Influence of The Menstrual Cycle Hormones On Autonomic Nervous System Tests

Melike ŞAHİNER[1], Başak YILDIRIM[2]
Denizli-Turkey

OBJECTIVE: To evaluate effects of estrogen and progesterone on autonomic nervous system by non-invasive electrophysiological autonomic tests such as sympathetic skin response (SSR) test and R-R interval.
STUDY DESIGN: Twenty-one subjects aged between 22-35 years were evaluated in EMG laboratory. SSR and R-R interval tests were performed twice, first in the early follicular (EF) phase and for a second time during the midluteal (ML) phase respectively.
RESULTS: SSR latency parameter was significantly shorter in follicular than midluteal phases ($p<0.05$) without indicating any correlation with the level of the hormones (FSH, LH, estrogen and progesterone).
CONCLUSION: Hormonal fluctuations that occur during the menstrual cycle alter the sympathetic skin response latency but not baroreflex regulation of heart rate.
(Gynecol Obstet Reprod Med 2004; 10:98-100)

Key Words: Autonomic nervous system, Estrogen, Progesterone R-R interval, Sympathetic skin response

There is not enough data regarding the effects of hypothalamus on autonomic nervous system but currently it was considered that hypothalamus is a coordination center rather than a motor nucleus. There is not so much data available concerning the impact of hormonal changes during the menstrual cycle on autonomic nervous system in women. All of the studies about this topic have focused on the cardiovascular effects of sympathetic and parasympathetic nervous system.[1-3] Recent work on estrogen and progesterone has focused on independent roles these hormones play in modulating the production of, or sensitivity to, the substances that vasodilate and/or constrict the vascular endothelium or underlying smooth muscle.[4]

Sympathetic skin response (SSR), the long latency electrical response obtained from the skin surface by the stimulation of the peripheral nerve, is considered an index of peripheral autonomic nerve fiber function.[5,6] Fagius and Wallin demonstrated with microneurography techniques that vasomotor as well as sweat-controlling fibers are involved in the SSR.[4] Shahani et al have shown the diagnostic value of SSR that can easily be performed in an electromyography (EMG) laboratory.[7]

[1]Pamukkale University Medical Faculty, Department of Physiology, [2]Pamukkale University Medical Faculty, Department of Obstetrics and Gynecology, Denizli-Turkey

Address of Correspondence *Melike Şahiner*
University of Pamukkale,
Faculty of Medicine,
Department of Physiology
Denizli-Turkey

Submitted for Publication: 19.12.2003
Accepted for Publication: 13.03.2004

Variation of the R-R interval in ECG is another test, which can provide useful information about the function of the parasympathetic nervous system.[8] There are very few studies investigating menstrual hormone effects on autonomic tests and to our knowledge SSR and R-R interval has not been previously applied in menstrual cycle periods.

Materials and Methods

Twenty-one subjects who did not taking any drug or drugs that could effect the autonomic system were evaluated; their ages ranged between 22-35 years (mean 29±3.53 years). Subjects had to abstain from coffee and alcoholic beverages for at least 12 h prior to the study. Written consent was obtained from each subject subsequent to a through explanation of the purposes and the methodology to be used in the present study.

SSR recordings were performed in a semi-darkened room, and in the relaxed and supine position. SSR recordings in all of the subjects were performed by a Medelec Premiere (UK, 1996) electromyograph and according to the method described by Shahani et al.[11] Stainless steel disk electrodes in 6 mm diameter were used for SSR recordings. The active electrodes were attached to the right hand palm where the reference electrode was attached to the dorsum of the hand. Bandpass filters were set between 1 to 1000 Hz and the sensitivity was between 0.5 to 2 mV/division. Square wave electrical pulses in 0.1 msec duration and 20 mA intensity were applied to the skin of the right wrist of each subject for 10 times, one in every 10 sec and the averaged SSR was recorded. The electrical pulses were applied at low frequency to minimize the motion artifact. Habituation was not encountered during the successive electrical pulses. The latency and amplitude measurements in SSR were performed manually. The amplitude was measured in mV from the

peak of the negative component to baseline. The area under the negative component of SSR was also recorded automatically in mVs.

