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## TREATMENT OF ARTERIAL HYPERTENSION AND QTc INTERVAL DURATION THROUGH CLINICAL PRACTICE

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This clinical case presents the treatment of arterial hypertension (AH) with improvement levels of daily average blood pressure (BP) in comparison with the initial level at the background of increasing the proportion of elongated corrected interval QTc and a violation of the average daily profile. The patient K. receiving ramipril in the morning 5 mg and 10 mg evening after 3 months during the control of daily monitoring of BP and ECG there is a decrease of average daily SBP and DBP daily average. Normalization of the average daily profile of DBP from «excessive degree of nocturnal BP reduction «in the» normal degree of nocturnal BP reduction». At the same time, however, there is an increase in the number of episodes of lengthening the interval corrected QTc and increase the proportion of elongated corrected interval QTc as well as the conversion of the average daily profile SBP «excessive degree of nocturnal BP reduction» in the «insufficient degree of nocturnal BP reduction», which increases the risk of acute cardiovascular events and requires further adjustment of therapy. This case demonstrates the individual patient's response to antihypertensive therapy in view of increased psycho-emotional stress associated with the specifics of her work.

**KEY WORDS:** arterial hypertension, ambulatory blood pressure monitoring, ECG monitoring, the insufficient degree of night BP decrease, excessive degree of nocturnal BP reduction, normal degree of nocturnal BP reduction

### ТЕРАПІЯ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ І ТРИВАЛІСТЬ ІНТЕРВАЛУ QTc ЧЕРЕЗ КЛІНІЧНУ ПРАКТИКУ

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Описано клінічний випадок терапії гіпертонічної хвороби з поліпшенням середньодобових цифр АТ порівняно з початковим рівнем на тлі підвищення питомої ваги подовженого коригованого інтервалу QTc і порушенням середньодобового профілю. У пацієнтки К. на фоні прийому раміприлу 10 мг вранці і 5 мг ввечері через 3 місяці при проведенні контрольного добового моніторингу АТ та ЕКГ відзначається зниження середньодобового САТ і середньодобового ДАТ. Нормалізація середньодобового профілю ДАТ з «надмірного нічного зниження АТ» до «нормального ступеню нічного зниження АТ». При цьому, проте, відзначається збільшення числа епізодів подовження коригованого інтервалу QTc і підвищення питомої ваги подовженого коригованого інтервалу QTc, а також конвертація середньодобового профілю САТ з «надмірного нічного зниження АТ» до «недостатнього ступеню нічного зниження АТ», що збільшує ризик гострих серцево-судинних подій і вимагає подальшої корекції терапії. Даний клінічний випадок демонструє індивідуальну відповідь пацієнтки на гіпотензивну терапію з урахуванням підвищеного психоемоційного навантаження, що пов'язано зі специфікою її роботи.

**КЛЮЧОВІ СЛОВА:** гіпертонічна хвороба, добове моніторування артеріального тиску, добове моніторування ЕКГ, недостатня ступінь нічного зниження АТ, надлишкова ступінь нічного зниження АТ, нормальна ступінь нічного зниження АТ

### ТЕРАПИЯ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ И ПРОДОЛЖИТЕЛЬНОСТЬ ИНТЕРВАЛА QTc ЧЕРЕЗ КЛИНИЧЕСКУЮ ПРАКТИКУ

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Описан клинический случай терапии гипертонической болезни с улучшением среднесуточных цифр АД по сравнению с исходным уровнем на фоне повышения удельного веса удлиненного

корректированного интервала QTc и нарушения среднесуточного профиля. У пациентки К. на фоне приема рамиприла 10 мг утром и 5 мг вечером через 3 месяца при проведении контрольного суточного мониторирования АД и ЭКГ отмечается снижение среднесуточного САД и среднесуточного ДАД. Нормализация среднесуточного профиля ДАД с «чрезмерного ночного снижения АД» до «нормальной степени ночного снижения АД». При этом, однако, отмечается увеличение числа эпизодов удлинения корректированного интервала QTc и повышение удельного веса удлиненного корректированного интервала QTc, а также конвертация среднесуточного профиля САД с «чрезмерного ночного снижения АД» до «недостаточной степени ночного снижения АД», что увеличивает риск острых сердечно-сосудистых событий и требует дальнейшей коррекции терапии. Данный клинический случай демонстрирует индивидуальный ответ пациентки на гипотензивную терапию с учетом повышенной психоэмоциональной нагрузки, что связано со спецификой ее работы.

