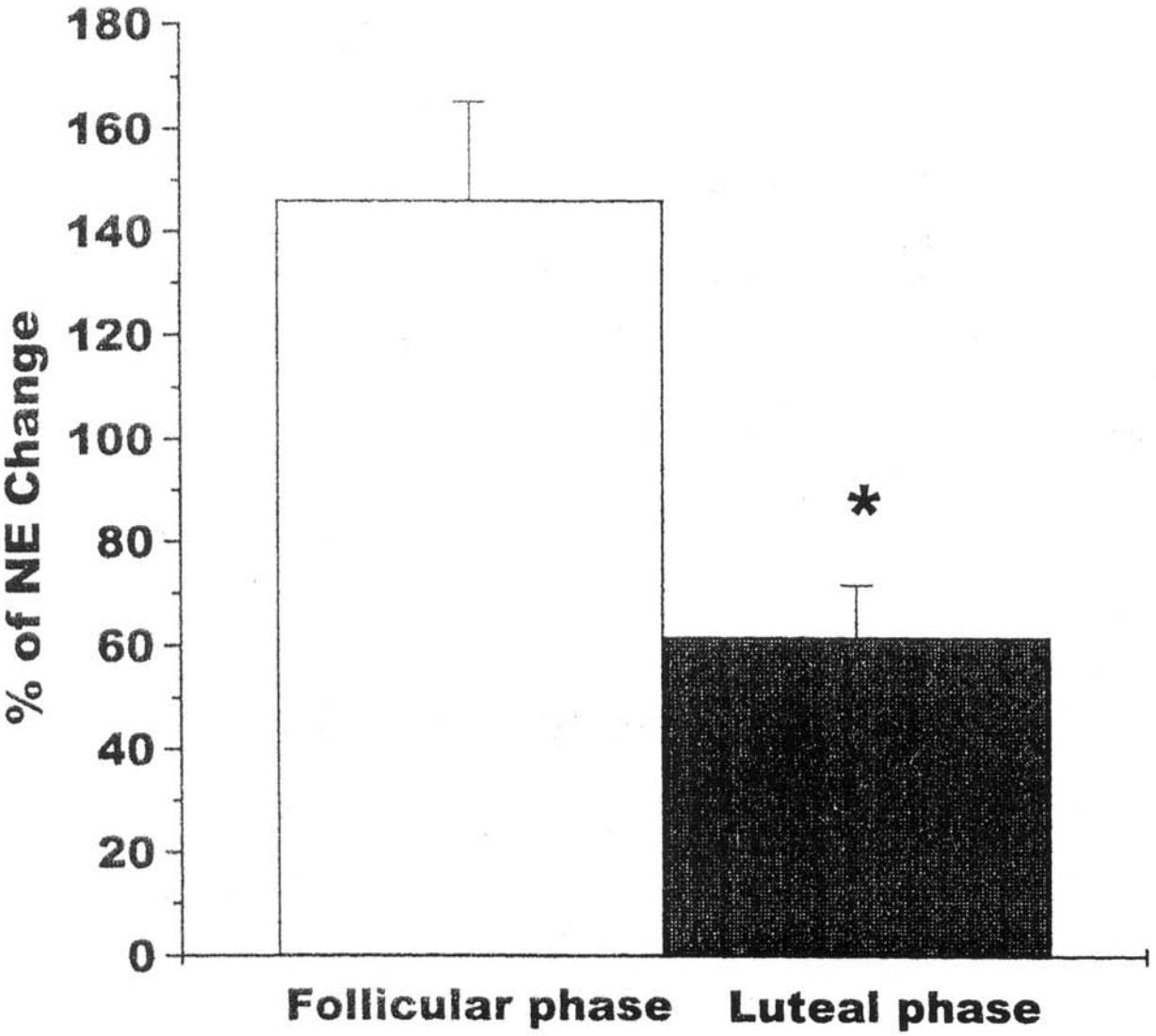

Figure 2: Neurohormonal responses to orthostatic stress. The norepinephrine (NE) response to standing, expressed as a percentage change to correct for the higher baseline levels of plasma NE, was significantly smaller ($p < 0.001$) in the luteal phase of the menstrual cycle.