For RRIV recordings, with the patient lying supine, one surface disc electrode was placed on the dorsum of each hand, the active being placed on the left.[12] A circular ground electrode was placed around one wrist. The bandpass was 1 to 100 Hz and the sensitivity was 0.5 to 2 mV/division. By using the triggering mode and the delay line, two QRS complexes were displayed on the screen. Because the first displayed complex is the triggering potential, the variation in timing of the second complex represents the R-R interval variation.

Five groups of QRS complex pairs were recorded at rest and two groups of 20 pairs of QRS complexes were recorded during deep breathing at 5 or 6 breaths per min. The range in the 20 pairs of R-R interval is termed -a-, and the mean of the 20 pairs of R-R intervals is termed as -b-. RRIV was expressed as a percentage of the average R-R interval using the formula RRIV= a/bx100. The average of five recordings at rest was termed as R% and those two recordings during deep breathing as D%. The differences between D% and R% and the ratio of D% to R% were also calculated.

F wave response study and conduction velocity measurement in two "motor and sensory" nerves (n.medianus and n.ulnaris) were performed to exclude the subjects with abnormal findings due to subclinical polyneuropathy, by using the usual criteria for diagnosis.[6,12]

FSH, LH estrogen and progesterone levels of each subject were obtained twice during 14^{th} and 21^{st} days of the menstruation.

Statistical analysis was performed using t-test by SPSS for MS Windows.

Results

All of the subjects' peripheral nerve conduction velocities were in normal limits. Configuration of the SSR waveform was a biphasic or triphasic potential. We accepted the time from the stimulus to the initial deflection as latency value and we performed SSR tests twice in the early follicular (EF) phase (2-4 days after the onset of menstruation) and once during the midluteal (ML) phase (8-10 days after the luteinizing hormone surge). Latency was significantly longer in the 21^{st} day of the cyclus than 14^{th} day (1.47s±10.2; 1.50s±26.5 $p<0.005$). The amplitude of SSR varied from a few microvolts to several milivolts even in the same subject but the averaged responses had more consistent waveforms. SSR amplitudes (1.9 mV±0.40; 2.2±0.46 $p>0.05$) and areas (8.7 mVs±0.15; 9.2 mVs±0.5 $p>0.05$) had shown non-significant differences in 14^{th} and 21^{st} days of the cyclus (Table 1). R-R interval values (D%, R%, D%-R% and D%: R%) did not show any significant difference between the 14^{th} and 21^{st} days of the menstruation. Mean values of RR intervals are shown in Table 2. Hormone levels did not show any significant correlation with SSR and RR parameters.

Table 1. Means of sympathetic skin response latencies, amplitudes and areas

Days	Latencies (s)	Amplitudes (mV)	Area (mVs)
14^{th}	1.47±10.2[a]	1.9±0.40	8.7±0.15
21^{st}	1.50±26.5[a]	2.2±0.46	9.2±0.50

[a] Statistically significant difference from normal controls ($p<0.05$)

Table 2. Mean Value of RRIV

Days	Rest (R%)	Deep breath (D%)	D% - %R	D% / R%
14^{th}	16.48±5.07	20.51±8.21	4.03±7.73	1.28±0.47
21^{st}	16.70±6.54	18.69±5.58	1.99±3.85	1.11±0.45

Discussion

The hypothalamus serves as the integrating mechanism of the autonomic nervous system and limbic system. The regulatory activity of the hypothalamus is accomplished in two ways; through direct pathways that descend into the brainstem and spinal cord and through the pituitary and thence other endocrine glands.[9]

Beyond the spinal cord the efferent part of the sympathetic pathway is composed of type B pre-ganglionic (thin, intermediate-slow myelinic) fibers originating from the cells of the lateral horns of the spinal cord and type C post-ganglionic (slow amyelinic) fibers. They synapse in the sympathetic laterocervical ganglia by means of excitatory and inhibitory postsynaptic potentials of extremely long duration. The afferent part runs closely with the somatic sensory fibers up to the spinal ganglia.[10,11]

According to the electrophysiological data obtained from the patient group, none of the patients had shown peripheral neuropathy so we were able to exclude peripheral nerve pathologies as a reason for the significant latency differences in 14^{th} and 21^{st} days of menstrual cyclus. It is obvious that hormonal changes effects sympathetic pathways and/or sympathetic neurons and delays SSR in the 21^{st} day of menstrual cyclus but it is not easy to guess the exact localization for this delay in the long pathway of sympathetic nervous system. Thus, further research is needed to more fully explore the relative contribution of estrogen and progesterone on latency period of SSR.