**КЛЮЧЕВЫЕ СЛОВА:** гипертоническая болезнь, суточное мониторирование артериального давления, суточное мониторирование ЭКГ, недостаточная степень ночного снижения АД, избыточная степень ночного снижения АД

## INTRODUCTION

The duration of the QTc interval is not just electrophysiological phenomenon, but the most important parameter characterizing the electric systole of the heart [1]. Its shortening and lengthening reflect gross violations of the heart, which are associated with the risk of severe clinical syndromes including sudden cardiac death. Its reaction to the drug candidate determines be it so or not.

Clinical practice has deal with real patients, each of which can respond and responds to the already approved and included in the standard of care drugs, and these reactions may differ materially from those anticipated according to instructions attached to it.

That this is so, and that in clinical practice, the physician is obliged to rely not on the instructions but on patient's response to drug was demonstrated by our clinical case.

## CLINICAL CASE

Patient K., 50 years old, lives in Kharkiv, works as supervisor in extracurricular institutions for over 15 years.

**Complaints during the initial examination:** recurrent headaches with pressing nature often in the occipital region against the backdrop of increasing blood pressure to 160/90 mmHg, associated with emotional stress or weather condition.

Constant tinnitus, which get worse in the middle of the day. Periodical pressing pain in the heart after emotional stress without irradiation, accompanied by numbness of the left hand fingers. All symptoms are relieved by exercise (walking). Drug therapy is not accepted.

Periodical strong compressive pain in the middle and lower third of the sternum, burning sensation associated with psycho-emotional stress and without connection with food intake.

Periodical hunger pains. Bitterness in the morning, heaviness in the right upper quadrant.

**History of the disease:** first time high blood pressure (BP) was mentioned in 1995 during second pregnancy. For 16 years BP control was absent. In 2011 was fixed high blood pressure after a strong stress. Maximum level was 180/110 mmHg. Treatment in day hospital: ramipril 5 mg, bisoprolol 2,5 mg, polokard 75 mg, mildronate 5,0 ml.

Until July 2014 she was not treated. Sometimes she registered increasing of blood pressure to 160/100 mmHg. Periodically taking ramipril 5mg in the morning.

**Life history:** born in a large city, second child in the family. Sexual development is according to her age. Start working in 17 years old. Working and living conditions are satisfactory. The nature of the work is associated with increasing of emotional load. Lifestyle is satisfactory. Married. Has 2 children.

**Postponed diseases:** chickenpox, measles, mumps, cold, tonsillitis, acute bronchitis, pneumonia, primary varicose expansion of right saphenous vein, chronic cholecystitis, cholelithiasis, esophagitis.

Injuries are denied. In 1996 was removed uterus with appendages due to bleeding during second delivery.

Tuberculosis, viral hepatitis, sexually transmitted diseases are denied.

**Family history** of diabetes mellitus, cancer, mental illness, tuberculosis is not burdened.

Mother in 19 years old was operated because of thyroid goiter, she has AH for 20 years. Her mother, grandmother and aunt on the maternal line suffered from acute ischemic stroke. Mother suffered from malaria in childhood.

Her father had chronic gastritis with low acidity. In 65 years old 2/3 of the stomach was removed due to polyps. More than 50 years he smoked about 2 packs of cigarettes a day, drank alcohol. Blood pressure was low.

Allergic anamnesis is not burdened.

She does not have bad habits.

**Objective examination:** general condition was relatively satisfactory. Skin and visible mucous membranes was clean, normal in color. Peripheral lymph nodes were not enlarged. Weight gain: weight - 95 kg, height - 164 cm, BMI - 35.3, waist - 103cm.

Heart sounds were muffled, rhythmic, accent of 2 tone on the aorta, heart rate - 86 beats/min, BP - 150/100 mmHg. In the lungs was vesicular breathing. Tongue was clean, damp. Abdomen was soft on palpation, painless, increased in size due to the subcutaneous fat. There was moderate pain in the thoracic region of the spine during palpation.

Symptom effleurage on the lumbar region was negative on both sides. Physiological functions were normal. Peripheral edema did not present.

CVD risk factors: overweight, family history of cardiovascular disease in mother.