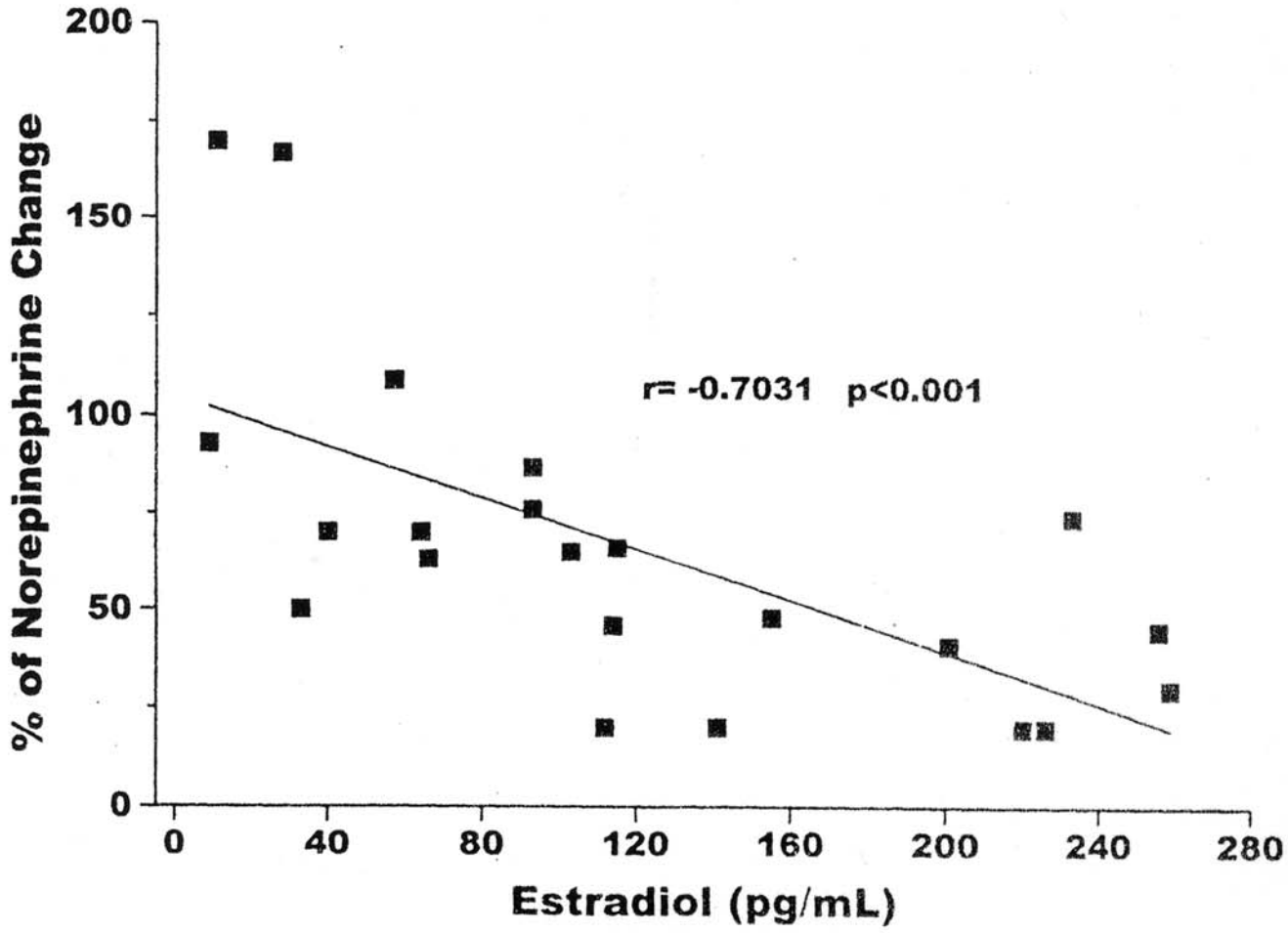

Figure 3: Baseline estradiol and percentage change in plasma NE, during standing, in the follicular and luteal phases of the menstrual cycle. There was a significant and inverse correlation between the sympathetic response to standing and the baseline levels of estradiol.