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Philosophy of Medicine

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INTERNAL DISEASES: THE TIME OF GLOBAL SOMATIC RISK

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This manuscript revises the problem of risk factors in somatic diseases. Singular risk factor and combination of risk factors are important and significantly affect the prognosis, the course, and outcomes of the disease. Today many global indexes have been introduced to assess the impact of risk factors, such as total cardiovascular risk in arterial hypertension, global cardiovascular risk in heart disease and diabetes mellitus, and global somatic risk in somatic diseases. Global somatic risk is based and generalized from total cardiovascular risk in arterial hypertension.

KEY WORDS: clinical medicine, internal diseases, cardiology, risk factors

ВНУТРІШНІ ХВОРОБИ: ЧАС ГЛОБАЛЬНОГО СОМАТИЧНОГО РИЗИКУ

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У статті порушено проблему факторів ризику соматичних захворювань. Розглядаються фактори ризику та сукупний вплив факторів ризику на прогноз, перебіг та наслідки хвороби. Обговорюються тотальний кардіоваскулярний ризик при артеріальній гіпертензії, загальний кардіоваскулярний ризик при хворобах серця і цукровому діабеті, глобальний соматичний ризик при соматичних захворюваннях. Глобальний соматичний ризик при соматичних захворюваннях пропонується будувати на базі загального кардіоваскулярного ризику при артеріальній гіпертензії.

КЛЮЧОВІ СЛОВА: клінічна медицина, внутрішні хвороби, кардіологія, фактори ризику

ВНУТРЕННИЕ БОЛЕЗНИ: ВРЕМЯ ГЛОБАЛЬНОГО СОМАТИЧЕСКОГО РИСКА

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В статье поднята проблема факторов риска соматических заболеваний. Рассматриваются факторы риска и совокупное влияние факторов риска на прогноз, протекание и последствия болезни. Обсуждаются тотальный кардиоваскулярний риск при артериальной гипертензии, общий кардиоваскулярный риск при болезнях сердца и сахарном диабете, глобальный соматический риск при соматических заболеваниях. Глобальный соматический риск при соматических заболеваниях предлагается строить на базе общего кардиоваскулярного риска при артериальной гипертензии.

КЛЮЧЕВЫЕ СЛОВА: клиническая медицина, внутренние болезни, кардиология, факторы риска

Risk factors are a key concept in the clinical practice. World Health Organization (WHO) determines risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury [1].

Due to a significance of combination of various risk factors on the development of disease,

a term risk factors has been accepted for general use instead of a singular risk factor term [2].

According to the WHO, all risk factors are divided to the internal and external, controlled and non-controlled risk factors [2]. Non-controlled external risk factors include multiple environmental elements, while non-controlled internal risk factors include sex, age (astronomical), and heredity. Controlled risk factors include changes in the blood cholesterol level and composition, high or low arterial blood pressure, active or passive smoking, alcohol abuse, hyper- and hypoglycemia, body weight, disorders in the reactivity and immune system, low and excessive physical activity, psychosocial distress, age (biological), habits and the living conditions (including water and nutrition), etc. [3].

Each risk factor contributes to a probability and complication of the disease. Combination of risk factors significantly exacerbates the risk of development of the disease, its severity, a possibility of early complications, and outcomes [2].

To evaluate the effect of risk factors on the prognosis, the course, and the outcomes of the disease, it is important to introduce a global index (or global score) as an integral measure.

The one successful attempt in this area has concluded in «2007 Guidelines for the Management of Arterial Hypertension», when the total cardiovascular risk (TCVR) was introduced [2]. The idea was effective and TCVR was carried into the new 2013 ESH/ESC Guidelines for the management of arterial hypertension [4].

Six years later, D.M. Eddy suggested expanding the concept of TCVR from the application in the arterial hypertension to a larger scope of heart disease and diabetes mellitus. In April 2013, D. M. Eddy introduced a new integral measure, the Global Cardiovascular Risk score (GCVR) [5]. In the «Pioneering Ideas» blog, the GCVR index was considered as «A New Performance Measure for Prevention» [6].

It is important to mention, that earlier in 2010–2011, in the Russian-speaking scientific environment, our group has suggested expanding the existing TCVR to the «Global Somatic Risk» (GSR) score [3, 7]. According to the principle of symmetry, the GSR is a generalization of TCVR [8].

The evaluation of TCVR in the guidelines of European Society of Hypertension (ESH) and European Society of Cardiology (ESC) is based on the WHO recommendations. These recommendations identify low, moderate, high, and very high risks in cardio-vascular morbidity and mortality for the next 10 years. GSR classifies the risks of somatic diseases in a similar manner. With a little modification, the TCVR is transformed into GSR, and can be used for the evaluation of a whole variety of somatic conditions.

The inclusion of outcomes of the disease and individualized treatment goals into the Eddy's GCVR is noteworthy, and we believe this is a prospective approach which should be used in many other global scores today and in the future [5].

However, risk factors are not that simple. It is important to consider an absolute level of quantitative measure of the risk factor and its duration, the assessment of single risk factor value in the global index, the philosophy of global index, and all of these are uneasy tasks.

It is not always possible to identify and correctly quantify all the risk factors, outcomes, and other important factors for the systemic composition of global index. The more precisely they are defined, the more accurately GSR is estimated, therefore the better the prognosis and the diagnosis are, the more likely the optimal preventive and therapeutic strategies are used, and the better the results are.

Medicine operates with non-strict sets and it is appreciated that not all of the factors are identified in the global indexes today. Along with a discovery of new risk factors, systematic work with patients and scientific research, the more risk factors will be included in the global indexes. Thus, it is not just a time of GCVR, but the time of GSR has come.

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Clinical researches

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GASTRIC MUCOSAL MICROCIRCULATION IN PATIENTS WITH DUODENAL PEPTIC ULCER AGAINST THE BACKGROUND OF ERADICATION THERAPY

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The article presents the results of investigation of gastric mucosal microcirculation with the help of laser-Doppler flowmetry in acute phase of duodenal ulcer during 7 and 14-day eradication therapy. The study enabled to obtain some data on effectiveness of the two therapeutic eradication regimens as well as their impact on gastric mucosal microcirculation in the process of ulcer defects healing.

KEY WORDS: microcirculation, peptic ulcer, duodenum, eradication therapy

СТАН МІКРОЦИРКУЛЯЦІЇ СЛИЗОВОЇ ОБОЛОНКИ ШЛУНКА У ХВОРИХ НА ВИРАЗКОВУ ХВОРОБУ ДВАНАДЦЯТИПАЛОЇ КИШКИ НА ФОНІ ЕРАДІКАЦІЙНОЇ ТЕРАПІЇ

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У статті наведені результати дослідження мікроциркуляції слизової оболонки шлунку методом лазерної допплерівської флуометрії в гостру фазу виразкової хвороби дванадцятипалої кишки, на тлі 7 і 14-денної ерадикаційної терапії. Отримано дані про ефективність двох схем ерадикаційної терапії, вплив різних схем на стан мікроциркуляції слизової шлунку на тлі загоєння виразкового дефекту.

КЛЮЧОВІ СЛОВА: мікроциркуляція, виразкова хвороба, дванадцятипала кишка, ерадикаційна терапія

СОСТОЯНИЕ МИКРОЦИРКУЛЯЦИИ СЛИЗИСТОЙ ЖЕЛУДКА У БОЛЬНЫХ С ЯЗВЕННОЙ БОЛЕЗНЬЮ ДВЕНАДЦАТИПЕРСТНОЙ КИШКИ НА ФОНЕ СТАНДАРТНОЙ ЭРАДИКАЦИОННОЙ ТЕРАПИИ

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В статье приведены результаты исследования микроциркуляции слизистой оболочки желудка методом лазерной допплеровской флуометрии в острую фазу язвенной болезни двенадцатиперстной кишки, на фоне 7 и 14-дневной эрадикационной терапии. Получены данные об эффективности двух эрадикационных схем терапии, влияние различных схем на состояние микроциркуляции слизистой желудка на фоне заживления язвенного дефекта.

КЛЮЧЕВЫЕ СЛОВА: микроциркуляция, язвенная болезнь, двенадцатиперстная кишка, эрадикационная терапия

Gastric and duodenal peptic ulcer (PU) is one of the major problems of contemporary clinical medicine. Despite successful implementation of diverse Helicobacter pylori (H. pylori) eradication therapies, PU is still among leading diseases of digestive system [1, 2]. In accordance with classical views, the processes of ulcerogenesis, chronization of arisen ulcers and their recurrence are closely associated with insufficient blood supply to gastroduodenal zone, hemodynamic disturbances in abdominal cavity vessels as well as in micro-

circulation in stomach wall, and, therefore, in injured tissues trophism [3–5]. All intensive processes in mucosa, including its rehabilitation, physiologic and reparative regeneration of epithelial and glandular cells, can be supported by adequate regional blood supply only [6–10]. The assumption that vascular injury (as a fact of ultimate injury in ulcerogenesis) is directly induced by bacterial chemotactic products and is one of the mechanisms of injury as well as the target of realized by H. pylori factors, renewed interest in investigation of regional blood flow in mucosa of gastroduodenal zone [11–13]. However, there is still a need for complete and conclusive conception of pathogenetic significance of microcirculation disturbances in injured tissues and its association with H. pylori infection.

The aim of the study was to investigate characteristics of gastric mucosa in patients with duodenal PU treated with standard triple eradication therapy.

MATERIALS AND METHODS

For the aims of this study we examined 68 patients with common and complicated clinical courses of chronic duodenal PU. 35 of the patients were male and 33 female. Age of the patients ranged 22–64 years (mean age 43,2 ± 6,3 years). The control group consisted of 25 preventively examined practically healthy middle-aged people. The groups were comparable in age (48,47 ± 0,82 years) and gender (12 males and 13 females) composition. Patients with H. pylori positive duodenal PU were enrolled.

All the patients underwent esophagogastroduodenoscopy (EGDS) with gastric mucosa biopsy of ulcer defect area. The examination was conducted twice with 1 month's interval.

Regional perfusion was studied using laser-Doppler flowmetry (LDF) (LAKK – 02, SPE «Lazma», Russia). Mucosal microcirculation was examined with cavitary sensor inserted through bioptic canal of Gastroduodenoscope into stomach and duodenal lumen. In course of the study were registered and evaluated: arithmetical mean of microcirculation (M), measured in (pf.sb.), standard deviation fluctuation range of blood supply from M (SD) measured in (pf.sb.), coefficient of variation (K_V), index of microcirculation effectiveness (IME). The examination was conducted in acute phase during ulcer defect scarring (phase of red and white scar) 1–3 month after remission of acute conditions.

After initial examination all the patients with H. pylori-associated duodenal PU were divided into two groups. Group I was formed by 34 patients, who underwent first-line eradication therapy for 7 days. Group II included 34 patients with duodenal PU, who underwent first-line 14-day eradication therapy. The therapy included a proton pump inhibitor — rabeprazole (20 mg twice daily) and 2 antibacterial agents: clarithromycin (500 mg twice daily), amoxicillin (1 g twice daily, for 7 or 14 days), pre- and probiotics (Maastricht-4, 2010) [10, 14]. Effectiveness of treatment was evaluated regarding reduction of duodenal PU clinical signs, indices of frequency of HP eradication (the results of validated laboratory monoclonal H. pylori stool antigen test in 4 weeks) and scarring of ulcer defect (phase of red scar in 4 weeks and phase of white scar in 12 weeks) after the therapy [1, 15, 16].

Mathematical treatment of the results was carried out using statistical package of programs «STATISTICA» 6.0. Normality of index distribution was checked using Kolmogorov-Smirnov criterion. For statistical estimate of results parametric criteria were used — mean value (M) and standard deviation (sd). Reliability of differences between samples was assessed using Wilcoxon-Mann-Whitney criteria. Estimation of correlation between pairs of independent signs marked in a numerical scale was done using Spearman's rank correlation coefficient (r). Significance of correlation coefficients was assessed comparing the estimated coefficients with the critical ones. Differences were considered significant at $P < 0,05$ level.

RESULTS AND DISCUSSION

Estimation of effectiveness of the H. pylori eradication was conducted 4 weeks onwards the therapy (Maastricht-4, 2011). The data obtained are shown in Fig. 1.

Eradication by 7-day therapy was reached in 72,3 % of the cases (24 patients). 14-day therapy appeared to be more effective as eradication rate made up 92,4 % in group II (32 patients). The data obtained match the results, cited in Consensus Maastricht-4 (2010) [1, 10, 17–19].

Additionally, 14-day anti-Helicobacter therapy regimen was followed by development of side effects in 33,4 % of the patients.

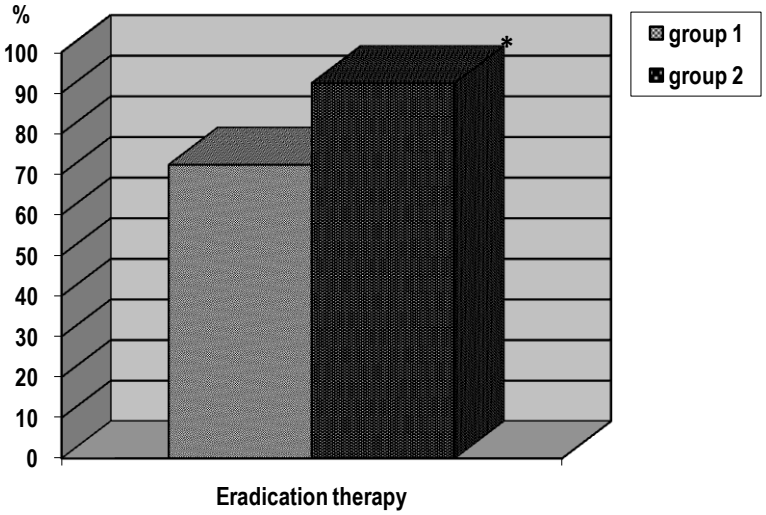

Fig. 1. H. pylori eradication rate in the groups of patients (%)

Comment:
* — differences between the groups are reliable (P < 0,05)

That was the reason for cessation of the therapy in some of the patients. In most cases the patients experienced general weakness (21,4 %), liquid stool (7,8 %), giddiness and headache (11,3 %), abdominal distension and rumbling (8,6 %), nausea (11,4 %). By 7-day anti-Helicobacter therapeutic regimen insignificant side effects were observed in 18 % of the patients with duodenal PU.

The data obtained by LDF 1 month onwards the therapy indicated improvement of microcirculation during ulcer defect scarring (table 1).

Table 1

Dynamics of microcirculation indices in patients with duodenal PU one month onwards the therapy (M ± sd)

Region	Index	Control group (n = 25)	Duodenal PU, acute phase (n = 68)	Duodenal PU (n = 68)	
				Group I (n = 34)	Group II (n = 34)
Fundal region	M (pf.sb.)	6,1 ± 0,15	9,22 ± 0,15	8,22 ± 0,35*	7,69 ± 0,21*º
	SD (pf.sp.)	0,66 ± 0,02	0,32 ± 0,02	0,36 ± 0,03	0,42 ± 0,07*
	K_V (%)	10,9 ± 0,2	4,9 ± 0,3	6,41 ± 0,5*	7,52 ± 0,2*º
	IME	1,95 ± 0,14	1,62 ± 0,14	1,67 ± 0,01	1,82 ± 0,02*º
Andral region	M (pf.sb.)	5,9 ± 0,08	4,2 ± 0,08	5,24 ± 0,09*	5,52 ± 0,04*º
	SD (pf.sb.)	0,58 ± 0,05	0,33 ± 0,05	0,38 ± 0,1	0,46 ± 0,12*
	K_V (%)	9,8 ± 0,4	8,67 ± 0,4	9,03 ± 0,4	9,19 ± 0,23*
	IME	2,2 ± 0,19	1,3 ± 0,19	1,68 ± 0,09*	1,85 ± 0,12*º

Comment:
* — differences from indices in acute phase are significant (P < 0,05);
º — differences from indices of group I are significant (P < 0,05)

As it can be seen from the given data, positive dynamics was observed one month onwards the therapy in the both groups, realized in the form of significant decrease of M and increase of SD, IME и K_V. In patients of group I we attested positive changes in the form of significant decrease of M in antral region in combination with increase in this index in fundal region. The decrease of M was not significant and had a character of a tendency. It should be noted that the lowest frequency of HP eradication was observed in this group. Correlation analysis between these indices has shown negative correlation of mean force (r = –0,24, P < 0,05). In the patients of group II the rate of decrease in index M in fundal region and increase in antral region was higher compared with the rate before the treatment in this group of patients (P < 0,05). This index was significantly increased compared to the indices before the treatment (by 13 %, P < 0,05), and to group I (by 18 %, P < 0,05). The was also noticed increase in SD by 14 % compared to the original (P < 0,05), IME by 22 %

($P < 0,05$) and K_V by 17 % ($P < 0,05$). Hence, a tendency towards normalization of microcirculation indices 1 was noticed in all the patients month onwards the therapy. The most evident changes were recorded in patients of group II.

3 month onwards the therapy in all the patients with duodenal PU was recorded significant decrease of microcirculation index in antral region, increase in SD, K_V and IME in fundal region ($P < 0,05$). Additionally, in group II no significant differences were recorded in most of the indices of gastric mucosal microcirculation compared to the control measures. In patients of group I reduction of K_V in fundal region and IME in antral region retained ($P > 0,05$) (Table 2).

Table 2

Dynamics of indexes of microcirculation in patients with duodenal PU 3 month onwards the therapy (M ± sd)

Region	Index	Control group (n = 25)	Duodenal PU, acute phase (n = 68)	Duodenal PU (n = 68)	
				Group I (n = 34)	Group II (n = 34)
Fundal region	M (pf.sb.)	6,1 ± 0,15	9,22 ± 0,15	7,31 ± 0,35*	6,24 ± 0,21º
	CKO (pf.sb.)	0,66 ± 0,02	0,32 ± 0,02	0,56 ± 0,03	0,58 ± 0,07
	KV (%)	10,9 ± 0,2	4,9 ± 0,3	7,32 ± 0,5*	8,32 ± 0,2º
	IME	1,95 ± 0,14	1,62 ± 0,14	1,74 ± 0,01*	1,82 ± 0,02º
Andral region	M (pf.sb.)	5,9 ± 0,08	4,2 ± 0,08	5,24 ± 0,09*	5,52 ± 0,04
	CKO (pf.sb.)	0,58 ± 0,05	0,33 ± 0,05	0,42 ± 0,1*	0,46 ± 0,12*º
	KV (%)	9,8 ± 0,4	8,67 ± 0,4	9,03 ± 0,4*	9,19 ± 0,23
	IME	2,2 ± 0,19	1,3 ± 0,19	1,68 ± 0,09	1,85 ± 0,12*º

Comment:
* — differences from indices in acute phase are significant ($P < 0,05$);
º — differences from indices of group I are significant ($P < 0,05$)

As it can be seen from the data, the most evident alterations were also fixed in group II in 3 month. Mean square deviation of microcirculation index in patients of group II in fundal region decreased by 34 % in compassion to the indices before the treatment ($P < 0,05$), in andral region it increased by 47 % ($P < 0,05$). This index was not significantly different from the control, but different from the index in group I ($P < 0,05$). SD in fundal and antral regions increased to $0,63 \pm 0,06$ and $0,58 \pm 0,09$ pf.sb. correspondingly and was not significantly different from the indices of the control group ($P < 0,05$). Significant differences were noticed only between indices of the control group and group II ($P < 0,05$). Index of variation K_V also increased $9,1 \pm 0,4$ %. That was significantly different from indices of group I ($P < 0,05$). Significant differences in IME of the control group, group I and II were also recorded 3 month after the therapy, in contrast to corresponding measures in 1 month ($P < 0,05$).

The conducted analysis enabled to establish strong dependency of alterations in state of gastric mucosal microcirculation on duration of anti-Helicobacter therapy and its efficacy. 14-day eradication regimen has proved to be more effective in patients with duodenal PU, however, more often followed by side-effects. Besides, disturbances in gastric mucosal microcirculation persisted 3 months onwards the conducted 7-day eradication therapy. More evident alterations in gastric mucosal microcirculation state have been recorded in patients who underwent 14-day therapy. 3 month onwards the therapy most of the indices were not different from the control measures. The mentioned differences in effectiveness of the regimens may be associated with different rate of H. pylori eradication after the treatment and different duration of proton pump inhibitors intake.

CONCLUSIONS

Having compared two standard regimens of eradication therapy we established that 14-day triple regimen is more effective for H.pylori eradication and correction of disturbances in gastric mucosal microcirculation in patients with duodenal PU than the 7-day regimen.

PERSPECTIVES OF FURTHER RESEARCH

Further investigation of gastric mucosal microcirculation in different phases of PU course by application of different therapeutic regimens, as well as study of influence of original microcirculation state on the effectiveness of

eradication therapy, will help to increase efficacy of therapeutic measures and reduce the frequency of relapses and complications after PU.

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IVABRADINE AND QUALITY OF BIOFEEDBACK IN THE LOOP OF PACED BREATHING UNDER THE CONTROL OF HEART RATE VARIABILITY PARAMETERS IN HEALTHY VOLUNTEERS

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On 15 healthy volunteers aged from 18 to 22 years the effect of ivabradine on the quality of biofeedback in the loop of paced breathing under the control of heart rate variability parameters were estimated. It was found that ivabradine contributes to an earlier onset and more significant optimization of regulatory systems in systematic sessions of biofeedback that allows to expand the indications for its clinical use.

KEY WORDS: ivabradine, heart rate variability, paced breathing, regulation

ІВАБРАДИН ТА ЯКІСТЬ БІОЛОГІЧНОГО ЗВОРОТНЬОГО ЗВ'ЯЗКУ В КОНТУРІ МЕТРОНОМІЗОВАНОГО ДИХАННЯ ПІД КОНТРОЛЕМ ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ЗДОРОВИХ ДОБРОВОЛЬЦІВ

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На 15 здорових добровольцях у віці від 18 до 22 років оцінили вплив івабрадину на якість біологічного зворотнього зв'язку в контурі метрономізованого дихання під контролем параметрів варіабельності серцевого ритму. У ході дослідження було встановлено, що івабрадін сприяє більш ранньому настанню і більш істотною за ступенем оптимізації регуляторних систем у систематичних сеансах біологічного зворотнього зв'язку, що дозволяє розширити показання до його клінічного використання.

КЛЮЧОВІ СЛОВА: івабрадін, варіабельність серцевого ритму, метрономізоване дихання, регуляція

ИВАБРАДИН И КАЧЕСТВО БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В КОНТУРЕ МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ ПОД КОНТРОЛЕМ ПАРАМЕТРОВ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА У ЗДОРОВЫХ ДОБРОВОЛЬЦЕВ

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На 15 здоровых добровольцах в возрасте от 18 до 22 лет оценили влияние ивабрадина на качество биологической обратной связи в контуре метрономизированного дыхания под контролем параметров вариабельности сердечного ритма. В ходе исследования было установлено, что ивабрадин способствует более раннему наступлению и более существенной по степени оптимизации регуляторных систем в систематических сеансах биологической обратной связи, что позволяет расширить показания к его клиническому использованию.

КЛЮЧЕВЫЕ СЛОВА: ивабрадин, вариабельность сердечного ритма, метрономизированное дыхание, регуляция

Heart rate is one of the most important physiological characteristics of the organism and has predictive significance in health and illness [1]. Its functional range is formed by sympathovagal and neurohumoral balance of regulation [2]. Distress, especially chronic, causes overstrains of regulatory systems of the organism and upsets the balance of the regulation that is reflected, in particular, in the high heart rate at rest [3].

One of the perspective ways is to optimize the balance of regulation during biofeedback sessions [4, 5] in the loop of paced breathing under the control of heart rate variability (HRV) parameters [6–8].

We showed before that systematic biofeedback sessions in healthy volunteers [6, 7] and in patients with arterial hypertension [8] optimizes regulatory systems by restoration sympatovagal and neurohumoral balance of regulation with reproducibility of these results for 3 months [9].

Ivabradine is positioned as a drug that selectively lowers heart rate by specific suppression of the sinus node If-channels [10]. Whereas heart rate is controlled by regulatory systems of the organism, especially by sympathovagal balance, ivabradine effect on heart rate may have an effect on regulatory systems. However, there is no such information in literature.

Considering to this, it is interesting to evaluate the effect of ivabradine on the regulatory systems during biofeedback sessions in the loop of paced breathing with more effective start with free breathing [7].

The study is conducted as a part of research project of V. N. Karazin Kharkiv National University «Development and research of automatic control of heart rate variability», registration No. 0109U000622.

Research objective: to evaluate the effect of ivabradine on the regulatory systems during biofeedback sessions starting with free breathing in the loop of paced breathing.

MATERIALS AND METHODS

The study involved 15 conventionally healthy volunteers aged from 18 to 22 years (average age is 19,53 ± 1,55). Exclusion criteria: pernicious habits, medication taking last 3 months, heart rate less than 60 bpm at rest.

The study is conducted with computer diagnostic complex «CardioLab 2009» («KhAI-Medica») with special module «Biofeedback» that contains programmatically connected aural-visual breathing metronome and algorithm of HRV parameters estimation.

HRV parameters were estimated in slide buffer for 1 minute through dynamic spectral decomposition by fast Fourier transform of R-R intervals sequence of lead I ECG records with 1000 Hz digitization frequency. All calculations were conducted in real-time during 7-minute biofeedback session. Power of low (V, up to 0,05 Hz), medium (L, 0,05–0,15 Hz) and high (H, 0,15–0,40 Hz) HRV parameters were estimated [11], then they were transformed into two-dimensional coordinate space with L/H and V/(L+H) axes, which correspond to power of sympathovagal and neurohumoral balances of regulation.

During biofeedback session, initialization of adaptation algorithm of biofeedback module was conducted in first 2 minutes, when volunteer breathe in his normal rhythm. After that for each following minute exact frequency of paced breathing was set through frequency rearrangement of aural-visual breathing metronome. Adaptation algorithm consists in automatic seeking of such frequency, when current L/H and V/(L+H) values are maximally approximate to optimum zone.

Biofeedback quality estimation was based on optimality (O), sensitivity (S), effectiveness (E) parameters both for whole regulatory system (D) and sympathovagal (L/H) and neurovagal (V/(L+H)) sections of regulatory system, and also on BQI integral index [6] that reflects all qualitative changes of biofeedback process.

In compliance with research objective, volunteers were conducted two series of 7-day biofeedback sessions in loop of paced breathing under HRV control with a 3 months interval between sessions [9]. In second session, biofeedback series were conducted 1 hour after oral intake of 5 mg ivabradine.

Values calculations of O, S, E parameters for D, L/H, V/(L+H) indicators and of BQI index were carried out using MathCAD 15 software program.

Statistical analysis of the results for each volunteer was carried out using Microsoft Excel 2003 software program. Average values (M) and standard deviation (sd) of O, S, E parameters for D, L/H, V/(L+H) indicators of first and last records of each volunteer were put down in spreadsheet.

The differences reliability of each parameter between first and second sessions and in each session was determined by Wilcoxon signed-rank test [12].

RESULTS AND DISCUSSION

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1st and 7th sessions of 1st and 2nd biofeedback series on conventionally healthy volunteers are shown in the table. Biofeedback series with ivabradine led to more rapid approach of examined rates levels to the optimum, while levels of reference values of both series were nearly equal.

Table

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1st and 7th sessions of 1st and 2nd biofeedback series on healthy volunteers

Parameter		Series			
		1		2	
		Session 1	Session 7	Session 1	Session 7
D	O	–5,08 ± 5,42	–1,11 ± 5,31†	–2,93 ± 4,58*	–0,60 ± 4,52*†
	S	0,85 ± 0,31	0,91 ± 0,30†	0,77 ± 0,25*	0,88 ± 0,21*†
	E	0,23 ± 0,22	0,26 ± 0,28†	0,21 ± 0,23*	0,35 ± 0,26*†
L/H	O	–5,88 ± 10,84	–3,84 ± 5,30†	–4,18 ± 6,96*	–3,80 ± 1,48*†
	S	5,08 ± 1,04	6,39 ± 2,28†	5,15 ± 2,99*	8,87 ± 1,76*†
	E	0,78 ± 0,02	0,99 ± 0,40†	0,95 ± 0,09*	1,00 ± 0,01*†
V/(L+H)	O	–1,72 ± 1,08	–1,43 ± 0,90†	–2,65 ± 0,30*	–1,39 ± 1,40*†
	S	1,36 ± 2,14	1,44 ± 2,00†	0,23 ± 0,03*	0,38 ± 2,72*†
	E	0,35 ± 0,37	0,37 ± 0,38†	0,13 ± 0,13*	0,14 ± 0,46*†

Note:
* — P > 0,05 between series;
**— P < 0,01 between series;
† — P > 0,05 in the series against the baseline values;
‡ — P < 0,01 in the series against the baseline values

The figure shows the changes of BQI index level of all subjects of first and second biofeedback series for 7 sessions. Systematic biofeedback sessions in loop of paced breathing under HRV control led to expected approaching of BQI index level to the optimum in both series. Biofeedback series with ivabradine led to more rapid approach of BQI index level to the optimum starting from the second session.