### **SPECIAL INVESTIGATIONS**

Complete blood count (24/10/2014): all figures were in normal range.

Urinalysis (10/24/2014): all figures were in normal range.

Biochemical analysis indicators (09.07.2014) were in normal range, except blood sugar - 5.69 mmol/L (normal 3.33 - 5.55 mmol/L).

Glycosylated Hb (24.10.2014g.) was 6.4 mkmol fructose/g Hb (normal rate 3.5 - 7.0 mkmol fructose/g Hb).

Glucose tolerance test (20.03.2015g.): glycaemia on empty stomach - 6.16 mmol/L (venous blood); 2 hours after glucose load - 7.47 mmol/l.

In lipid profile (10/24/2014) was noted increasing level of total cholesterol, low density lipoprotein (LDL), atherogenic factor, and decreasing of high-density lipoprotein

(HDL). The results are summarized in table 3. The risk of fatal cardiovascular event according to SCORE scale is 1 %.

Ultrasound of the heart (08/10/2014): left ventricular hypertrophy (LVMH), additional chord in the apical segment of the left ventricle, ejection fraction (LVEF) – 57 % (normal rate 55 – 80 %).

Ultrasound of abdomen and kidneys (11/06/2013): cholelithiasis (calculus to 5 mm in diameter), uric acid diathesis.

Fibrogastroscopy (11/06/2014): catarrhal gastritis, surface duodenopathies.

ECG (02/10/2014): sinus rhythm, right, heart rate - 76 beats/min, electrical axis of heart was horizontal, moderate signs of left ventricular hypertrophy were present. The length of the waves on ECG were P - 114 ms, PQ - 146 ms, QRS - 84 ms, QT - 392 ms, QT corrected (QTc) - 442 ms.

On the basis of home blood pressure monitoring for 3 weeks (from 10.10.2015 to 03.11.2015) the average figures of BP in the morning were from 140/100 mm Hg up to 160/110 mm Hg, on the evening – from 130/90 mm Hg up to 150/110 mm Hg. Taking into account these home monitoring for patient was assigned ramipril 5 mg in the morning and 5 mg in the evening.

Daily monitoring of ECG and blood pressure (05/11/2014) [2-4].

During the daily monitoring, average figure of BP was 144/85 mm Hg and heart rate - 81 beats/min. Elevated systolic blood pressure (SBP), more than 135 mmHg in the daytime and 120 mmHg at night was during 68 % of the daily monitoring time, including 80 % in the daytime and 27 % at night. Normal SBP was in 31 % of the daily monitoring, 20 % in the daytime and 67 % at night. Elevated diastolic blood pressure (DBP), more than 85 mmHg in the daytime and 70 mmHg at night was recorded over 60 % of daily monitoring time, including 68 % in the daytime and 33 % at night. Normal DBP was in 40 % of the daily monitoring time, including 32 % in the daytime, 67 % at night. Reduction degree of blood pressure at night above normal, SBP - 23,1 % - «overdipper» [5], DBP - 23.8 % (normal 10-20 %) in background of using ramipril 5 mg in the morning and 5 mg in the evening. Results of ABPM presented in table 1, 2.

During ECG monitoring average heart rate was 76 beats/min (day - 84 beats/min, night -

65 beats/min). It has been recorded 156 episodes of sinus tachycardia, total duration - 3 hour 6 min (153 in daytime and 3 at night) with average heart rate in an episode of 97 beats/min and maximum heart rate to 139 beats/min during daytime hours (14:25:55) at the end of the meal. Minimum heart rate was 51 beats/min in the early morning hours (6:35:55). Most episodes of tachycardia were an adequate response to emotional and physical stress and were registered in the period of wakefulness. Circadian index was in the normal range - 1,30. During the period of observation in sinus rhythm was registered single ventricular extrasystoles, total number - 17 and single supraventricular arrhythmias, total number - 13. Episodes of ST-segment depression with total duration of 21 minutes were registered. During the day (14:28:45), at the end of the meal, on the background of an episode of tachycardia (heart rate - 118 beats/min) an episode of ST segment depression (-147mkV) during 12 min 30 sec was registered. It was recorded 26 episodes of lengthening corrected QTc interval, which occupying 32 % of the registration period time. The average length of corrected QTc was 434 ms. Episode of maximum QTc (480 ms) was in 19:00:15 during 7 minutes (in time of cooking) and an episode of the maximum duration of QTc prolongation to 477 ms was in 00:38:15 during 41 min 30 sec with heart rate - 75 beats/min.

