Heart Rate Variability Predicts the Ovulation in Young Women: Possible Implications for Mobile Medicine Services

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***Abstract*—Here we report on a variety of traditional statistic and spectral parameters, and nonlinear parameters of heart rate variability (HRV) of 23 young females (19-24 years) during 4 phases (the early and late follicular phases, the ovulation, and the luteal phase) of the menstrual cycle (MC), in spring and autumn seasons. We found that in the ovulation phase of the MC, unlike to other phases, most of parameters of HRV have significantly changed. In springtime, these changes were significantly accentuated in comparison with autumn. All HRV parameters during ovulation shifted in the direction of decrease of the parasympathetic nervous system activity with reciprocal increase of the hormone-hypothalamic level of cardiovascular regulation and inference of the sympathetic nervous system. Additionally, we found that heart rate during the ovulation phase was controlled by a lesser number of regulating sensory inputs (2 in comparison with 3 characteristic of other phases of the MC). We discuss potential usability of this finding in respect with mobile medicine applications to strengthen awareness of a woman about forthcoming ovulation that would help planning their physical and behavioral activities.**

I. Introduction

The female's menstrual cycle (MC) attracts persistent interest among physiologists and health care specialists due to growing engagement of women in the professions and sport activities that were previously considered as strictly "masculine" ones. For example, women increasingly master such professions as cosmonaut/astronaut and military. Women participate in boxing, weightlifting, football and a variety of other sport activities which demand perfect endurance, power, coordination and speed characteristics. In a way, all the time the list of "ultimately masculine" professions is restricting. Physical and mental activity of the man largely depends on adequate circulation, and, hence, oxygen provision to tissues including the skeletal muscles. In many studies, sport achievements in females were attributed to a specific phase of the MC [1, 2]. However, there are papers, which provide no evidence for such correlation [3].

Additionally, many of modern women are very eager to be engaged in health supporting activities, such as fitness, aerobic training, and training of flexibility of joints, weight control etc. Both sports and these "moderate" health care motor activities are potentially dangerous in respect with tendon rapture, bone fracture, muscle tension, and even trauma caused by fallings or other accidents. It is known that there is higher incidence of, for example, patellofemoral pain syndrome in women, which presumably depend on the phase of MC [4]. Knowing the effect of a specific phase of the MC on neuromuscle condition or circulation may help preventing a woman from excessive motor practices at that time.

It is also acknowledged that the psychological status of women and their mental health and behavior is correlated with the MC phase. In particular, the episodes of depression, paranoidal thinking, decreased self-esteem, or suicidal behavior are believed to take place mostly in the paramenstrual period (several days pre, during and right post the menstruation) due to low concentration of estrogens and progesterone [5], [6], [7].

Current techniques aimed to perfectly detect specific phase of the MC are rather costly. Some are based on estimation of sex hormones [8], others relay on ultrasound search for follicular rupture during ovulation [9]. Measurement of the basal temperature graphs, cervical mucous assessment or ovulation test strips are regarded as the most practical, especially in lower-income women, though the least accurate method [10].

Earlier we have shown that some parameters of the motor system may be indicative of the ovulation phase of MC. In particular, we found that the nonlimear parameters of the surface electromyogram, such as fractal and correlation dimension and entropy are statistically significantly decreased in comparison with other phases of MC thus evidencing increased synchronicity of motor unit activity [11]. Also, we found that the motor units modulate their frequency depending on phase of the MC [11].

Some earlier studies have shown that values of heart rate variability (HRV) parameters are correlated with phases of the MC. However, only two or three phases were usually taken in consideration (the follicular, the luteal and the menstruation phase) [12, 13].

We hypothesize that the nonlinear HRV parameters may also be indicative of the ovulation. If it was true, one can consider applying HRV as a candidate predictor or indicator of the ovulation. To verify that hypothesis we collected samples

of electrocardiogram (ECG) from young female volunteers at four phases of the MC (the early and late follicular, the ovulation, and the luteal phase) in springtime (March-May) and autumn (October-November). If that hypothesis holds, a smart service based on the mobile information and communication technologies (ICT) can be designed to help women to be aware of their MC phase.