We showed before [9] that biofeedback in loop of paced breathing under HRV control is reproducible for 3 months. This allows to estimate the contribution of ivabradine in optimization of regulatory systems on a single cohort of volunteers by carrying out two series of biofeedback sessions with this interval, adding ivabradine to the sessions of second series.

These results demonstrate the influence of ivabradine on the regulatory systems of the organism, showed by changes of studied biofeedback reflective parameters (O, S, E for D, L/H, V/(L+H), BQI). Biofeedback series with ivabradine led to more rapid and significant optimization of regulatory systems of the organism.

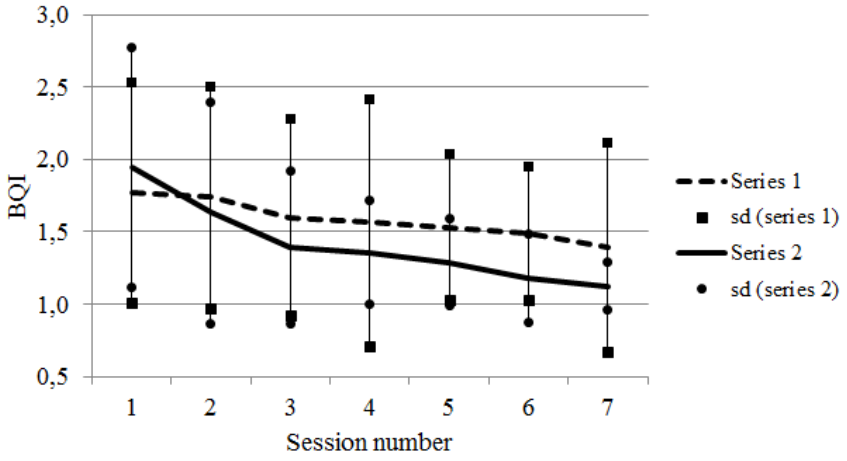

Fig. BQI changes at the first and second biofeedback series in all volunteers

Note:
* — P < 0,01 in the series against the baseline values;
**— P > 0,05 in the series against the baseline values;
† — P > 0,05 on the close sessions of the series;
‡ — P > 0,05 between series on the current session

These changes of the regulatory systems under the influence of ivabradine is a ground for its future pharmacodynamics studies with a perspective expansion of its clinical indications for use.

CONCLUSIONS

Systematic biofeedback sessions in the loop of paced breathing under HRV control optimizes regulatory systems of the organism.

Systematic biofeedback series with ivabradine led to more rapid and significant optimization of regulatory systems of the organism.

Ivabradine effects in biofeedback on regulatory systems of the organism requires a focused study and may become a ground for expansion of its indications for use.

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COMPARATIVE ANALYSIS OF SYSTOLIC BLOOD PRESSURE AND HEART RATE ORTHOSTATIC REACTIONS IN HEALTHY SUBJECTS AND ARTERIAL HYPERTENSION PATIENTS

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Age and gender difference of SBP orthostatic reaction types and HR in healthy subjects and AH patients were found. Rate of SBP hyper- and hypotensive reaction types decrease with age. Frequency of hypertensive type in AH is increased. HR increases in orthostasis disregarding SBP reaction type, the extent of growth increases from hyper- to hypotensive reaction. HR reactivity is higher in males.

KEY WORDS: arterial hypertension, orthostatic reactions, orthostatic hypotension, heart rate, systolic blood pressure

ПОРІВНЯЛЬНИЙ АНАЛІЗ ОРТОСТАТИЧНИХ РЕАКЦІЙ СИСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ ТА ЧАСТОТИ СЕРЦЕВИХ СКОРОЧЕНЬ У ЗДОРОВИХ ОСІБ І ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

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Виявлені вікові та статеві відмінності розподілу типів ортостатичних реакцій САТ та ЧСС у здорових осіб та у пацієнтів з АГ. Частота гіпер- та гіпотензивних типів реакції САТ знижуються з віком. Частота гіпертензивного типу при АГ підвищена. В ортостазі ЧСС зростає незалежно від типу реакції САТ, ступінь зростання збільшується від гіпер- до гіпотензивної реакції. Реактивність ЧСС вища у чоловіків.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, ортостатична реакція, ортостатична гіпотензія, частота серцевих скорочень, систолічний артеріальний тиск

СРАВНИТЕЛЬНЫЙ АНАЛИЗ ОРТОСТАТИЧЕСКИХ РЕАКЦИЙ СИСТОЛИЧЕСКОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И ЧАСТОТЫ СЕРДЕЧНЫХ СОКРАЩЕНИЙ У ЗДОРОВЫХ ЛИЦ И ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Обнаружены возрастные и половые отличия распределения типов ортостатических реакций САД и ЧСС у здоровых лиц и у пациентов с АГ. Частота гипер- и гипотензивных типов реакции САД снижаются с возрастом. Частота гипертензивного типа при АГ повышена. В ортостазе ЧСС возрастает вне зависимости от типа реакции САД, степень прироста увеличивается от гипер- к гипотензивной реакции. Реактивность ЧСС выше у мужчин.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, ортостатические реакции, ортостатическая гипотензия, частота сердечных сокращений, систолическое артериальное давление

Three main types of systolic blood pressure (SBP) and heart rate (HR) orthostatic reactions can be identified in both healthy subjects and in arterial hypertension (AH) patients: increase, no changes and decrease [1–3].

Persons in age 22–30 years are characterized with fast and high reactivity of SBP and HR, opposite to elderly people of age 65–75 years, in which lower reactivity, but longer duration of reaction is observed [3].

Normal and pathologic types of SBP and HR can be identified.

Normal type is characterized by average decrease of SBP on 6,5 mm (from –19 to 11 mm)

and by average increase of HR on 12,3 beats per minute (from –6 to +27 beats per minute. Pathologic type of SBP and HR orthostatic reactions include orthostatic systolic hypotension — decrease of SBP not less than per 20 mm; and orthostatic tachycardia — increase of HR for 30 beats per minute and more (or more than 108 beats per minute) [2].

SBP in healthy subjects of young age were investigated during the orthostatic test [3, 4]. Frequency distribution of main BP reaction types were studied [2] and hypertensive type of SBP reaction was found in 54 %; isotensive in 3%, and hypotensive in 43 %.

According to existing scientific data [1] three types of SBP orthostatic reactions were identified in AH patients — hypertensive, isotensive and hypotensive with a frequency distribution 67 %; 12 % and 21 % correspondingly.

According to multicenter clinical trials data hypotensive type of SBP reaction in orthostatic test, in particular orthostatic hypotension (SBP decrease on more than 25 mm) is an independent predictor of vascular mortality, risk factor of stroke [5], coronary syndrome [6], factor with clear negative prognostic meaning [7].

Comparative analysis of SBP and HR orthostatic reactions frequency distribution peculiarities in healthy subjects and AH patients data are absent in world and native scientific literature.

Aim of Research: to compare the peculiarities of SBP and HR orthostatic reactions distribution features in healthy subjects of various age groups and in AH patients in order to identify their clinical meaning.

MATERIALS AND METHODS

Three follow up groups were identified: healthy subjects of young and elder age (256 persons in total) and elder AH patients (154 patients in total).

Group of healthy subjects consisted of 2 sub-groups: 1^{st} — 218 persons (93 males and 125 females, age 20,8 ± 2,1 years, and 2^{nd} — 38 persons (17 males and 21 females, age 60,8 ± 4,4 tears).

Group of AH patients consisted of 58 males and 96 females, age 63,0 ± 7,0 years. Average AH anamnesis duration was 10,4 ± 7,8 years. 83 patients had I grade AH, 36 had II grade AH, and in 35 patients — III grade AH.

Patients that had myocardial infarction, stroke, heart failure (IV functional class), obesity III–IV grade, secondary hypertension were not included into study [4, 6].

Examinations were done in the morning, coffee, alcohol, medications were prohibited for 24 hours period. Physical load restricted for 30 minutes before the test.

BP was measured with Korotkoff method with a Microlife BP AG1-20 tonometer in a supine position (clinostasis) after 5 minutes rest and in 3 minutes after transition into standing position (orthostasis).

HR was calculated according to 5 minutes ECGs traces performed with computer electrocardiograph Cardiolab 2000.

According to SBP changes in orthostatic test healthy subjects and AH patients were split into 3 groups: 1^{st} — hypertensive type; 2^{nd} — isotensive type; 3^{rd} — hypotensive type. Criteria of SBP increase and decrease were its changes in a volume not less than 5 mm. Gender of healthy subjects and AH patients were taken into account in SBP and HR orthostatic reaction evaluation.

Distribution peculiarities of SBP and HR orthostatic reactions in healthy young and old subjects and in AH patients were studied.

Parametric criteria were used for evaluation of statistical estimations (mean meaning — M and standard deviation — sd).

RESULTS AND DISCUSSION

Fig. 1, reflects the results of SBP orthostatic reactions distribution research in young and old healthy subjects, and gender dependence.

Hypertensive SBP reaction type was found in 54 % of healthy young (45 % males, 60 % females) and in 45 % of healthy old (42 % males, 49 % females); Isotensive type in 3 % of healthy young (6 % males, 0 % females) and in 18 % of healthy old (21 % males, 17 % females); Hypotensive type in 43 % of healthy young (49 % males, 40 % females) and in 37 % of healthy old (37 % males and 34 % females).

SBP hyper and hypo orthostatic reactions types are predominating in healthy persons, but the old age group demonstrates a tendency for isotensive type frequency increase. Hypertensive type frequency is markedly higher in young healthy females, if compared to males, but in the old age group this difference greatly diminishes.

Relative increase of isotensive orthostatic SBP reactions frequency together with hypertensive and hypotensive reactions decrease

that is seen in old healthy subjects can be explained with the age diminishing SBP reactivity [3, 8].

Fig. 2, reflects the results of SBP orthostatic reactions distribution research in old healthy subjects and old AH patients, and gender dependence.

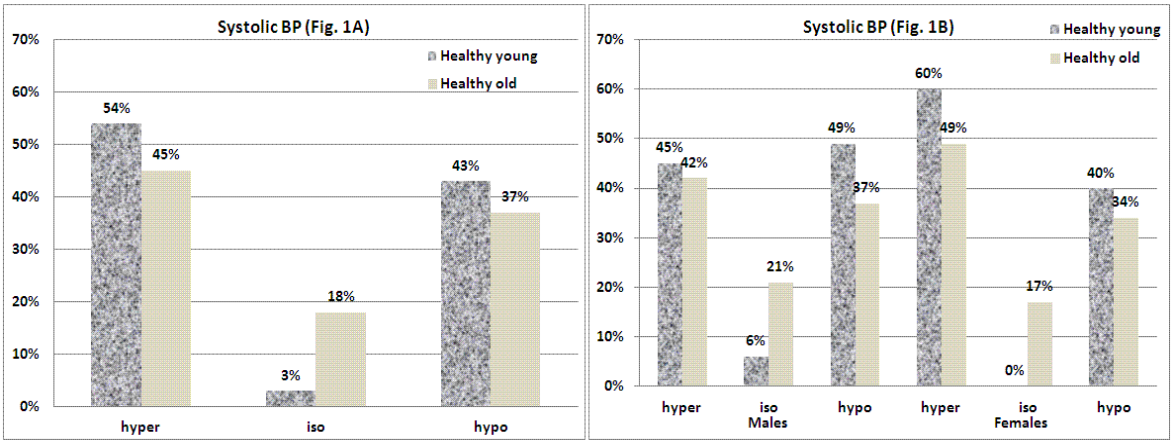

Fig. 1A. Distribution of SBP orthostatic reactions in young and old healthy subjects

Fig. 1B. Distribution of SBP orthostatic reactions in the same groups depending on gender

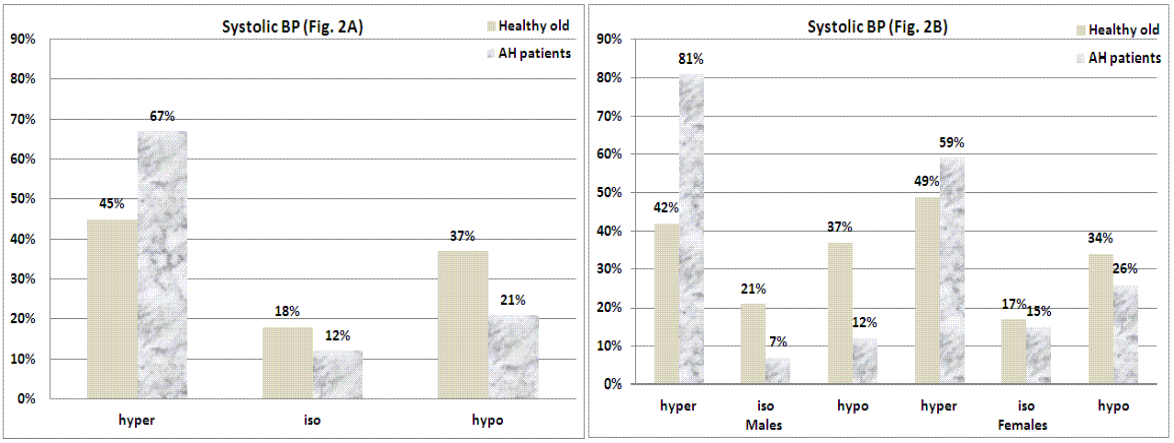

Fig. 2A. Distribution of SBP orthostatic reactions in old healthy and AH patients

Fig. 2B. Distribution of SBP orthostatic reactions in the same groups depending on gender

Hypertensive SBP reaction type was found in 45 % of healthy old (42 % males, 49 % females), and in 67 % of AH patients (81 % males, 59 % females); isotensive type in 18 % of healthy old (21 % males, 17 % females) and in 12 % of AH patients (7 % males, 15 % females); hypotensive type in 37 % of healthy old (37 % males, 34 % females) and in 21 % of AH patients (12 % males, 26 % females).

Hypertensive type is much frequently and hypotensive type is less frequently seen in AH patients, on the opposite to healthy old age. Hypertensive type is almost two times higher in male AH patients, while iso- and hypotensive types are almost three times lower in male AH patients, if compared to old healthy males. That makes hypertensive type absolutely dominating in AH male patients.

In female AH patients hypertensive type is somewhat higher, while isotensive is almost equal and hypertensive is slightly lower, if compared to old healthy females. Thus, hypertensive type is predominating in AH female patients, but the other two types can also be seen quite often.

Higher frequency of hypertensive orthostatic SBP reactions, that is seen in AH patients, is present mainly in males, and probably connected with the peculiarities of male and female organism aging [5, 7]. It also can be a reason of different frequency of more severe current and more aggressive complications of AH in males and females of older age [5].

Fig. 3, reflects the HR increase in identified types of SBP orthostatic reactions in young and old healthy subjects, and gender dependence.

In SBP orthostatic reaction hypertensive type, HR increased per 15 % in young healthy (16 % in males, 14 % in females) and per 12 % in old healthy (13 % in males, 11 % in females); In isotensive type, HR increased per 18 % in young healthy (19 % in males, 16 % in females) and per 15 % in old healthy (16 % in males, 14 % in females); In hypotensive type, HR increased per 20 % in young healthy (22 % in males, 19 % in females) and per 18 % in old healthy (19 % in males, 17 % in females).

HR increase is higher in young healthy, in all types of orthostatic reactions, if compared to old healthy subjects. Disregarding age, males demonstrate slightly higher rate of HR increase in all types of orthostatic reactions. Data obtained cannot be compared as no similar data was found available in world literature.

Fig. 4, reflects the HR increase in identified types of SBP orthostatic reactions in old healthy subjects and AH patients.

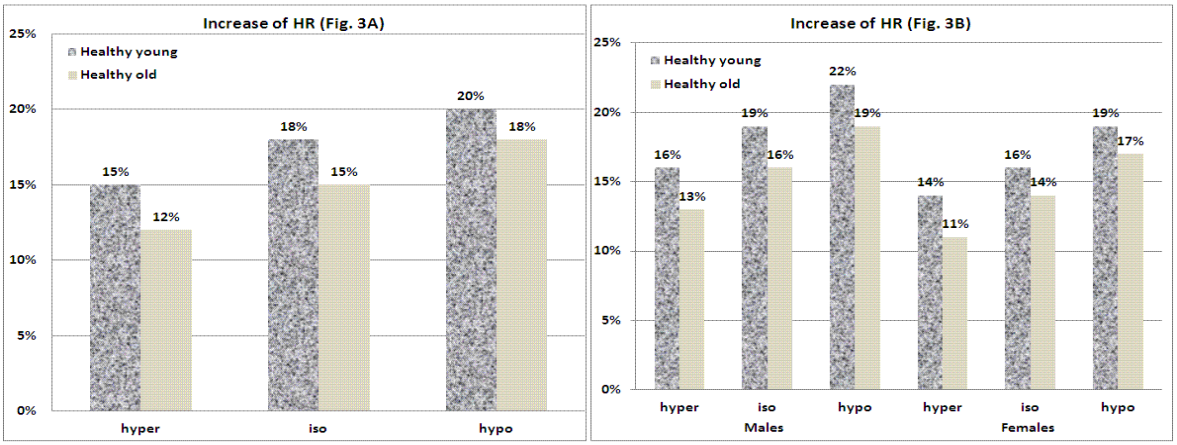

Fig. 3A. HR orthostatic increase peculiarities in the identified types of SBP orthostatic reactions in young and old healthy subjects

Fig. 3B. HR orthostatic increase gender dependence in the orthostatic types in young and old healthy subjects

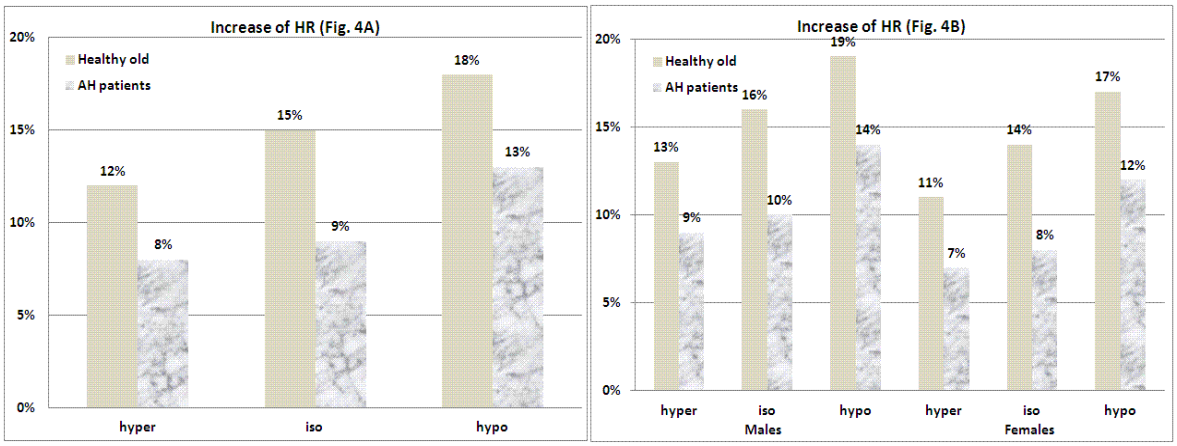

Fig. 4A. HR orthostatic increase peculiarities in the identified types of SBP orthostatic reactions in old healthy subjects and AH patients

Fig. 4B. HR orthostatic increase gender dependence in the orthostatic types in old healthy subjects and AH patients

In hypertensive type, HR increased per 12 % in old healthy (13 % in males, 11 % in females) and per 8 % in AH patients (per 9 % in males and 7 % in females); In isotensive type, HR increased per 15 % in old healthy (16 % in males, 14 % in females) and per 9 % in AH patients (10 % in males, 8 % in females); In hypotensive type, HR increased per 18 % in old healthy (19 % in males, 17 % in females) and per 13 % in AH patients (14 % in males, 12 % in females).

HR increases less in AH patients, in all types of orthostatic reactions, if compared to old healthy subjects. Both old healthy subjects and AH patients of male gender demonstrate slightly higher HR increase in all orthostatic reactions types.

HR changes are tightly connected with SBP orthostatic reactions. In all types of SBP orthostatic reactions HR increases during orthostatic tests both in young and old healthy subjects and AH patients. The extent of orthostatic HR increase raises from hypertensive to hypotensive SBP orthostatic reaction types. These data correspond to results obtained earlier [7]. The extent of HR increase in tilt tests diminishes not only with age but also in AH patients, and can be another additional sign of cardiovascular system reduced reactivity in AH. In males reactivity of HR in orthostasis is higher than in females per 2 % on average, that correspond to data obtained [7].

CONCLUSIONS

In healthy subjects SBP hyper- and hypotensive orthostatic reaction rates drops with age, while isotensive orthostatic reaction rate markedly grows. Gender difference in young and old healthy subjects has no significant importance.

In AH patients SBP hypertensive orthostatic reaction type predominates and is seen in 67 % of cases. In AH male patients, hypertensive type is markedly dominating.

In young and old healthy subjects and in AH patients HR increases in the tilt test in all types of SBP orthostatic reaction, but in AH patients the extent of increase is seen to be lower. The extent of HR increase drops from hypotensive to hypertensive type of SBP reactions. HR increase extent in tilt test diminishes with age. In males, HR reactivity is slightly higher in all age groups and reaction types.

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DEPRESSIVE DISORDERS MANAGEMENT IN ISCHEMIC HEART DISEASE PATIENTS

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OBJECTIVE: To study the dynamics of clinical, instrumental and psychological parameters in patients with ischemic heart disease (IHD) and comorbid depressive disorders on the stages of standard baseline therapy and additional tianeptine intake to develop proposals to improve management of such patients.

METHODS: 142 patients (77 males and 65 females) with the painful form of IHD in age from 45 to 60 years were examined. Quality of life (QoL), levels of depression, anxiety, pain perception; functional classes (FC) of stable angina pectoris and HRV indices were studied in patients with IHD in groups with a presence and absence of the depressive disorders at the beginning, in 3 weeks, 3, 6 and 12 months of baseline therapy and before and after 4 weeks of tianeptine adding to baseline therapy.

RESULTS: It was determined, that the depressive disorders result in worsening of QoL and HRV indexes. It was shown, that basic IHD therapy in the group of depressed patients with positive dynamics doesn't allow to achieve QoL and HRV indexes registered in the group of non-depressed patients. Also adding of tianeptine to baseline IHD therapy in depressed patients allows not only to improve QoL and HRV indexes, but also to attain the values of the proper indexes as in non-depressed group.

CONCLUSIONS: Patients with IHD should be examined for the presence of depressive disorders. In patients with IHD and clinically significant depression diagnosed antidepressant tianeptine must be added to baseline therapy.

KEY WORDS: ischemic heart disease, depressive disorders, heart rate variability, quality of life, tianeptine

ЛІКУВАННЯ ДЕПРЕСИВНИХ РОЗЛАДІВ У ПАЦІЄНТІВ З ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ

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МЕТА ДОСЛІДЖЕННЯ: вивчити динаміку клінічних, інструментальних і психологічних параметрів у пацієнтів з ішемічною хворобою серця (ІХС) та супутніми депресивними розладами на етапах стандартної терапії та її доповнення тіанептіном для розробки пропозицій щодо вдосконалення лікування таких хворих.

МЕТОДИ: У дослідження включили 142 пацієнтів (77 чоловіків і 65 жінок) з больовою формою ІХС у віці від 45 до 60 років. У всіх пацієнтів з ІХС в групах з наявністю і відсутністю депресивних розладів вивчали якість життя (ЯЖ), рівні депресії, тривоги, сприйняття больових відчуттів; функціональних класів (ФК) стабільної стенокардії і варіабельності серцевого ритму (ВСР) при початку, в 3 тижні, 3, 6 і 12 місяців стандартної терапії і до і після 4 тижнів додання до базисної терапії тіанептину.

РЕЗУЛЬТАТИ: Встановлено, що депресивні розлади призводять до погіршення якості життя і зниження показників ВСР. Було показано, що стандартна терапія ІХС у групі пацієнтів з депресивними розладами при позитивній динаміці не дозволяє досягти якості життя і значень ВСР, зареєстрованих у групі пацієнтів без депресії. Додання тіанептину до стандартної терапії у пацієнтів з депресивними розладами дозволяє не тільки поліпшити якість життя і ВСР, а й досягти значень, отриманих у групі пацієнтів без депресивними розладами.

ВИСНОВКИ: У пацієнтів з ІХС повинен проводитися скринінг на наявність депресивних розладів. У пацієнтів з ІХС та клінічно значущою депресією до стандартної терапії необхідно додання антидепресанту, наприклад тіанептину.

КЛЮЧОВІ СЛОВА: ішемічна хвороба серця, депресивні розлади, варіабельність серцевого ритму, якість життя, тіанептин

ЛЕЧЕНИЕ ДЕПРЕССИВНЫХ РАССТРОЙСТВ У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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ЦЕЛЬ ИССЛЕДОВАНИЯ: изучить динамику клинических, инструментальных и психологических параметров у пациентов с ишемической болезнью сердца (ИБС) и сопутствующими депрессивными расстройствами на этапах стандартной терапии и её дополнения тианептином для разработки предложений по совершенствованию лечения таких больных.

МЕТОДЫ: В исследование включили 142 пациентов (77 мужчин и 65 женщин) с болевой формой ИБС в возрасте от 45 до 60 лет. У всех пациентов с ИБС в группах с наличием и отсутствием депрессивных расстройств изучали качество жизни (КЖ), уровни депрессии, тревоги, восприятия болевых ощущений; функциональных классов (ФК) стабильной стенокардии и вариабельности сердечного ритма (ВСР) при начале, в 3 недели, 3, 6 и 12 месяцев стандартной терапии и до и после 4 недель добавления к базисной терапии тианептина.

РЕЗУЛЬТАТЫ: Установлено, что депрессивные расстройства приводят к ухудшению качества жизни и снижению показателей ВСР. Было показано, что стандартная терапия ИБС в группе пациентов с депрессивными расстройствами при положительной динамике не позволяет достичь качества жизни и значений ВСР, зарегистрированных в группе пациентов без депрессивных расстройств. Добавление тианептина к стандартной терапии у пациентов с депрессивными расстройствами позволяет не только улучшить качество жизни и ВСР, но и достичь значений, полученных в группе пациентов без депрессии.

ВЫВОДЫ: У пациентов с ИБС должен проводиться скрининг на наличие депрессивных расстройств. У пациентов с ИБС и диагностированной клинически значимой депрессией к стандартной терапии должен быть добавлен антидепрессант, например — тианептин.

КЛЮЧЕВЫЕ СЛОВА: ишемическая болезнь сердца, депрессивные расстройства, вариабельность сердечного ритма, качество жизни, тианептин

Ischemic heart disease (IHD) is one of the world's most prevalent disease of the cardiovascular system. IHD is the cause of more than half of all cardiovascular deaths [1]. It should also take into account the great socio-economic significance of IHD, which leads to a relatively early disability. Recent studies show that in addition to such factors as age, dyslipidemia [1], smoking, depressive disorders produce significant impact on the development, course and prognosis of the disease [2].

Depression in its various manifestations, including outpatient and inpatient patients with IHD occurs in 10–33 % of cases [3]. The frequency of depressive disorders in the population is 4,7–25,8 % in women and 2,1–12,3 % in men, and it is steadily progressing with age. Depressive disorders and heart disease are commonly comorbid [4]. The presence of depression is associated not only with a decreasing of patients' quality of life (QoL) [5], but also with an increased risk of cardiovascular complications [2] and death [6]. One possible pathogenetic mechanisms of the relationship of depression and cardiovascular disorders may appear imbalance between influences the parasympathetic and sympathetic nervous systems [7].