### **CLINICAL SYNDROMES**

Obesity, II degree. Hyperlipidemia IIa. Impaired glucose tolerance.

Syndrome of arterial hypertension with night blood pressure reduction, type «overdipper», 2 stage, 2 degree, high risk.

Syndrome of acquired QTc interval prolongation.

Syndrome of primary saphenous varicose veins in right leg.

GERD syndrome: chronic non-erosive esophagitis, remission.

Cholelithic syndrome. Chronic cholecystitis, clinical remission.

### **CLINICAL DIAGNOSIS**

Arterial hypertension, 2 stage, 2 degree, high risk. LVMH. Syndrome of acquired QTc interval prolongation. HF 0 degree. Obesity, II degree. Hyperlipidemia IIa. Impaired glucose tolerance. Chronic cholecystitis, clinical

remission. GERD: chronic non-erosive esophagitis, remission. Primary saphenous varicose veins in right leg.

### **THERAPY**

Ramipril 10 mg in the morning and 5 mg in the evening, atorvastatin 5 mg per day [6-7].

On the basis of the identified data changes ABPM and ECG (table 1 and 2; fig. 1a, 2a), taking into account the level of SBP night reduction: 20,6 %, «overdipper» (> 20), and DBP night reduction: 22, 1 %, «overdipper» (> 20), with insufficient reduction of blood pressure during the day, dose of ramipril in the morning was increased to 10 mg, in the evening dose was remained on 5 mg.

### **REPEATED EXAMINATION**

Repeated examination (11.03.2015) of ABPM and ECG (table 1 and 2; fig. 1b, 2b).

During the daily monitoring, average BP level decreased from 144/85 mmHg to 136/81 mm Hg to and heart rate - from 81 to 73 beats/min. SBP value remained high for 57 % (initial value - 68 %) of the daily monitoring time, including 57 % of daytime (initial value - 80 %) and 58 % at night (initial value - 27 %), maximum HR during the day - 96 beats/min. Normal SBP during the whole period of monitoring was registered in 43 % (initial value - 31 %), 43 % in daytime (initial value - 20 %), 42 % at night (initial value - 67 %). Increasing of DBP was over 49% (initial value - 60 %) of daily monitoring time, including 41 % in daytime (initial value - 68 %) and 68% at night (initial value - 33 %). Normal DBP during the day was in 59 % (initial value - 67 %), at night - 32 % (initial value - 67 %). Degree of BP reduction at night was below normal, SBP - 9,2 % - «nondipper» (> 0 and < 10), DBP in the normal range was in 12.7 % (normal 10-20 %) on the background of ramipril 10 mg in the morning and 5 mg in the evening. Transition of SBP from «overdipper» (20,6 %) to «nondipper» (9,2 %), and DBP from «overdipper» (22,1 %) to «dipper» (12,7 %). It remains insufficient degree of BP reduction most likely due to sleep disorders (patient woke up twice at night from 01 hour 40 min to 02 h 30 min and 04 hour 10 min to 04 hour 40 min on the background of increased emotional state).

During ECG daily monitoring (11.03.2015), average HR was 72 beats/min (79 beats/min in daytime, 62 beats/min at night). Maximum HR

was 120 beats/min in the morning, minimum HR - 47 beats/min in the early morning hours (5:17:35). Circadian index was 1,27. Increasing the numbers of QTc corrected elongation episodes to 77 from 26 and average duration QTc to 442 (previous - 434) ms, QTc above normal was registered in 56 % (previous - 32 %). Increasing of maximum QTc interval prolongation and indicators with maximum period of QTc interval prolongation. Episode

with the maximum QTc interval prolongation was 496 ms with total duration - 17 minutes 30 seconds, HR in episode was 83 beats/min (previous QTc was 480 ms with total duration of 7 minutes) and episode with maximum period of QTc interval prolongation - 1 hour 18 min 00 sec with interval prolongation to 479 ms, HR in episode was 65 beats/min (1:06:15), (previous - QTc - 41 min 30 sec with interval prolongation - 477 ms (00:38:15)).