II. Subjects and Methods

A total of 29 healthy young females (aged 18-24 years, mean age ±SD was 19,9±1,4 years) volunteered to participate in the study. All females were non-smokers; they did not take contraception hormones at the time of the study and prior to it, all subjects signed their informed consent. The protocol was approved by the local Ethical Committee (the Ministry of Health Care and Social Development of the Republic of Karelia).

In average, based on the individual basal temperature graphs, the early follicular phase (F1) was tested on the 7th day of MC, the late follicular phase (F2) – on the 13th, the ovulation (OV) – on the 16th, and the luteal phase (LU) – on the 24th day of MC that corresponds with the sampling protocol in other studies [14].

Mean duration of the MC in autumn was 28,8±0,3 days, and in springtime - 28,6±0,7 days ($p>0,05$). The ovulation coming was verified by daily measuring the basal body temperature. The subjects were instructed to measure temperature intrarectally, early in the morning, before standing up and taking meals, 30 s long using an individual electronic thermometer (DT-520, A&D Company Ltd., Tokyo, Japan). Then subjects had to map the temperature data in an individual graph. On this temperature graph, the first day of ovulation was defined as the first day of sustained temperature rise after basal body temperature nadir [4, 14]. In some cases, subjects had to rebuild their temperature graphs during the next MC due to uncertainty of the ovulation point. Mean values of the basal temperature through the MC in springtime and autumn are presented on Fig. 1.

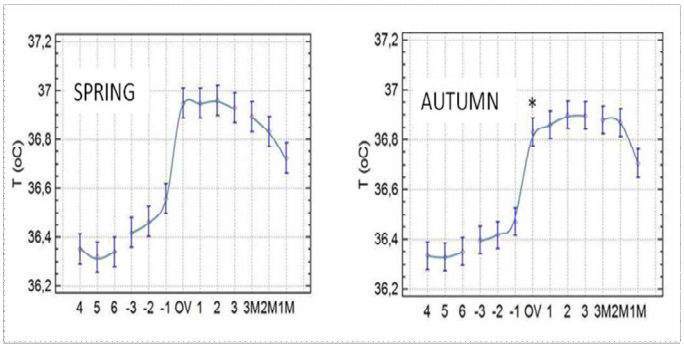

Fig. 1. Basal temperature along the menstrual cycle. OV – ovulation point, 3M-1M – days of menstruation. 1, 2, 3, -1, -2, -3 – days pre- and post ovulation. T – rectal temperature. * - difference between autumn and springtime at $p<0,05$

The ECG samples were collected with help of the VNS-Spectr device (Neirosoft Inc., Ivanovo, Russia) using the Lead II probe position within 300 s (5 min), strictly between 10:00 and 12:00 AM in the morning to avoid inference of hormonal diurnal shifts; in a shadowed, deprived of noise room, at thermoneutral air temperature (20-22 °C), without preceding physical and emotional stress, not earlier than 1,5-2,0 hours after last consuming meals. Prior to ECG recording the subjects were allowed to quietly lay on a horizontal surface (medical bed) for 30 minutes to help get adapted and relaxed. The ECG was sampled under condition of quite breathing, in laying position, with switched-off cellular phones. Subjects were asked to avoid swallowing saliva, coughing, and gasping. The arterial blood pressure (both systolic – SAD, and diastolic pressure - DAD) and heart rate (HR) were monitored using a UA-705 device (A&D Company Ltd., Japan).