Despite the current standards of therapy of IHD [1] the search for more effective medicines for the treatment of concomitant depressive disorders remains relevant. According to K. Beliles, in most cases antidepressants must be prescribed to control depression [8]. Due to the fact that tricyclic antidepressants have cardiotoxic effects [2], monoamine oxidase inhibitors and, rarely, serotonin reuptake inhibitors may lead to the development of severe hypotensive reactions, the choice of the safest antidepressant to treat depression in patients with IHD is quite problematic [9]. At the same time, long-term effectiveness of basic therapy and its impact on QoL indices and heart rate variability (HRV) in patients with IHD with concomitant depressive disorders were not covered in the literature. In particular, the possibility of baseline therapy complementing with tianeptine is not studied, although there are reasons to believe that this drug, which is well tolerated, have mild antidepressant and anxiolytic effects can be quite effective in such patients. A study of the mechanisms of physiological functions regulation in patients

with IHD and depressive disorders can provide significant aid in both predicting patient status and effective management of such patients.

Objective. To study the dynamics of clinical, instrumental and psychological parameters in patients with IHD and comorbid depressive disorders on the stages of standard baseline therapy and additional tianeptine intake to develop proposals to improve management of such patients.

MATERIALS AND METHODS

142 patients with painful form of IHD who were admitted to cardiology department «Central Clinical Hospital of Ukrainian Railways Ukrzaliznytsi». The duration of the study was from 2003 to 2006. Totally 77 males and 65 females aged 45 to 60 years (mean age for men — 49,7 ± 5,8, years, women — 54,0 ± ± 3,7 yrs.) were observed.

According to the criteria of the Canadian Cardiovascular Society all patients had stable angina pectoris ranged from I to III functional classes (FC). I FC of stable angina pectoris (SAP) was found in 45 patients (32 ± 4 %), II FC — in 52 (36 ± 3 %) and III FC — in 45 patients (32 ± 4 %). 57 patients had previous acute myocardial infarction (AMI) with subsequent development of post-infarction cardiosclerosis (PICS). In 132 patients chronic heart failure (CHF) of FC I–III according to New York Heart Association (NYHA) classification and I–IIA stages according to Ukrainian Scientific Society of Cardiology classification was diagnosed. I FC of CHF according to NYHA classification was detected in 27 (19 ± 3 %), II FC CHF — in 76 (53 ± 3 %) and III FC CHF — in 32 patients (21 ± 3 %); I stage heart failure according to Ukrainian Scientific Society of Cardiology classification was detected in 85 patients (60 ± 3 %), II A stage — in 29 (20 ± 5 %). 123 patients had concomitant arterial hypertension (AH). According to the criteria of the Ukrainian Association of Cardiology [10], a mild degree was found in 33 of them (23 ± 3 %), moderate — in 61 (35 ± 3 %) and severe — in 28 (19 ± 3 %).

64 patients had depressive disorders according to the criteria of the International Classification of Diseases, 10th revision (WHO, 1995). Thus somatogenic depression (F06.32) was noted in 9 patients, psychogenic depression (F43.21) was met in 33 patients (52 ± 6 %), endogenous depression (F32.0–F32.2) was met in 22 patients (34 ± 5 %).

The inclusion criteria was a painful form of IHD with stable angina pectoris I–III FC.

Exclusion criteria were: stable angina pectoris IV FC, acute myocardial infarction, valvular defects, heart failure IIb–III stages, IV FC CHF, implanted pacemakers, AV conduction disorders, endocrine disorders (diabetes, thyroid disease), peptic and duodenal ulcer in acute phase, renal and hepatic failure, acute cerebrovascular events or its consequences.

Research methods. In all patients were assessed Ferrans & Powers quality of life (QoL) overall and in four domains: health/functioning, psychological/spiritual, social/economic, and family [11], the levels of depression and anxiety with HDRS and HADS scales, pain perception with McGill Pain Questionnaire (MPQ), blood pressure on both arms, heart ultrasound. Heart rate variability (HRV) assessment was conducted in accordance with the recommendations of the Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [12] — total power (TP) of HRV spectrum and its components — domains of very low frequency (VLF, associated of neurohumoral regulation and heat regulation), low (LF, relating to the regulation of sympathetic link), high (HF, associated with the element of parasympathetic regulation). Also the ratio LF/HF was determined which is considered as a measure sympathovagal balance.

At first 103 patients with IHD were examined — 60 males and 43 females. The study showed that in 25 observed patients (24 %, 11 males and 14 females), depressive disorders were found. Second, 39 IHD patients (17 males and 22 females) with concomitant depressive disorders were additionally included in a study for a more detailed study of depressive disorders in patients with IHD.

Patients were divided into 2 groups: the first group (64 patients) had depressive disorders while the second group (78 patients) did not. The distribution of patients into groups was based on the presence or absence of criteria for depressive disorders according to ICD-10 and on the results of HDRS.

Therapy was performed in two phases: In first phase all patients in both groups received baseline therapy, as recommended by the Ukrainian Association of Cardiology [1], in the second phase in patients with depressive disorders tianeptine was added to basic therapy. The duration of the first phase was 1 year, the

second — 4 weeks. Registration of QoL and HRV indices was performed in the first stage before treatment, after 3 weeks, 3 months. 6 months. baseline and 1 year of therapy and the second stage — after 4 weeks of tianeptine intake.

Baseline therapy included beta-blockers, calcium channel blockers, aspirin, statins and nitrates [1]. Tianeptyn administered 12,5 mg 3 times a day.

The criteria for the efficacy of therapy were: QoL and HRV improvement, SAP FC decline.

Statistical procedures included mean (M), standard deviation (sd), parametric and non-parametric tests: Student's t-test, T-Wilcoxon test (for related samples) and Mann-Whitney U-test (for independent samples) [13]. For the determining the probability of differences between groups 95 % confidence interval (CI) was used. Frequency characteristics of indices studied — the percentage (%) and the percent deviation (pD) was calculated [14].

RESULTS AND DISCUSSION

In the group of depressed patients prevailing of women were observed, with higher angina and CHF FCs, degree of hypertension, higher scores of MPQ. In contrast, in the group of non-depressed patients dominance of males were observed, lower angina and CHF FCs and lower incidence of hypertension (Table 1).

Table 1

Clinical characteristics of patients with painful form of IHD in groups with the presence and absence of depressive disorders, (M ± sd; n (% ± pD))

Index				Groups	
				Depressed patients (64)	Non-depressed patients (78)
Sex				Male	28 (44 ± 6)	49 (63 ± 5)
				Female	36 (56 ± 6)	29 (37 ± 5)
Age, years (M ± sd)					51,16 ± 6,17	51,61 ± 5,31
IHD			SAP FC	I	10 (16 ± 4)	35 (45 ± 5)
				II	21 (33 ± 6)	31 (40 ± 5)
				III	33 (51 ± 5)	12 (15 ± 4)
			AP FC (M ± sd)		2,36 ± 0,74	1,71 ± 0,72
Quantity of patients with PICS					29 (45 ± 6)	28 (36 ± 5)
CHF	FC			I	10 (16 ± 4)	17 (22 ± 4)
				II	31 (48 ± 6)	45 (58 ± 5)
				III	18 (28 ± 5)	11 (14 ± 3)
	(M ± sd)				1,96 ± 0,87	1,79 ± 0,76
	Stage			I	41 (64 ± 6)	44 (56 ± 5)
				IIA	20 (31 ± 6)	12 (15 ± 3)
Quantity of patients with AH					61 (95 ± 2)	62 (79 ± 4)
AH stage				1	6 (9 ± 3)	27 (35 ± 5)
				2	40 (63 ± 6)	21 (27 ± 5)
				3	15 (23 ± 5)	13 (17 ± 3)
MPQ, points					17,21 ± 3,1	14,37 ± 3,74

Initially, in group of depressed patients were observed significantly lower levels ($p < 0,05$) of QoLI (12,4 ± 1,04 points vs 16,7 ± 1,8), health and functioning (9,8 ± 1,0 points vs. 13 5 ± 1,3), psychological/ spiritual (10,3 ± 1,2 points vs 15,0 ± 1,9) and family (15,3 ± 1,9 points vs 20,3 ± 2,6) and insignificantly lower social and economic domains (14,9 ± 1,9 points vs 18,3 ± 3,4) ($p > 0,05$) comparing with the group of non-depressed patients.

Also obtained results indicate that initially in group of depressed patients in comparison with group of non-depressed patients were observed significantly higher depression levels measured by HDRS (12,1 ± 1,8 points vs 5,6 ± 2,0) and HADS (12 ± 1,6 points vs 4,4 ± 1,9) scales and the anxiety levels measured by HADS scale (8,0 ± 1,3 points vs 4,2 ± 2,3) ($p < 0,05$).

HRV research showed a similar pattern — in group of depressed patients were observed lower TP (497,24 ± 298,37 ms^2 vs 769 ± 386), VLF (253 ± 147 ms^2 vs 392 ± 217), LF (167 ± 115 ms^2 vs 249 ± 198), HF (77 ± 76 ms^2 vs 132 ± 141) and the ratio LF/HF (2,78 ± 1,32 vs. 3,5 ± 3,49) indices comparing with group of non-depressed patients

(p > 0,05). This pattern, which was observed in both groups, indicates that depression leads to changes in autonomic balance toward activation of sympathoadrenal system, reducing the efficiency baroreflex regulation and stress regulatory systems, which has an adverse prognostic significance.

Results obtained on further stages of the study showed that the most pronounced improvement in QoL, decline in depression and anxiety levels, pain perception (MPQ), SAP FC was achieved in the early stages of the study (3 weeks and 3 months of basic therapy) where further minor variations of these indicators were registered.

Despite the positive trend in patients with depressive disorders in comparison with the group of patients without depressive disorders QoL, decline in depression and anxiety levels, pain perception (MPQ), SAP FC still remained significantly higher.

Also, despite the presence of significant positive improvement of HRV indices, even after 1 year of baseline treatment in patients with depressive disorders compared with a group of patients with depressive disorders ratio LF/HF still remained higher (p > 0,05), and TP, VLF, LF and HF indexes — lower (p < 0,05). Thus, despite the positive dynamics in patients with depressive disorders (increased total power and its subdomains, including parasympathetic level, sympathovagal balance normalization) as previously observed decrease in the power spectrum of HRV, occurs excessive sympathetic activation and parasympathetic inhibition. Based on the concept that the cardiovascular system is an indicator of the body's adaptive abilities such HRV indices that depression leads to a decrease in the functional capacity of the organism and increase the «price» for physiological adaptation in patients with depressive disorders.

The aim of the next study stage was to explore the influence of tianeptine intake on QoL, depression and anxiety levels in patients with IHD with depressive disorders.

Tianeptine intake in a standard dose of 37,5 mg for 4 weeks in a group of patients with depressive disorders allowed to increase QoL levels, decrease depression and anxiety levels, lower pain perception (MPQ) results and increase all HRV indices (TP, VLF, LF and HF) (Table 2).

Table 2

Quality of life, depression and anxiety levels and HRV indices on different sudy phases in group of depressed patients (M ± sd)

Indices	Study stages				
	1st phase — baseline therapy			2nd phase — adding of tianeptine to baseline therapy	
	Admittance	3 weeks	1 year	Initially	4 weeks
QoL, (M ± sd)	13,7 ± 3,14	14,8 ± 2,94	15,5 ± 3,54	15,9 ± 3,14	22,1 ± 3,6123
HDRS, (M ± sd)	12,3 ± 3,94	11,2 ± 3,74	11,1 ± 3,44	11,0 ± 3,24	3,2 ± 1,5123
HADS, depression scale, (M ± sd)	8,4 ± 3,44	8,1 ± 2,84	7,5 ± 2,34	7,3 ± 2,74	3,4 ± 1,2123
HADS, anxiety scale (M ± sd)	5,1 ± 2,13,4	4,6 ± 1,7	2,8 ± 1,41	2,7 ± 1,61	2,1 ± 0,712
TP ВСР, мс^2	759 ± 1664	767 ± 189	981 ± 219	1066 ± 2311	1278 ± 2531,2
VLF, мс^2	442 ± 1044	474 ± 126	597 ± 114	633 ± 1491	654 ± 113,71,2
LF, мс^2	249 ± 564	287 ± 52	306 ± 68	335 ± 75	456 ± 103 1,2
HF, мс^2	65 ± 23,44	76 ± 35,1	84 ± 29,7	98 ± 34	159 ± 68,712
LF/HF	4,1 ± 1,3	3,9 ± 1,1	3,8 ± 1,0	3,7 ± 1,1	2,9 ± 1,2

Notes:
[1] — the differences comparing to the levels on admittance point are significant;
[2] — the differences comparing to the results on 3rd week of the first phase of treatment are significant;
[3] — the differences comparing to the results after 12 months are significant;
[4] — the differences comparing to the results for the 4th week of tianeptine intake are significant

Our data about greater burden of IHD course due to the depressive disorders is supported by recent publications, e. g. article by O. Mittag and T. Meyer, confirming that association of depression and IHD seems independent from pivotal demographic variables (gender, marital status or education) [15].

Similar results were obtained by GV Pogosov and et al. [16], where the authors noted significant QoL improvement in patients with IHD on the background of baseline IHD ther-

apy and tianeptine intake in dose 37,5 mg daily for 6 weeks.

Increase of HRV indices (TP, VLF, LF and HF) and decreasing of LF/HF ratio in patients receiving tianeptine was not reflected in the literature, but similar results were obtained in a study by AV Trofimov et al. [17]. Dynamics of the HRV indices in patients with acute MI and depressive disorders while taking paroxetine were studied. As a result of paroxetine intake in patients with MI were reduction of depressive symptoms and a more favorable course of postinfarction period. In addition, were found significant increasing HRV indices, accompanied by a significant increase in parasympathetic influences.

Significant decline in the subjective perception of pain on a MPQ scale when adding tianeptine to baseline treatment of IHD in patients with depression was not reflected in the literature also.

CONCLUSIONS

1. Among the IHD patients with depressive disorders compared with the group without depressive disorders higher SAP FC ($p > 0,05$), CHF FC ($p > 0,05$) and the degree of hypertension, higher values of depression and anxiety ($p < 0,05$), higher values on a scale perception of pain MPQ ($p > 0,05$), lower rates of capacity HRV (TP, VLF, LF and HF) ($p > 0,05$) were observed.

2. In the group of patients with depressive disorders comparing with patients without depression lower QoL levels, health and functioning, psychological/spiritual, family, social and economic QoL domains were also observed.

3. Despite positive changes when using baseline therapy in patients with IHD and depressive disorders compared with patients without depression higher levels of depression and anxiety ($p < 0,05$), pain perception MPQ ($p > 0,05$), SAP FC ($p > 0,05$) and lower — QoL levels, health and functioning, psychological/spiritual ($p < 0,05$), social and economic ($0,1 > p > 0,05$), family domains ($p > 0,05$).

4. In IHD patients with in the presence and the absence of depressive disorders baseline therapy enables achieve improvements in all indices of HRV spectrum and reduce the LF/HF ratio ($p > 0,05$), but at the same time in patients with depressive disorders lower ($p > 0,05$) spectral indices and higher LF/HF ratio of ($p < 0,05$) are found, compared with patients without depressive disorders, indicating the exhaustion of adaptation reserves and an imbalance of autonomic regulation in patients with depressive disorders.

5. Adding tianeptine to baseline therapy in all patients with IHD and depressive disorders helps to achieve increasing of QoL to levels observed in patients without depressive disorders and optimizing HRV indices and reduce the LF/HF ratio almost to the level observed in the absence of depressive disorders.

6. Patients with IHD should be examined for the presence of depressive disorders. In patients with IHD and clinically significant depression diagnosed antidepressant tianeptine must be added to baseline therapy.

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THE QTc INTERVAL DURATION CLASS AND CLINICAL FEATURES OF PATIENTS WITH PACEMAKERS IN THE ACUTE POSTOPERATIVE PERIOD

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The clinical features of 124 patients (63 men and 61 women) in the acute postoperative period after implantation of the pacemaker (ECS) in the various classes of corrected QTc interval duration of stimulated complexes were investigated. Evaluation was made by sex and age of the patients, chronic forms of ischemic heart disease (CIHD): postinfarction cardiosclerosis, stable angina (I–IV functional classes (FC)); stable angina (I–IV FC), arterial hypertension (AH) — 1–3 degrees and stages (1–4), type of diabetes mellitus (DM), atrial fibrillation (AF) (paroxysmal and persistent, permanent), chronic heart failure (CHF) — stages I–III, I–IV FC; functional indicators before pacemaker implantation and in the acute postoperative period (3–5 days after surgery): QTc interval duration, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP); ejection fraction (EF) of the left ventricle (LV), anterior-posterior size of the left atrium (LA), end-systolic volume (ESV) and end-diastolic volume (EDV), the thickness of the back wall of the left ventricle (AP LV), the thickness of the interventricular septum (IVS), left ventricular mass (LVM). The patients were divided into 3 classes: class 1 — normal QTc (320–440 ms) — 27 (22 %) patients, class 2 — elongated QTc (> 440 ms) — 97 (78 %) patients. Standard statistical procedures using Microsoft Excel were applied for data processing. The results showed that QTc interval duration of stimulated complexes in the acute postoperative period after pacemaker implantation can be established in a physiological range in 22 % of patients, and in 78 % — it remains longer or even elongated. Elongation associated with a higher incidence and the increase of FC and stages of heart failure, high values of ESV and EDV, mostly in the pacing mode VVI/VVIR and DDD/DDDR. Patients with a pacemaker require more careful monitoring the stimulation parameters as well as ongoing drug therapy.

KEY WORDS: pacing, cardiac resynchronisation therapy, electrocardiography, interval QTc

КЛАС ТРИВАЛОСТІ ІНВАЛУ QTc ТА КЛІНІЧНІ ОСОБЛИВОСТІ ПАЦІЄНТІВ З ІМПЛАНТОВАНИМИ ЕЛЕКТРОКАРДІОСТМУЛЯТОРАМИ В ГОСТРОМУ ПІСЛЯОПЕРАЦІЙНОМУ ПЕРІОДІ

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Досліджені клінічні особливості 124 пацієнтів (63 чоловіків и 61 жінка) в гострому післяопераційному періоді після імплантації електрокардіостимуляторів (ЕКС) в різних класах тривалості коригованого інтервалу QTc стимульованих комплексів. Оцінювали: стать, вік пацієнтів; форми хронічної ішемічної хвороби серця (ХІХС): постінфарктний кардіосклероз, функціональні класи (ФК) стабільної стенокардії (I–IV); стадії артеріальної гіпертензії (АГ) (I–III) ті ступіні АГ (1–3), тип цукрового діабету (ЦД); форми фібріляції передсердь (ФП) (пароксизмальна та персистуюча, постійна); ФК (I–IV) та стадії (I–III) хронічної серцевої недостатності (ХСН); функціональні показники до імплантації ЕКС та в гострому післяопераційному періоді (на 3–5 добу): тривалість коригованого інтервалу QTc, частоту серцевих скорочень (ЧСС), фракцію вигнання (ФВ), кінцево-систолічний та кінцеводіастолічний об'єми (КСО та КДО) лівого шлуночку (ЛШ), товщину задньої стінки (ЗС) ЛШ, товщину міжшлуночкової перетинки (МШП), масу міокарду лівого шлуночку (ММЛШ), передньо-задній розмір лівого передсердя (ЛП). Пацієнти були розділені на класи: клас 1 — нормального QTc (320–440 мс) — 27 пацієнтів (22 %), клас 2 — подовженого QTc (> 440 мс)) — 97 (78 %) пацієнтів. Для обробки даних були використані стандартні статистичні процедури за допомогою Microsoft Excel. Результати показали, що в гострому післяопераційному періоді після імплантації ЕКС у 22 % пацієнтів тривалість інтервалу

QTc стимульованих комплексів можна встановити в фізіологічному діапазоні значень та у 78 % — вона продовжує залишатися довгою чи навіть подовжується. Подовження асоціюється з більшою частотою розвитку та збільшенням ФК і стадій ХСН, більшими значеннями КСО и КДО, насамперед в режимах стимуляції VVI/VVIR та DDD/DDDR. Пацієнти з ЕКС потребують більш ретельного контролю як параметрів стимуляції, так і терапії, що проводиться.

КЛЮЧЕВІ СЛОВА: електрокардіостимуляція, кардіоресинхронізуюча терапія, електрокардіографія, інтервал QTc

КЛАСС ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QTc И КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРАМИ В ОСТРОМ ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ

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Исследованы клинические особенности 124 пациентов (63 мужчин и 61 женщина) в остром послеоперационном периоде после имплантации электрокардиостимулятора (ЭКС) в различных классах продолжительности корригированного интервала QTc стимулированных комплексов. Оценивали пол, возраст пациентов; формы хронической ишемической болезни сердца (ХИБС): постинфарктный кардиосклероз, функциональные классы (ФК) стабильной стенокардии (I–IV); стадии артериальной гипертензии (АГ) (I–III) и степени АГ (1–3), тип сахарного диабета (СД); формы фибрилляции предсердий (ФП) (пароксизмальная и персистирующая, постоянная); ФК (I–IV) и стадии (I–III) хронической сердечной недостаточности (ХСН); функциональные показатели до имплантации ЭКС и в остром послеоперационном периоде (на 3–5 сутки): продолжительность корригированного интервала QTc, частоту сердечных сокращений (ЧСС), фракцию выброса (ФВ), конечно-систолический и конечно-диастолический объемы (КСО и КДО) левого желудочка (ЛЖ), толщину задней стенки (ЗС) ЛЖ, толщину межжелудочковой перегородки (МЖП), массу миокарда левого желудочка (ММЛЖ), переднезадний размер левого предсердия (ЛП). Пациенты были разделены на классы: класс 1 — нормального QTc (320–440 мс) — 27 (22 %) пациентов, класс 2 — удлиненного QTc (> 440 мс) — 97 (78 %) пациентов. Для обработки данных использовались стандартные статистические процедуры с помощью Microsoft Excel. Результаты показали, что в остром послеоперационном периоде после имплантации ЭКС у 22 % пациентов продолжительность интервала QTc стимулированных комплексов удается установить в физиологическом диапазоне значений и у 78 % — она продолжает оставаться дольшей или даже удлиняется. Удлинение ассоциируется с большей частотой развития и увеличением ФК и стадий ХСН, большими значениями КСО и КДО, преимущественно в режимах стимуляции VVI/VVIR и DDD/DDDR. Пациенты с ЭКС нуждаются в более тщательном контроле как параметров стимуляции, так и проводимой медикаментозной терапии.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимуляция, кардиоресинхронизирующая терапия, электрокардиография, интервал QTc

Output of corrected QT interval duration (QTc) values beyond physiological scope, so-called qualified shortening and elongation, is an important prognostic factor among patients with sinus rhythm and with implanted pacemakers (PM) [1–3].

However, the possible link of the stimulated QTc interval duration complexes and clinical features of patients with implanted pacemakers in the acute postoperative period is not reported in the literature.

Aims: to evaluate the link between the classes of stimulated QTc interval duration under different modes of permanent cardiac pacing with the clinical features of patients in the acute postoperative period.

MATERIALS AND METHODS

124 patients aged 68 ± 8 (M ± sd) (61 — female, 63 — male) were examined in the department of ultrasound and instrumental diagnostics with miniinvasive interventions of SI «Zaycev V. T. Institute of General and Urgent Surgery of NAMS of Ukraine», among them — 29 patients has sinus node dysfunction (SND), 78 patients — atrio-ventricular block (AVB) (57 — III degree, 16 — II degree, 5 — I degree), 40 — atrial fibrillation (AF), 7 —

dilated cardiomyopathy (DCMP). All patients were underwent permanent pacing therapy from 2006 to 2012 in modes: DDD (25 patients) and DDDR (42 patients), among them 29 patients with mainly atrial pacing (more than 90 %), VVI (36 patients), VVIR (12 patients), cardiac resynchronization therapy (CRT) (9 patients).

Evaluation was made by sex and age of the patients, chronic forms of ischemic heart disease (CIHD) — postinfarction cardiosclerosis, stable angina (I–IV functional classes (FC)) [4]; stable angina (I–IV functional classes (FC)), arterial hypertension (AH) — 1–3 degrees and stages (1–4), type of diabetes mellitus (DM), atrial fibrillation (AF) (paroxysmal, persistent and permanent), chronic heart failure (CHF) — stages I–III, I–IV (FC)) [4]; functional indicators before pacemaker implantation and in the acute postoperative period (3–5 days after surgery): QTc interval duration, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP); figures echocardiography: ejection fraction (EF) of the left ventricle (LV), anterior-posterior size of the left atrium (LA), end-systolic volume (ESV) and end-diastolic volume (EDV), the thickness of the back wall of the left ventricle (AP LV), the thickness of the interventricular septum (IVS), left ventricular mass (LVM).

To measure the duration of the QT interval and heart rate of the patients before and after pacemaker implantation (3–5 days after surgery) were recorded on a computer ECG electrocardiograph «Cardiolab+» (HAI-Medica). The stimulated QTc interval duration was measured after the removal of the stimulus artifact in three consecutive complexes of the Q wave to the beginning of the descending segment of the return of the T wave in leads to the contour II, V5, and V6 with choosing of a maximum value. The corrected QT interval duration (QTc) of the patients with spontaneous rhythm and pacing was calculated by the Bazett formula: QTc = QT / (RR ^ 0,5). For patients with AF, QTc was calculated using the formula QTc = QT + 0,154 × (1000 – RR) Fermingem study for patients with atrial fibrillation [12], the measurement accuracy — 0,5 ms. SBP and DBP were measured by tonometer Microlife BP AG1-20 Korotkov method, the measurement accuracy — 1 mm Hg.

Echocardiography was conducted by the ultrasound machine Siemens Cypress and Toshiba Applio 400. RA, LA, RV sizes, end-systolic size (ESS), end-diastolic size (EDS) and AP LV, IVS thickness was measured. EDV and ESV were calculated by the method of Simpson. LVEF was calculated using the formula LVEF = (EDV – ESV) / EDV *100 %. Left ventricular mass (LVM) was calculated according to the formula Devereux: LVM = 1,04 * (AP LV + IVS + ESS)^3 – ESS^3) – 13,6 [2]. The measurement accuracy was 0,5 mm. For the calculation of ejection fraction (EF) using the formula PV = SV / EDV [5].

The patients with pacemakers were divided into 3 classes of stimulated QTc interval duration: Class 1 — normal (in the physiological range of values) — 320–439 ms, Class 2 — (qualified) an elongated QTc — > 440 ms, and Class 3 — (qualified) shortened the QTc — < 320 ms [10]. Values and/or frequency of clinical signs in the classes were estimated in the total sample, and electrophysiological parameters, moreover, a separate group with mainly atrial pacing.

The data were processed after formation the Microsoft Excel and Statistica base. For statistical evaluation of the results, the parametric criteria (mean — M, standard deviation — sd) and nonparametric ones (absolute (n, number) and relative (percentage of (p, %) and the mean percentage error (sP), the criterion χ^2) units) were used. The probability of differences between groups was determined using a nonparametric U — Mann-Whitney test. The expected result is determined by levels of reliability $p < 0,01$ and $p < 0,05$.

RESULTS AND DISCUSSION

Distribution of QTc interval duration in the studied group of patients before pacemaker implantation was close to normal with the mode in the physiological range. Ventricular stimulation did not change its shape, but moved stimulated QTc interval duration to higher values (Fig. 1A). Sex differences were not found (Fig. 1B, C).

