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Clinical Investigations

Estrogen Does Not Prevent Endothelial Dysfunction Caused by Cigarette Smoking

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Summary

Background: Estrogen favors endothelial function while acute tobacco use provokes dysfunction. Previous studies have not examined the effect of smoking one cigarette at different stages of the menstrual cycle.

Hypothesis: Favorable actions of estrogen on endothelial function are transitorily abolished by smoking one cigarette.

Methods: Brachial artery endothelium-dependent dilation was measured noninvasively before, 10 min, and 1 h after smoking in 17 healthy premenopausal women. Studies were done in the first 3 days (early stage) and repeated between Days 9 and 13 of the menstrual cycle (middle stage). Estradiol was measured after each study.

Results: At basal conditions, women in the middle stage of their cycles, when estradiol was 20 times higher than in the early stage, had significantly more endothelial-dependent brachial dilatation. No difference in the marked depression caused by cigarette smoking was found between the two stages. One h recuperation was complete in both phases.

Conclusion: Cigarette smoking abolishes the protection of circulating estrogen on endothelial function.

Key words: atherosclerosis, endothelial function, menstrual cycle, estrogen, smoking

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Introduction

Estrogen prevents endothelial dysfunction, partially limiting the progress of atherosclerosis.[1, 2] This is generally accepted as the cause of at least 10 years' delay in the appearance of coronary heart disease in women.[3]

During menses, when estrogen is lowest, the incidence of effort and variant angina increases significantly.[4, 5] Myocardial infarction, though rare in premenopausal women, is more likely to occur when circulating estrogen is low.[6] Mendelsohn and Karas[7] have reviewed the consistent finding of protective vasodilating properties of estrogen.

On the other hand, chronic smoking leads to coronary endothelial vasomotor dysfunction.[8] Even one cigarette or chewing gum containing nicotine can cause transitory dysfunction.[9, 10]

Considering that atherosclerosis begins in the early stages of life[11] and that arterial endothelium is one of the first barriers to atherosclerosis, we decided to compare the endothelium-dependent vascular response to smoking in women at two distinct stages of the menstrual cycle.

Methods

Seventeen apparently healthy women, aged 30 to 50 years, with normal menstrual cycles and not receiving exogenous hormones, were included in the study. Each had smoked a maximum of 10 cigarettes per day for < 5 years.

Endothelial function was determined by a noninvasive ultrasound procedure in the brachial artery.[12] Studies were done in each case between Days 1 to 3 (early stage) and repeated at Days 9 to 13 (middle stage) of the menstrual cycle.

Each study was begun in medication-free subjects after 15 min of supine rest in an undisturbed 22˚C to 24˚C surrounding, following overnight fasting, and at least 8 h without smoking.

After recording the internal diameter of the brachial artery, a blood pressure cuff positioned in the forearm was inflated to 200 mmHg for 5 min and a new recording was made 1 min after deflating the cuff; the diameter mean values were termed endothelial dependent. This procedure was repeated 10 and 60 min after smoking a cigarette.

TABLE I Demographic and clinical data

Variable, mean ± standard deviation
Number of women, 17 paired observations
Age 38.8 ± 5.1 years
Mass index 24.2 ± 2 kg/m^2
Systolic arterial pressure 99.4 ± 13.4 mmHg
Diastolic arterial pressure 65.8 ± 11.9 mmHg
Heart rate 72.2 ± 8.2 beats/min
Total cholesterol 3.77 ± 0.62 mmol/l
Triglycerides 1.14 ± 0.19 mmol/l
HDL-cholesterol 0.85 ± 0.16 mmol/l
LDL-cholesterol 2.40 ± 0.63 mmol/l

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

A 7.5 MHz linear array transducer with high-resolution ultrasound equipment was used. The zoom-amplified diameter of the brachial artery was measured at least 5 times by an observer blinded to the menstrual cycle phase.

Observer variability, calculated as the difference ± standard deviation of brachial artery diameter before and 60 min after smoking, was 0.0403 ± 0.012 mm.

At the end of each study a blood sample was obtained to determine estradiol levels by radio immunoassay (ESTR-CTRIA CIS Bio International, Gif-sur-Yvette Cedex/France).

Wilcoxon signed rank test was performed to compare the percent increase after smoking between the early and middle phases of the menstrual cycle. A two-tailed Z for a p value of < 0.05 was accepted as significant.

