Menstrual Cyclic Variation of Myocardial Ischemia in Premenopausal Women with Variant Angina

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Background: **An abundance of ovarian hormones is assumed to be a major contributor to the low incidence of ischemic heart disease in premenopausal women. However, the effects of ovarian hormones remain undetermined.**

Objective: **To examine whether the variation in ovarian hormone levels throughout a menstrual cycle affects myocardial ischemia in women with variant angina.**

Design: **Prospective, observational study.**

Setting: **University medical center in Japan.**

Participants: **10 premenopausal women with variant angina.**

Measurements: **Frequency of spontaneous ischemic episodes, flow-mediated dilation of brachial artery, and serum levels of estradiol and progesterone.**

Results: **Frequency of ischemic episodes was highest from the end of the luteal phase to the beginning of the menstrual phase and was lowest in the follicular phase. Flow-mediated vasodilation and estradiol levels were lowest from the end of the luteal phase to the beginning of the menstrual phase and were highest in the follicular phase.**

Conclusions: **In premenopausal women with variant angina, we documented a cyclic variation in endothelial function and the frequency of myocardial ischemia that was associated with the variation in estrogen levels.**

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Coronary spasm plays an important role in the pathogenesis of not only variant angina but also ischemic heart disease in general (1, 2). Ischemic heart disease is relatively uncommon in premenopausal women (3). The abundance of endogenous ovarian hormones is commonly assumed to be a major contributor to this phenomenon (3).

Estrogen slows the development and limits the adverse effects of atherosclerosis in part by alleviating vascular endothelial dysfunction (4). Because endothelial dysfunction is one of the reasons for coronary spasm (5), estrogen may also be effective for suppressing coronary spasm itself. We examined whether the variation of ovarian hormones during a menstrual cycle affects the frequency of myocardial ischemia in premenopausal women with variant angina.

Methods

We defined variant angina as recurrent attacks of chest symptoms that occur spontaneously at rest, are associated with ST-segment elevation on electrocardiography, and are rapidly relieved by nitroglycerin. Ten premenopausal women were eligible for enrollment (age range, 33 to 51 years; mean age, 44.8 years). All women had had regular menstrual cycles for more than 3 months before study entry (range, 27 days to 32 days; mean, 29.2 days). All antianginal drugs, except sublingual nitroglycerin, were withdrawn during the study. All participants gave written, informed consent, and the study was approved by the ethics committee at our institution in Kumamoto, Japan.

Coronary angiography was performed before study entry by using the Judkins technique (6). All participants had coronary spasm demonstrated by chest symptoms and by ST-segment elevation after intracoronary injection of acetylcholine, which causes vasodilation when endothelium is functioning normally (7–9). One participant showed 50% organic stenosis of the left anterior descending coronary artery, and the other participants showed no fixed stenosis after receiving an intracoronary injection of nitroglycerin.

The study was performed from 2 to 3 days before the participants' predicted beginning of menstruation (menses) to 2 to 3 days after the beginning of the next menstruation. Participants underwent 24-hour ambulatory electrocardiographic monitoring on every day of the study to evaluate the frequency of spontaneous ischemic episodes. The data were transmitted from the participant to a computer system by wireless telemetry, were displayed on a monitor in the nurse center, and were simultaneously stored on computer hard drive (Telemetry System, Nihon Kohden, Tokyo, Japan). Data were evaluated daily by reviewing the information on the computer disk. An ischemic episode was defined as a period of ST-segment depression (horizontal or downsloping) of at least 0.1 mV or elevation of at least 0.2 mV, lasting at least 1 minute before recovery to baseline, and separated from another episode by an interval of at least 2 minutes.

Endothelial function was evaluated by flow-mediated dilation of the brachial artery every other morning by using a 7.5-MHz linear array transducer (SSH-160A, Toshiba, Tokyo, Japan) (10–15). Participants lay quietly for 10 minutes before the first scan. After baseline measurements of the diameter and flow velocity, a blood pressure cuff placed around the forearm was inflated with a pressure of 250 to 300 mm Hg and was released after 5 minutes. The measurements were continuously taken during cuff inflation and after cuff deflation. After confirmation that the diameter and the flow velocity had returned to baseline levels, sublingual nitroglycerin, 0.3 mg, was administrated, and the final measurements were obtained 3 to 4 minutes later.