Table 1

The results of ABPM during daytime hours (07:00 - 22:00)

Indicators	Observation stages		Standards
	05.11.14	11.03.15	
Avg. SBP	151 mmHg	139 mmHg	>90 and <135
Avg. DBP	90 mmHg	82 mmHg	>60 and <85
Time index of SBP	78,2%	44,8%	<15
Time index of DBP	64,2%	26,2%	<15
VAR1 SBP	19,7 mmHg	15,1 mmHg	<15
VAR1 DBP	10,1 mmHg	12,0 mmHg	<14

Table 2

The results of ABPM during night hours (22:00 - 7:00)

Indicators	Observation stages		Standards
	05.11.14	11.03.15	
Avg. SBP	120 mmHg	127 mmHg	> 80 and <120
Avg. DBP	70 mmHg	73 mmHg	> 50 and < 70
Time index of SBP	33,7 %	47,4 %	< 15
Time index of DBP	20,9 %	31,9 %	< 15
VAR1 SBP	13,1 mmHg	13,9 mmHg	< 15
VAR1 DBP	16,7 mmHg	9,0 mmHg	< 12
Degree of nocturnal SBP reduction	20,6 % «overdipper»	9,2 %«nondipper»	> 10 and <20
Degree of nocturnal DBP reduction	22,1 % «overdipper»	12,7 % «dipper»	> 10 and <20

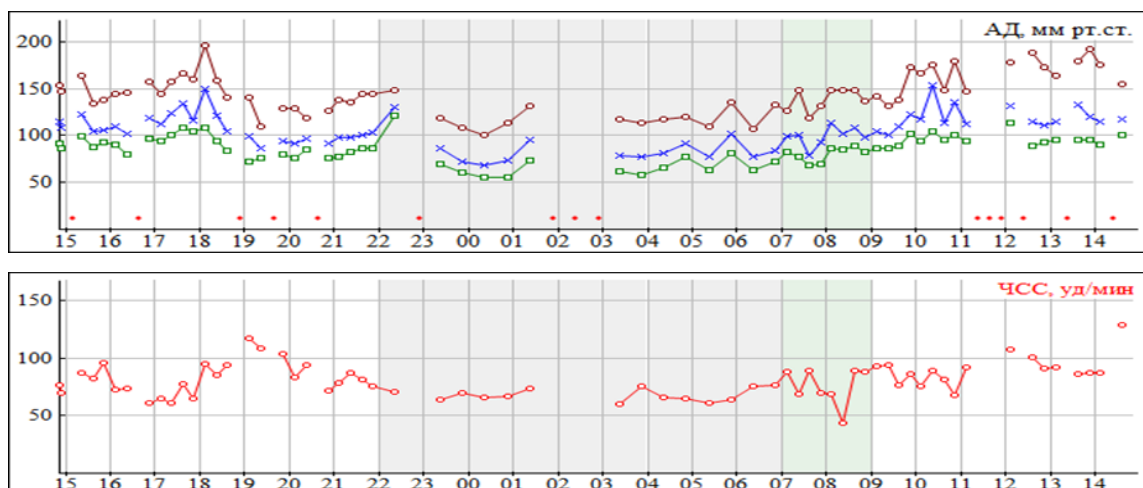


Fig.1a. Daily changes of SBP, DBP and HR (05/11/2014)