The statistical (time-domain) and spectral (frequency-domain) HRV parameters were computed online. The following parameters were taken into consideration:

1) SDNN (ms) – the standard deviation of all normal-to-normal RR intervals (ms). SDNN characterizes the variability of the heart rate.
2) RMSSD (ms) - root mean square of successive RR interval differences.
3) PNN50 (%) - percentage of successive RR intervals with difference bigger than 50 ms (PNN50). PNN50 is believed to depend on the respiratory cycle and, hence, on the parasympathetic nervous system.
4) High frequency (HF, Hz) spectral power characterizes RR variation at 0.15-0.40 Hz. It correlates with the respiratory cycle and may reflect the parasympathetic influence on HRV.
5) Low frequency (LF, Hz) spectral power– spectral power characterizes RR variation at 0.04-0.15 Hz. It correlates both with the sympathetic and the parasympathetic influence on HRV.
6) Very low frequency (VLF, Hz) spectral power characterizes RR variation at 0.003 до 0.04 Hz. Presumably, VLF reflects the hormonal inference (renin-angiotensin-aldosteron system, catecholamine, etc).
7) HF, % - the spectral power in HF band.
8) LF, % the spectral power in LF band.
9) TP (Hz) - all variation in RR interval within the measured frequency band.

Additionally, the non-linear parameters were used to characterize HRV. Computation of these was performed off-line using the Kubios 2.2 HRV software (BSAMIG, University of Eastern Finland, Kuopio, Finland) [15].

The following non-linear parameters were considered in the study:

10) Correlation dimension (D_c) – a measure of complexity of attractor of a chaotic process. Mathematically, D_c can be regarded as a number of dynamic variables (equations) needed to model the underlying system [16]. Physiologically, D_c may be a representative of the number of sensory or other inputs which affect the cardiovascular control centers [17].

11) Percent of recurrence (REC,%) derived from the recurrence quantitative analysis (RQA) is a representative of a share of recurring fragments in a given time series.
12) Approximate (ApEn) and sample (SampEn) entropy is a commonly used measure of complexity in data.
13) The Poincaré plot (a scatter plot between successive RR intervals) provides indexes for short-term variability (SD1) and long-term variability (SD2), where both SD1 and SD2 are non-linearly connected to time-domain parameters [18].

Statistics was performed using the Statgraphics 15.0 Centurion software (Statpoint Technologies Inc., Warrenton, USA). The Mann-Whitney test (for pair comparisons) and the Kruskall-Wallis test (for multiply comparisons) were applied to validate difference between factors of phase of the MC and season.

III. Results

Of 29 volunteers, 3 withdrew their agreement to participate for different personal reasons, 1 subject had anovulatory MC, and 2 subjects – irregular MC, and, hence, were excluded from further analysis. Thus, the data was collected from 23 remaining females (79,3%).

HR, the SAD and DAD values are presented in Table I. HR was higher in the ovulation phase that was most clearly seen in springtime (10 beats per minute higher than in other phases, $p<0,05$). HR was still elevated in the luteal phase, though insignificantly. SAD and DAD values were higher in OV by 2-6 mmHg in springtime in comparison to other phases, though insignificantly.

The time-domain parameters (SDNN, RMSSD, and PNN50) did not differ between seasons, though they were significantly decreased in the ovulation phase both in autumn and springtime (Table II). The SD of the mean was very big, thus reflecting high variability of values between women.

All frequency-domain parameters of HRV have also decreased during the ovulation phase (Table III).

The portion of HF, LF and VLF bands was modulated in the direction of decrease of HF at the expense of VLF growth in the ovulation phase (Table III).

The nonlinear parameters of HRV presented the same pattern of variation across the MC phases and seasons. Namely, such parameters as correlation dimension (Dc), percent of recurrence (REC%) and SD1 and SD2 have decreased in the ovulation phase of the MC. For example, D_c has decreased from ~3,1 in phases F1, F2 and LU to 2,2 in the ovulation phase (Table IV). Percent of recurred fragments has increased from ~25 to 31%, SD1 has decreased to 35 and SD2 – to 60 in the ovulation phase (table IV).With respect to season, the difference of the ovulation phase from the other phases by the non-linear parameters was even more prominent. For example, in springtime D_c has decreased to 1,7 (Fig. 2), and SD1 – to 28.

