Parameters of the spectral analysis of the heart rate variability in treating depression

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Key words: endogenous depression; chronobiology; circadian rhythm; autonomic nervous system; spectral analysis of the heart rate variability.

Summary. The objective of this work was to study circadian rhythms of the indicators of the spectral analysis of the heart rate variability in case of depression.

Materials and methods. A total of 37 patients, with a mean age of 46.7±10.3 years, were examined. According to the International Classification of Disease, 10th revision (ICD-10), endogenous depression was diagnosed for all of them (F 31.3–31.4, F 32.0–32.2, F 33.0–33.2). To assess the variability of the heart rhythm, the spectral analysis was used. The patients were examined at 1 AM, 7 AM, 1 PM, 7 PM prior to the beginning of treatment, following one week, and upon leaving the inpatient department. The control group consisted of 15 mentally healthy people.

Results. Before the beginning of treatment, desynchronization of circadian rhythms of the indicators studied and the sleep-wake cycle, the increase in the spectrum power within low-frequency (LF) range, and the decrease in the spectrum power within high-frequency (HF) range were observed. Reduction of depression symptoms was followed by resynchronization of the rhythms under study, with a spectrum power within LF range being increased and that within HF range – decreased.

Conclusions. Changes in depression symptoms and chronobiological disorders testify to their close pathogenetic link.

Introduction

Major depression is the most common mental illness in the general population, with a lifetime prevalence of 4–18% (1). It is estimated that up to 20% of patients (2) who contact primary healthcare services have current depression, but despite its high prevalence, major depression is unrecognized or misdiagnosed in approximately 50% to 75% of affected individuals (3–6). According to the present conception about neurophysiological mechanisms of pathogenesis of affective psychosis, hypothalamic-limbic structures of the brain play an important role within their development (7–10). In 50% of the patients suffering from endogenous depression, the activity of the hypothalamus-hypophysial system is increased, the circadian rhythms of producing individual hormones, cortisol in particular, are disturbed (11). Polysomnographic investigations revealed that the decrease in the length of a slow-wave sleep, the reduction of the latent period of the rapid eye movement (REM) phase, the disturbance of markers of its continuity are characteristic of a depressive episode (12). These changes attest to desynchronization of the circadian rhythms and the sleep-wake cycle, the shift of their phases towards the earlier hours of the day. Periodicity in affective disorders (from seasonal recurrence to 48-h rapid cycling) is the clinical observation; diurnal variation of mood, early morning awakening, and sleep disturbances are the classical symptoms that have linked depression with circadian rhythm function. Many rhythms, such as core body temperature, cortisol, monoamine metabolism, are different in depressive patients: phase advanced (timed earlier) with respect to the sleep-wake cycle, diminished in amplitude, and/or with day-to-day variability in their synchronization to social cues (13). It is assumed that these neurophysiological changes reflect much deeper pathological mechanisms of endogenous depression. At the same time, the disturbance of sleep and dysregulation of biological rhythms, apparently, in their turn, play an important role in the pathogenesis of the development of depression (14–20). Since the role of chronobiological disorders in the pathogenesis of depression is rather vague, the study of the question of correlation between the clinical manifestation of depression and the disturbance of circadian rhythms is of great interest.

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One of the methods for assessing functions of the hypothalamic structures is studying the indices of the activity of the autonomic nervous system, an autonomic regulation of the cardiovascular system, in particular (21).

The objective of this work was to study circadian rhythms of the indicators of the spectral analysis of the heart rate variability in case of depression.

**Methods**

The study was performed at the Republican Vilnius Psychiatric Hospital (Vilnius, Lithuania). It was approved by Ethic Committee of the Hospital. Subjects gave their written informed consent to participate in the study.