There are a 27 (22 %) patients in class 1 (male — 16, female — 11, in the stimulation mode DDD / DDDR — 11 patients (41 %), VVI/VVIR — 16 patients (59 %), patients with mainly atrial pacing — 10 (37 %)) and 97 patients (78 %) in class 2 (male — 47, female — 50, in the stimulation mode DDD/DDDR — 56 patients (58 %), VVI/VVIR — 32 patients (33 %) , CRT — 9 patients (9 %)), patients with mainly atrial pacing — 19 (20 %)). In class 3, there was not a single patient. Average duration of the QTc interval in class 1 patients has not

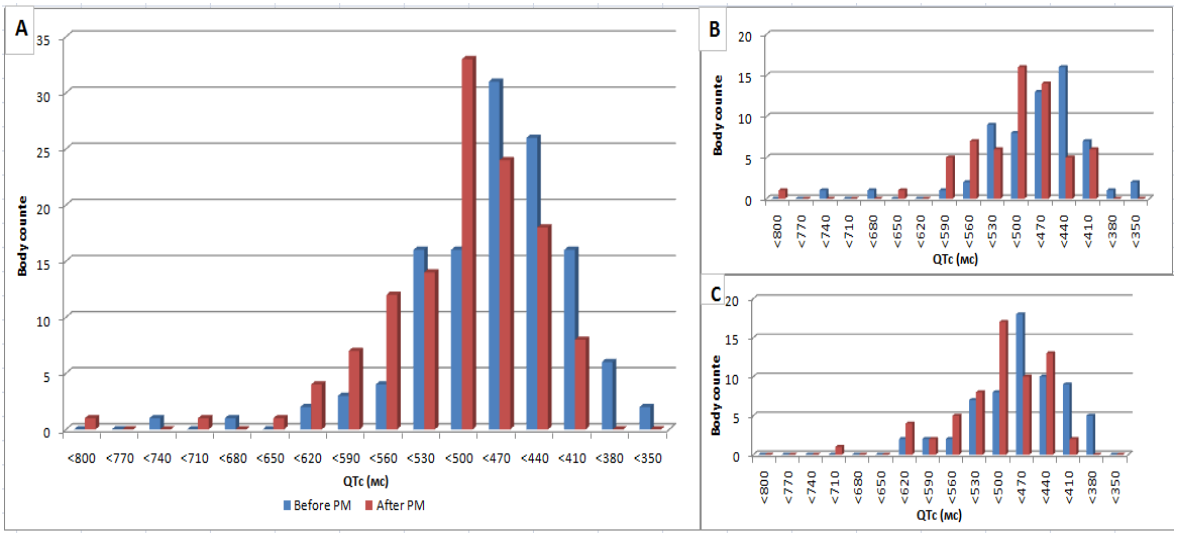
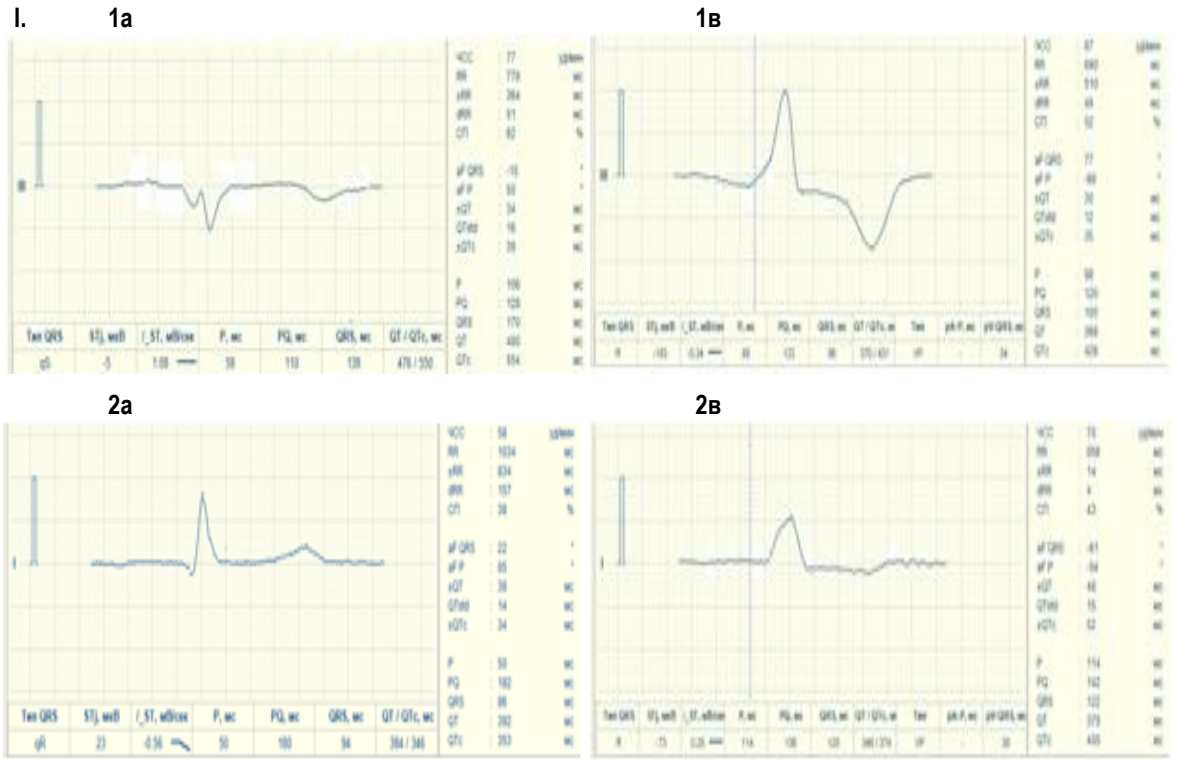


Fig. 1. Distribution of QTc interval duration before and after (stimulated) pacemaker implantation in the studied group of patients, including those of female (B) and male (C) sex

changed (from 420 ± 53 ms, to 419 ± 14 ms) and class 2 patients — lengthened (from 460 ± 48 ms to 506 ± 42 ms), but neither in the first nor the second did not reflect the essence of individual patient.

QTc interval duration before and after pacemaker implantation in acute postoperative period in 15 (56%) patients of class 1 was within the physiological range of values and in 12 (44%) – initially extended and shortened to class 1 after pacemaker implantation. QTc interval before and after pacemaker implantation was lengthened in 61 (63%) patients of class 2, and in 36 (37%) — extending from physiological values to class 2 after pacemaker implantation. Individual changes in the QTc interval duration in response to the pacing for classes 1, 2, and transitions between them are shown in Fig. 2.



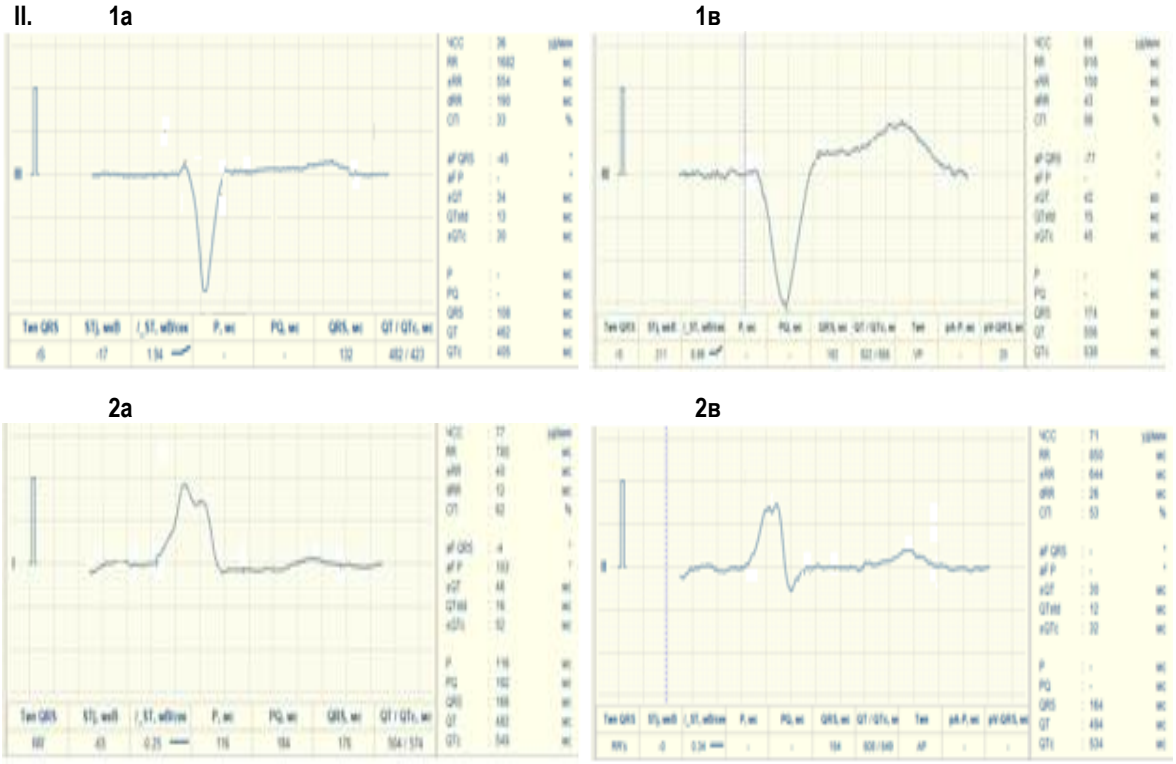


Fig. 2. Individual changes in the QTc interval duration of the in patients' response to the pacing

Legend:
I — class 1:
1 — shortening initially extended to normal QTc, 2 — changes within class 1;
II — class 2:
1 — elongation initially normal to lengthened QTc, 2 — changes within class 2;
a — before pacemaker implantation, b — after pacemaker implantation

QTc interval duration in patients with mainly atrial pacing was similar to that of the total sample before and after pacing in classes (in the class 1: 421 ± 35 ms before and 412 ± ± 12 ms after stimulation vs 420 ± 53 and 419 ± 14 ms in the total sample (p > 0,05); in the class 2: 432 ± 57 ms and 505 ms ± 39 vs 460 ± 48 and 506 ± 42 (p > 0,05), respectively).

Clinical features of patients with pacemakers are presented in the classes of stimulated QTc interval duration in the acute postoperative period in Table 1.

Table 1

Clinical features of patients with pacemakers in the classes of stimulated QTc interval duration in the acute postoperative period (% ± p)

Clinical features				All off patients, the proportion of total (n, % ± p)	Class of stimulated QTc interval duration	
					Class 1	Class 2
Sex (n, % ± p)		Male		63, (51 ± 4)	25 ± 5	75 ± 5
		Female		61, (49 ± 4)	18 ± 5	82 ± 5
Age (M ± sd, years)				124	68 ± 7	68 ± 9
Diseases	CIHD	Postinfarction cardiosclerosis (n, %±p)		16, (13 ± 3)	7 ± 5	14 ± 4
		Stable angina (n, % ± p)	Total	49, (40 ± 4)	48 ± 10**	37 ± 5
			FC I	13, (27 ± 6)	38 ± 13	22 ± 7
			FC II	22, (45 ± 7)	62 ± 13*	39 ± 8*
			FC III	11, (22 ± 6)	–	31 ± 8*
			FC IV	3, (6 ± 3)	–	8 ± 5

Continuation of table 1

	Arterial hypertension (n, % ± p)	Total		102, (82 ± 3)	85 ± 7	81 ± 4
		Stage	I	5, (5 ± 2)	4 ± 4	5 ± 2
			II	56, (55 ± 5)	57 ± 10*	54 ± 6*
			III	39, (40 ± 5)	39 ± 10	41 ± 6
		Degree	1	39, (40 ± 5)	43 ± 10*	41 ± 6*
			2	27, (26 ± 4)	17 ± 8	29 ± 5
			3	13, (13 ± 3)	9 ± 6	10 ± 3
	Diabetes mellitus (n, % ± p)	Total		17, (14 ± 3)	4 ± 4	16 ± 4**
		Type 1		1, (6 ± 6)	–	6 ± 6
		Type 2		16, (94 ± 6)	100	94 ± 6*
Clinical syndromes	Atrial fibrillation (n, % ± p)	Total		40, (32 ± 4)	41 ± 9**	30 ± 5
		Paroxysmal and persistent		22, (55 ± 8)	64 ± 15*	52 ± 9
		Permanent		18, (45 ± 8)	36 ± 15	48 ± 9
	CHF (n, % ± p)	Total		92, (74 ± 4)	67 ± 9	76 ± 4**
		FC	I	9, (10 ± 3)	22 ± 10	7 ± 3
			II	42, (46 ± 5)	44 ± 12*	46 ± 6*
			III	35, (38 ± 5)	33 ± 11	39 ± 6
			IV	6, (6 ± 2)	–	8 ± 3
		Stage	I	11, (12 ± 3)	17 ± 9	11 ± 4
			IIA	55, (60 ± 5)	72 ± 11*	55 ± 6*
			IIB	24, (26 ± 4)	6 ± 5	31 ± 5
			III	2, (2 ± 1)	–	3 ± 2

Comment :
p — average percentage error, M — mean value, sd — standard deviation;
* p < 0,05 — between the values in the classes after pacemaker implantation,
** p < 0,05 — a class of values before and after pacemaker implantation

Age, sex, the proportion of patients with postinfarction cardiosclerosis, AH, the ratio of the degrees and stages of hypertension (prevalence of stage II, and 1 degree) in classes 1 and 2 were not statistically different. Stable angina was more frequent in the class 1 ($p < 0,05$), which was dominated by patients with FC II. In class 2 equally often met II and III angina. Patients with III and IV FC stable angina were represented only in class 2.

The amount of patients with type 2 diabetes in the 1 was smaller than in class 2 ($p < 0,05$). Diabetes mellitus type 1 was observed only 1 patient in Class 2.

AF was more frequent in class 1 than in class 2 ($p < 0,05$). In class 1 prevailed over paroxysmal and persistent AF constant ($p < 0,05$), in class 2 statistically significant differences in their frequencies were not. CHF was observed more frequently in class 2 ($p < 0,05$). In both classes of patients with FC II and stage IIA CHF are prevail ($p < 0,05$), III and IV CHF stage was more frequent in class 2.

Functional performance in the classes of stimulated QTc interval duration before pacemaker implantation and in the acute postoperative period are shown in Table 2.

The average heart rate after pacemaker implantation in both classes was established more than before to 7 1/min in class 1 and 13 1/min in class 2.

Systolic and diastolic blood pressure, ejection fraction, antero-posterior size of the LA, the thickness of the IVS and AP LV, and average LVM did not differ significantly in classes of patients, and in each of them before and after pacemaker implantation, except for the mean value of ESV and EDV, which were larger before pacemaker implantation, and have a direct correlation with the QTc interval duration ($p < 0,05$).

Distribution of the QTc interval within adults was close to normal [6]. Our data regarding it among patients with bradyarrhythmia before and after pacemaker implantation are new.

In the present study confirmed the individuality of the QTc interval duration reactions to stimulation with shortening and lengthening among some other patients after pacemaker implantation. Prochnau at al. [7] were observed QTc interval shortening among patients with CRT and Medina-Ravell VA at al. [8] — its elongation among patients with biventricular

Table 2

Functional performance in the classes of stimulated QTc interval duration in the acute postoperative period before and after pacemaker implantation (M ± sd)

Functional performance		Class of stimulated QTc interval duration			
		Class 1		Class 2	
		Before pacing	Paced	Before pacing	Paced
HR (M±sd, 1/min)		61 ± 11	68 ± 6**	58 ± 16	71 ± 9**
BP	SBP (M ± sd, mm Hg)	143 ± 19	137 ± 17	145 ± 15	145 ± 17
	DBP (M ± sd, mm Hg)	83 ± 10	82 ± 10	84 ± 11	84 ± 10
Figures echocardiography	EF (M ± sd, %)	45 ± 8	52 ± 9	41 ± 10	51 ± 13
	LA (M ± sd, sm)	4,6 ± 0,5	4,4 ± 0,5	4,7 ± 0,6	4,5 ± 0,7
	ESV (M ± sd, ml)	62 ± 27*	41 ± 32**	109 ± 35*	87 ± 55**
	EDV (M ± sd, ml)	170 ± 31*	149 ± 36**	226 ± 42*	179 ± 60**
	AP LV (M ± sd, sm)	1,23 ± 0,1	1,23 ± 0,11	1,2 ± 0,16	1,19 ± 1,15
	IVS (M ± sd, sm)	1,22 ± 0,15	1,23 ± 0,13	1,2 ± 0,14	1,2 ± 0,18
	LVM (M ± sd, g)	331 ± 63	337 ± 71	341 ± 90	331 ± 86

Comment :
M — mean value, sd — standart deviation;
* p < 0,05 — between the values in the classes,
** p < 0,05 — a class values before and after pacemaker implantation

pacing, which was associated with an unfavorable increase in transmural dispersion of repolarization.

The possibility of lengthening the duration of the QTc interval with a qualified going beyond the physiological range of values was shown in all studied modes of stimulation performed by us, unlike J.A. Chiladakis et al. [9]. The probable reason for this is the large amount of patients with baseline repolarization disorders and borderline QTc values before pacemaker implantation among some patients [10], a few CRT implantations for economic reasons, as well as the selection of sub-optimal stimulation parameters and drug therapy.

We also found that the duration of the QTc interval among patients with SND after pacemaker implantation with mainly atrial pacing is similar to that among patients with other modes of stimulation.

A large proportion of heart failure, higher stage and CHF FC, FC stable angina, higher EDV and ESV among patients with impaired repolarization and a prolonged QTc interval were identified by us, as T. Ishikawa at al. [11]. As for the greater incidence of type 2 diabetes mellitus in the class of QTc prolongation in patients with a pacemaker, such data in the literature was not found.

Taking into consideration that the lengthening of the QTc interval associated high risk of acute cardiovascular events up to sudden cardiac death [7, 12, 13], these results require a dedicated research.

Patients with a qualified lengthening of the QTc interval after pacemaker implantation for permanent pacing in the acute postoperative period require more attention and in optimazation of its parameters, and in therapeutic management.

CONCLUSIONS

1. Pacemaker implantation in all modes of stimulation has a modifying effect on the QTc interval duration in the acute postoperative period, with 22 % of patients in the physiological range of values, and in 78 % — it continues to be long or even elongates.

2. Prolongation of stimulated QTc interval duration associated with the increase in FC and stages of heart failure, high values of CSR and EDV, mainly in VVI/VVIR and DDD/DDDR modes of stimulation.

3. Patients require more careful monitoring of the stimulation parameters and ongoing drug therapy, because of the potential for permanent pacemaker lengthening of the QTc interval.

PROSPECTS FOR FURTHER RESEARCH

It seems appropriate to investigate the relationship changes of the QTc interval duration among patients with implanted pacemaker due to the stimulation parameters and characteristics of ongoing drug therapy.

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COMPARATIVE EFFICACY OF ANTICOAGULANT AND THROMBOLYTIC THERAPY IN PATIENTS WITH ACUTE THROMBOSIS OF THE INFERIOR VENA CAVA

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138 patients with thrombosis in the system of the inferior vena cava was examined and treated. Thrombolytic therapy (TLT) as a basic method of treatment was used in 52 (37,7 %) patients. Of these, 20 (14,5 %) was performed catheter-controlled thrombolysis and 32 (23,2 %) patients had systemic thrombolytic therapy. The 86 (62,3 %) patients in the basic treatment had anticoagulant therapy (ACT). In the long-term results of thrombolytic therapy significantly exceed the results of ACT. The 70 % of this patients had signs of post-thrombotic disease with mild chronic venous insufficiency, and 100% of patients with ACT had more forms of postthrombotic disease.

KEY WORDS: acute thrombosis in the inferior vena cava, anticoagulant therapy, thrombolytic therapy

СРАВНИТЕЛЬНАЯ ОЦЕНКА ЭФФЕКТИВНОСТИ АНТИКОАГУЛЯНТНОЙ И ТРОМБОЛИТИЧЕСКОЙ ТЕРАПИИ У БОЛЬНЫХ С ОСТРЫМ ТРОМБОЗОМ В СИСТЕМЕ НИЖНЕЙ ПОЛОЙ ВЕНЫ

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Проведено обследование и лечение 138 пациентов с тромбозами в системе нижней полой вены. Тромболитическая терапия (ТЛТ) в качестве базового метода лечения была применена у 52 (37,7 %) пациентов. Из них у 20 (14,5 %) был осуществлен катетер-управляемый тромболизис и у 32 (23,2 %) пациентов была применена системная тромболитическая терапия. У 86 (62,3 %) пациентов базовым методом лечения была антикоагулянтная терапия (АКТ). В отдаленном периоде результаты ТЛТ значительно превосходят результаты АКТ. У 70 % пациентов, пролеченных ТЛТ, наблюдали в отдаленном периоде признаки посттромбофлебитической болезни (ПТФБ) с лёгкой степенью хронической венозной недостаточностью (ХВН), а у 100 % пациентов, получавших курс АКТ, отмечены более тяжелые формы ПТФБ.

КЛЮЧЕВЫЕ СЛОВА: острый тромбоз в системе нижней полой вены, антикоагулянтная терапия, тромболитическая терапия

ПОРІВНЯЛЬНА ОЦІНКА ЕФЕКТИВНОСТІ АНТИКОАГУЛЯНТНОЇ ТА ТРОМБОЛІТИЧНОЇ ТЕРАПІЇ У ХВОРИХ НА ГОСТРИЙ ТРОМБОЗ У СИСТЕМІ НИЖНЬОЇ ПОРОЖНИСТОЇ ВЕНИ

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Проведено обстеження і лікування 138 пацієнтів з тромбозами у системі нижньої порожнистої вени. Тромболітична терапія (ТЛТ) в якості базового методу лікування була застосована у 52 (37,7 %) хворих. З них у 20 (14,5 %) був здійснений катетер-керований тромболізис та у 32 (23,2 %) пацієнтів була застосована системна тромболітична терапію. У 86 (62,3 %) пацієнтів базовим методом лікування була антикоагулянтна терапія (АКТ). У віддаленому періоді результати ТЛТ значно перевершують результати АКТ. У 70 % пацієнтів, пролікованих ТЛТ, спостерігали у віддаленому періоді ознаки посттромбофлебітичній хвороби (ПТФХ) з легким ступенем хронічною венозною недостатністю (ХВН), а у 100 % пацієнтів, котрі отримали курс АКТ, відзначені більш важкі форми ПТФХ.

КЛЮЧОВІ СЛОВА: гострий тромбоз у системі нижньої порожнистої вени, антикоагулянтна терапія, тромболітична терапія

Acute deep vein thrombosis (DVT) in the inferior vena cava is more than 95% of venous thrombosis and is often complicated by pulmonary embolism (PE) [1, 2]. In Ukraine, each year about 260 cases of DVT and its complications per 100 thousand people with mortality from pulmonary embolism at the level of 20–25 % [3, 4]. In addition to a life-threatening pulmonary embolism, deep venous thrombosis is a serious consequence of the post-thrombosis disease (PTD) with severe manifestations of chronic venous insufficiency (CVI) of the lower extremities [4, 5]. Subsequent progression PTD accompanied by the formation of venous ulcers, which constitute 19,7 % of the etiology of venous ulcers [1, 6].

Despite the use of different methods of treatment of deep venous thrombosis in the inferior vena cava, the immediate and long-term results of their application can not fully meet the professionals [7–10]. This fact was the basis for a comparative analysis of the effectiveness of various methods of treatment of acute deep venous thrombosis in the inferior vena cava.

In our study, we conducted a comparative evaluation of the efficacy of thrombolytic therapy compared with anticoagulation in patients with deep venous thrombosis of the pelvis and lower extremities, and to determine the severity of chronic venous insufficiency caused PTD.

The purpose of the study is to evaluate the efficacy of thrombolytic and anticoagulant therapy in patients with deep venous thrombosis of the pelvis and lower extremities, and to determine the severity of CVI due PTD, in the long term.

Work performed as part of the scientific program of the SI «Institute of General And Emergency Surgery» NAMS of Ukraine and a fragment of a comprehensive the research work: «To develop a differentiated therapeutic, diagnostic and preventive tactics in patients with acute thrombosis of the inferior vena cava» (№ state registration 011V002288).

MATERIALS AND METHODS

The examination and treatment of 138 patients with DVT of the pelvis and lower extremities, in 20 cases complicated by pulmonary embolism. Said patients have been applied to different types of treatment in 52 (37,7 %) — thrombolytic and in 86 (62,3 %) — anticoagulant therapy.

The examinees were 79 (57,2 %) men and 59 (42,8 %) of women aged 20 to 78 years. Patients came for treatment in terms of 3 to 20 days after onset of clinical signs of disease. Anamnestic prescription thrombosis in 83 (60,1 %) of the patients was 7 or more days. Under the complex clinical and instrumental and laboratory examination, including ultrasound scanning of and on the testimony of a radiopaque angiography revealed widespread acute thrombosis involving the iliac-femoral and/or femoral-popliteal venous segments. All patients were identified occlusive thrombi specified location. 20 patients hospitalized for DVT, PE is complicated, while 18 (90 %) of them had sub massive and 2 (10 %) — massive form of the disease. Patients admitted to hospital with DVT combined with PE, were in a state of moderate severity.

Thrombolytic therapy as a basic method of treatment was used in 52 (37,7 %) patients. Of these, 20 (14,5 %) performed catheter-controlled thrombolysis (CCT) [11] using the Streptase at 100 000 units/hour with an average duration of treatment up to 3 days. The drug was administered through a catheter inserted in the posterior tibial vein thrombosis affected lower limb.

For systemic thrombolytic therapy (STLT) [6, 7] in 32 (23,2 %) patients used Streptokinase (100,000 units/hour), Urokinase (4400 U/kg/h) and Actilyse (100 mg for 2 hours).

In 86 (62,3 %) patients had baseline treatment anticoagulant therapy (ACT) using low molecular weight heparin (LMWH), 57 (41,3 %) and unfractionated heparin (UFH) 29 (21 %) patients. Low molecular weight (fractionated) heparin (mainly — Enoxaparin) administered at a dose of 1mg/kg body weight of the patient two times per day subcutaneously to a patient on Warfarin transfer when the target INR. Also used UFH, which was administered once intravenously at a dose of 5000 ED.i then continued treatment by continuous intravenous infusion at a daily dose of UFH 20000–35000 units, ensuring the maintenance of APTT values are 1,5–2 times larger than the original and controlling her every 6 hours. The duration of infusion of UFH was a minimum of 5 days or more, depending on the performance INR. Patients treated with ACT, parallel to the prescribed anticoagulants of indirect action (AIA). The dose of these drugs were selected individually under the control of prothrombin ratio (50–60 %) or INR (2,0–3,0), and recommended taking AIA for at least 4–6 months in an outpatient setting. In addition to this therapy during the

hospital stay, patients received Movalis, Detralex, Flebodia, Cyclo 3 Fort in standard doses, use elastic bandages or compression stockings individualized.

In accordance with the protocol of the study, all patients were assessed hemostasis prior to and throughout the hospital treatment period.

Assessment of the immediate results of the treatment of patients with acute deep vein thrombosis of the lower limbs and pelvis was performed with the following parameters:

- the dynamics of the regression of clinical symptoms;
- the degree of patency of the venous bed;
- the effectiveness of the prevention of pulmonary embolism;
- the type and number of complications associated with treatment.

Assessment of long-term results of treatment was carried out in the absence or presence of clinical signs and PTD indicators such as:

- functional class CVI according to the International Classification of CEAP;
- the degree of patency of the venous bed (partial or complete recanalization) according to duplex scanning.

Statistical analysis was performed using a standard office suite «Microsoft Office XP» with the application package «Microsoft Excel» and statistical software for biomedical research «Biostatistics» (Statistical Graphics Corp., USA), Version 4.03 for Windows.

RESULTS AND DISCUSSION

In general, the immediate clinical outcomes were positive in 83 (74,1 %) patients.

In patients who received CCT, there was a rapid regression of the main clinical signs of acute iliofemoral venous thrombosis. By the end of the first day in these patients significantly reduced bursting pain in the lower extremities. On the third day of the CCT remained only mild pain in the limbs, the volume of which was significantly smaller than the original. On the 12th day of the clinical manifestations of the disease were absent.

An ultrasound and angiography in 14 of 20 patients receiving CCT, marked by full and 6 — partial lysis of blood clots. Under STLT after the first day of treatment start regression of clinical symptoms was observed in 6 (22,2 %), and on the third day — in 14 (51,9 %) patients. At 12 days of the clinical manifestations of DVT in 22 (83,3 %) patients were minimal. According to the ultrasound group STLT complete patency affected segments there thrombosis in 5 (18,5 %) and partial — 17 (63 %) patients. In this group, 24 patients (88,9 %) had normalization of hemodynamics in the pulmonary circulation, and only 3 patients (11,1 %) were observed moderately pronounced signs of pulmonary hypertension. System-administration of a thrombolytic agent was unsuccessful in 5 (18,5 %) patients. Importantly, treatment of thrombolytic agents are not accompanied by a clinically significant bleeding complications were observed only subcutaneous hematoma.

The results of anticoagulant and thrombolytic therapy in patients with acute venous thrombosis in the inferior vena cava in the table.

