Short-term effect of transdermal estrogen on autonomic nervous modulation in postmenopausal women

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Objective: To evaluate the effect of short-term transdermal estradiol-l7b on cardiac autonomic nervous modulation in postmenopausal women.
Design: Prospective study.
Setting: A tertiary medical center.
Patient(s): Twenty-one postmenopausal women.
Intervention(s): Transdermal estradiol or placebo therapy for 3 weeks in randomized, double-blinded, crossover fashion.
Main Outcome Measure(s): Heart rate variability measures in both time and frequency domains, serum biochemistry, and climacteric symptoms were compared among baseline, placebo and transdermal estrogen therapies.
Result(s): Plasma concentration of estradiol rose significantly from 11.0 ± 5.2 pg/ml to 48.2 ± 34.0 pg/ml after transdermal estrogen. The standard deviation of RR-interval increased significantly from 30.3 ± 9.9 ms (placebo) to 31.3 ± 7.4 ms (transdermal estrogen), and the coefficient of variation of RR-interval increased significantly as compared with the baseline session. The total power was marginally increased as compared among baseline, placebo, and transdermal estrogen sessions. The irritability symptom decreased significantly after transdermal estrogen therapy, as compared with baseline and placebo treatment.
Conclusion(s): Transdermal estradiol for 3 weeks could significantly increase the global heart rate variability and reduce the irritability symptom in the postmenopausal women. Short-term transdermal estrogen for 3 weeks could improve cardiac autonomic nervous modulation and climacteric symptoms, and might have some cardioprotective effect in postmenopausal women. (Fertil Steril® 2005;84:1477–83. ©2005 by American Society for Reproductive Medicine.)

Key Words: Autonomic nervous modulation, climacteric symptoms, heart rate variability, menopause, transdermal estrogen

Menopause is a global reality that has become a 20th-century phenomenon simply because women are living longer. Female longevity itself no longer is a major issue, but the quality of this expanded lifespan certainly is an important trend because the incidence of cardiovascular diseases, which are the leading cause of death in women, increases sharply after menopause (1, 2). This phenomenon of menopause has led to an ever-increasing societal health issue: the care of elderly women.

Postmenopausal women often have vasomotor symptoms that are thought to arise from lability of the autonomic nervous system and that are effectively controlled by estrogen (E) therapy (3). Previous studies have demonstrated that menopause is associated with a shift toward increased sympathetic activity and significantly reduces both mean RR interval and the standard deviation in postmenopausal women (4, 5). Although the cause of the postmenopausal upsurge in cardiovascular morbidity and mortality is not clear, there is a strong link between the onset of menopause and the cessation of ovarian function, changes in the autonomic nervous modulation, and increased cardiovascular risk (6, 7).

Postmenopausal hormone therapy (HT) was found to be associated with reduced risk of cardiovascular risk; however, the mechanisms remain obscure (8). Unfortunately, the results of some randomized trials that have assessed the effect of E alone on cardiovascular disease are inconsistent in recent years. Hormone therapy regimens have been reported to increase the risk of breast cancer and endometrial cancer by using estrogen therapy alone and have numerous side effects, which reduce the long-term adherence of the postmenopausal women and the use of these agents by these women (9–11). Therefore, the majority

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of postmenopausal women do not take HT long enough to have an impact on chronic disease risk (12–15), despite some beneficial effects of HT. The ongoing controversy about the potential benefits of hormone replacement was fueled by a recently published research work (9). The recent findings of the Women's Health Initiative and several large-scale randomized clinical trials have demonstrated that the protection from cardiovascular disease is not an indication for the use of E plus progestin among postmenopausal women (10, 16, 17). It also was shown that E plus progestin did not confer cardiac protection and might increase the risk of coronary heart disease among generally postmenopausal women, especially during the first year after the initiation of hormone use; therefore, the treatment of E plus progestin should not be prescribed for the prevention of cardiovascular disease (18). At present, it has been difficult to determine whether it is beneficial or harmful to use estrogen therapy in postmenopausal women on the basis only of one-sided evidence.