Thirty-seven right-handed patients (mean age, 46.7±10.3 years; range, 18–73 years) – 19 females (mean age, 49.6±10.5 years; range, 18–73 years) and 18 males (mean age, 43.6±9.8; range, 18–68 years) – have been examined. According to ICD-10 criteria (22), depression was diagnosed for all of them (columns: F 31.3–31.4; F 32.0–32.2; F 33.0–33.2). Exclusion criteria were organic pathology of central nervous system (tumors, etc.) and history of alcohol dependence. The degree of severity of depression was assessed according to the Hamilton Depression Rating Scale (HAM-D, 17 items) (23). The patients were treated with citalopram (20–60 mg/day). To assess the effectiveness of depression therapy, the absolute values attested to an intensification of sympathicotonia (at 7 \text{AM}, 1 \text{PM}, 7 \text{PM}, LF 7 \text{AM}/1 \text{PM}, 1 \text{PM}/7 \text{PM}, 7 \text{PM}/7 \text{PM}, 7 \text{PM}/1 \text{AM}, 7 \text{AM}/1 \text{AM} – 0.93, 1.08, 0.94, 0.95, respectively; in the depression group LF 7 \text{AM}/1 \text{PM}, 1 \text{PM}/7 \text{PM}, 7 \text{PM}/1 \text{AM}, 7 \text{AM}/1 \text{AM} – 1.10, 0.99, 0.91, 0.99, respectively). The absolute values attested to an intensification of sympathicotonia (at 7 \text{AM}, 1 \text{PM}, 7 \text{PM}, 1 \text{AM}, LF\% values in the control group were 4.84±20.91, 52.00±19.75, 47.93±18.82, 51.12±18.59, respectively; in the depression group – 56.19±23.15, 51.08±23.05, 51.46±20.13, 56.76±19.28, respectively) (Fig. 1, Table 1). In most cases, the depression status had a completely typical structure with the prevalence of a depression triad, anxiety, reduced excitation, and attraction characteristic of vital-somatic derangements. Such quite clearly expressed phenomena as awakening early in the morning, 24-h depressive variations, clinical features of sympathicotonia. Emotional instability, sensory hyperesthesia, deterioration of the status in the evening, dissociative changes in a vegetative structure with the prevalence of a depression triad, anxiety, reduced excitation, and attraction characteristic of vital-somatic derangements. Such quite clearly expressed phenomena as awakening early in the morning, 24-h depressive variations, clinical features of sympathicotonia. Emotional instability, sensory hyperesthesia, deterioration of the status in the evening, dissociative changes in a vegetative

**Results**

Before the therapy, desynchronization of the circadian rhythms of the parameters of spectral analysis of the heart rate variability and the sleep-wake rhythm were observed. This manifested itself in the shift of the phase of the circadian rhythms of the parameters under study toward the earlier time of the day (in the control group LF 7 \text{AM}/1 \text{PM}, 1 \text{PM}/7 \text{PM}, 7 \text{PM}/1 \text{AM}, 7 \text{AM}/1 \text{AM} – 0.93, 1.08, 0.94, 0.95, respectively; in the depression group LF 7 \text{AM}/1 \text{PM}, 1 \text{PM}/7 \text{PM}, 7 \text{PM}/1 \text{AM}, 7 \text{AM}/1 \text{AM} – 1.10, 0.99, 0.91, 0.99, respectively). The absolute values attested to an intensification of sympathicotonia (at 7 \text{AM}, 1 \text{PM}, 7 \text{PM}, 1 \text{AM}, LF\% values in the control group were 4.84±20.91, 52.00±19.75, 47.93±18.82, 51.12±18.59, respectively; in the depression group – 56.19±23.15, 51.08±23.05, 51.46±20.13, 56.76±19.28, respectively) (Fig. 1, Table 1). In most cases, the depression status had a completely typical structure with the prevalence of a depression triad, anxiety, reduced excitation, and attraction characteristic of vital-somatic derangements. Such quite clearly expressed phenomena as awakening early in the morning, 24-h depressive variations, clinical features of sympathicotonia. Emotional instability, sensory hyperesthesia, deterioration of the status in the evening, dissociative changes in a vegetative

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Fig. 1. Curve of daily changes in the indices at the initial stage of depression
LF – low frequency; HF – high frequency.