Table

Comparative evaluation of the effectiveness of anticoagulant and thrombolytic therapy in patients with acute venous thrombosis

The result of treatment (number of patients n)	TLT		ACT		Total
	STLT	CCT	LMWH	UFH	
The treatment	32 (23,2 %)	20 (14,5 %)	57 (41,3 %)	29 (21,0 %)	138 (100 %)
Examined the results of Treatment	27 (84,4 %)	20 (100 %)	48 (84,2 %)	17 (58,6 %)	112 (81,2 %)
Positive direct results	22 (81,5 %)	20 (100 %)	32 (66,7 %)	9 (52,9 %)	83 (74,1 %)
The development of severe chronic venous insufficiency (C5-C6)	3 (11,1 %)	0	11 (22,9 %)	5 (29,4 %)	19 (17,6 %)

Of the 65 patients who received a course of ACTs in 41 (63,1 %), there was progression of the thrombotic process. In 12 (18,5 %) patients had an ultrasound examination revealed signs of recanalization of the thrombosed veins, and earlier recanalization was observed in patients treated with LMWH. In 24 (36,9 %) cases, the course of the ACP has not led to a positive effect of the treatment due to progression of the thrombotic process. However, in any case for DVT is not complicated by pulmonary embolism. Conducted a comprehensive treatment of deep vein thrombosis of the pelvis and lower extremities prevented the development of pul-

monary embolism. Recurrence of DVT, no deaths reported in all groups of patients.

In the long-term in terms from 3 months to 10 years were examined 108 (80,5 %) patients, of whom 43 (39,8 %) patients received TLT and 65 (60,2 %) — a course of ACT.

In 20 patients, the treatment of which was the base of TCS, in the late period showed no signs of chronic venous insufficiency associated with PTD. In the group of 32 patients, the primary treatment which was to STLT, and 4 marked C1-C2, and 4 — C3-C4 and 3 — C5-C6 CVI (CEAP). In patients who received TLT, there was varying degrees (from full to partial) recanalization of the deep veins by ultrasound. In the group of 57 patients who were treated with LMWH, 12 registered C2-C3 and 10 — and 11 C4-C5-C6 CVI (CEAR). Among the 29 patients treated with UFH, in 3 marked C2 in 6 — C3-C4, and 5 — C5-C6 CVI (CEAP).

Application TLT patients with DVT pelvis and lower limbs and pulmonary embolism caused rapid regression or complete elimination of the major clinical signs of venous thrombosis and pulmonary embolism, while in anticoagulant treatment in 16 (52,3 %) patients remained significant clinical manifestations of CVI.

In 14 (70 %) of 20 patients who received CCT, there was a complete and in 6 (30 %) — a partial lysis of blood clots. Under full restore patency STLT deep vein was observed in 18,5 % and partial — 63 % of patients. The resumption of blood flow in the major tributaries of the iliac and femoral veins contributed to the rapid improvement of venous hemodynamics and eliminate clinical symptoms of DVT. In the course of the TLT clinically significant bleeding complications were not recorded, and subcutaneous hematoma occurred gradually disappeared without treatment. According to the results of the late period TLT methods significantly outperform the conservative therapy with anticoagulants. 70 % of patients treated with TLT had a long-term PTD with mild to moderate chronic venous insufficiency. In contrast, all patients who received a course of ACP marked PTD, with more severe manifestations of chronic venous insufficiency observed in those who was treated with UFH and LMWH are not.

Thus, the use of anticoagulant and thrombolytic therapies makes it possible to reduce the likelihood of PTD and reduce the severity of chronic venous insufficiency of the lower extremities in the long term.

CONCLUSIONS

1. Application of thrombolytic therapy in patients with DVT pelvis and lower limb leading to rapid regression or complete elimination of the major clinical signs of venous thrombosis. According to the results of the late period TLT methods significantly outperform the conservative therapy with anticoagulants. Thus, only three (6,3 %) patients treated TLT had a pronounced long-term signs PTD while treatment with anticoagulants in 16 (52,3 %) patients remained severe clinical manifestations of CVI.

2. According to our observations, the regional administration of thrombolytics more fully and quickly in comparison with systemic thrombolytic therapy allows you to resume the blood flow in the deep veins of the pelvis and lower extremities. Thus, in 14 (70 %) who received CCT, there was a complete and in 6 (30 %) — a partial lysis of blood clots. In the group of patients treated with STLT full recovery of deep vein patency was observed in 5 (18,5 %) of 27 patients and partial — in 17 (63 %) patients.

3. The use of ACT has prevented the progression of the thrombotic process in 41 (63,1 %) patients, of whom 32 (66,7 %) of patients receiving LMWH and in 9 (52,9 %) — NFG. In addition, an ultrasound examination, the earlier recanalization of the thrombosed veins was observed in patients treated with LMWH course. In 24 (36,9 %) cases, the course of the ACP has not led to a positive effect of the treatment due to progression of the thrombotic process. However, in any case for DVT is not complicated by pulmonary embolism.

4. ACT does not remove the blood clots deep veins of the pelvis and lower extremities, accompanied by a sustained regression of clinical signs of DVT and in the long term often leads to the development of moderate to severe PTD. However, the ACP may be effective in preventing pulmonary embolism. When ACT drugs of choice are the LMWH. These drugs should be used after the CUT or STLT in prevention of recurrence of DVT.

Prospects for future research is to study and compare the effectiveness of methods of regional and systemic thrombolysis in patients with acute thrombosis in the inferior vena cava.

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QRS COMPLEX DURATION AND CLINICAL FEATURES OF PATIENTS WITH PERMANENT PACEMAKERS

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125 patients (57 — women, 68 — males) with permanent pacing were examined. Among the indications for pacemaker installation there were atrio-ventricular block (AV-block) — 77 people (62 ± 4 %), sick sinus node syndrome (SSNS) — 32 patients (26 ± 4 %), bradysystolic AF — 8 patients (6 ± 2 %). 8 patients with cardioresynchronization therapy (6 ± 2 %) were also included. Average age was 69 ± 7 years. The patients were divided into two groups: first — patients with QRS complex duration under 120 mc, second — QRS duration complex with more than 120 mc. It was found that QRS complex duration with more than 120 mc is associated with males and patients with postinfarction cardiosclerosis, heavier functional class of heart failure and atrial fibrillation. Given the trend towards more clinically significant cardiovascular disease in patients with a QRS complex duration with more than 120 mc, this group of patients needs optimal therapeutic management. The results show the feasibility of and prospects for further study of this group of patients.

KEY WORDS: permanent pacing, cardioresynchronization therapy, chronic heart failure

ТРИВАЛІСТЬ QRS КОМПЛЕКСУ ТА КЛІНІЧНІ ОСОБЛИВОСТІ ПАЦІЄНТІВ З ПОСТІЙНОЮ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ

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Було досліджено 125 пацієнтів (57 — жінок, 68 — чоловіків) з постійною електрокардіостимуляцією. Серед показань до імплантації електрокардіостимулятора було передсердно-шлуночкова блокада (АВ — блокада) — 77 осіб (62%) , синдром слабкості синусового вузла (СССУ) — 32 пацієнтів (26%) , брадісістоліческая форма фібриляції передсердь — 8 пацієнтів (6%). Були також досліджені 8 пацієнтів з кардіоресінхронізірующей терапією (6%). Середній вік пацієнтів склав 69 ± 7 років. Пацієнти були розділені на дві групи: перша — пацієнти з тривалістю QRS комплексу менше 120 мс, друга — більше 120 мс. Було виявлено, що тривалість QRS комплексу більше 120 мс асоціювалася з чоловічою статтю , постінфарктним кардіосклерозом, більш важким функціональним класом хронічної серцевої недостатності та фібриляції передсердь. З урахуванням тенденції до більш клінічно значущих серцево-судинних захворювань у пацієнтів з тривалістю QRS комплексу більше 120 мс, ця група пацієнтів потребує оптимального терапевтичному менеджменту. Результати показують можливості та перспективи для подальшого вивчення цієї групи пацієнтів.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, кардіоресинхронізуюча терапія, хронічна серцева недостатність

ПРОДОЛЖИТЕЛЬНОСТЬ QRS КОМПЛЕКСА И КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ПАЦИЕНТОВ С ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ

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Было исследовано 125 пациентов (57 — женщин, 68 — мужчин) с постоянной электрокардиостимуляцией. Среди показаний к имплантации электрокардиостимулятора было предсердно-желудочко-

вой блокада (АВ-блокада) — 77 человек (62 %), синдром слабости синусового узла (СССУ) — 32 пациентов (26%), брадисистолическая форма фибрилляции предсердий — 8 пациентов (6 %). Были также исследованы 8 пациентов с кардиоресинхронизирующей терапией (6 %). Средний возраст пациентов составил 69 ± 7 лет. Пациенты были разделены на две группы: первая — пациенты с продолжительностью QRS комплекса менее 120 мс, вторая — более 120 мс. Было обнаружено, что продолжительность QRS комплекса более 120 мс ассоциировалась с мужским полом, постинфарктным кардиосклерозом, более тяжелым функциональным классом хронической сердечной недостаточности и фибрилляции предсердий. С учетом тенденции к более клинически значимым сердечно-сосудистым заболеваниям у пациентов с продолжительностью QRS комплекса более 120 мс, эта группа пациентов нуждается в оптимальном терапевтическом менеджменте. Результаты показывают возможности и перспективы для дальнейшего изучения этой группы пациентов.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, кардиоресинхронизирующая терапия, хроническая сердечная недостаточность

Permanent pacing is the primary method of treatment of bradysystolic rhythm disturbances and medical refractory chronic heart failure (CHF) [1].

The effectiveness of pacing is defined by the QRS complex duration. For example, a wide QRS complex is associated with frequent hospitalizations and a higher risk of cardiac death [2–4].

So far, we haven't found any publications containing with comparing clinical conditions of patients with pacemakers in different QRS complex duration.

The purpose of this paper is to analyze the clinical features of patients with pacemakers depending on the QRS complex duration.

MATERIALS AND METHODS

125 patients (57 — women, 68 — men) who underwent permanent pacing therapy were examined in the department of ultrasound and instrumental diagnosis with miniinvasive interventions of SI «Zaycev V. T. Institute of General and Urgent Surgery NAMS of Ukraine». The average age was 69 ± 7 years.

Evaluation was made of the age and sex of the patients, the availability of diseases (chronic ischemic heart disease (CIHD) and its forms — postinfarction cardiosclerosis, stable angina (I–IV functional classes (FC)), arterial hypertension (AH) — 1–3 degrees and stages 1–4), and the presence of clinical syndromes (atrial fibrillation (AF) (paroxysmal, persistent and permanent), chronic heart failure (CHF) — stages I–III, I–IV (FC)). Also, left ventricle ejection fraction (LVEF), end-diastolic and end-systolic volumes, interventricular septum (IVS) thickness, left (LA) and right atrium (RA), right ventricular (RV) sizes, systolic (SBP) and diastolic blood pressure (DBP) were estimated.

CIHD and AH were diagnosed in accordance with the recommendations of the Ukrainian Association of Cardiology (2007). CHF stage and FC were assessed in line with the guidelines of the Ukrainian Association of Cardiology (2012) [5]. Evaluation of AF and its forms was made according to the Working Group of Cardiac rhythm disorders [7].

SBP and DBP were measured by Korotkov's method as recommended by the Association of Cardiologists of Ukraine to prevent and treat hypertension through using tonometer Microlife BP AG1 — 20 after 5 minute rest. The measurement accuracy was 2 mm Hg.

Electrocardiogram (ECG) was performed with computer electrocardiograph Cardiolab+ 2000 in the early postoperative period (the third — fifth day after the pacemaker installation). The stimulated QRS complex duration was measured in leads II, V5, V6 (the average of three consecutive complexes) with choosing of a maximum value. The measurement accuracy was 1mc.

Echocardiography was conducted by the ultrasound machine Toshiba. LF, RF, RV sizes and IVS thickness was measured. EDV and ESV were calculated by Teichholz's formula. $EDV = (7 \cdot EDD^3) / (2{,}4 + EDD)$, $ESV = (7 \cdot ESD^3) / (2{,}4 + ESD)$. LVEF was calculated using the formula LVEF = (EDV — ESV) / EDV * 100 %. The measurement accuracy was 0,5 mm.

The patients were divided into two groups: 1 — with the QRS complex duration under 120 mc, 2 — more than 120 mc. The age and sex of the patients, along with the availability of diseases, clinical syndromes and functional values were assessed and compared in the selected groups.

The data were brought into the Microsoft Excel base. For statistical evaluation of the re-

sults, the parametric criteria (the mean — M, sd — the average deviation) and nonparametric ones (absolute (n, the number) and relative (p, %) units) were used. The probability of differences between groups was determined using a non-parametric U — Mann-Whitney test. The expected result is determined by levels of reliability $p < 0,01$ and $p < 0,05$.

RESULTS AND DISCUSSION

Table 1 shows the distribution of patients with installed pacemakers into groups according to the QRS stimulated complex duration. The average age of the patients in the groups was the same ($p > 0,05$). In the first group the predominant patients were women, and in the second — men ($p < 0,05$).

Table 1

Clinical characteristics of patients with pacemakers

Clinical data					Total	QRS complex duration	
						Under 120 mc	More than 120 мс
Age, years (M ± sd)					125	69 ± 8	69 ± 7
Sex (n, % ± sP)			F		57	65 ± 9	40 ± 5*
			M		68	35 ± 9	60 ± 5*
Diseases	CIHD	Postinfarction cardiosclerosis, (n, % ± sP)			14	3 ± 1	14 ± 4*
		Stable angina (n, % ± sP)	Total		41	38 ± 9	31 ± 8
			FC I		10	–	33 ± 9
			FC II		19	63 ± 15	40 ± 9
			FC III		10	37 ± 15	20 ± 7
			FC IV		2	–	7 ± 5
	Arterial hypertention (n, % ± sP)		Total		102	83 ± 7	81 ± 4
			Degree	0	23	14 ± 6	19 ± 4
				1	39	26 ± 8	33 ± 5
				2	52	50 ± 9	40 ± 5
				3	11	10 ± 6	8 ± 3
			Stage	0	23	14 ± 6	19 ± 4
				1	3	7 ± 5	2 ± 1
				2	60	38 ± 9	51 ± 5*
				3	39	41 ± 9	28 ± 5*
	Diabetes mellitus, (n, % ± sP)		Type	1	–	–	–
				2	15	14 ± 6	12 ± 3
			Severity	Light	–	–	–
				Medium	10	10 ± 6	8 ± 3
				Heavy	5	4 ± 3	4 ± 2
Clinical syndromes	CHF (n, % ± sP)		Stage	Total	95	70 ± 5	78 ± 4
				I	7	10 ± 6	4 ± 2
				IIA	60	31 ± 9	51 ± 5*
				IIБ	25	24 ± 8	19 ± 4
				III	3	4 ± 4	2 ± 1
			FC	I	5	10 ± 6	3 ± 2
				II	48	66 ± 9	50 ± 7
				III	29	21 ± 8	39 ± 6*
				IV	6	3 ± 3	8 ± 4
	AF (n, % ± sP)		Total		40	24 ± 8	34 ± 5
			Paroxysmal and persistent		20	10 ± 6	17 ± 4
			Permanent		20	14 ± 6	17 ± 4

Comment:
* $p < 0,05$; ** $p < 0,01$ — the level of significance of differences;
sP — percent average error,
M — mean value,
sd — standard deviation

In the structure of CIHD, the proportion of patients with postinfarction cardiosclerosis was lower in group 1 than in group 2 ($p < 0,05$). The distribution of patients with stable angina

in both groups was even. In the first group the patients with II and III stable angina FC were predominant. The patients with hypertension were also divided into groups evenly. The differences between the groups in degrees of AH have not been detected ($p > 0,05$). There were less patients with stage 2 hypertension in the first group and more with stage 3 ($p < 0,05$). The number of patients with stage 2 hypertension was prevailing in group 2 ($p < 0,05$). The proportion of the patients with CHF and AF was lower in group 1, but the differences were not significant ($p > 0,05$). The patients with type 1 diabetes have not been identified. The distribution of patients with type 2 diabetes in both groups was uniform ($p > 0,05$).

The significance levels of heart rate, systolic and diastolic blood pressure, as well as echocardiographic parameters in patients with pacemakers are presented in Table 2.

Table 2

Functional performance in patients with pacemakers

Functional value	QRS complex duration		
	Under 120 mc	More than 120 mc	
BP, (M ± sd, mm. Hg)	SBP	149 ± 20	145 ± 17
	DBP	88 ± 10	84 ± 9
HR, (M ± sd, beats/min)	Spontaneous	54 ± 13	50 ± 11
	Stimulated	69 ± 6	69 ± 9
	EF (M ± sd, %)	53 ± 13	50 ± 10
	ESV (M ± sd, ml)	82 ± 56	85 ± 47
	EDV (M ± sd,ml)	152 ± 64	151 ± 46
	IVS, (M ± sd, cm)	1.15 ± 0.2	1.2 ± 0.1
	LA (M ± sd, cm)	4.5 ± 0.7	4.3 ± 0.6
	RA (M ± sd, cm)	4.3 ± 0.7	4,4 ± 0,6
	RV (M ±м sd, cm)	2.9 ± 0.6	3.2 ± 0.6

Comment:
* P < 0,05 — the level of significance of differences

Functional characteristics of patients in groups did not vary significantly ($p > 0,05$).

QRS complex duration is estimated as a useful indicator of ventricular function, in patients with own rhythm [3] and those with pacemakers [4, 7].

QRS complex widening in patients with pacemakers, as well as with their own rhythm, is associated with the higher prevalence of comorbid conditions. CHF severity and consequent increase in the frequency of hospitalizations were showed by Shukla [2]. In our study, CHF also proved to be more serious in patients in QRS complex duration with more than 120 mc. The high rate of occurrence of permanent atrial fibrillation in patients with widened QRS complex [9, 10] is reflected in our work.

The relationship between QRS complex duration and the changes in the functional parameters in patients with pacemakers has been studied to a much lesser extent. The decrease in SBP in QRS complex widening patients with pacemakers was showed by Young J. H. et al. Sumiyoshi et al. associated the lower LVEF and LV EDV in patients with pacemakers with QRS complex widening, which is confirmed by other studies. Our research has found no significant differences in terms of echocardiography in patients with pacemakers in different rates of QRS complex duration.

The fact that there is no statistically significant differences in most clinical parameters in patients with pacemakers in different rates of QRS complex duration is positive. The higher prevalence of postinfarction cardiosclerosis, CHF FC, AF in patients with QRS duration with more than 120 mc and their sex differences should be taken into account in the course of therapeutic management after the pacemaker installation.

CONCLUSIONS

1. QRS complex duration is associated with clinical features of patients with permanent pacemakers. Among the patients with QRS complex duration with more than 120 mc vs that under 120 mc, predominant are males and patients with postinfarction cardiosclerosis, heavier functional class of chronic heart failure and atrial fibrillation.

2. Patients with QRS duration more than 120 mc require thorough therapeutic management.

It seems appropriate to undertake a further clinical insight into features of patients with permanent pacemakers, taking into account QRS complex duration.

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EFFICACY OF CORMOBID OCTEOARTHROSIS WITH ARTERIAL HYPERTENSION CONTROL CONSIDERING THE TYPES OF ORTHOSTATIC REACTIONS AND CARCADIAN PROFILES OF ARTERIAL PRESSURE

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Clinical peculiarities, heart rate variability and effectiveness of comorbid osteoarthrosis with arterial hypertension control considering the types of orthostatic reactions and circadian profiles of blood pressure were established. In patients with comorbid osteoarthrosis with arterial hypertension all three types of systolic and diastolic blood pressure orthostatic reactions with the prevalence of hypertensive were observed, and all of four types of diurnal profiles — with a prevalence of non-dipper on systolic blood pressure and dipper for diastolic. The detrimental types of arterial pressure orthostatic responses were observed in 12 % of systolic and in 15 % of diastolic type in patients with comorbid OA with AH then with isolated one. Migration regularities of blood pressure orthostatic reactions in patients with comorbid osteoarthrosis with arterial hypertension on the stages of therapy were revealed and it was determined that migration of systolic blood pressure was higher into the hypertensive type, diastolic — into hypotensive. It was determined that comorbid with arterial hypertension osteoarthrosis had no effect on baseline indexes of heart rate variability, but affected the reactions on orthostasis. In the management of patients it should be taken into account that in hypotensive and isotensive of orthostatic reactions, dipper and night-peaker circadian profiles of systolic blood pressure and night-peaker profiles of diastolic blood pressure require more intensive antihypertensive therapy. In studied clinical signs and heart rate variability indices statistically significant criteria of arterial hypertension comorbid with osteoarthrosis efficacy control were patients age and sympatho-vagal balance ratio.

KEY WORDS: hypertension, osteoarthrosis, comorbidity, orthostatic reactions, circadian profile, blood pressure

ЕФЕКТИВНІСТЬ КОНТРОЛЮ КОМОРБІДНОЇ З ОСТЕОАРТРОЗОМ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ З УРАХУВАННЯМ ТИПІВ ОРТОСТАТИЧНИХ РЕАКЦІЙ І ДОБОВИХ ПРОФІЛІВ АРТЕРІАЛЬНОГО ТИСКУ

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Встановлені клінічні особливості, варіабельність серцевого ритму і ефективність контролю коморбідної з остеоартрозом артеріальної гіпертензії у залежності від типів ортостатичних реакцій і добових профілів артеріального тиску. У хворих на коморбідну з ОА АГ спостерігалися три типи ортостатичних реакцій артеріального тиску з переважанням гіпертензивного за систолічним (47 %) і діастолічним (44 %). Несприятливі типи ортостатичних реакцій артеріального тиску зустрічалися на 12 % по систолічному і на 15% по діастолічному частіше у хворих на коморбідну з ОА АГ, ніж на ізольовану. Виявлено, що у хворих на коморбідну з остеоатрозом артеріальну гіпертензію спостерігалися три типи добових профілів систолічного артеріального тиску (dipper, non-dipper, night-peaker) з переважанням non-dipper (43 %) та всі чотири типи добових профілів діастолічного з переважанням dipper (52 %). Виявлені закономірності міграції ортостатичних реакцій артеріального тиску у хворих на коморбідну з остеоартрозом артеріальну гіпертензію на етапах терапії та встановлено, що міграція систолічного артеріального тиску більшою мірою відбувалася у гіпертензивний тип, діастолічного — у гіпотензивний. Встановлено, що коморбідність артеріальної гіпертензії з остеоартрозом не впливала на вихідні показники варіабельності серцевого ритму, але при цьому порушувала реакції на ортостаз. У менеджменті хворих на коморбідну з остеоартрозом артеріальну гіпертензію необхідно враховувати те, що при гіпотензивній та ізотензівній ортостатичних реакціях, dipper та night-peaker добових профілях систолічного артеріального тиску та night-peaker діастолічного — необхідна більш інтенсивна антигіпертензивна терапія. Серед сукупності вивчених клінічних ознак і показників варіабельності серцевого

ритму статистично значимими критеріями ефективності контролю АТ у хворих на коморбідну з остеоартрозом артеріальну гіпертензію виявилися вік хворих та співвідношення симпато-вагального балансу.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, остеоартроз, коморбідність, ортостатичні реакції, добові профілі, артеріальний тиск

ЭФФЕКТИВНОСТЬ КОНТРОЛЯ КОМОРБИДНОЙ С ОСТЕОАРТРОЗОМ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ В ЗАВИСИМОСТИ ОТ ТИПОВ ОРТОСТАТИЧЕСКИХ РЕАКЦИЙ И СУТОЧНЫХ ПРОФИЛЕЙ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ

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Установлены клинические особенности, вариабельность сердечного ритма и эффективность контроля коморбидной с остеоартрозом артериальной гипертензии с учетом типов ортостатических реакций и суточных профилей артериального давления. У больных коморбидной с остеоартрозом артериальной гипертензией наблюдались три типа ортостатических реакций артериального давления с преобладанием гипертензивной по систолическому (47 %) и диастолическому (44 %). Неблагоприятные ортостатические реакции артериального давления встречались на 12% чаще по систолическому артериальному давлению и на 15 % по диастолическому у больных коморбидной с остеоартрозом артериальной гипертензией, чем с изолированной. У больных коморбидной с остеоартрозом артериальной гипертензией наблюдались три типа суточных профилей систолического артериального давления с преобладанием non-dipper (43 %) и все четыре диастолического с преобладанием dipper (52 %). Выявлены закономерности миграции ортостатических реакций артериального давления у больных коморбидной с остеоартрозом артериальной гипертензией на этапах терапии и установлено, что миграция систолического артериального давления в большей степени происходила в гипертензивный тип, диастолического — в гипотензивный. Установлено, что коморбидность артериальной гипертензией с остеоартрозом не влияла на исходные показатели вариабельности сердечного ритма, но при этом нарушала ее реакции на ортостаз. При ведении больных коморбидной с остеоартрозом артериальной гипертензии с гипотензивной, изотензивной ортостатическими реакциями, dipper и night-peaker суточными профилями систолического артериального давления и night-peaker диастолического рекомендуется болем интенсивная антигипертензивная терапия. Среди совокупности изученных клинических признаков и показателей вариабельности сердечного ритма статистически значимыми критериями эффективности контроля артериального давления у больных коморбидной с остеоартрозом артериальной гипертензей оказались возраст больных и соотношение симпатовагального баланса.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, остеоартроз, коморбидность, ортостатические реакции, суточные профили, артериальное давление

Problem of comorbidity becomes more important in the patients managements and its actuality is raising especially for arterial hypertension (AH) and osteoarthrosis (OA) [1–3]. Increase of morbidity with age, common risk factors and pathogenic mechanisms [4–7], and also possibility of mutual aggravation lead to worsening of patients quality of life and to economic losses of State as a result.

Investigation of orthostatic reactions (OR) of blood pressure (BP) [8–11], diurnal profiles (DP) of BP [12, 13] and heart rate variability (HRV) [14, 15] reflects the degree of stresses in the regulatory systems which play an important role in AH and OA pathogenesis.

The data of BP control efficacy in patients with comorbidity of OA with AH and depending on the type of OR and DP of BP were not found in the literature in spite of the problem actuality.

Target. To define the cormobid osteoarthrosis with arterial hypertension control efficacy considering the types of orthostatic reactions and diurnal profiles of arterial pressure.

MATERIALS AND METHODS

111 patients: 31 men and 80 women (58 ± 11 years old) who have been consulted at the Kharkov city clinics №6 during 2007–2010 years were included to the current study. 98 (88 %) patients were diagnosed with AH including 26 with mild (26 %), 49 with moderate (51 %) and 23 with severe (23 %) rates. Stage I of AH was diagnosed in 11 (11 %) patients, stage II — in 71 (73 %), stage III — in 16 (16 %). 56 patients were with chronic heart

failure (HF) of I and II A stages (I — in 31 (55 %) and II A — in 25 (45 %)) by classification of Strazhesko-Vasilenko. The I-st functional class of HF was diagnosed in 25 patients (45 %), II — in 31 (55 %) according to the NYHA classification. OA was diagnosed in 58 patients (52 %) including 32 (58 %) with II stage (58 %) and 26 (42 %) with III, the I-st stage of OA was not detected.

The work deals with the estimation of the effectiveness of control of arterial hypertension and osteoarthritis comorbidity depending on types of orthostatic reactions and diurnal profiles of blood pressure.

45 patients of total 111 were examined with comorbidity of AH and OA (observation group — AH + OA), 53 with isolated arterial hypertension (first comparison group — IAH) and 13 — with isolated OA (2nd comparison group — IOA). Control group (CG): 36 mostly healthy individuals of the same age as the patients in the observation group.

The criteria for involving to the study were: AH of 1, 2 and 3 rates of I–III stage and primary OA. Exclusion criteria from the study were: myocardial infarction, unstable angina, stable angina of IV functional class, stroke in history card, arterial fibrillation, implanted pacemakers, severe arrhythmias and conduction of the heart, HF IIb–III stage, III–IV functional class HF by NYHA, diabetes mellitus, obesity of III–IV rate, chronic respiratory disease, ulcer disease, thyroid disease, IV stage joints injury radiographycally by Kellgren-Lawrence classification.

The diagnosis of AH was verified according to the Ukrainian Association of cardiologists of the prevention and treatment of arterial hypertension recommendations (2008). The diagnosis of OA was stated according to the Association of rheumatologists of Ukraine and the Association of orthopedists, traumatologists of Ukraine recommendations (2004).

AP measurement was done early in the morning according to Korotkov method by Microlife BP AG1–40 blood pressure monitor in clinostasis after 5-minutes rest and in 3 minutes after transfer to orthostasis. During orthostatic sample procedure increase of systolic and diastolic AP in 5 and more mm Hg was classified as hypertentional OR, decrease of systolic and diastolic AP in 5 and more mm Hg — as hypotentional OR, change of systolic and diastolic AP not more than 5 mm Hg — as isotensive OR.

