Cardiac Symptoms Related to Paroxysmal Atrial Fibrillation Varied With Menstrual Cycle in a Premenopausal Woman

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Summary

Atrial fibrillation, an arrhythmia observed more frequently in men than women, is induced by both sympathetic and parasympathetic autonomic nerve activations. The menstrual cycle in premenopausal women has been reported to modulate the autonomic nervous system: parasympathetic activity is dominant in the follicular phase and sympathetic activity is dominant in the luteal phase. However, the relationship between atrial fibrillation and the menstrual cycle has not yet been reported, because this arrhythmia is very rarely detected in premenopausal women. We experienced a 38 year-old woman with paroxysmal atrial fibrillation. Her menstrual cycle was 30.4 ± 0.5 days and the menstrual period was 3.9 ± 0.2 days for 22 cycles. Although she had taken flecainide 200 mg/day, bepridil 200 mg/day, and propranolol 20 mg/day, she sometimes experienced mild palpitations. QTc intervals measured at her visits to our clinic were 440 ± 3 msec in the follicular phase and 425 ± 2 msec in the luteal phase (P = 0.01). These changes in QTc intervals during the menstrual cycle are compatible with earlier reports. During the 22 menstrual cycles, she felt palpitations on 3.2 ± 0.7 days in the menstrual period, 6.4 ± 0.3 days in the follicular phase, and 4.1 ± 0.4 days in the luteal phase (P = 0.01). Afterward, the medication was changed from daily to periodic administration for one week beginning a couple of days before the expected menstrual time, and she did not feel symptomatic variation in her menstrual cycle. These data suggest that her symptoms related to atrial fibrillation might have been dependent on parasympathetic activity. (Int Heart J 2013; 54: 107-110)

Key words: Follicular phase, Luteal phase, Autonomic nerve system, Parasympathetic activity, QTc interval

Gender differences are well known to exist in atherosclerotic disease, but have recently been elucidated also in some arrhythmias. For example, congenital long QT syndrome is more often detected in females. The QTc interval might be influenced by female sex hormones and may change with the menstrual cycle in premenopausal women.3,4 Atrial fibrillation is, in contrast, observed much more often in males. This arrhythmia increases gradually with age in men. It is extraordinarily rare in premenopausal age women and increases after menopause. On the other hand, female sex hormones may modulate the autonomic nervous system, which is already well known to influence the occurrence of atrial fibrillation.4,5 Therefore, the hormones might play important roles in the genesis of this arrhythmia. However, there have been no reports, to the best of our knowledge, about the roles of the menstrual cycle in atrial fibrillation, because this arrhythmia is very rare in premenopausal women. We here present a premenopausal female patient whose cardiac symptoms related to paroxysmal atrial fibrillation may have changed during her menstrual cycle.

Statistical analysis: Values are expressed as the mean ± SE. The unpaired Student t-test was used to assess the differences between two groups. The ANOVA test was used to examine differences among three groups. P values < 0.05 were considered to be statistically significant.

Case Report

A woman had experienced mild palpitation attacks (irregular tachycardia) since her late thirties. When she was 37 years old, an electrocardiogram (ECG) during the symptom was recorded for the first time at another hospital. The ECG showed atrial fibrillation (Figure 1). When she was free from any chest symptoms, an ECG revealed normal sinus rhythm. Her thyroid function tests were normal, and an ultrasonocardiogram did not show any abnormal findings. Thus, a diagnosis of lone paroxysmal atrial fibrillation was established. She did not smoke, and was just a social drinker. Medication was started, but her bearable palpitation attacks were not completely controlled. The attacks occurred not only in daytime but also in evenings, and especially after drinking alcohol. When she first visited our department at the age of 38, an ECG showed normal sinus rhythm (Figure 2) while taking flecainide 200 mg/day, bepridil 200 mg/day, and propranolol 20 mg/day. For two years (22 menstrual cycles) after the first visit, her medication was never changed and we asked her to keep a record of symptomatic
days. An ECG was recorded on every visit to our clinic. Her menstrual cycle was 30.4 ± 0.5 days and the menstrual period was 3.9 ± 0.2 days for the 22 cycles. We did not observe any more atrial fibrillation at our clinic during the two years. QTc intervals were 440 ± 3 msec in the follicular phase and 425 ± 2 msec in the luteal phase (P = 0.01) (Figure 3). These changes in QTc intervals during a menstrual cycle are compatible with the findings of earlier reports.

During the 22 menstrual cycles, she was symptomatic on 3.2 ± 0.7 days in the menstrual period, 6.4 ± 0.3 days in the follicular phase, and 4.1 ± 0.4 days in the luteal phase (P = 0.01) (Figure 4). After these 22 menstrual cycles, she wished to discontinue the medication because she felt the chest symptoms were bearable. Based on the findings during the observation period, we did not choose complete discontinuance, but rather a switch from daily medication to periodic administration for a week beginning a couple of days before her expected menstrual time. She did not experience either worsening of the palpitations or changes in the symptom with her menstrual cycle so she stopped recording her symptomatic days in detail. ECG event recorder monitoring was not performed because she did not wish to undergo a detailed examination about her bearable symptoms. Five years later, when she felt the symptom at a regular visit to our clinic, an ECG revealed atrial fibrillation (Figure 5).