The ultrasonography images were recorded on a videocassette recorder (BR-S601M, Victor, Tokyo, Japan), and the diameter was measured by using ultrasonic calipers. The diameters at four cardiac cycles were analyzed for each scan and were averaged. The peak diameter for reactive hyperemia was measured for 45 to 90 seconds after cuff deflation. Blood flow was calculated by multiplying the velocity–time integral of the Doppler flow signal by the heart rate and the vessel cross-sectional area. Increase in the blood flow was calculated by dividing the maximal flow within the first 15 seconds after cuff deflation by the flow at baseline.

The interobserver and intraobserver variabilities (±SD) for the repeated measurements of resting diameter performed by two of the authors were 0.05 ± 0.02 mm and 0.02 ± 0.02 mm, respectively. When these procedures were performed at the same time on 2 separate days in 20 volunteers, the average intraparticipant test–retest difference for the measurements of the diameter during the reactive hyperemia was 0.05 ± 0.04 mm (13).

The menstrual cycle was divided into three phases: the menstrual (menstruation) phase, the follicular phase, and the luteal phase (the period from ovulation to menstruation). In each participant, the phases were determined according to serum estradiol and progesterone concentrations, dates of the last menstrual cycle, basal body temperature, and timing of genital bleeding. The levels of estradiol and progesterone were measured by performing a specific immunoradiometric assay every other day from blood samples obtained when the participant was in a fasting state (10).

The Tukey–Kramer test was used to evaluate pairwise mean differences among the three phases. We analyzed the effects of estradiol and progesterone levels on flow-mediated vasodilation by using a linear multiple regression model. We used a Poisson multiple regression model to analyze the effects of estradiol, progesterone, flow-mediated vasodilation, and nitroglycerin-induced vasodilation on the frequency of ischemic episodes. As explanatory variables, we also adapted two dummy variables that represent the relative effects of the follicular phase and the luteal phase compared with the effect of menstrual phase. The response variables of each participant were assumed to have a first-order autoregressive correlation structure.

We used SAS/STAT software, version 6.12 (SAS Institute, Inc., Cary, North Carolina), for all statistical analyses. Statistical significance was defined as a *P* value less than 0.05. All data are expressed as the mean (±SE).

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Results

All participants tolerated the studies well. The ischemic episodes were highest from the end of the luteal phase to the beginning of the menstrual phase and were lowest in the follicular phase (**Figure 1**). The levels of estradiol and flow-mediated vasodilation were lowest from the end of the luteal phase to the beginning of the menstrual phase and were highest in the follicular phase. The progesterone level increased only in the luteal phase.