Table 1. Parameters of spectral analysis of the heart rate variability in case of the manifestation of depression, LF (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>7 AM M±SD</th>
<th>1 PM M±SD</th>
<th>7 PM M±SD</th>
<th>1 AM M±SD</th>
<th>7 AM / 1 PM</th>
<th>1 PM / 7 PM</th>
<th>7 PM / 1 AM</th>
<th>7 AM / 1 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression group (n=37)</td>
<td>56.19±23.11</td>
<td>51.08±23.05</td>
<td>51.46±20.13</td>
<td>56.76±19.28</td>
<td>1.10</td>
<td>0.99</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td>Control group (n=15)</td>
<td>48.41±20.91</td>
<td>52.00±19.75</td>
<td>47.93±17.82</td>
<td>51.12±18.59</td>
<td>0.93</td>
<td>1.08</td>
<td>0.94</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 2. Parameters of spectral analysis of the heart rate variability at the end of the first week, LF (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>7 AM M±SD</th>
<th>1 PM M±SD</th>
<th>7 PM M±SD</th>
<th>1 AM M±SD</th>
<th>7 AM / 1 PM</th>
<th>1 PM / 7 PM</th>
<th>7 PM / 1 AM</th>
<th>7 AM / 1 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression group (n=37)</td>
<td>51.51±23.30</td>
<td>50.81±22.69</td>
<td>55.51±21.78</td>
<td>56.11±21.29</td>
<td>1.01</td>
<td>0.93</td>
<td>0.99</td>
<td>0.92</td>
</tr>
<tr>
<td>Control group (n=15)</td>
<td>48.41±20.91</td>
<td>52.00±19.75</td>
<td>47.93±17.82</td>
<td>51.12±18.59</td>
<td>0.93</td>
<td>1.08</td>
<td>0.94</td>
<td>0.95</td>
</tr>
</tbody>
</table>
In the process of the therapeutic dynamics of depression, alongside the reduction of affective disorders, resynchronization of the rhythms of the parameters under study took place. At the end of the third week, phases of the rhythms were already insignificant shifted toward the earlier hours of the day. At the final stage of the study, reduction of depression symptoms was followed by resynchronization of the rhythms under study, with a spectrum power within LF range being increased and that within HF range – decreased. The absolute values attested to an intensification of sympathicotonia (Fig. 2, Table 3). HAMD-17 was 7.3±1.0 (P<0.001, the first week compared to discharge).

Discussion
This study showed that in case of depression, central mechanisms, which synchronize the circadian

![Fig. 2. Curve of daily changes in the indices at the final stage of depression](image)

**LF**

**HF**

**Hours**

**Table 3. Parameters of spectral analysis of the heart rate variability upon the discharge from the inpatient department, LF (%)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>7 AM M±SD</th>
<th>1 PM M±SD</th>
<th>7 PM M±SD</th>
<th>1 AM M±SD</th>
<th>7 AM / 1 PM</th>
<th>1 PM / 7 PM</th>
<th>7 PM / 1 AM</th>
<th>7 AM / 1 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression group (n=37)</td>
<td>53.73±23.24</td>
<td>54.92±18.07</td>
<td>51.19±21.84</td>
<td>56.14±19.77</td>
<td>0.98</td>
<td>1.07</td>
<td>0.91</td>
<td>0.96</td>
</tr>
<tr>
<td>Control group (n=15)</td>
<td>48.41±20.91</td>
<td>52.00±19.75</td>
<td>47.93±17.82</td>
<td>51.12±18.59</td>
<td>0.93</td>
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rhythms, become affected. This manifested itself in
the pronounced shift of the phase of the parameters
under study toward the earlier hours of the day.

Psychological, behavioral, physiological, and hor-
monal rhythms are specifically and functionally timed
(entrained or synchronized) with respect to sleep and
the day-night cycle. Rhythmic characteristics of mood
disorders were precisely described as far back as an-
cient times. However, it is still unclear whether circra-
dian rhythms are reliably linked with psychopathol-
yogy, if they provide clues to underlying mechanisms,
and how they can be understood with respect to the
established neurotransmitter models of depression.

Both circadian- and wake-dependent factors con-
tribute to a subjective measure such as mood. This has
been demonstrated in healthy subjects in both proto-
cols (16, 28–30). The day-to-day change in patterns
diurnal mood variation in a forced desynchrony
protocol has remarkable similarities to the day-to-day
variability in diurnal mood variation found in depressi-
ve patients and even more similarity to the mood pat-
terns following a phase advance of sleep-wake cycle
(31). Thus, mood fluctuations can indeed be under-
stood in terms of abnormal or changing phase rela-
tionships.