TABLE I. HEART RATE AND BLOOD PRESSURE OF WOMEN IN VARIOUS PHASES OF THE MENSTRUAL CYCLE AND SEASONS

Phase/ season	Autumn	Springtime
SAD, mm Hg		
F1	107,3±7,0	106,7±6,1
F2	108,2±6,2	103,7±6,2 (p=0,056)
OV	108,5±7,2	103,8±8,0
LU	107,6±7,5	105,1±8,6
DAD, mm Hg		
F1	68,7±5,9	66,5±5,49
F2	69,2±5,2	64,0±6,1 ** to autumn
OV	69,1±6,8	65,28±7,10
LU	66,4±6,6	66,2±5,26
HR, minute^{-1}		
F1	71±11	69±9
F2	68±7	67±6
OV	74±6 # to F2	76±5 ## to F1, ### to F2, # to LUT
LU	72±9	71±7

Note: * - p<0,05, ** - p<0,01 in comparison to autumn, # - p<0,05, ## - p<0,01 between-phases comparisons

TABLE II. TIME-DOMAIN PARAMETERS OF HRV

Phase/ season	Autumn	Springtime
SDNN, ms		
F1	60,67±23,61	52,32±19,86
F2	65,1±28,01	58,71±17,26
OV	**44,12±12,93** * to F1, F2, LU	**40,27±24,15** * to F1, F2, LU
LU	57,5±15,97	59,86±22,30
SDNN, ms		
F1	32,27±22,49	31,27±20,64
F2	35,98±20,90	39,17±19,83
OV	18,69±17,95 p=0,052 to F1, * to F2	16,11±28,12 (n=11) * to F1; ** to F2, LUT
LU	30,50±17,70	33,48±22,34
PNN50, %		
F1	32,27±22,49	31,27±20,64
F2	35,98±20,90	39,17±19,83
OV	**18,69±17,95** p=0,052 to F1, * к F2	**16,11±28,12** * to F1; ** to F2, LU
LU	30,50±17,70	33,48±22,34

Note: * - p<0,05, ** - p<0,01 in comparison to autumn, # - p<0,05, ## - p<0,01 between-phases comparisons.

IV. Discussion

The major finding of the present study was that values of practically all parameters of HRV, either linear (time- and frequency-domain) or the nonlinear were synchronized with phases of the menstrual cycle. The same pattern was the characteristic of the electromyographic parameters fluctuation along the menstrual cycle found in our earlier study [11]. A presentation of such pattern is pictured on Fig. 3. Altogether, we found that the power of all spectral bands of HRV, the portion of high-frequency band, SDNN, PNN50 and correlation dimension has decreased during the ovulation phase. Alternatively, per cent of the very low frequency band has increased. The factor of a season also did matter. In fact, in springtime all shifts of HRV parameters were more profound.

TABLE III. FREQUENCY-DOMAIN PARAMETERS OF HRV

Phase/ season	Autumn	Springtime
TP, ms^2		
F1	4733,0±3315,72	3418,64±2546,0
F2	5615,55±4282,27	4071,18±2219,74
OV	2360,92±1497,12 # to F1, ## to F2, LU	1891,27±1637,01 # to F1, ### to F2, ## to LU
LU	4309,09±2132,6	4556,1±2732,93
VLF, ms^2		
F1	1032,38±563,66	723,41±684,93 *
F2	992,6±487,96	1130,06±631,51
OV	691,58±331,94	732,55±660,37 # to F2
LU	986,41±455,56	1171,52±935,54
LF, ms^2		
F1	1546,14±1678,29	942,91±1013,38 *
F2	1385,85±914,57	859,53±559,99 *
OV	589,35±423,22 # to F1, ## to F2, LUT	616,98±664,64 # to LUT
LU	1374,41±1053,04	1097,38±741,04
HF, msc^2		
F1	2154,48±1914,18	1752,82±1653,28
F2	3237,15±3791,54	2081,47±1707,44
OV	1080,08±1024,61 # to F1, LUT, ## to F2	541,64±442,16 # to F1, ### to F2, LUT
LU	1948,5±1193,19	2286,9±1775,69
%VLF		
F1	26,50±10,88	29,51±23,05
F2	23,77±13,31	32,67±18,83
OV	35,74±15,27 # to F1, F2	42,87±17,89 # to LU
LU	26,34±12,87	27,66±14,94
%LF		
F1	30,36±14,68	25,11±11,82
F2	26,60±9,93	21,14±8,15
OV	24,7±7,94	28,74±11,05 # to LU
LU	30,57±11,57	24,93±7,14
%HF		
F1	43,13±14,18	45,39±18,63
F2	49,63±16,45	46,19±15,76
OV	39,58±14,15 p=0,059 to F2	28,41±11,32 *, # to F1, ## to F2, LU
LU	43,11±10,91	47,41±13,79