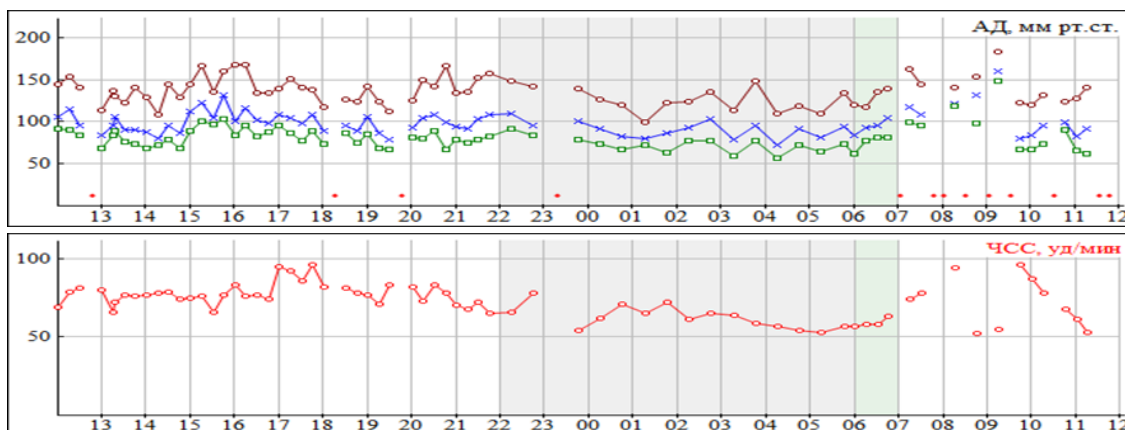


Fig.1b. Daily changes of SBP, DBP and HR 10.03.2015

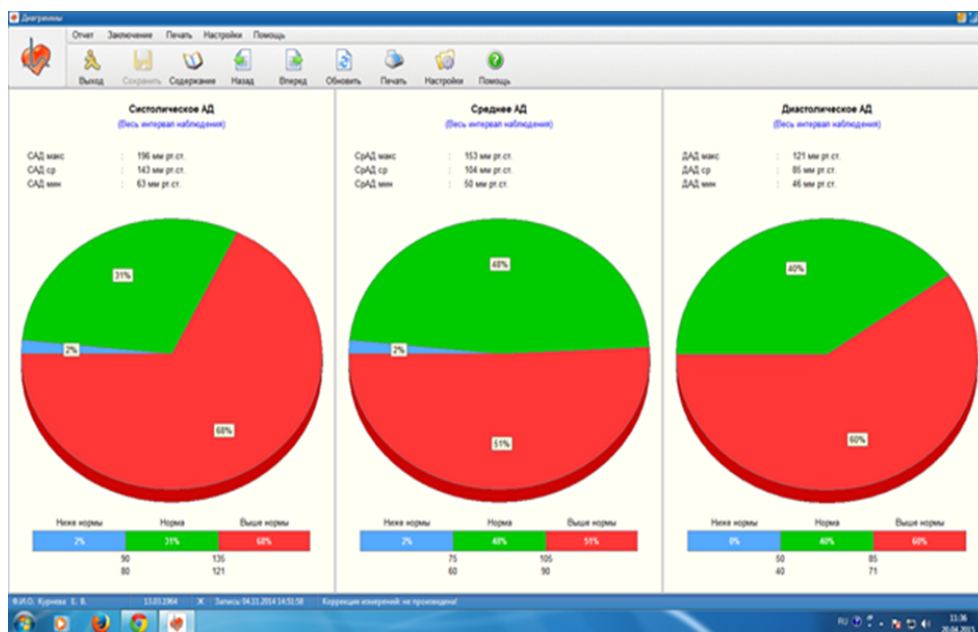


Fig.2a. Circadian profile of BP (05/11/2014)

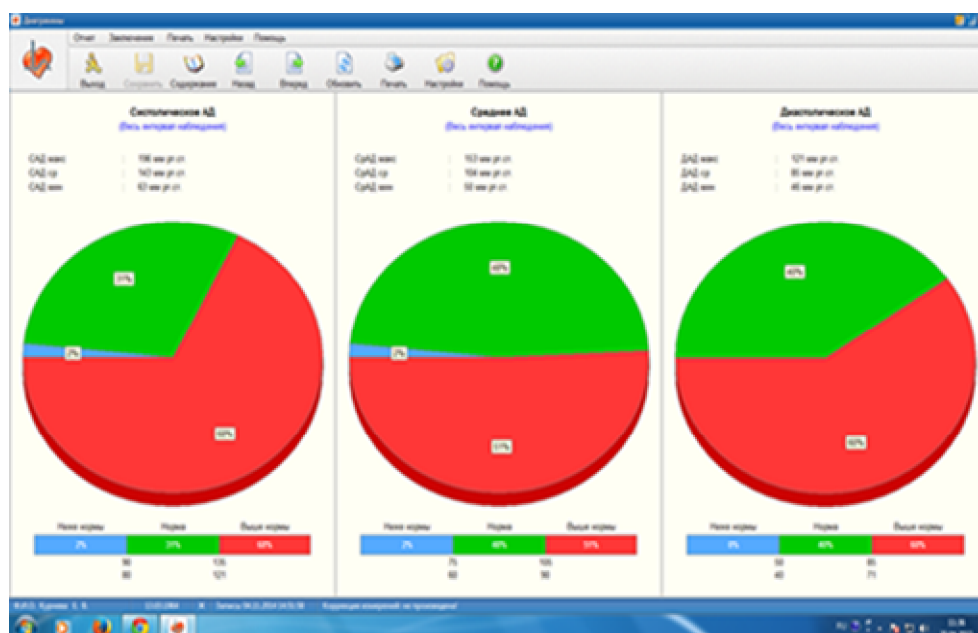


Fig.2b. Circadian profile of BP (10/03/2015)

Lipid profile has been improved during the second investigation (table 3).