Mood-related cognitive and attributional disturban-
ces have been postulated to be sequelae of shifting
circadian rhythms. This is an important point for the
above findings. If patients with seasonal affective
disorder (SAD) are vulnerable to short winter days, is
this an abnormality of the biological clock, or is it
rather a subjective interpretation of internal temporal
disorder? The following findings are perhaps relevant
to this argument. Some subjects in experiments where
they live free of time cues manifest spontaneous in-
ternal de-synchronization, in that their sleep-wake
cycle desynchronizes from circadian rhythms such as
core body temperature. They do not notice that this
phenomenon has occurred or they do not show any
decrement in mood or performance; on the contrary,
they feel rather well. This is in marked contrast to the
situation resulting from external desynchronization,
when sleep timing is shifted by shift work or trans-
meridian travel. Here the internal desynchronization
between sleep and the clock is additionally in conflict
with light and social zeitgebers in the outer world,
and it is postulated that this aspect may underlie the
often-associated depressive disturbances (32).

It may not only be phase relationships that are im-
portant, but perhaps also the light-dark ratio (day
length or photoperiod). Some of the evidence for SAD
suggests that the duration of nocturnal melatonin
secretion is important for triggering psychopathology
in winter (33). Conversely, in a study of healthy sub-
jects kept on long winter nights, one volunteer became
severely suicidal, even though all the others felt re-
markably well on this protocol (34).

Diurnal variation or instability of mood can thus
be quite well explained by considering changing phase
relationships between processes C and S. Even in
healthy subjects, some phase relationships are favo-able, others unfavorable. Modest but reliable mood
decrements occur after a phase delay of the sleep-wake
cycle (35). Sudden delays (as induced by night shift
or westwards flights across time zones) can even pre-
cipitate depressive symptoms in predisposed indivi-
duals with a history of affective illness (36). This
points to a particular vulnerability of mood state when
sleep is shifted later with respect to circadian rhythms.
Such an association also appears to be valid for the
circadian sleep disorder of delayed sleep phase syn-
drome (inappropriately late sleep timing with respect
to the endogenous circadian clock). In these persons,
there is a high comorbidity of depressive symptoms
(37). Conversely, flying east may be more correlated
with hypomanic or manic states (36).

The present investigation showed that desynchro-
nization of circadian rhythms is observed not only in
such clinical phenomena as changes in the mood
depending on the part of day, early waking up, changes
in the energy tonus, appetite, sexual attraction, dis-
turbance of sleep, but also in disagreement between
the sleep-wake cycle and the circadian rhythms of
parameters of the autonomic activity that allow assess-
ing the function of the hypothalamic structures. The
study showed that both sympathetic and parasymp-
pathetic regulation of the cardiac rhythm was disturbed
in the patients who suffered from depression: the sym-
pathetic tonus was increased, whereas the parasymp-
pathetic tonus was weakened. Reduction of depression
symptoms was followed by resynchronization of the
circadian rhythms of the indicators of the spectral
analysis of the heart rate variability and sleep-wake
cycle. Direct relation between clinical manifestations
of depression and a pronounced negative effect on
the mechanisms that synchronize circadian rhythms
allow us to make a supposition that there exists a close
pathogenetic link between them.
Širdies ritmo variabilumo spektrinės analizės parametrai gydant depresiją

Sergejus Andruškevičius
Respublikinė Vilniaus psychiatrijos ligoninė

Raktažodžiai: endogeninė depresija, chronobiologija, cirkadianinė ritmika, autonominė nervų sistema, širdies ritmo variabilumo spektrinė analizė.


Rezultatai. Pradinio etapo metu stebėta registruojamų parametrų cirkadianinių ritmų ir miego-būdavimo ciklo tarpusavio desinchronizacija, LF (angl. low frequency) diapazono galios padidėjimas, HF (angl. high frequency) diapazono galios sumažėjimas. Depresijos simptomų redukcija lydęjo tirtų ritmų resinchronizacija, LF diapazono galios padidėjimas, HF diapazono galios sumažėjimas.

Išvados. Depresijos simptomų ir chronobiologinių sutrikimų pokyčiai rodo artimą jų patogenezinį ryšį.

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References