Note: * - p<0,05, ** - p<0,01 in comparison to autumn, # - p<0,05, ## - p<0,01 between-phases comparisons

TABLE IV. NON-LINEAR PARAMETERS OF HRV

Parameter	F1	F2	OV	LU
D_c	3,15±0,98	3,09±0,97	2,21±1,27 # to F1, F2, LU	3,16±0,96
SD1	44,11±22,64	43,25±22,59	35,39±36,47	48,80±23,53
SD2	73,71±24,00	72,35±22,69	59,78±36,25 # to LU	81,96±29,33
REC%	24,30±12,31	20,62±7,04	31,09±16,74 # to F2	28,19±17,20

Note: Regardless of season. # - p<0,05 between-phases comparisons

Lower values of SDNN, pNN50, and RMSSD seen during the ovulation phase, irrespective of season, might evidence the decrease of the variability of heart rate. That, in turn, may be indicative of the weakened contribution of the parasympathetic nervous system in the net control of heart rate during ovulation. Decrease of the power of high-frequency band indicates the same [19]. Decrease of the total power of HRV spectrum reflects the general decrease of heart rate variability under ovulation, whereas growth of the very low frequency band power prompts increased contribution of the hormonal (neuro-humoral) factors in heart rate control [19].

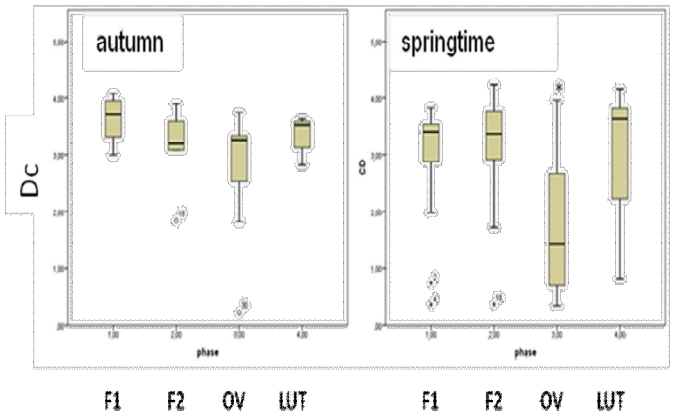

Fig. 2. Correlation dimension (Dc) across phases of the menstrual cycle and seasons