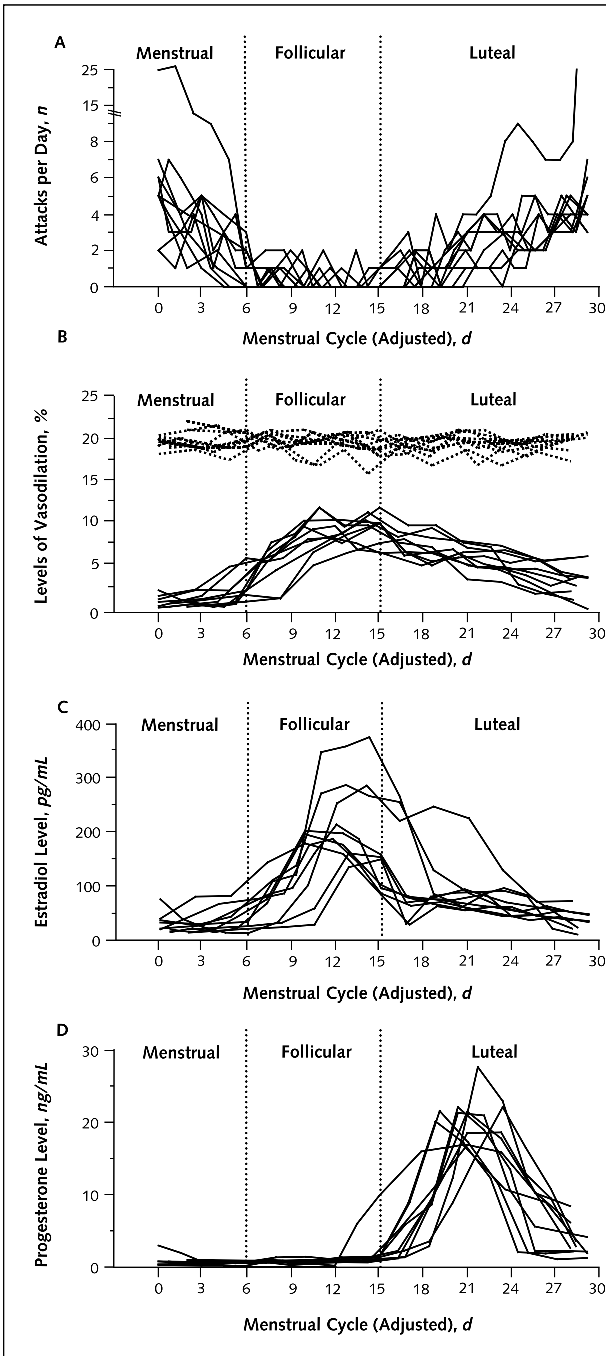
The average frequency of ischemic episodes was highest in the menstrual phase and was lowest in the follicular phase. The mean frequency in the luteal phase was lower than that in the menstrual phase (3.9 ± 0.6 episodes/d during the menstrual phase, 0.3 ± 0.1 episodes/d during the follicular phase, and 2.6 ± 0.2 episodes/d during the luteal phase) ($P < 0.001$ for comparison of luteal vs. follicular and menstrual vs. follicular mean values; $P = 0.01$ for comparison of menstrual vs. luteal mean values). The levels of flow-mediated vasodilation and estradiol were lowest in the menstrual phase and highest in the follicular phase (1.67% ± 0.23% and 118.6 ± 13.2 pmol/L [32.3 ± 3.6 pg/mL], respectively, during the menstrual phase; 8.16% ± 0.35% and 565.0 ± 47.0 pmol/L [153.9 ± 12.8 pg/mL] during the follicular phase; and 5.69% ± 0.25% and 264.7 ± 23.1 pmol/L [72.1 ± 6.3 pg/mL] during the luteal phase) ($P = 0.005$ for comparison between any two mean values). Nitroglycerin-induced vasodilation remained unchanged across the three phases (the mean values were 19.62% ± 0.18% during the menstrual phase, 19.47% ± 0.17% during the follicular phase, and 19.45% ± 0.11% during the luteal phase). The progesterone levels were highest in the luteal phase (mean menstrual level, 2.3 ± 0.3 nmol/L; mean follicular level, 3.8 ± 0.7 nmol/L; mean luteal level, 32.6 ± 1.5 nmol/L [$P < 0.001$ for comparison of menstrual vs. luteal and follicular vs. luteal mean values]).

In the linear regression analysis for flow-mediated vasodilation, the regression coefficients for estradiol, progesterone, and follicular and luteal phases (contrasted with menstrual phase) were 0.019% · mL/pg ($P < 0.001$), 0.032% · mL/ng ($P = 0.2$), 3.0% ($P < 0.001$), and 2.2% ($P < 0.001$), respectively. The auto-correlation coefficient was 0.570. In the Poisson regression analysis for ischemic episodes, the regression coefficients for estradiol level, progesterone level, follicular phase, luteal phase, and flow-mediated and nitroglycerin-induced vasodilation were −0.0048 mL/pg per day ($P = 0.004$), −0.0070 mL/ng per day ($P > 0.2$), −0.63/d ($P < 0.001$), 0.12/d ($P > 0.2$), −0.11%/d ($P = 0.001$), and 0.012%/d ($P > 0.2$), respectively. The auto-correlation coefficient was 0.566. Estradiol had a significant effect on flow-mediated vasodilation but progesterone did not. **Figure 2** depicts the relationships between estradiol level and frequency of ischemic episodes. Estradiol level and flow-mediated vasodilation had a significant effect on the frequency of ischemic episodes, but progesterone level did not.