DPAP was done with the help of cardiogtaphic complex «CARDIOSENSE». According to the results of the investigation DPAP was estimated after the level of their night decrease (LND): 1 — over-dipper — LND > 20 %, 2 — dipper — 10 % < LND < 20 %; 3 — non-dipper — LND < 10 %; 4 — night-peaker — LND < 0 %.

HRV was defined with the help of electrocardiograph «CARDIOLAB». For HRV analysis ECG was registered in other standard allotment consequently in clinostasis and orthostasis (HRV sample for orthostasis). Spectral analysis of HRV was done with the help of Fourier quick transformation. The spectrum total power (Total power — TP, мс^2) and proportion of sympathetic balance (Low Frequency/High Frequency — LF/HF) were studied. The sample of metronomized breathing was performed, the respiratory rate was defined individually for each patient in proportion: inhale (3 seconds) — exhale (4 seconds). Average 5 minutes of 7-minutes monitor ECG record were treated.

The AH therapy was based on the Ukrainian Association of cardiologists recommendations, OA — on the Association of rheumatologists of Ukraine and the Association of orthopedists, traumatologists of Ukraine recommendations.

Before the beginning of the therapy the patients in all groups were categorized into subgroups according to OR of SAP type and OR of DAP type into: hypertensive, isotensive, hypotensive types of OR. Before the beginning of the therapy the patients in all groups were categorized into subgroups according to DP of SAP type and DP of DAP type into: with DP, dipper, non-dipper, over-dipper and night-peaker.

The patients were examined before the therapy, after 2 weeks, 1, 3, 6 and 12 months from the beginning of the therapy.

The received results were processed after database formation in «Microsoft Excel 2007». Statistic procedures were executed with the help of the programs «Microsoft Excel 2007», «Mathcad 14.0». The Mann-Witney criterion was used for statistical estimation of the results. In defining the differences between the groups authenticity the confidential intervals 95 % and 99 % were used. The features incidence studied was indicated in percentage, average errors of the percentage were indicated in the tables by V. S. Genes.

RESULTS AND DISCUSSION

Cormobid OA with AH in compareson with isolated one was characterized by more prominent frequency of occurence and more severe manifestations of HF (table 1).

Table 1

Clinical charactristics of the patients with AH+OA and IAH taking into account age, sex, level and stage of the disease (% ± Sp), M ± sd)

Indices		Groups of the patients	
		AH+OA	IAH
Number of the patients	total	46 ± 9	54 ± 9
	men	27 ± 8	36 ± 9
	women	73 ± 8	64 ± 9
Age, years (M±sd)		58 ± 11	58 ± 11
Level of AH (%± Sp)	1	20 ± 7	32 ± 8
	2	56 ± 10	45 ± 8
	3	24 ± 8	23 ± 7
Stage of AH (%± Sp)	I	7 ± 4	15 ± 6
	II	69 ± 8	76 ± 7
	III	24 ± 8	9 ± 5
Stage HF (%± Sp)	0	29 ± 8	48 ± 9
	I	47 ± 9	43 ± 9
	IIA	24 ± 8	9 ± 5
FC of HF (%± Sp)	I	76 ± 8	89 ± 6
	II	24 ± 8	11 ± 6
Stage of OA (%± Sp)	I	–	–
	II	56 ± 9	–
	III	44 ± 9	–

All three types of OR of SAP with hypertensive prevalence were observed in groups AH + OA and IAH. Hypotensive type of OR of SAP was found more frequently in the group AH+OA, isotensive — in the group with IAH. In the group with IOA the patients with isotensive type of OR of SAP dominated (fig. 1).

In all comparative groups including the group with HC all three types of OR of DAP with hypertensive prevalence were observed. Hypotensive type of OR of DAP was observed more frequently in the group AH + OA, isotensive — in the group IAH (fig. 2).

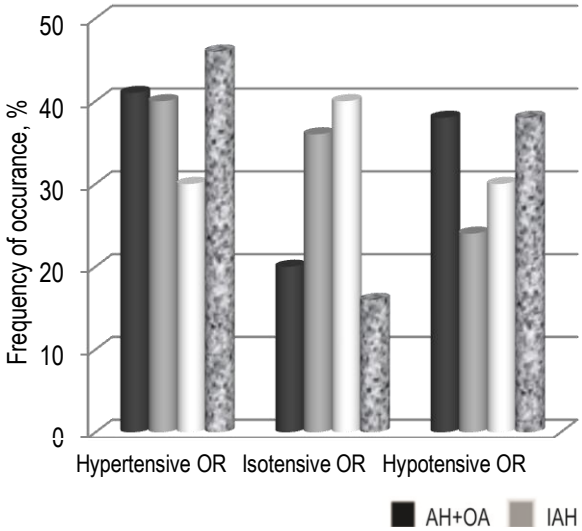

Fig. 1. Frequency of occurance of OR of SAH in the limits of defined groups AH+OA, IAH, IOR and HC

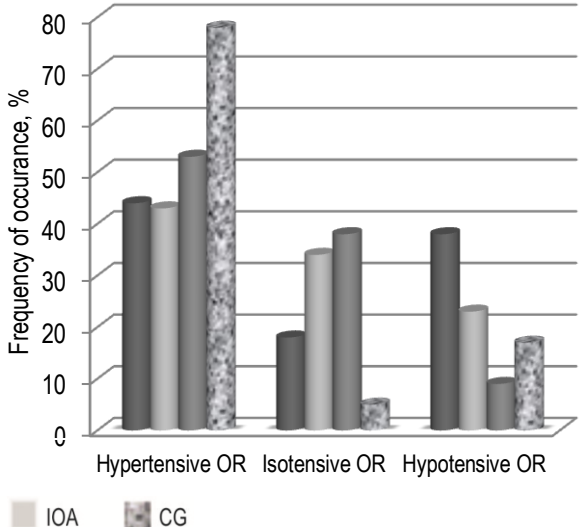

Fig. 2. Frequency of occurance of various types of OR of DAP in the limits of defined groups AH+OA, IAH, IOA and HC

Regardless all types of OR of SAP and OR of DAP under AH + OA the level and stage of AH, functional classes and stages of HF were higher. Three types of DP of DAP with non-dipper prevalence were observed. Night-peaker were found more frequently in the group AH+OA, dipper — in the group IAH. Over-dipper was not found in any group (fig. 3).

All three types of DP of DAP with dipper prevalence were observed in the groups AH + OA and IAH. Non-dipper was observed more frequently in the group AH + OA and night-peaker and over-dipper — in the group IAH. In the group IOA dipper and non-dipper were found with the same frequency (fig. 4).

Combination of detrimental DP of SAP and DP of DAP were observed more frequently (7 %) in patients with cormobid OA with AH than with isolated AH.

HRV was identically low in the groups AH + OA and IAH than in the groups IOA and HC before the beginning of TR therapy. Correlation LF/HF was greater under AH + OA, than under IAH, IOA and HC. Improper reaction was observed in the group AH + OA before the beginning of therapy, in the groups IAH and IOA — the reaction on orthostasis was proper. In three comparison groups proper reaction on metronomized breathing was observed (table 2).

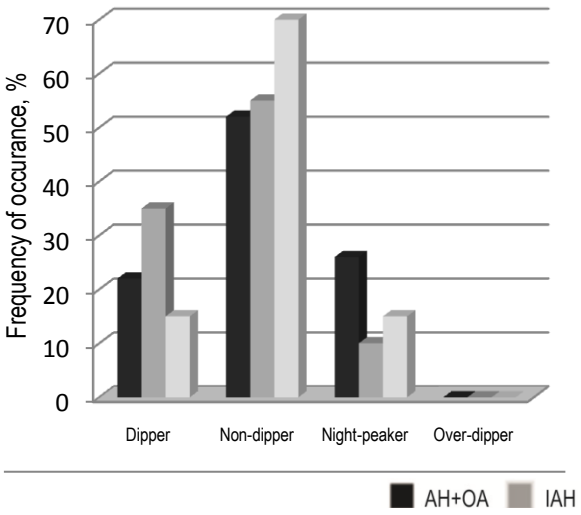

Fig. 3. Frequency occurance of various types of DP of SAP in the limits of defined groups AH+OA, IAH and IOA

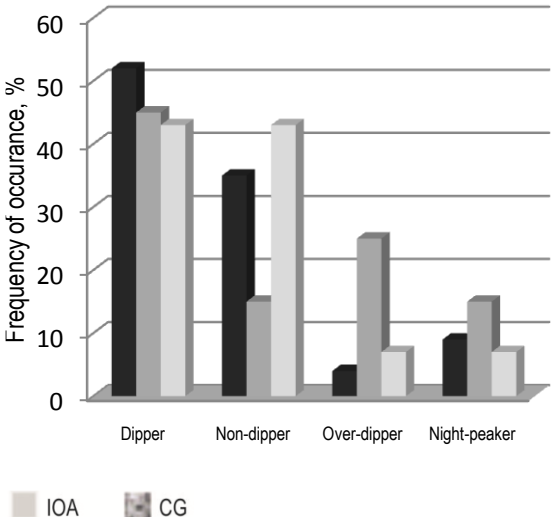

Fig. 4. Frequency occurance of various types of DP of DAP in the limits of defined groups AH+OA, IAH and IOA

Table 2

TR and LF/HF (M ± sd) in the limits of defined groups AH+OA, IAH, IOA, HC

HRV indices	Samples	Groups of patients			
		AH+OA	IAH	IOA	HC
TR, мс^2	clinostasis	1301,3 ± 1011	1369 ± 927,8	1423,6 ± 1131,1	2120 ± 1674
	orthostasis	1313,1 ± 1046,6	1300 ± 929,2	1358 ± 963	1850 ± 1298##
	metronom. breathing	2180,0 ± 1731,5##	2394,1 ± 1689,1##	3513,8 ± 2534##	3580 ± 2107##
LF/HF, dimentionless	clinostasis	3 ± 1,8	2,4 ± 1,7	2,6 ± 1,7	1,2 ± 1,2
	ortostasis	5 ± 3,5##	4,2 ± 3##	4,7 ± 4,1##	5,3 ± 1,5##
	metronom. breathing	3,9 ± 3,2##	4,6 ± 3,6##	4,2 ± 3##	4,9 ± 1,2##

Note:
# p< 0,05, ## p < 0,01 — between indises inside the groups on the corresponding stages of the investigation

Adequate control of AP led to the improvement of HRV indices in patients with regeneration of proper reactions on orthostasis. In the groups AH + OA, IAH, IOA in patients with various types of OR and DP of SAP and DAP no essential differences in HRV indices were found (p > 0,05). The output SAP in patients with AH+OA was higher, than in patient with

IAH (p > 0,05). Efficacy control of SAP under AH + OA was lower than under IAH. The output DAP under AH + OA was higher than under IAH (p > 0,05), while therapy was similarly effective in both groups (p > 0,05). SAP and DAP lowered consequently in 24 % and 18 % in the group AH + OA, in 22 % and 18 % in the group IAH in 12 months (table 3).

Table 3

Changes of SAP and DAP on the stages of therapy in groups of the patients AH+OA and IAH (M ± sd)

Stages of therapy	Groups of patients			
	AH+OA		IAH	
	SAP	DAP	SAP	DAP
To 2 weeks	175 ± 14	100 ± 11	166 ± 13	99 ± 12
2 weeks	160 ± 16	90 ± 9	140 ± 10	85 ± 12
1 month	148 ± 10	86 ± 10	134 ± 11*	84 ± 11
3 months	138 ± 6	83 ± 11	140 ± 10	85 ± 11
6 months	134 ± 8	82 ± 8	132 ± 9	82 ± 6
12 months	133 ± 7##	82 ± 9##	130 ± 9#	81 ± 7

Note:
* p < 0,05, — in current indices inside the group AH + OA and IAH against baseline indices;
# p < 0,05, ## p < 0,01 — between the indices in the groups on the corresponding stages of the investigation

Comorbidity of AH with OA influenced the baseline level of AP in patients with all types of OR of SAP and OR of DAP. SAP was more effectively controlled in patients with hypertensive than with hypotensive and isotensive types of OR of SAP.

DAP was more effectively controlled in the patients with hypertensive and hypotensive types of OR of SAP under AH + OA and with all types of OR of SAP under IAH. SAP was more effectively controlled in both groups of patients with hypertensive type of OR of SAP and DAP — in both groups of patients irrespective the type of OR of DAP. Comorbidity of AH with OA did not essentially influence the baseline level of AP under any type of DP of AP. The AP control efficacy was higher in patients with non-dipper DP of SAP, with dipper, non-dipper and over-dipper DP of DAP and lower — with dipper and night-peaker DP of SAP and night-peaker DP of DAP.

Corresponding to the analysis of the publications comorbidity of AH with OA occurs in 48–65 % cases [16], which is confirmed by the results of our investigation. We did not find any information about the investigation of AP efficasy control in the patients with AH + OA and IAH depending on DP of SAP and DP of DAP in the literature, thus, the results of our investigation are new. Moreover, as for the results, received by us the AP control was effective in both groups AH+OA and IAH, it occurred different for SAP and DAP and was connected with the types of DP of SAP and DP of DAP. More low control efficacy of SAP in comparison with DAP can be explained by lower influence of antihypertension therapy on the level of DAP [17]. Identical control efficacy of SAP and DAP which should be taken into account in patients with non-dipper DP of SAP and lower of DAP — in dipper and night-peaker can be considered as different influence of DP of SAP on the chronobiology of SAP and DAP which is necessary to take into account during the patients management. Though control efficacy of SAP and DAP in patients with DP of DAP dipper, non-dipper, over-dipper and lower DAP — in night-peaker can be considered as more severe course of cormobid AH with OA and isolated AH with the data of DP of DAP which should be taking into account during the patients management.

CONCLUSIONS

1. Comorbid OA with AH in comparison with isolated one is characterized by high frequencies of more severe stages of AH and HF (15 %). The detrimental hypotensive type of OR of AP was found in 12 % in SAP in 15 % in DAP more frequent in patients with AH cormobid with OA than with isolated one.

The detrimental night-peaker DP occurred in 16 % in SAP, but non-dipper — in 20 % in DAP more frequent in patients with AH comorbid with OA than with isolated one. The comorbidity of AH with OA in patients with various types of OR and DP of AP did not authentically lower the indices of HRV but led to their reaction on orthostasis disruption.

2. Therapy in the way of standard schemes of antihypertensive preparations provided the AP effective control in patients with AH comorbid with OA with AP hypertensive type of OR with non-dipper DP of SAP and dipper, non-dipper and over-dipper DAP. Patients with hypotensive and isotensive types of OR, dipper and night-peaker DP of SAP and night-peaker DAP need more intensive antihypertensive therapy. Adequate control of AP in patients with AH comorbid with OA promoted the improvement of HRV indices with proper reaction on orthostasis regeneration.

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THE ROLE OF MODERN MEDICAL IMAGING TECHNOLOGIES AT DISTANT RADIATION THERAPY PLANNING

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The possibilities of use of modern multimodal imaging technologies during the distant radiation therapy treatment planning are analyzed. The conditions for carrying out of different modality tomography research for needs of treatment planning are determined. The issues of informativity of the hybrid images for target volume finding are considered.

KEY WORDS: distant radiation therapy, radiation treatment planning, target volume, multimodal imaging, image fusion, computed tomography, positron-emission tomography, magnetic resonance tomography

РОЛЬ СУЧАСНИХ ТЕХНОЛОГІЙ МЕДИЧНОЇ ВІЗУАЛІЗАЦІЇ У ПЛАНУВАННІ ДИСТАНЦІЙНОЇ ПРОМЕНЕВОЇ ТЕРАПІЇ

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Проаналізовані особливості застосування сучасних технологій мультимодальної томографічної візуалізації в процесі планування дистанційної променевої терапії. Визначені умови проведення томографічних досліджень різної модальності для цілей планування променевої терапії. Розглянуті питання інформативності гібридних зображень при визначенні об'ємів мішені.

КЛЮЧОВІ СЛОВА: дистанційна променева терапія, планування променевого лікування, об'єм мішені, мультимодальна візуалізація, злиття зображень, комп'ютерна томографія, позитронно-емісійна томографія, магніторезонансна томографія

РОЛЬ СОВРЕМЕННЫХ ТЕХНОЛОГИЙ МЕДИЦИНСКОЙ ВИЗУАЛИЗАЦИИ В ПЛАНИРОВАНИИ ДИСТАНЦИОННОЙ ЛУЧЕВОЙ ТЕРАПИИ

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Проанализированы возможности применения современных технологий мультимодальной томографической визуализации в процессе планирования дистанционной лучевой терапии. Определены условия проведения томографических исследований различной модальности для целей планирования лучевой терапии. Рассмотрены вопросы информативности гибридных изображений при определении объемов мишени.

КЛЮЧЕВЫЕ СЛОВА: дистанционная лучевая терапия, планирование лучевого лечения, объем мишени, мультимодальная визуализация, слияние изображений, компьютерная томография, позитронно-эмиссионная томография, магниторезонансная томография

Modern imaging technologies are playing an increasingly important role in ensuring the quality of radiation therapy preplanning and realization of radiation treatment. Without exaggeration, we can assume that the development of methods of medical imaging has led to fundamental changes in approaches to planning and implementation of modern radiotherapy (RT). The transition from traditional planar medical images to volumetric tomographic imaging of the body structure caused the need to rethink the principles of radiation semiotics,

reconsider pathomorphological characteristics of tumor processes, which could not affect at the strategy of modern radiation treatment.

Now three-dimensional (3D) computer tomographic imaging of different modalities is not only the source of anatomical and topological information about the degree of the prevalence of tumor process and its boundaries, but it is a necessary methodological and technological basis of all phases of modern three-dimensional conformal radiotherapy (3D-CRT) [1, 2]. However, the determination of the place of each of the imaging techniques and the prospects for its use for technological improvement of the radiation treatment is always a relevant task. This is primarily due to the permanent development of imaging technologies themselves: they become not only more clinically informative, but also provide new unique methodological and technical capabilities for distant radiation therapy (DRT) and other treatments for which the use of volumetric anatomical imaging is necessary.

The purpose of this work is analytical review of information about the possibilities and limitations of use of the modern medical imaging technologies from viewpoint of improving the quality of distant radiation therapy planning (DRTP).

The use of visual information for DRTP

During the DRTP the anatomical-clinical and topological analysis of previously obtained radiologic diagnostic images is done. These images allow define (fig. 1): Gross Tumor Volume (GTV); Clinical Target Volume (CTV); Planning Target Volume (PTV); Treated Volume (TV); Irradiated Volume (IV). Also the boundaries of Organs at Risk (OAR) are determined [3]. These data are used for DPTP (selection the optimal number of radiation fields; calculation the individual maps of dose distribution; determining the proper area of capture of the target volume and the evaluation of radiation dose in organs at risk). Thus, all the stages of the DPTP process anyway based on the initial data on the topology of the tumor.

Nearly a century the only source of visual information about the topology of the tumors was classic planar radiograph [4]. A limited number of standard two-dimensional projections allowed create a very simplified volumetric model of the target volume; there were no objective visual data for the optimal choice of fields and directions of irradiation. Thus, considerable uncertainty in the distribution

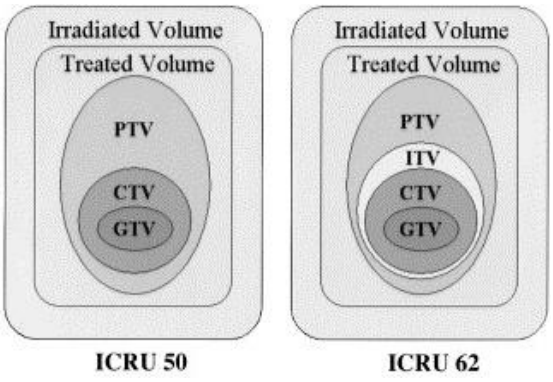


Fig. 1. Schematic illustration of the boundaries of the target volumes defined by ICRU [3]

of doses was formed already at the first stage of treatment planning. In a long time this circumstance restrained the process of improving of DRT equipment. Due to the lack of comprehensive information about the anatomical structure of the patient there was no sense in creation a more effective means of treatment. Patients suffered significant radiation injuries due to excessive irradiation of healthy body parts; it was impossible to simulate accurately the distribution of individual doses of radiation at a given depth and in a given direction. Ideally the shapes of radiation fields has to repeat the outlines of the tumor and dose distribution should provide the most intensive irradiation of the tumor and a sharp decrease of dose in the surrounding tissues. So, for the future there were identified two basic principles of DPT improvement — *conformality* of the radiation fields and *spatial modulation of the radiation intensity* in the therapeutic beam (fig. 2).

The idea of 2D-conformal DPT was realized by applying of standard shielding blocks. Individual dose fields of complex shape created by the beam modifiers — wedge-shaped lead filters and flattening compensators — boluses), which reduced the errors of reproduction of theoretical dose distribution caused by the individuality of the patient's body structure (fig. 3). However, in practice the use of heavy shielding blocks was very uncomfortable, especially for creating of several radiation fields during one treatment session. Boluses were made individually that also required precise anatomical and topographical data and high technological costs. The most difficult was to make correct positioning of all this equipment relative to beam isocentre and ensure its alignment with the target marks on the patient's body. Usually, in practice, irradiation carried out simplistically — by rectangular fields with

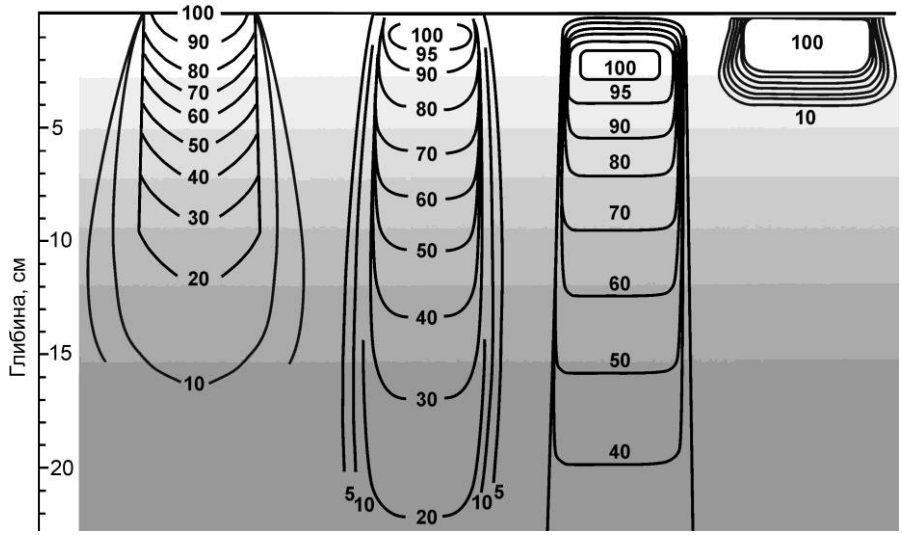


Fig. 2. Charts of depth isodose distribution for photon and electron beams in water:
1 — X-photons 0,2 MeV; 2 — γ-photons ^{60}Co 1,25 MeV; 3 — bremsstrahlung 6 MeV; 4 — electrons 6 MeV

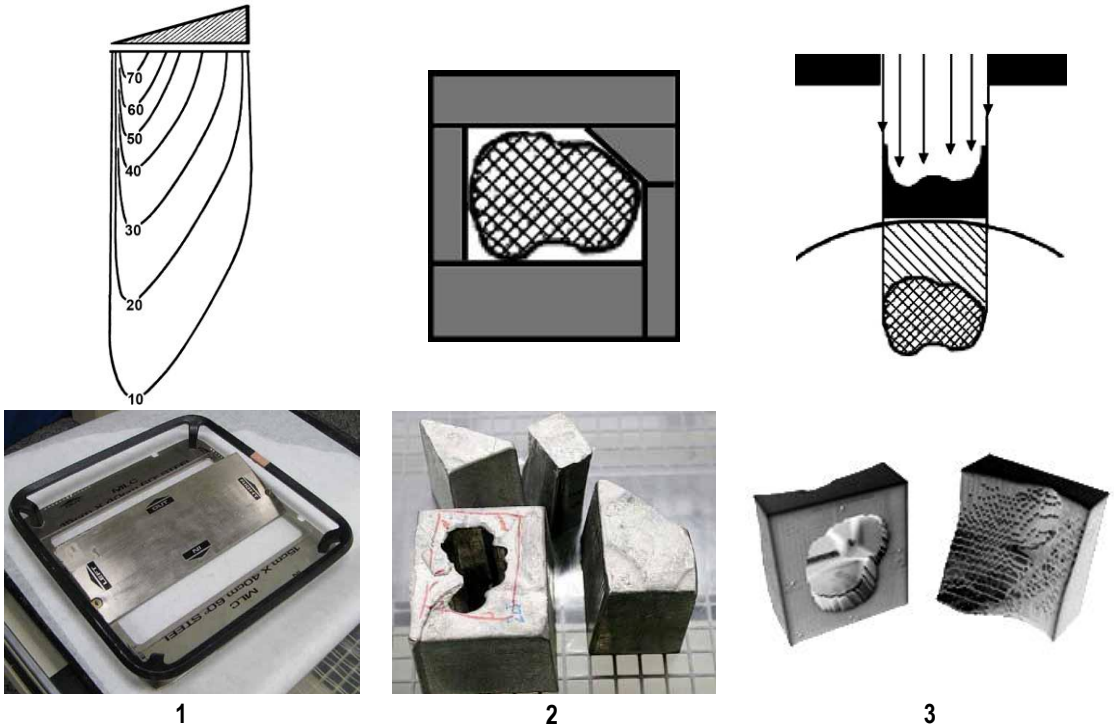


Fig. 3. Means for the forming of individual dose fields:
1 — wedge-shaped filter (http://www-personal.umich.edu);
2 — shielding blocks (http://thestar.com.my/health);
3 — flattening compensators-boluses (http://www.dotdecimal.com)

significant coverage of healthy tissues and non-optimal depth dose distribution. Thus, the development of all technological stages of DRT was constrained primarily due to the lack of comprehensive anatomic imaging.

Computed tomography — an informational basis of modern DRTP technologies

The real breakthrough in the development of radiation therapy was the implementation of a unique method of volumetric anatomical imaging — X-ray computed tomography (CT). Computed tomogram (axial CT scan) is a result of imaging of array of CT numbers (Hounsfield units), calculated after processing of CT scanning data (fig. 4). Computer tomograms are synthesized as digitally reconstructed radiographs (DRRs) which are used to create volumetric (voxel) model of the body — a «virtual patient» (fig. 5). Technology of computed

3D imaging allows synthesizing a virtual cross-section of the body at any given plane [5] (fig. 6). But the most important advantage of CT is the lack of superposition shadows of anatomical structures, their separated imaging (according to CT numbers, computed for them). All these new features allow implementing of previously unavailable technology of 3D-DRTP with calculation of volumetric dose distribution. Generating of patient's anatomical 3D-model allows additional images rendering for each of the selected radiation fields and further use of these images to verify an individual plan of radiation treatment and checkup of patient positioning during irradiation (fig. 6). According to the CT data it is possible to create real volumetric model of tumor. For this purpose up to 100 CT scans can be used, for each of which the contours of the target and outlines of adjacent organs at risk must be marked according to fig. 1. Now, with use the 3D-model of tumor it is possible to accurately identify the boundaries of target for any direction of irradiation. This possibility allowed solving the problem of conformal radiation by another way. The creation of multileaf collimator (MLC) allowed to waive the application of inconvenient protective blocks (fig. 3) and to create technology of automated profiling of therapeutic beam in accordance with the contour of target for each of the planned fields of irradiation (fig. 7, 8). Realization of all the advantages of 3D-DRTP is possible only in case of no less precise technologies of dose delivery which now are based on use of linear electron accelerators. Accelerators deprived of basic disadvantages of cobalt machines (large geometric penumbra of beam, low energy of radiation, non-optimal dose distribution), they are more manageable and easily integrated into a joint hardware-software DRT-complex.

Use of CT technology for DRTP together with the undeniable advantages has several peculiarities which change the standard CT protocol in some aspects [6]:

1. Special flat couch is used for recreate the treatment position of patient, but it is somewhat reduces the CT image quality.

2. It is necessary to use the laser positional indicators which provide coordinate reference marks for reproducible positioning of patient during DRTP verification and radiation treatment.

3. Positioning the patient during CT scanning at once should be the same as for irradiation, if necessary — with use of individual immobilization devices which must be transparent for x-rays.

4. During the scanning shallow breathing is permitted (as during irradiation), but the quality of the CT scans is reduced through the respiratory movements.

5. Quality of 3D-plan for DRT worsens in case of significant changes of volume of patient's fillable organs. It is recommended CT scanning and correction of plan anew.