**Discussion**

Recently, gender differences are being examined in relation to the occurrence of some arrhythmias. Congenital long QT syndrome is more often detected in females and the risk of a cardiac event in adults with this syndrome is higher in
women according to the International LQTS registry.\(^7\) While male sex hormone has been shown to shorten the QT interval,\(^9\) there have been some reports on the influence of female sex hormones on the QTc interval and the relationship between this interval and the menstrual cycle. Burke, et al revealed that QTc intervals changed during the menstrual cycle in premenopausal women; namely, it was the longest in the follicular phase and the shortest in the luteal phase.\(^2\) Rodriguez, et al showed that drug-induced QT prolongation by a group III antiarrhythmic agent, ibutilide, was prominent in the follicular phase and related to the serous progesterone level and progesterone/estrogen ratio, but not to the serous estrogen level.\(^7\) The menstrual cycle-related changes in QTc intervals in the present case (Figure 3) were compatible with these earlier results.

In contrast, atrial fibrillation is observed much more often in males, and increases gradually with age in men. In women, it is extremely rare before menopause and increases only after menopause. Therefore, female sex hormones have been considered to influence the occurrence of this arrhythmia. There have been some reports on the effects of female sex hormones on the electrophysiological characteristics of the atria. Rapid pacing-induced pathological shortening of atrial refractoriness was reported to be rectified by a female sex hormone, estrogen, in an animal model\(^10\) and was shown to have a gender difference and change after menopause in a clinical study.\(^10\) These results suggest that estrogen may reduce atrial arrhythmias. On the other hand, the menstrual cycle has been reported to modulate autonomic nerve function: parasympathetic activity is dominant in the follicular phase and sympathetic activity is dominant in the luteal phase.\(^8,11\) Both sympathetic and parasympathetic nerve activations can induce atrial fibrillation.\(^8\) Therefore, the roles of female sex hormones and the menstrual cycle in atrial fibrillation should be very interesting. To the best of our knowledge, however, there have been no reports on this topic because this arrhythmia is very rare in premenopausal women.

We have already reported that gender differences in subjective symptoms related to paroxysmal atrial fibrillation might also be detectable in postmenopausal women.\(^12\) In this report, we speculated that the gender difference in symptoms related to paroxysmal atrial fibrillation might depend not only on sex hormones, but also on intrinsic or social gender differences. In contrast, we have shown here that cardiac symptoms related to paroxysmal atrial fibrillation were varied during the menstrual cycle in a premenopausal woman.

The present case, without any underlying heart disease or hyperthyroidism, had mild palpitation attacks not only in daytime but also at night, especially after consuming alcohol, since her late thirties. Her symptoms occurred more often in the follicular phase when the parasympathetic nervous system is dominantly activated.\(^12\) Either sympathetic or parasympathetic nervous activation can induce atrial fibrillation,\(^12\) and the latter type is often characterized by its occurrence at night or its relation to alcohol drinking, a young age, and the absence of underlying cardiac diseases. The characteristics of palpitation attacks in the present case are compatible with those of paroxysmal atrial fibrillation related to parasympathetic nerve activation, as described above. Thus, we speculate that her palpitations may be induced by paroxysmal atrial fibrillation related to parasympathetic nerve activation during the menstrual cycle. We subsequently changed the medication from daily to periodic administration for one week beginning a couple days before the start of her expected menstrual cycle according to this speculation, and as a result she no longer experienced symptomatic variation during her menstrual cycle.

Since female sex hormones, especially estrogen, act as an anti-atherosclerotic factor, coronary artery disease is very rare in premenopausal women. Vasospastic angina is also rarely observed in premenopausal women, and may be related to the menstrual cycle. Kawano, et al found that episodes of anginal attack were reduced and flow-mediated dilatation of the brachial artery was augmented with increases in serum estrogen levels during the follicular phase in 10 premenopausal women with vasospastic angina.\(^8\) They stated that estrogen might suppress coronary artery spasm by activating endothelium-derived nitric oxide synthesis\(^11\) and/or by relaxing vascular smooth muscle with its calcium channel antagonistic action.\(^10\) The female sex hormone was shown to influence QT time, as described above.\(^8,13\) We have demonstrated here a case with a variation in paroxysmal atrial fibrillation attacks during her menstrual cycle. Thus, female sex hormones may also play important roles in various non-atherosclerotic cardiovascular diseases.

**Study limitations:** We only assessed subjective symptoms of the patient, and did not evaluate her arrhythmia objectively. Some of the symptoms might not have been caused by atrial fibrillation, but rather by other arrhythmias, such as frequent supraventricular premature contractions. On the other hand, some attacks of paroxysmal atrial fibrillation might have been asymptomatic. It is, however, difficult to objectively record attacks in outpatients with paroxysmal atrial fibrillation over long periods of time like a month. We detected sinus rhythm on all of more than 20 ECGs obtained during her asymptomatic visits to our clinic, but atrial fibrillation on both ECGs performed during palpitations. Therefore, we concluded that her palpitations were most likely related to paroxysmal atrial fibrillation.

**References**