Informed consent was voluntarily signed by each participant.

Results

Demographic and clinical data are shown in Table I.

Table II shows endothelium-dependent data at the early and middle stages of the menstrual cycle. There was a significant higher endothelial-dependent dilatation during the middle stage than at the early stage.

After smoking, endothelial function was markedly depressed, yet there was no significant difference between the two study periods (Fig. 1).

Endothelial-dependent dilation was restored entirely 60 min after smoking, but with a nonsignificant tendency to be less during the early stage of the menstrual cycle.

Estradiol plasma levels were more than 20 times higher during the middle stage.

Discussion

The protective action of natural estrogen has been alleged to be the main cause of differing gender cardiovascular morbidity and mortality.[3] However, several epidemiologic studies in smokers have found a higher incidence of nonlethal myocardial infarction or cardiovascular mortality in premenopausal women than in men of similar age.[13–15] Furthermore, women smokers have an earlier menopause, which could reduce the gender difference in cardiovascular morbidity and mortality.[3]

At baseline in this study, women with slight tobacco abuse had an increased artery diameter at the middle stage of the menstrual cycle, when plasma levels of estradiol were higher. This confirms similar previous results in nonsmokers, in which endothelial function is preserved during the mid follicular phase.[7]

Increased levels of circulating estrogen were incapable of preventing marked deterioration of endothelial function caused by smoking one cigarette. This could partially explain a reduction in gender difference morbidity and mortality in smokers, although a comparison with men is necessary to determine whether women are more prone to the endothelial effects of tobacco use.

Estrogen has consistently been found to preserve endothelial function;[7] this is also manifested in our study by a signifi-

TABLE II Endothelial-dependent brachial dilatation

Variable	Early stage	Middle stage	p Value
Basal brachial diameter (mm)	3.09 ± 0.39	3.08 ± 0.34	
ED diameter (mm)	3.50 ± 0.42	3.57 ± 0.30	
Percent diameter increase	13.17 (7–20.1) [a]	16.0 (9.09–32) [a]	< 0.05
Basal brachial diameter 2 (mm)	3.07 ± 0.36	3.08 ± 0.33	
ED diameter after smoking (mm)	3.21 ± 0.35	3.24 ± 0.36	
Percent diameter increase	4.98 (0–13.6)	5.13 (0–13.4)	NS
Basal brachial diameter 3 (mm)	3.07 ± 0.37	3.08 ± 0.34	
ED diameter 60 min after smoking (mm)	3.51 ± 0.39	3.57 ± 0.34	
Percent diameter increase	14.60 (7.2–28.5) [a]	16.4 (6.7–27.8) [a]	NS
Mean plasma beta estradiol (pmol/l)	27.33	588.33	< 0.001

Mean ± standard deviation or (minimum-maximum).

[a] $p < 0.001$ compared with percent diameter after smoking.

Abbreviation: ED = endothelial-dependent.

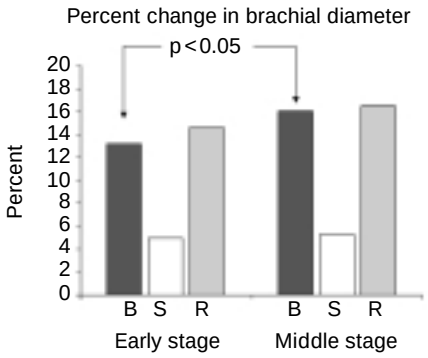

FIG. 1 Percent increase at baseline (B), 10 min (S), and 60 min after (R) cigarette smoking, at two different stages of the menstrual cycle. There was a significant reduction 10 min after smoking ($p < 0.001$) and no significant difference between stages, except at baseline flow-mediated dilation.

cant increase in brachial artery diameter during the middle phase, when circulating levels of estradiol were highest. However, in postmenopausal women, recent randomized studies have shown negative or a higher risk than benefit in preventing cardiovascular disease.[16, 17] This apparent contradiction raises the question of how many of these older women, most of them with clinical or subclinical cardiovascular disease, may have had risk factors, such as cigarette smoking, that counteracted a possible action of estrogen treatment.

Observer variability was much less than the differences encountered;[18] therefore, it is unlikely these could be due to technical limitations.

Conclusion

Transitory endothelial dysfunction caused by smoking one cigarette cannot be prevented by peak naturally occurring estrogen.

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