6. The precise calculation of CT numbers during reconstruction of tomograms significantly affects the accuracy of further calculation of doses. It is important to ensure correct positioning of the patient in the «circle of reconstruction» of CT scanner.

The presence of implants near the target leads to artifacts on CT scans, which worsens the conditions of definition of target volume and dose distribution.

7. Choice of CT slices thickness affects the accuracy of 3D-reconstruction and creation of additional projections (fig. 6).

8. The use of contrast agents in CT scanning makes it easy delineate the tumor and surrounding soft tissues on tomograms, but may affect the accuracy of calculation of doses.

Thus, there are the elements of uncertainty at the use of X-ray CT imaging technology in DRTP, they are caused by the deviation in positioning of patient, target, organs at risk, by features of the CT imaging and its limitations in rendering of the patient's anatomical models. However, CT is the basic technology of data acquisition for adequate dose planning for DRT.Common factor in this process is the use of bremsstrahlung with similar physical nature but with different energy levels. Any other supporting imaging technology which is applied to refine the details of the DRTP should be agreed with the data of CT as the reference method of anatomical and topological visualization and spatial orientation.

Application of tomographic visualization of other modalities for DRTP. Recently, there are actively explored the possibilities of applying tomographic data of other modalities in systems for 3D-CRT planning. Special hopes are assigned to the application of multi-modal and hybrid imaging technologies, which allow co-registration or fusion of medical images of different modalities. Such approach should deepen understanding of metabolic, functional and other factors of the tumor process, which

will help improve the algorithms of determining the topology of the tumor and refine DRTP [6, 7].

Development of methods for *emission tomography* and growth of their diagnostic significance in oncology led to review of approaches to the definition of tumor volumes in DRTP. It was proposed the concept of biological target volume — BTV (fig. 8), which provided differentiated dose delivery to the target sub- volumes in accordance with the specifics of their functional state which is detected by diagnostic imaging of other modalities [8]. This is particularly important in determining the boundaries of the CTV (fig. 1), which takes into account the area of subclinical dissemination of tumor that can be visualized by positron emission tomography (PET). Molecular functional imaging with the use of radiopharmaceuticals combined with structural anatomical CT imaging (fig. 10) [9], creates the best conditions for accurate determination of CTV [10]. According to [11] due to the use of hybrid PET/CT technology the following DRTP changes occurred: GTV correction — in 58 % of cases, dose correction — 14 %, configuration of fields — 15 %, choice of other modality of radiation treatment — 5,4 %. Visualization of biological heterogeneities within tumor sub-volumes can be used to adapt the dose according to their local radiosensitivity. PET-technology is prospective not only for the detection of fractions of hypoxic cells, but also to study other specific biological parameters (proliferation, angiogenesis, apoptosis, etc.), which may further modify the existing approaches to defining target volumes and even influence the choice of radiation treatment strategy [12]. Another perspective application of PET is to determine the functional changes in the irradiated volume during radiation treatment and appropriate current adaptation of DRTP. PET study is indispensable in planning DPT for patients after surgery, for which irradiated volume can be adequately estimated only by the result of molecular functional imaging [13]. Peculiarity of emission imaging is that each of radiopharmaceuticals has its own bio-distribution and dynamics of visual characteristics, so the rules of imaging areas of fixing radiopharmaceuticals and contouring of the tumor should be individual for each radiopharmaceutical [14]. Variability of results of determination of the target volume by PET imaging depends on various factors: technical (the dependence of image quality on characteristics of the detecting block of PET scanner, algorithm of visualization), pharmacological (adequately choosing the type of radiopharmaceutical and its activity in a particular clinical case), physiological (features of individual absorption of radiopharmaceutical, uncertainty time limits of studied processes, etc.). With all the unique capabilities of PET imaging there is a physical limit of spatial resolution of these images — about 4 mm in advanced PET systems. Imprecision of the contours of damaged areas, identified on PET images, makes it impossible to make an objective visual estimation of target volume. Only color coding of PET image and its fusion with the appropriate CT scan enables simultaneously compensate deficiencies of PET imaging and limitations of CT in determining the real limits of tumor proliferation. The use of PET imaging in practice gives rise to many questions: how to determine the required PET target volume for DRTP, who can mark the contours of PET target volume: radiologist-oncologist or a physician of nuclear medicine? The experience of radiologists is proved that the use of emission tomography is indisputably an important factor in improvement of radiotherapy. However, experts not in vain called this method is «Pandora's Box»: it is important to achieve a correct interpretation of the obtained information and apply it for the benefit to the aim pursued — improving the quality of DRTP [15].

Method of *magnetic resonance imaging* (MRI) is indispensable for planning radiation treatment of tumors in soft tissues because in such cases CT imaging is uninformative due to small tissue contrast. The rich palette of MRI imaging modes allows you to select the best conditions for imaging of tumor, contours of which are detected due to the difference of nuclear magnetic resonance signals from tumors compared to normal surrounding tissues. MRI visualization of brain structures (fig. 11), chest, abdomen and pelvis in many cases is more informative for determine the PTV, than the corresponding CT images [16].

However, MRI technology has particular warnings to be taken into account when it used for DRTP. Necessary that when laying the patient on MRI in radiotherapy position used immobilization devices did not prevent properly positioning RF coil (fig. 12, 13). On MRI images with a large field of view the geometric distortions can be formed due to the nonli-

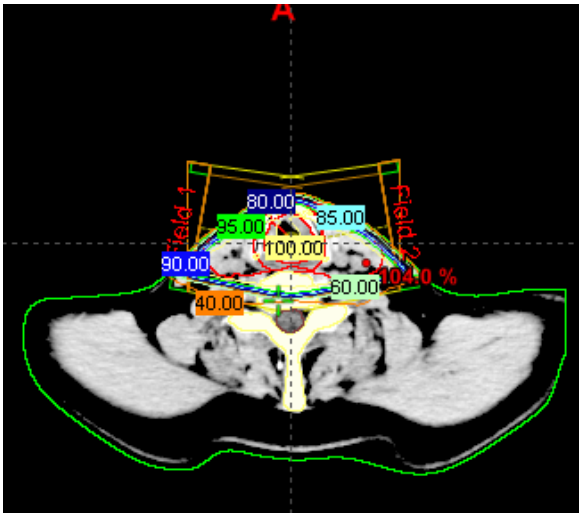


Fig. 4. CT-scan with chart of isodoses

Fig. 5. Voxel CT-anatomical model

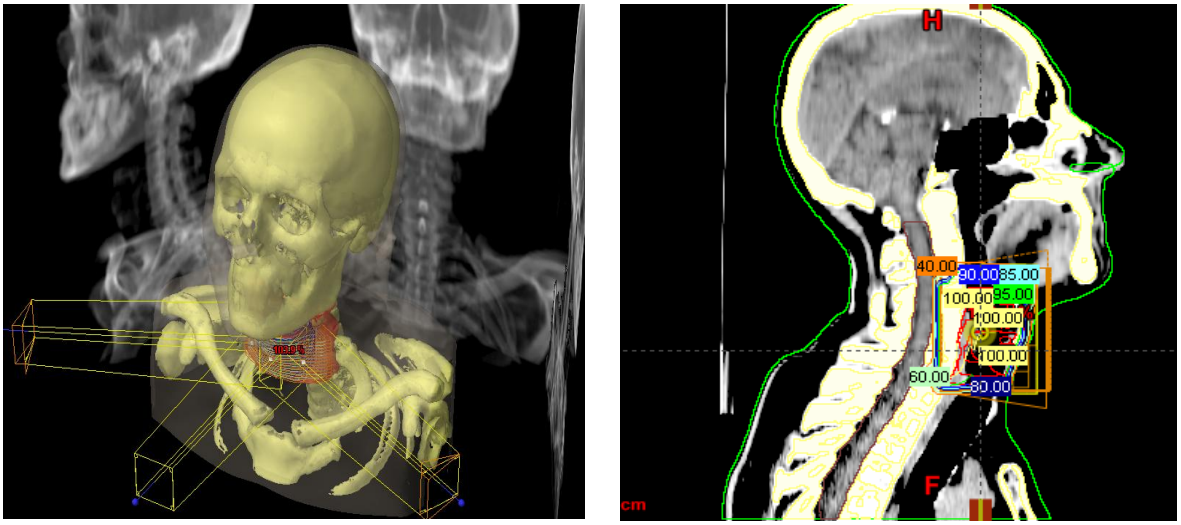


Fig. 6. Simulation of 3D dose distribution and synthesis of additional CT-anatomical projections

Fig. 7. Multileaf collimator (MLC)

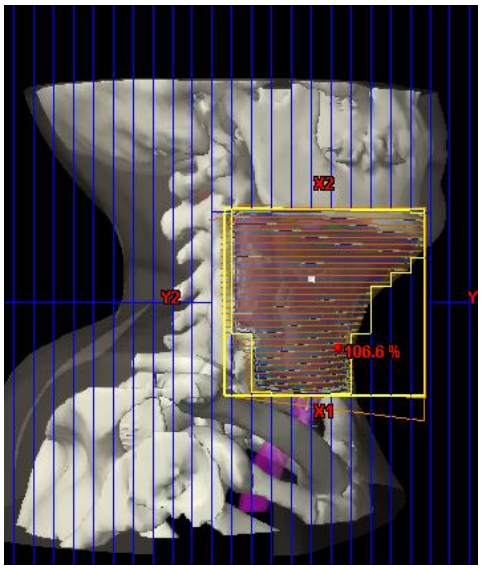


Fig. 8. Programmed positioning of MLC plates according to the target contour

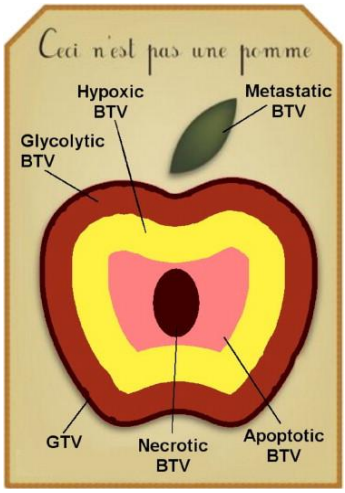
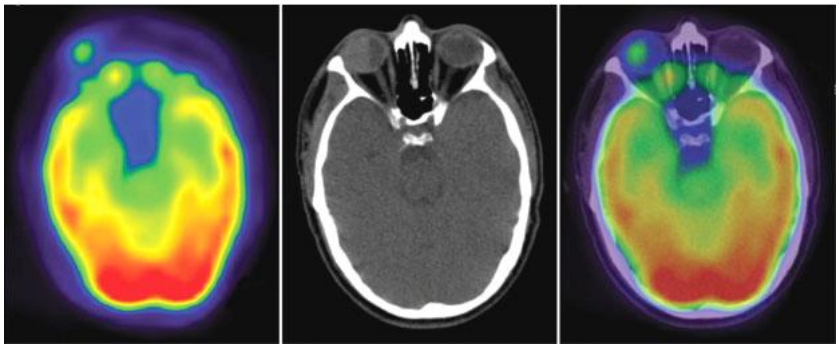


Fig. 9. R. Magritte. BTV mosaic



PET CT PET/CT

Fig. 10. Tomografical visualization of choroidal melanoma [9]. Focus of hypermetabolic activity in the intraocular tumour

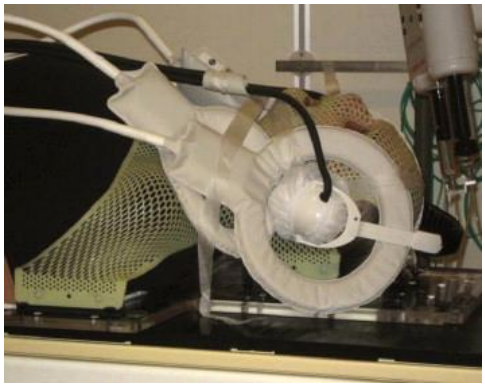
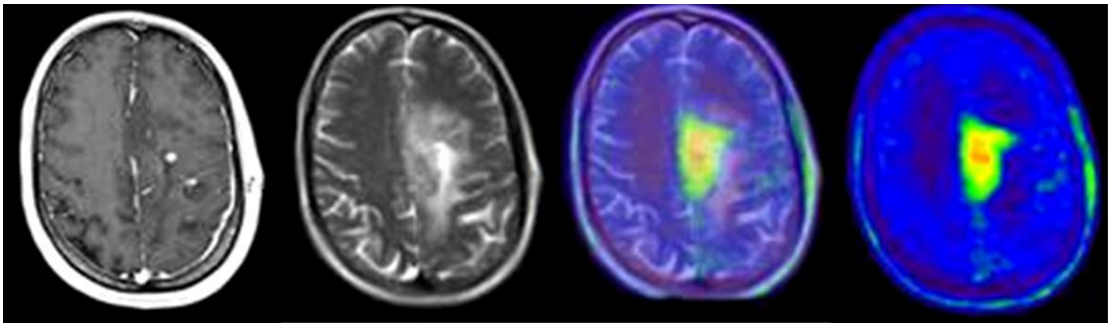
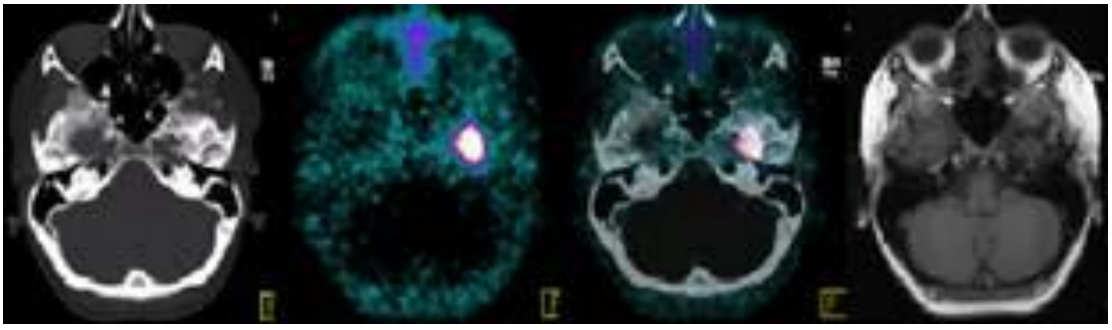


Fig. 12. Head coil for MRI, attached to a radiotherapy fixation mask [19]

Fig. 13. MRI Head Coil for DRTP (http://www.hellotrade.com/magmedix)



1 MRI T1 MRI T2 PET/MRI PET



2 CT PET CT/PET MRI

Fig. 15. The results of tumor detection on CT/PET/MRI-scans (http://www.vivantes.de)

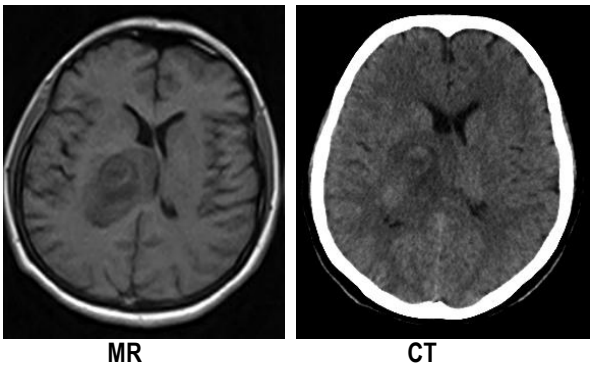


Fig. 11. Brain astrocytoma on MRI and CT-scans [16]

nearity changes the gradients of magnetic field. Unlike CT, MRI studies are lengthy procedure in which it impossible to avoid motion artifacts on MR scans that affect the accuracy of the GTV determining. In radiotherapy MRI mainly used as a duplicate method for anatomical imaging of tumors. But now actively explored the possibility of using MRI instead of CT for DRTP [16]. It is important to remember that there is no match between the intensity of MR signals from protons in tissues and the values of the electron density of the same tissues on CT images. In [17] made an attempt to modify MR images with replacement values of its intensity on CT numbers using the standard data on the density of the tissues [18]. It is proved that this modified MR image can be successfully used instead of CT without losing accuracy of calculation of doses. This avoids excessive radiation load on the patient, systematic errors due to fusion of MR and CT images and reduces the costs for additional CT study. In [19] pointed out that the best option in determining the GTV for DRT of prostate is a fusion of CT and MR images made in radiotherapy position of patient. Are studied the possibilities of use functional MRI (fMRI) with contrast enhancement to estimate radiosensitivity of tumor and identify areas that need more intensive irradiation [20].

Discussion features of applying hybrid tomographic images in DRT

The performed review of modern approaches to determining tumor volume shows that the use of hybrid multi-modal imaging technologies for DRTP doesn't give unequivocal results and requires thorough study [21]. The results of an experiment to determine the GTV using various combinations of tomograms are shown in fig. 14. The results show that in determining the GTV of studied tumor the growth of target volume through the use of PET was low. The added volume through the use of MRI is significantly influenced the result of a common definition of GTV. One can predict that degree of influence each method of tomographic imaging on the result of determining GTV will vary depending on the histopathological type of tumor and clinical estimation the pathological process.

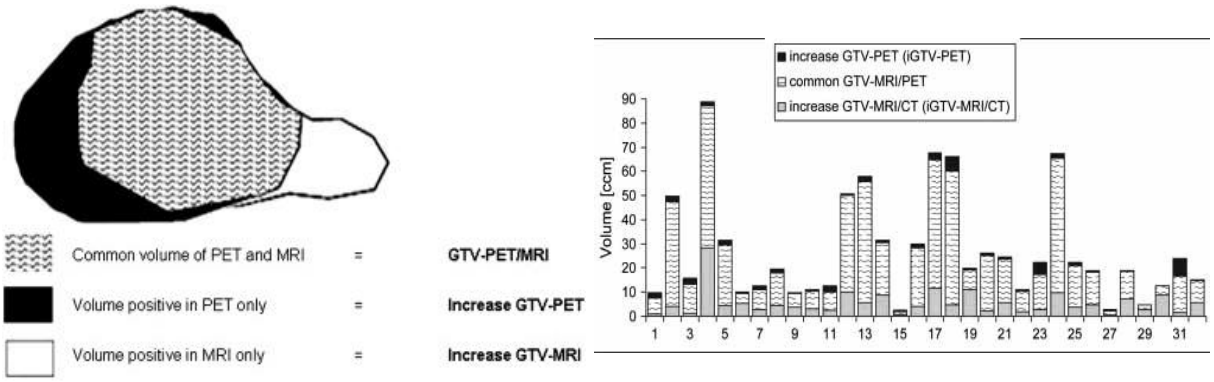


Fig. 14. Illustration of the definition of increase GTV-MRI and GTV-PET [21]

Let's consider specific examples of hybrid tomographic imaging to determine the GTV (Vivantes International Medicine group, http://www. vivantes.de).

Fig. 15-1 shows the results of topological evaluation of tomograms in different modalities when preparing for stereotactic radiotherapy (recurrence of malignant brain tumor). Researches: MRI (T1-weighted with contrast and T2-weighted) and PET tracer F18-FET (tyrosine). Combined PET/MRI images enable to determine the contour of the tumor and separate the areas of necrosis from tumor growth zones. Fig.15-2 shows the results of imaging PET/CT with tracer Ga68-DOTATATE, which showed recurrence of meningioma with in-

filtration of the bones of the skull base. The tumor is visualized on PET due to the presence of somatostatin receptors and is not determined by MRI.

CONCLUSIONS

The analysis of the opportunities offered by modern technology of topographical imaging in DRTP showed that each one can visualize a predominant property of the tumor, depending on its histopathological variant. Thus, in determining the GTV radiologists should analyze what imaging modality is the most informative for a particular case. Often when planning DRT anatomical CT images are used, but protocol of CT scanning should be coordinated with the technology of planning and realization of radiation treatment. MRI method demonstrates indisputable advantages of anatomical imaging for tumors of brain, chest, abdomen and pelvis in determining the GTV. In perspective can be used the functional MRI imaging to clarify the boundaries of tumor. However, significant duration of MRI study, technical complexity, limited patient positioning and lack of accurate coordinate binding between patient, scanner, simulator and accelerator restrains use of MRI as a basic anatomical imaging modality of the target. The use of PET imaging in some cases allows very accurately differentiate tumor boundaries, but physician must decide exactly which variant of PET image fully corresponds to the nature of the tumor and can be considered as suitable for clarify the boundaries of GTV. Taking into account economical factors and technological features, the most available and necessary in the planning of radiation treatment are technologies of CT and MRI. Actual task for the future is to develop protocols of multi-modal tomographic imaging and topometrical estimation of hybrid images for planning DRT considering histopathological variants of tumors and their morphological and functional features.

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ORTHOSTATIC REACTIONS OF VENTRICULAR RATE IN MEDICAL CONTROL OF PERMANENT ATRIAL FIBRILLATION

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Article is devoted to studying the Significance of orthostatic reactions of ventricular rate (OR VR) in the clinical course of permanent atrial fibrillation (AF) to improve the effectiveness of its control. It was found that among patients with AF there are all 3 types of OR VR as during sinus rhythm, positive OR VR predominate over negative and absent. It was shown, that positive OR are favorable to reduce the severity of symptoms of AF, according to European Heart Rhythm Association (EHRA), less favorable — absent, and unfavorable — negative OR VR. It was established, that the control of AF with by beta adrenergic antagonists (BAA) is possible in any type of OR VR except qualified positive, combination of BAA and amiodarone — for BAA inefficiency, and control of AF with amiodarone is preferable in qualified positive and negative OR VR and when there are contraindications to BAA.

KEY WORDS: atrial fibrillation, orthostatic reactions of ventricular rate, positive, negative, absent types of orthostatic reaction ventricular rate, antiarrhythmic therapy

ОРТОСТАТИЧНІ РЕАКЦІЇ ЧАСТОТИ ШЛУНОЧКОВИХ СКОРОЧЕНЬ ПРИ МЕДИКАМЕНТОЗНОМУ КОНТРОЛІ ПОСТІЙНОЇ ФІБРИЛЯЦІЇ ПЕРЕДСЕРДЬ

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Робота присвячена вивченню значення ортостатичних реакцій частоти шлуночкових скорочень (ОР ЧШС) в клінічному перебігу постійної фібриляції передсердь (ФП) з метою поліпшення ефективності її контролю. Встановлено, що у пацієнтів з ФП мають місце всі 3 типи ОР ЧШС як і при синусовому ритмі, позитивні ОР ЧШС переважають над негативними і відсутніми. Виявлено, що у контролі ФП сприятливими для зменшення тяжкості симптомів пов'язаних з ФП за шкалою EHRA є позитивні, менш сприятливими — відсутні, і несприятливими — негативні ОР ЧШС. Показано, що контроль ФП бета-адреноблокаторами БАБ можливий при будь-якому типі ОР ЧШС, за винятком кваліфікованого позитивного, а комбінацією БАБ і аміодарону при неефективності БАБ, контроль ФП аміодароном переважніше при кваліфікованих позитивних і негативних ОР ЧШС та наявності протипоказань до БАБ.

КЛЮЧОВІ СЛОВА: фібриляція передсердь, позитивний, негативний, відсутній тип ортостатичної реакції частоти шлуночкових скорочень

ОРТОСТАТИЧЕСКИЕ РЕАКЦИИ ЧАСТОТЫ ЖЕЛУДОЧКОВЫХ СОКРАЩЕНИЙ ПРИ МЕДИКАМЕНТОЗНОМ КОНТРОЛЕ ПОСТОЯННОЙ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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Работа посвящена изучению значения ортостатических реакций частоты желудочковых сокращений (ОР ЧЖС) в клиническом течении постоянной формы фибрилляции предсердий (ФП) с целью улучшения эффективности ее контроля. Установлено, что у пациентов с ФП имеют место все 3 типа ортостатических реакций частоты желудочковых сокращений как и при синусовом ритме, позитивные ОР ЧЖС преобладают над негативными и отсутствующими. Выявлено, что в контроле ФП благоприятным для уменьшения тяжести симптомов связанных с ФП по шкале Европейской ассоциации

сердечного ритма EHRA являются позитивные, менее благоприятными — отсутствующие, и неблагоприятными — негативные ОР ЧЖС. Показано, что контроль ФП бета-адреноблокаторами (БАБ) возможен при любом типе ОР ЧЖС, за исключением позитивного квалифицированного, а комбинацией БАБ и амиодарона при неэффективности БАБ, контроль ФП амиодароном предпочтительнее при квалифицированных позитивных и негативных ОР ЧЖС и наличии противопоказаний для БАБ.

КЛЮЧЕВЫЕ СЛОВА: фибрилляция предсердий, позитивный, негативный, отсутствующий тип ортостатической реакции частоты желудочковых сокращений

Atrial fibrillation (AF) is the most occurred chronicle ventricular rate irregularity which is found among 1–2 % of people in total population. AF morbidity growth annually and during following 50 years it may be reduplicated [1–9].

Irregular rhythm and high ventricular rate (VR) cause strengthening of heard symptoms connected with AF according to European Heart Rhythm Association (EHRA) scale which are the defining factors of the patients quality of life. Adequate VR control allows decreasing the symptoms and making the hemodynamic better preventing the development of tachicardiomiopathy [1, 2].

Antiarrhythmic therapy of the patients with AF is directed to the achievement of VR control and decrease of symptoms severity class connected with AF according to EHRA scale, but it also influences the autonomous regulation of cardio vascular activity, the objective criteria of which are orthostatic reactions (OR) of VR [10, 11]. The problem of antiarrhythmic preparations influence on OR of VR in patients with AF is not covered in the world scientific literature.

The study of OR of VR under control of permanent AF by beta adrenergic antagonists (BAA), amiodarone and their combination became the aim of the work.

The work is done in accordance with the main plan of SRW of V. N. Karazin Kharkov National University of the Ukrainian HCM «Elaboration and research of the automatic control system of heart rate variability» included into the coordination plan of priority directions of scientific research, approved by the Ministry of Education and Science of Ukraine (№ state registration 0109U000622).

MATERIALS AND METHODS

132 patients (60 men and 72 women) at the age of 55 ± 15 years old with permanent form of AF remoteness 6 ± 5 years were examined on the basis of cardiologic department of MTPE «Central clinical hospital Ukrzaliznytsya (Ukrainian Railway)» and Kharkov city policlinics № 6.

According to the classification of symptoms connected with AF EHRA I was found in 4 %, EHRA II — 18 % and EHRA III — 78 % of patients. Stable voltage angina of the I functional class (FC) (according to the classification of Canadian Cardiologists Association) was found in 35 %, II FC — in 65 % of patients, III FC — was absent. In 5 % of patients myocardial infarction was in the history card. In 16 % of patients I degree arterial hypertension (AH) was detected, in 35 % — II and in 49 % — III degree. The AH I stage was diagnosed in 13 %, II — in 77 % and III — in 10 % of patients. In 97 % of patients the symptoms of heart failure (HF) were found. According to the classification of Strazhesko N. D.–Vasilenko V. Ch. HF I was diagnosed in 30 %, II A — in 70 %, IIB and III stages were absent. According to NYHA classification in 11 % of patients HF of the I FC was found, in 58 % — HF of the II FC, in 31 % — HF of the III FC. 5 % of patients had violation of cerebral circulation. The patients with stable voltage angina of the IV FC, acute coronary syndrome, HF of the IV FC were not included into the investigation.

The comparison group consisted of 73 patients (43 men and 30 women) with sinus rhythm (SR) without AF in the history card of the same age category (55 ± 15 years) as the observation group. Stable voltage angina of the I FC was in 37 %, II FC — in 63 % of patients, III FC was absent. In 4 % of patients MI was in the history card. In 20 % of patients I degree AH was found, in 35 % — 2 and in 45 % — 3 degree. I stage AH was diagnosed in 15 %, II — in 75 % and III — in 10 % of patients. In 90 % of patients symptoms of HF were detected. According to the classification of Strazhesko N. D.–Vasilenko V. Ch. I stage HF was diagnosed in 35 %, II A — in 65 %, IIB and III stages were absent. According to NYHA classification in 15 % of patients I FC HF was detected, in 54 % — II FC HF, in 31 % — III FC HF. 7 % of patients had violation of cerebral circulation. The patients with stable voltage angina of the IV FC, acute coronary synd-

rome, HF of the IC FC were not included into the investigation.

OR of VR was estimated according to the data of its measurement on the 3rd minute of clinostasis after transformation into orthostasis. ECG was registered with the help of computer electrocardiograph «Cardiolab2000» in the II standard allotment fixing medium VR on the 3rd minute of clino- and orthostasis. VR changes in the range up to ± 5 % were classified as OR of VR absence, increase in 5 % and more — as positive, and decrease in 5 % and more — as OR of VR negative type. OR of VR increase or decrease in ≥ 15 % were classified as qualified type. The sample was done in the morning hours (from 9 to 12 a. m.) not earlier than in 2 hours after meals.