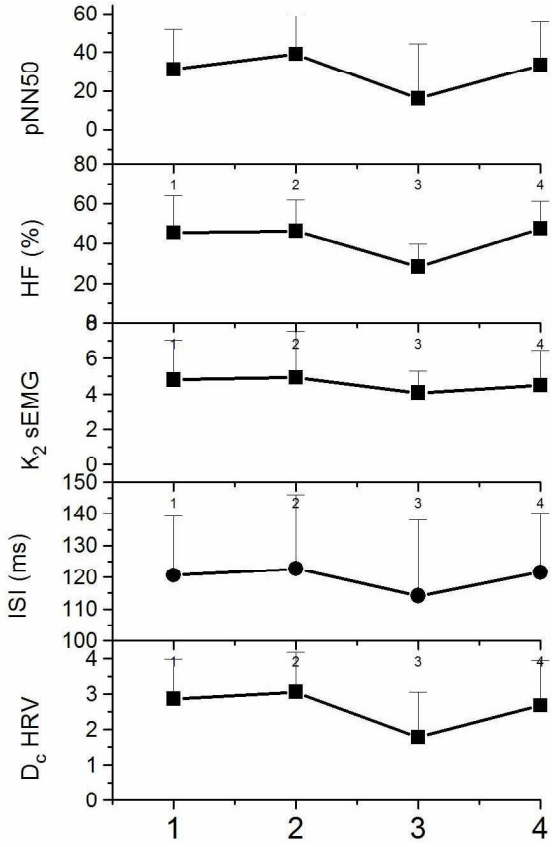

Fig. 3. Typical fluctuation of HRV and EMG parameters within the menstrual cycle. 1 – F1, 2 – F2, 3 – OV, 4 – LU phase. Data on ISI (interspike intervals, ms) of the motor unit impulsing and K_2 (correlation entropy) of EMG are borrowed from [11]

Thus, one can assume that the hallmark of the HRV modification throughout the MC is growing sympathetic nervous system inference in cardiac regulation during ovulation. This is in a good line with earlier studies, which have shown that the sympathetic activity prevails in the second (luteal) phase of the menstrual cycle [12], [13], [14]. In this study we have more precisely shown that this starts from the ovulation.

Presumably, such specific "sympathetic" bias of heart rate in the ovulation and, further, in the luteal phase may be associated with growing metabolism in women in the second part of the MC [20], that, in turn, could have been linked to their reproductive behavior.

Of the non-linear HRV parameters, correlation dimension and, to a lesser degree, the rate of recurrence, were linked to the menstrual cycle. Physiologically, the value of correlation dimension of any biosignal may be attributed to a minimal number of controlling inputs, either sensory or effector [14], [19]. Thus, decrease of correlation dimension from to 2,2 in upon ovulation from 3,1 in other phases of the menstrual cycle may merely reflect reduction of heart rate controlling inputs from 3 to 2. This corresponds well with elimination of the parasympathetic influence during ovulation. However, we did not document the same tendency for the luteal phase that raises further questions on the physiological nature of dimensionality of HRV in the menstrual cycle. The increase of the rate of recurrence of the heart cardiac intrevalogram supports the assumption that HRV in the ovulation phase is reduced to lesser number of regulating inputs. That is likely being true because the greater is the rate of similar fragments in a signal the lesser is number of independent oscillators and, therefore, the lesser is their interference. Thus, oscillatory generator of HRV becomes during ovulation less complex, or, in a sense, more "primitive".

Seasonality, i.e. the circannual cycle, proved to be a potent factor which interplays with the menstrual cycle (the inphradian rhythm). Indeed, we found that in springtime HRV bias to the sympathetic-control mode and less complex time structure is more prominent. One can attribute this to specific periodicity of some hormones. For example, springtime is characterized by elevated concentration of cortisol, whereas in the ovulation phase one could find decreased production of estrogens, progesterone, oxitocin, and, in contrary, increased concentration of testosterone and the follicle stimulating and luteinizing hormone [20].

V. Conclusions

In conclusion, we found that HRV parameters, either linear or nonlinear, are sensitive to the ovulation phase of the menstrual cycle in women. HRV during ovulation becomes less complex by its temporal structure and falls under influence of the sympathetic nervous system. These modifications of HRV were most readily seen in springtime.

Regardless of the physiological nature and biological purpose of these functional adjustments, this provides unique opportunity to invent an Internet-born, mobile medicine ICT channel for detection and recognition of the event of ovulation for further informing women about that. It would have raised awareness of women about their reproductive and physical state, and help them to make decision about daily activities.

We did not include such biologically important period of the MC, as the paramenstrual one into the protocol that can be regarded as a drawback and it restricted validity of the data. That should be done in our further studies. In ideal, an on-line day-to-day monitoring throughout the whole menstrual cycle with help of the ICT mobile medicine technique would be reliable to detect the ovulation.

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