Discussion

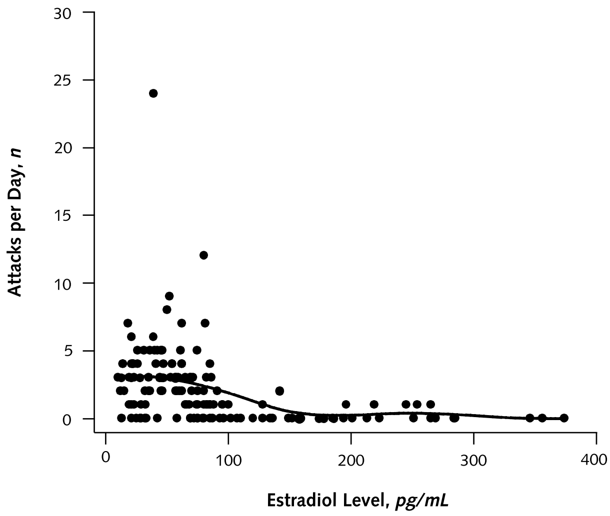
Estrogen increases nitric oxide synthase activity in the vascular endothelium (4). The magnitude of flow-mediated vasodilation of the brachial artery, which is

Figure 1. **Myocardial ischemic episodes and levels of vasodilation, estradiol, and progesterone in study participants, according to menstrual-cycle phase.**



In each panel, individual lines represent the 10 participants. For each participant, the days of the three menstrual phases were adjusted to the mean days (menstrual, 6.0 days; follicular, 9.1 days; luteal, 14.1 days). **A.** The frequency of spontaneous myocardial ischemic episodes per day. **B.** Flow-mediated (*solid lines*) and nitroglycerin-induced (*dotted lines*) vasodilation levels. **C.** Serum estradiol level. **D.** Serum progesterone level.

Figure 2. **Scatterplots and smooth curves of serum estradiol levels versus myocardial ischemic episodes.**



Smooth curves were fit by using kernel estimation.

mainly dependent on endothelium-derived nitric oxide (16), closely reflected the variation of estradiol level during the menstrual cycle. These results are consistent with our previous report and those of others (10–12) showing that the variation of ovarian hormones during a menstrual cycle affects the endothelial function of the brachial artery in healthy premenopausal women.

We have previously reported that patients with coronary spasm have a disturbance in endothelial function of coronary arteries as well as a hypercontractile response of vascular smooth muscle (5). We have provided further evidence for endothelial dysfunction, not only in the coronary arteries but also in the brachial arteries in the patients with coronary spasm (13). Because endothelial function of the brachial artery and of the coronary artery are closely related (13, 14), this modulation of endothelium-dependent dilation in the brachial artery probably occurs in the coronary arteries as well.

The precise mechanism of coronary spasm remains unknown. In this study, the frequency of myocardial ischemia was associated with the modulation of estradiol concentration and endothelial function. The ischemic episodes seldom occurred when estradiol and flow-mediated vasodilation increased and frequently occurred when estradiol and flow-mediated vasodilation decreased. Estrogen also directly relaxes vascular smooth muscle by antagonizing calcium channels (17). Therefore, it can be presumed that the variation of estrogen level affects endothelial and smooth-muscle function and contributes to the alteration of the frequency of myocardial ischemia.

Progesterone level did not seem to affect endothelial function or frequency of ischemic episodes. Considerable controversy still exists about the role of progesterone. Some investigators have suggested that the progesterone does not affect the beneficial effects of estrogen on endothelial function (12, 15); however, others have suggested that progesterone acts as an antagonist toward the beneficial effects of estrogen on endothelial function (11). Further studies are needed to establish the role of progesterone.

In some participants, the frequency of ischemic episodes decreased before the estradiol levels substantially increased. The physiologic alternation of other ovarian hormones may also affect the variation of endothelial function and ischemic episodes.

In premenopausal women with variant angina, we observed a cyclic variation in the frequency of myocardial ischemia and endothelial function. This variation is associated with the alteration of ovarian hormones, especially estrogen, in a menstrual cycle.

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