On the other hand we were not able to show any correlation with the level of the hormones (FSH, LH estrogen and progesterone) and SSR parameters but we can speculate that this will not be the evidence for irrelevance of sympathetic nervous system with menstrual hormones because it is well known that central nervous system has estrogen receptors on many localizations from spinal cord up to the diencephalic

structures and also it has been shown before that postmenopausal hormone replacement therapy effects some SSR parameters.[12]

SSR amplitude and area values of the subjects were not significantly changed in 14th and 21st the days of menstruation and these results seem to indicate that the number of excitable sympathetic neurons were constant, because Jasper reported that area under the curve which was recorded in electroneurographic studies provides the most direct estimate of the amount of functioning tissue that is generating the waveform.[13]

The integrity of the parasympathetic system could be assessed with several test based on cardiovascular reflexes. The heart rate variability termed R-R interval variation has been claimed to be the simplest and the most reliable test of vagal autonomic dysfunction. The neural mechanism depends on a parasympathetic reflex.[1-3]

Shahani et al. offered a simple test of vagal cardiac denervation that can be easily performed in the electromyography laboratory as well as SSR.[8] Their method depends on RRIV during normal breathing and deep breathing. In all age groups the vagal response to hyperventilation is to increase the R-R interval variability by deep breathing.[14] We observed that brainstem parasympathetic nucleus and its connections were not affected with menstrual hormone levels.

Because of some overlap test results between the 14th and 21st days of menstruation these two tests may not be able to sufficiently indicate autonomic test changes in an individual subject. Rather than, this study may indicate that as a group the subjects show some evidence of autonomic effects of hormones to sympathetic nervous system based on SSR.

References

1. Bosch E, Mitsumoto H. Disorders of peripheral nerves. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD (eds). Neurology in Clinical Practice. Stoneham: Butterworth-Heinemann, 1991:1755-71.
2. Persson A, Solders G. R-R variations: a test of autonomic dysfunction. Acta Neurol Scand 1984; 67:285-93.
3. Robinson BF, Epstein SE, Beiser GD, Braunwald E. Control of the heart rate by the autonomic nervous system. Studies in man on the inter-relation between baroreceptor mechanisms and exercise. Circ Res 1966; 19:400-11.
4. Fagius J, Wallin BG. Sympathetic reflex latencies and conduction velocities in normal man. J Neurol Sci 1980; 47:433-48.
5. Kimura J. Electrodiagnosis in disease of Nerve and Muscle. Philadelphia: Davis, 1983.
6. Maselli RA, Jaspan JB, Soliven BC, Green AJ, Spire JP, Arnoson BGW. Comparison of sympathetic skin response with quantitative sudomotor axon reflex test in diabetic neuropathy. Muscle Nerve 1989; 12:420-3.
7. Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response. A method assessing unmyelinated axon dysfunction in peripheral neuropathies. J Neurol Neurosurg Psychiatry 1984; 47:536-42.
8. Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol 1990; 47:659-64.
9. Adams RD, Victor M, Ropper AH. Principles of Neurology. New-York: McGraw-Hill, 1997.
10. Eizaguirre C. Physiology of the nervous system. Chicago: Year Book Medical, 1969.
11. Weight FF. Sympathetic mechanisms in autonomic ganglia. In: RN. Rosemberg (eds) Clinical Neurosciences, New York: Churchill Livingstone, 1983:267-85.
12. Sahiner T, Aktan E, Kaleli B, Oguzhanoglu A. The effects of postmenopausal therapy therapy on sympathetic skin response. Maturitas 1998; 30:85-8.
13. Jasper RD. Nerve conduction studies. In: Aminoff JM (eds) Electrodiagnosis in Clinical Neurology, New-York: Churchill and Livingstone, 1992:283-326.
14. Sundkvist G, Almer LO, Lilja B. Respiratory influence on heart rate in diabetes mellitus. Br Med 1979; 1:924-5.