In general, the autonomic nervous control of the heart can be studied by heart rate variability (HRV) analysis. Decreased HRV has been found to be a reliable indicator of decline in cardiac function and is useful in the prediction of adverse events after myocardial infarction (19). Reduced HRV predicts mortality not only in postinfarction patients but also in a population-based sample of elderly subjects (20). Altered HRV may contribute to mortality in a causal manner; the higher mortality observed in an elderly cohort with reduced HRV also may be caused by subclinical coronary artery disease. Alternatively, reduced HRV might simply identify subjects in poor health before death. It may be a marker of risk rather than an etiologic factor. Thus, it can be seen that any intervention that can increase the HRV of the subject may be beneficial to the subject, because the intervention improves cardiac autonomic function parameters and could partly explain the potential cardioprotective effect.

Because more and more women have relied on using short-term estrogen therapy to tide over their uncomfortable symptoms, it is important to know what might happen to the autonomic nervous modulation of postmenopausal women who have used short-term estrogen therapy for some weeks. The aim of this study was to determine whether the short-term administration of transdermal E for 3 weeks could modulate the autonomic nervous system and relieve the uncomfortable climacteric symptoms in postmenopausal women.

MATERIALS AND METHODS

Subjects

All women had had their last menstrual period ≥1 year ago, had serum E_2 concentration of ≤20 pg/mL and FHS ≥25 MIU/mL, and were not receiving hormonal therapy for ≥2 months before the study enrollment. None of the subjects had a history of smoking, cancer, endometrial hyperplasia, endometriosis, vaginal bleeding, arteriosclerotic or coronary artery disease, thromboembolic disease, hyperlipidemia, diabetes, migraine headaches, hypertension (systolic pressure >160 mm Hg or diastolic pressure >95 mm Hg), chronic neurological disorder, severe hepatic or renal dysfunction, or hypothyreosis. This study was reviewed and approved by the institutional review board of Taipei Veterans General Hospital. All procedures, risks, and benefits were explained to the subjects, and informed written consent was obtained from the subjects before the study.

Procedures and Protocols

All participants received each of the two treatments, placebo and transdermal E, in random order according to a double-blind cross-over design. The subjects were randomly assigned to either placebo or transdermal estrogen therapy by using a random number table. The treatment assigned to the subject was not disclosed to the physician caring for the subject or to the assistant who performed the treatment and electrocardiographic (ECG) recording for the subject. The two treatment modalities used in this study were a 7-day E matrix patch (Climara; Schering AG, Berlin, Germany) alone as a 50-μg patch once a week for 3 weeks and a placebo patch (a patch once a week) for 3 weeks. After a 2-week washout period, the women received another treatment for another 3 weeks. All subjects were studied before and after treatment by either transdermal E_2 or placebo.

The standards of measurement, physiological interpretation, and clinical use of HRV have been standardized by the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology (21). The methods used in this study are in accordance with the recommendation of the Task Force (21) and have been described in our previous studies (22). In brief, all subjects were requested not to drink caffeinated or alcoholic beverages for at least 24 hours before ECG recording and were requested not to take any solid or liquid food except water after dinner, the night before the study. The ECG recording was performed after 3 weeks' treatment, from day 22 to day 26. All women were studied at about the same time of the day (9:00 to 11:30 AM) to avoid the effects of circadian rhythms on HRV. All experiments were performed with the subjects in the sitting position. A 10-minute rest routinely was requested by the clinician before ECG recording. A continuous analog signal from standard lead II of the ECG was recorded for 10 minutes by a bedside ECG monitor (Biochem Vital Signs Monitor; BCI International, Waukesha, WI) and was transmitted to a personal computer for recording. The sampling frequency for ECG signals was 500 Hz. The recording was discontinued if there was any sign or symptom of intolerance to the sitting position, such as restlessness or pallor.

The recorded electrocardiographic signal was retrieved afterward to measure the consecutive RR intervals by using the software for the detection of the R wave. Sinus pauses and atrial or ventricular arrhythmias were deleted, and the last 512 stationary RR intervals were obtained in each treatment session for spectral HRV analysis. If the percentage of deletions was >5%, the subject was excluded from the study.

The mean, SD (SD_{RR}), coefficient of variation (CV_{RR}), root-mean-squared successive difference of RR intervals, and per-