Against the background of therapy in 3 months average daily SBP reduction from 143 mmHg to 136 mmHg and average daily DBP reduction from 85 mmHg to 81 mmHg was observed. Normalization of average DBP daily profile from «overdipper» to «dipper». At the same time, however, increasing the number of QTc corrected interval prolongation

episodes to 77 from 26 and increasing the proportion of elongated QTc corrected interval to 56 % against – 32 %, and conversion of the average SBP daily profile from «overdipper» to «nondipper» was detected. This condition contributes to the development of acute cardiovascular events, and therefore requires correction therapy. Our changes: ramipril 5 mg in the morning and 5 mg at night, melatonin 3 mg 30 minutes before bedtime.

Table 3

#### Indices of lipid spectrum

Indices	Results 24.10.14	Results 12.02.15	Norm (in SI units)
Total cholesterol	6,2	5,6	3,0 - 5,2 mmol/l - no risk 5,2 - 7,8 mmol/l – conditional risk > 7,8 mmol/l – high risk
Triglycerides	1,34	1,79	< 2,3 mmol/l
HDL	1,18	1,91	> 1,68 mmol/l - no risk 1,15 – 1,68 mmol/l – conditional risk < 1,15 mmol/l – high risk
LDL	4,73	2,67	< 2,59 mmol/l - no risk 2,59 – 4,12 mmol/l – conditional risk > 4,14 mmol/l – high risk
VLDL	0,28	0,98	0,26 – 1,00 mmol/l
Atherogenic ratio	4,2	1,9	< 3,0

Nearest goal is to restore physiological daily periodical of BP with shortening of QTc corrected interval and absolute improving patient's quality of life.

We hope that the recent intervention in the treatment regimen will lead to the expected result.

#### PROSPECTS FOR FUTURE STUDIES

It is interesting to re-evaluate studied parameters after 3 months on the background of therapy correction.

#### REFERENCES

1. Kulyk V.L. Interval QT v kardiologichniy klinitsi / V.L. Kulyk, M.I. Yabluchans'kyy // Visnyk Kharkivs'koho natsional'noho universytetu imeni V. N. Karazina, seriya «Medytsyna». – 2009. – № 18 (879). – S. 73-96.
2. Yabluchanskiy N.I. Ambulatoynaya elektrokardiografiya / N.I. Yabluchanskiy, A.V. Martynenko, L.A. Martim'yanova // Seriya: dlya nastoyashchikh vrachey. - KH.: - KHNU imeni. V.N. Karazina, 2015. - 113 s.
3. O'Brien E. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring / E. O'Brien, G. Parati, G. Stergiou [et al] // Journal of Hypertension. – 2013. – Vol. 31. – P.1731–1768.
4. International Society for Chronobiology. 2013 Ambulatory Blood Pressure Monitoring Recommendations for the Diagnosis of Adult Hypertension, Assessment of Cardiovascular and other Hypertension-associated Risk, and Attainment of Therapeutic Goals / International Society for Chronobiology // Chronobiology International. – 2013. – Vol. 30, Is. 3 – P. 355–410.
5. Alejandro de la Sierra. Prevalence and Factors Associated With Circadian Blood Pressure Patterns in Hypertensive Patients / Alejandro de la Sierra, Josep Redon, Jose´ R. Banegas [et al.] // Hypertension. – 2009. – Vol. 53. – P. 466-472.

6. Rekomendatsiyi Ukrayins'koyi Asotsiatsiyi kardiologiv z profilaktyky ta likuvannya arterial'noyi hipertenziiyi. Posibnyk do Natsional'noyi prohramy profilaktyky i likuvannya arterial'noyi hipertenziiyi. – K.: PP VMB; 2008. – 80 s.
7. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) // Journal of Hypertension. – 2013. – Vol. 31, Is. 7. – P. 1281-1357.