The AF symptoms severity class and ventricular rate (VR) control class were estimated in accordance with European Heart Rhythm Association recommendations [2].

The research was carried out in the morning hours. The day before the visit the patients did not drink coffee, strong tea or alcoholic beverage, limited physical activity 30 minutes before the examination.

For OR of VR role estimation 3 pharmacotherapeutic groups were derived for AF control efficacy: the group of BAA therapy (46 patients (35 %)), amiodarone therapy (44 patients (33 %)) and BAA and amiodarone combination therapy (42 patients (32 %)).

The patients were examined before the beginning of the therapy, in 2 weeks, 1, 6 months and 1 year after the beginning of the therapy. The AF therapy was based on the Working group on heart rhyme irregularity of the Cardiologists Association of Ukraine recommendations in 2010 [1]. All the patients received one of the antithrombotic preparations (vitamin K antagonist, acetylsalicylic acid (ASA), clopidogrel) or combination of ASA and clopidogrel.

VR control was carried out with the help of the following antiarrhythmic preparations and their combinations: BAA (bisoprolol in the dose 2,5–10 mg, metoprolol succinate in the dose 12,5–100 mg), amiodarone in the dose 100–200 mg a day. Minimal doses of BAA (bisoprolol in the dose 2,5–5 mg, metoprolol succinate in the dose 12,5–50 mg) and amiodarone in the dose 50–100 mg a day were used in the prescription of BAA and amiodarone combination.

Statistic procedures were executed with the help of the programs «Microsoft Excel 2010» and «Mathcad 14.0». The rate of the studied signs was indicated in percentage and average error of the percentage was calculated (Sp). Statistical estimation of the results was carried out with medium (M) and standard deviation (sd) estimation. The calculation of the parameters was done with the help of SPSS 15.0 for Windows. For estimation of samples similarity according to nominal signs the principle of statistical independence of two nominal signs according to the χ^2 criterion was used.

RESULTS AND DISCUSSION

In the studied population of the patients with AF all types of OR of VR were found before the beginning of the therapy. In 41 % of them positive took place, in 34 % — negative type and in 25 % OR of VR was absent. High frequency of qualified OR of VR occurrence was mentioned, both positive (27 %) and negative (40 %). In the comparison group in patients with SR positive type of OR was observed in 63 %, among which (58 %) were qualified, OR of VR was absent in 32 % and only 5 % comprised the negative type (fig. 1).

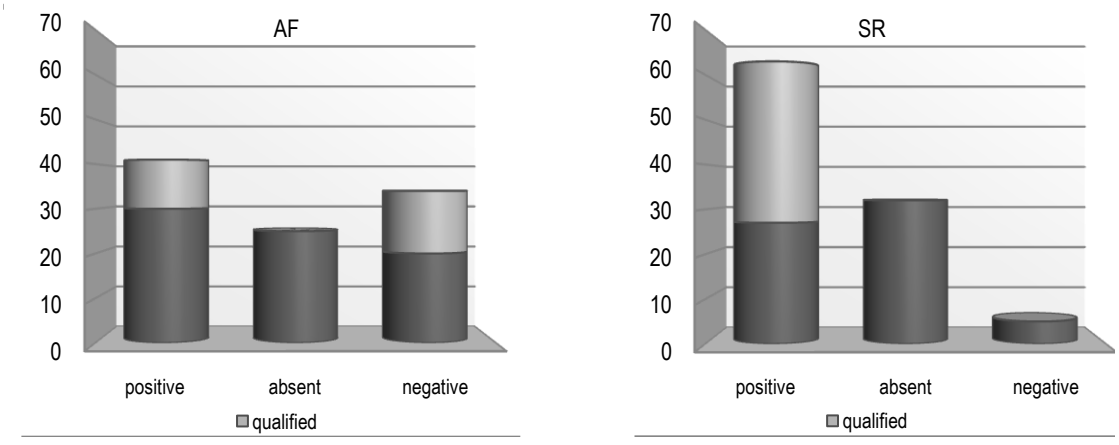

Fig. 1. Occurrence frequency of OR of VR (HR) various types in patients with AF and SR (%)

The received by us data about the occurrence frequency of OR of VR various types, symptoms of AF severity class according to EHRA scale and VR class before the beginning of pharmaceutical therapy in patients with AF are presented in table 1.

Table 1

Occurrence frequency of OR of VR various types (n (% ± Sp)) and clinical signs of AF before the beginning of the therapy

Data			Study groups								
			BAA			Amiodarone			BAA + Amiodarone		
Type of OR VR			positive	absent	negative	positive	absent	negative	positive	absent	negative
In all			19(41±7)	11(24±5)	16(35±7)	17(39±7)	12(27±7)	15(34±7)	18(43±8)	10(24±7)	14(33±7)
Grade of AF (EHRA)	I		4 ± 2	–	–	4,5 ± 2	–	–	5 ± 2	–	–
	II		9 ± 4	–	13 ± 5	11,5 ± 4	–	9 ± 4	14 ± 5	–	9 ± 4
	III		28 ± 6	24 ± 6	22 ± 6	23 ± 6	–	25 ± 6	24 ± 6	24 ± 6	24 ± 6
Type of VR control (at rest)	Strict (VR ≤80)		–	–	–	–	–	–	5 ± 3	–	–
	Lenient (VR ≤110)		13 ± 5	4 ± 3	5 ± 3	14 ± 5	4,5±3	22,5 ± 6	21 ± 6	7 ± 4	9 ± 4
	out of control	< 60	–	–	–	–	–	–	–	–	–
		> 110	28 ± 6	20 ± 6	30 ± 7	25 ± 6	22,5 ± 6	11,5 ± 5	17 ± 5	17 ± 5	24 ± 6

Before the beginning of the therapy in 41 % of patients positive OR of VR type was marked in the BAA therapy group, among which 18 % were qualified, 35 % — negative and 24 % — absent. 78 % (28 % with positive, 20 % with absent and 30 % with negative OR of VR type) had VR at rest > 110 bpm, 22 % of patients had VR in the range 80–110 bpm (13 % had positive, 5 % — negative and 4 % — absent OR of VR type).

In 74 % of patients the III class of symptoms severity connected with AF according to EHRA scale had place (28 % — positive, 22 % — negative and 24 % — absent OR of VR type), in 22 % — II (9 % had positive, 13 % — negative OR of VR type), in 4 % — I FC (all had positive OR of VR type).

Before the beginning of the therapy in amiodarone and BAA combination therapy group positive OR of VR type had place in 43 % of patients, among which 18 % were qualified, 33 % — negative and 24 % — absent. 44 % of patients had VR > 110 bpm (17 % — with positive and absent, 24 % — with negative OR of VR types), 37 % had VR in the range 80–110 bpm (21 % — with positive, 7 % — with absent and 9 % with negative OR of VR types), 5 % of patients had VR ≤ 80 bpm (all with positive OR of VR type). In 72 % of patients III class of symptoms severity connected with AF according to EHRA scale had place, 24 % — with positive, 24 % — with negative and 24 % — with absent OR of VR types, in 23 % — II class of symptoms severity connected with AF according to EHRA scale, in 14 % — with positive and 9 % — with negative OR of VR type, in 5 % — the I class of symptoms severity connected with AF according to EHRA scale only with positive OR of VR type.

Before the beginning of the therapy in the amiodarone therapy group positive OR of VR type had place in 39 % of patients, among which 18 % were qualified, 34 % — negative and 27 % — absent. 59 % of patients were on VR out of AF control of VR > 110 bpm (25 % — with positive, 22,5 % — with absent and 11,5 % — with negative OR of VR type), in 41 % of patients VR was in the range of 80–110 bpm before the beginning of the therapy (14 % — with positive, 22,5 % — with negative and 4,5 % — with absent OR of VR types). In 75 % of patients the III class of symptoms severity connected with AF according to EHRA scale had place, 23 % —with positive, 25 % — with negative and 27 % — with absent OR of VR types, in 20,5 % — II class of symptoms severity connected with AF according to EHRA scale in 11,5 % with positive and 9 % — negative OR of VR types, in 4,5 % — I class of symptoms severity connected with AF according to EHRA scale only with positive OR of VR type.

The data of the occurrence frequency of OR of VR various types according to EHRA scale and VR class in a year after the beginning of the therapy in patients with AF are presented in table 2.

Table 2

Occurrence frequency of OR of VR various types (n (% ± Sp)) and clinical signs of AF one year after the beginning of the therapy

Data			Study groups								
			BAA			Amiodarone			BAA + Amiodarone		
Type of OR VR			positive	absent	negative	positive	absent	negative	positive	absent	negative
In all			35(76±7)	7(15±5)	4(9±4)	18(41±7)	17(39±7)	9(20±6)	20(48±8)	18(43±8)	4(9±4)
Grade of AF (EHRA)	I		32 ± 7	4 ± 2	–	20 ± 6	5 ± 3	–	26 ± 6	24 ± 6	–
	II		44 ± 8	9 ± 4	7 ± 3	21 ± 6	24 ± 6	15 ± 4	22 ± 5	17 ± 5	4,5 ± 2
	III		–	2 ± 2	2 ± 2	–	10 ± 4	5 ± 2	–	2 ± 2	4,5 ± 2
Type of VR control (at rest)	Strict (VR ≤80)		18 ± 6	–	–	27 ± 7	21 ± 6	4,5 ± 3	31 ± 7	33,5 ± 7	4,5 ± 7
	Lenient (VR ≤ 110)		54 ± 7	15 ± 5	9 ± 4	14 ± 5	18 ± 6	15,5 ± 5	17 ± 5	9,5 ± 4	4,5 ± 3
	out of control	< 60	–	–	–	4,5 ± 3	–	–	–	–	–
		> 110	4 ± 3	–	–	–	–	–	–	–	–

During BAA therapy the increase of positive OR of VR frequencies was marked (from 41 % to 76 %) under simultaneous increase of qualified frequency (from 18 % to 35 %) at the expense of negative frequency decrease (from 35 % to 9 %) and absent (from 24 % to 15 %). During BAA therapy only in 8 % of patients VR tight control was achieved, moreover all of them had positive OR of VR type. The number of patients in the group of mild control comprised 78 % (54 % with positive, 15 % — with absent and 9 % — with negative OR of VR type). Part of the patients with VR > 110 bpm decreased from 78 % to 4 % (all had positive OR of VR type). During the therapy (in 6 months from the beginning of the therapy) 13 % of patients moved to the group out of AF control with VR < 60 bpm, moreover all of them had negative OR of VR type, these changes were not crucial and after BAA dose correction all the patients moved to the group of mild VR control. Gradual redistribution of the patients was detected — from higher III class of symptoms severity connected with AF according to EHRA scale to II and I. During the therapy the number of patients from III class of symptoms severity connected with AF according to EHRA scale decreased from 74 % to 4 % (2 % had absent, 2 % — negative OR of VR type) at the expense of the increase II from 22 % to 60 % (44% had positive OR of VR type, 9 % — absent and 7 % — negative) and I from 4 % to 36 % the class of symptoms severity connected with AF according to EHRA scale (among which 32 % had positive, 4 % — absent OR of VR type). With the class of symptoms severity connected with AF decrease according to EHRA scale gradual increase of physiological OR of VR was marked.

The estimation of the significance of differences between the studied groups with OR of VR various types demonstrated that the change of VR control classes partition ($\chi^2_{кр}$ = = 64,435 > $\chi^2_{0,95}(2)$ = 5,99) and classes of symptoms severity connected with AF according to EHRA scale ($\chi^2_{кр}$ = 48,097 > $\chi^2_{0,95}(2)$ = 5,99) before BAA therapy beginning and in a year are statistically significant.

During amiodarine and BAA combination therapy the positive OR of VR frequency increased in 19 % (from 24 % to 43 %) at the expense of negative frequency (from 33 % to 9 %) decrease. The frequency of unfavorable qualified decreased to 0. During the therapy part of the patients in the group of tight control comprised 69 % (31 % with positive, 33,5 % with absent and 4,5 % with negative OR of VR types). The group of mild control comprised 21 % (17 % with positive, 9,5 % with absent and 4,5 % with negative OR of VR types), all OR of VR became unqualified. During the therapy part of the patients having VR > > 110 bmp, decreased from 44 % to 0 %, the patients having VR < 60 bmp in 6 months from the beginning of the therapy (12 % — all with negative OR of VR type) moved into the groups of tight and mild VR control after amiodarone and BAA dose correction. Part of the patients with the III class of symptoms severity connected with AF according to EHRA scale decreased from 72 % to 6,5 % (among which 2% had absent and 4,5 % — negative OR of VR type) at the expense of part II increase from 23 % to 43,5 % (22 % with positive,

17 % — with absent and 4,5 % — with negative PR of VR type) and I from 5 % to 50 % (26 % with positive and 24 % — with absent OR of VR type). Increase of nonqualified OR of VR frequency was simultaneous with this.

The estimation of the significance of differences between the studied groups with OR of VR various types demonstrated that the change of VR control classes partition ($\chi^2_{кр} = 43,09 > \chi^2_{0,95}(2) = 5,99$) and classes of symptoms severity connected with AF according to EHRA scale ($\chi^2_{кр} = 40,072 > \chi^2_{0,95}(2) = 5,99$) before amiodarone and BAA combination therapy beginning and in a year are statistically significant.

The frequency of positive OR of VR during amiodarone therapy did not practically change (39 % against 41 %), the decrease of negative frequency was marked in 14 % (from 34 % to 20 %) at the expense of the increase of absent frequency (from 27 % to 39 %). The frequency of unfavorable qualified both positive and negative decreased from 18 % and 37 % to 0. During the therapy part of the patients in the group of tight control comprised 52,5 % (27 % — positive, 4,5 % negative and 21 % — OR of VR absent types). The number of patients in the group of mild control comprised 47,5 % (14 % with positive, 18 % — absent and 15,5 % — negative OR of VR types), all of which became physiologically unqualified. During the therapy part of the patients with VR > 110 bpm decreased from 59 % to 0, the patients having VR < 60 bpm in 6 months from the beginning of the therapy (4,5 % — all with OR of VR negative type) moved to the group of mild VR control after amiodarone dose correction. During the therapy part of the patients with the III symptoms severity class connected with AF according to EHRA scale decreased from 75 % to 15 % (10 % — of the had OR of VR absent type and 5 % — negative) at the expense of the II part of the class of symptoms severity connected with AF according to EHRA scale from 20,5 % to 62 % and I class of symptoms severity connected with EHRA scale from 4,5 % to 23 %. Increase of nonqualified OR of VR frequency was simultaneous with this.

The estimation of the significance of differences between the studied groups with OR of VR various types demonstrated that the change of VR control classes ($\chi^2_{кр} = 56,934 > \chi^2_{0,95}(2) = 5,99$) and the class of symptoms severity connected with AF according to EHRA scale ($\chi^2_{кр} = 33,782 > \chi^2_{0,95}(2) = 5,99$) before the amiodarone therapy beginning and in a year are statistically significant.

OR of HR was studied mainly under sinus rhythm in healthy people and patients with various somatic pathology [12-15]. Our investigation demonstrated that under AF as well as under SR all types of OR of VR take place which proves the data [16] in accordance with which vegetative regulation of cardiac biomechanics is not absolutely lost under AF which allows to use orthostatic testing for AF clinical management study [17, 18]. Moreover the received data about OR of VR various types diffusion under AF generally corresponds, our investigation demonstrated that OR of VR positive type under AF is more diffused (41 %), negative is more rare (34 %) and absent is the rarest (25 %). It was found in our investigation that patients with AF 7 times more frequently demonstrate negative OR of VR in comparison with SR including the qualified which are connected with deep violations of vegetative heart regulation and associated with high risk of cardio vascular events development [19]. As for antiarrhythmic preparations influence on clinical course of AF and OR of VR various types frequency there were not any investigations covered in the world literature.

Our investigation demonstrated that antiarrhythmic preparation therapy of various groups influence differentially on OR of VR, VR control efficacy and symptoms severity connected with AF according to EHRA scale. BAA appeared more favorable with regard to OR of VR positive frequency increase, the usage of amiodarone promoted decrease of qualified OR of VR. As for symptoms severity class connected with AF according to EHRA scale combination of amiodarone and BAA appeared more effective as the result of the therapy of which we achieved the increase of patients partition with EHRA I class from 4 % to 50 % (more than half of which had OR of VR positive type). Amiodarone and BAA monotherapy led to the decrease of symptoms severity class connected with AF according to EHRA scale, though preferentially up to II. As for the VR under AF control class combination of amiodarone and BAA demonstrated the greatest distribution of the patients into tight control class as the result of the therapy of which the number of patients in this group comprised 69 %. The greatest number of the patients in VR flexible control group was observed under BAA therapy and comprised 78 % (fig. 2).

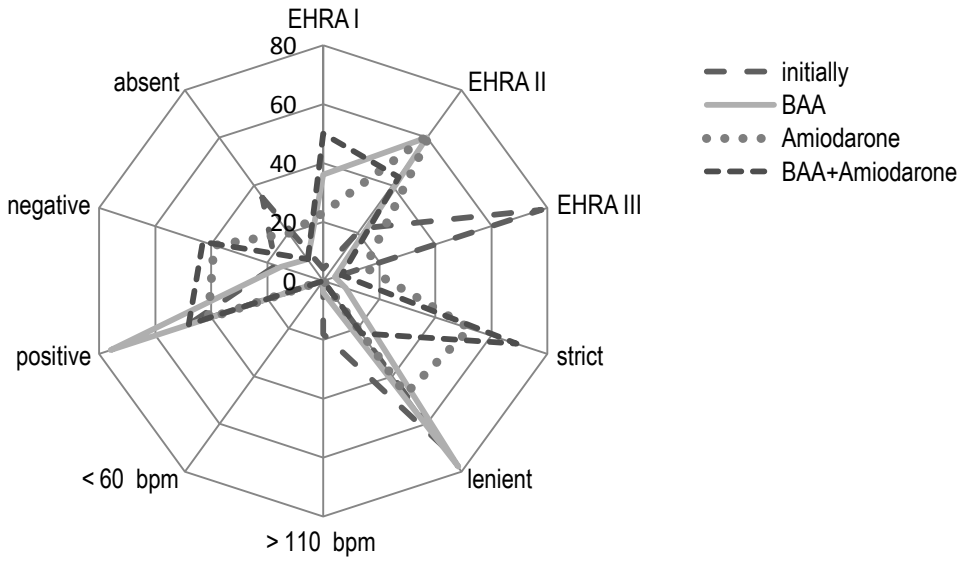

Fig. 2. OR of VR occurrence frequency, distribution of symptoms severity classes connected with AF according to EHRA scale initially and under a year's BAA, amiodarone therapy and their combination

CONCLUSIONS

1. In patients with atrial fibrillation positive (41 %), absent (25 %) and negative (34 %) types of orthostatic reactions of ventricular rate take place. Qualified positive orthostatic reactions of ventricular rate appear in 14 % and qualified negative — in 11 % of cases.

2. In control of atrial fibrillation more favorable for symptoms severity connected with atrial fibrillation decrease according to European Heart Rhythm Association scale are positive, less favorable — absent and unfavorable — negative orthostatic reactions of ventricular rate. It is necessary to tend to preserve initially positive and transfer to positive of others not allowing transfer to negative of orthostatic reactions of ventricular rate.

3. Atrial fibrillation control by beta adrenergic antagonists is possible under any type of orthostatic reactions of ventricular rate except positive qualified and combination of beta adrenergic antagonist and amiodarone under their inefficiency. Atrial fibrillation control by amiodarone is more preferable under qualified positive and negative orthostatic reactions of ventricular rate and presence of contra-indications to beta adrenergic antagonists.

4. Negative type of orthostatic reactions of ventricular rate needs the usage of beta adrenergic antagonists and amiodarone in minimal doses with careful monitoring of ventricular rate in connection with high risk of suppression < 60 bpm.

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Clinical case

UDC: 615.817:[616.12-008.3:616.126.4-089.87]

EXPERIENCE OF MANAGEMENT OF THE PATIENT WITH THE RESYNCHRONIZATION BIVENTRICULAR PACING WITHOUT DESTRUCTION OF ATRIO-VENTRICULAR NODE SUFFERING FROM CHRONIC HEART FAILURE AND PERMANENT ATRIAL FIBRILLATION

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The case of cardiac biventricular resynchronization without destruction of the atrio-ventricular node in patients with chronic heart failure (CHF) and permanent atrial fibrillation (AF) is described. The observation period was 14 months. The case demonstrates that biventricular resynchronization for severe heart failure with atrial fibrillation and significant atria size with theoretical and practical impossibility of its' transforming into the long-term persistent atrial fibrillation is a reasonable alternative of atrio-ventricular pacing. Though the destruction of the atrio-ventricular node can be delayed for a significant period of time, it should be done at the earliest opportunity. Pacemaker implantation does not cancel medical therapy, with the necessity for the latter to be according to the conducted biventricular pacing.

KEY WORDS: chronic heart failure, permanent pacing, atrio-ventricular ablation

ДОСВІД ВЕДЕННЯ ПАЦІЄНТА З РЕСИНХРОНІЗУЮЧОЮ ДВОШЛУНОЧКОВОЮ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ БЕЗ РУЙНУВАННЯ АТРІО-ВЕНТРИКУЛЯРНОГО З'ЄДНАННЯ З ПРИВОДУ ХРОНІЧНОЇ СЕРДЦЕВОЇ НЕДОСТАТНОСТІ ТА ПОСТІЙНОЮ ФОРМОЮ ФІБРИЛЯЦІЇ ПЕРЕДСЕРДЬ

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Наданий клінічний випадок ресинхронізуючої двошлуночкової електростимуляції без руйнування передсердно-шлуночкового вузла у пацієнта з хронічною серцевою недостатністю (ХСН) і постійною формою фібриляції передсердь (ФП). Термін спостереження 1 рік 2 місяці. Випадок демонструє, що ресинхронізує двошлуночкова електростимуляція при важкій ХСН з ФП і значних розмірах передсердь з теоретичної та практичної неможливістю переходу останньої в довгостроково персистируючу фібриляцію передсердь є обґрунтованою альтернативою передсердно-шлуночкової електростимуляції. Притому, що руйнування передсердно-шлуночкового вузла може бути відстрочено на тривалий проміжок часу, при найближчій можливості воно має бути виконано. Імплантація ЕКС не скасовує медикаментозної терапії, яка повинна знаходитись відповідно до проведеної двошлуночкової електростимуляції.

КЛЮЧОВІ СЛОВА: хронічна серцева недостатність, постійна електрокардіостимуляція, атріовентрикулярна абляція

ОПЫТ ВЕДЕНИЯ ПАЦИЕНТА С РЕСИНХРОНИЗИРУЮЩЕЙ ДВУХЖЕЛУДОЧКОВОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ БЕЗ РАЗРУШЕНИЯ АТРИО-ВЕНТРИКУЛЯРНОГО СОЕДИНЕНИЯ ПО ПОВОДУ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ И ПОСТОЯННОЙ ФОРМЫ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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Представлен клинический случай ресинхронизирующей двухжелудочковой электростимуляции без разрушения предсердно-желудочкового узла у пациента с хронической сердечной недостаточностью (ХСН) и постоянной формой фибрилляции предсердий (ФП). Срок наблюдения 1 год 2 месяца. Случай демонстрирует, что ресинхронизирующая двухжелудочковая электростимуляция при тяжелой ХСН с ФП и значительных размерах предсердий с теоретической и практической невозможностью перехода последней в длительно персистирующую фибрилляцию предсердий является обоснованной альтернативой предсердно-желудочковой электростимуляции. Притом, что разрушение предсердно-желудочкового узла может быть отсрочено на продолжительный промежуток времени, при ближайшей возможности оно должно быть выполнено. Имплантация ЭКС не отменяет медикаментозной терапии, которая должна находиться в соответствии с проводимой двухжелудочковой электростимуляцией.

КЛЮЧЕВЫЕ СЛОВА: хроническая сердечная недостаточность, постоянная электрокардиостимуляция, атрио-вентрикулярная абляция

Chronic heart failure (CHF) and permanent atrial fibrillation (AF) are common clinical syndromes in cardiology practice predetermining and burdening the development of each other [1–3].

Resynchronization therapy is an effective treatment for such patients, and can be done by setting pacemaker modes by atrio-ventricular (with the possibility of transition from permanent to long-persistent AF) or biventricular (permanent AF without the possibility of transition to long-term persistent) pacing with ablation of the atrio-ventricular node [4], followed by well-organized medication support [5, 6].

Destruction (ablation) of the AV node is a component of mandatory cardiac resynchronization therapy for these patients, providing a full replacement of biventricular pacing, together with a positive effect on the contractile function of the heart and health of the patient at a whole, as well as reducing the need for additional medical treatment. [7]

The patient is 75 years old, retired, villager; was hospitalized in the cardiac surgery department of SI IGES NASU for placing of cardioresynchronization device during the period of 25.11.2011–08.12.2011.

On admission, the patient complained for combined dyspnea, that appeared during mild exercise, and in the horizontal position, palpitation, weakness, and falling asleep dysfunction.

Exertional dyspnea (climbing the stairs to the second floor, walking about 500 m) came to be felt in 2000. The patient has neither been examined, nor treated for 7 years. The deterioration progressed: exercise tolerance decreased, dyspnea became noticeable during even mild exercise and in supine position. In January of 2008 patient have been admitted to the cardiac hospital for the first time, where he was diagnosed with ischemic heart disease (ICD): myocardial (unknown date) and atherosclerotic cardiosclerosis, permanent atrial fibrillation, eusistolic form. CHF II B, II FC (reduced systolic function of the left ventricular ejection fraction — 30 %). Since that time, the patient has been undergoing the hospital treatment every year.

In September 2011 there was a acute deterioration of overall condition with dyspnea during mild physical activity and activities of daily living disability appeared. Therefore, the patient was directed to SI IGES NASU for consultation, and later was hospitalized.

From the past medical history: since 1997 the patient is suffering from urolithiasis, chronic pyelonephritis, since 2003 — duodenal ulcer (DU), (in 2009 — acute gastrointestinal bleeding (AGIB) from duodenal ulcer). Allergic history is absent, tuberculosis and venereal diseases are actively denied.

On the admission to SI IGES NASU, patient's general condition is characterized as of

an average severity: clear conscience; pale skin color; peripheral edema on the feet; during auscultation — rough breath over the whole lungs surface with respiratory rate (RR) — 20 times/min; heart sounds are muffled at all points of auscultation and arrhythmic; systolic murmur at the apex; heart rate (HR) — 78 beats/min; pulse (Ps) — 68 beats/min; pulse deficiency — 10 beats/min; blood pressure (BP) — 110/70 mm Hg on the right arm, 126/70 mm Hg — on the left arm; borders of the relative cardiac dullness extended (right is in intercostal space III up to 1,5 cm outside from L.parasternalis dextra, upper — in intercostal space III on L. parasternalis sinister, left — in intercostal space V up to 1,5 cm laterally to L. clavicularis media.); soft and painless abdomen in all sections; liver is enlarged for 4 cm under the costal margin, firm consistency, painless; spleen is not palpable; Pasternatskiy syndrome is slightly positive on the both sides; normal stool and urine output.

Clinical blood analysis (CBA): hemoglobin (HGB) — 126 g/l, red blood cells count (RBC) — $4,0 \times 10^{12}$ / liter, color index — 0,9, white blood cells count (WBC) — $7,5 \times 10^{9}$/ l, stab leukocytes (SL) — 13 %, segmentonuclear leukocyte (SNL) — 72 %, eosinophils (EOS) — 4%, lymphocytes (LYM) — 9 %, monocytes (MONO) — 2 %, erythrocyte sedimentation rate (ESR) — 8 mm/h.

Clinical urine analysis (CUA): relative density — 1, 017, pH — 6.0, protein — 0,033 g/l, red blood cell — 2–4 on visual field (v/f), white blood cell — on all v/f.

Biochemical blood analysis (BBA): total protein — 74,4 g/L, total bilirubin — 23,4 mmol/L, conjugated bilirubin — 6,1 mmol/L, urea — 11,6 mg/day, creatinine — 0,122 umol/L, AST — 0,76 mmol/l × h, ALT — 0,77 mmol/ l × h, alkaline phosphatase — 7,1 mmol/l × h, glucose — 5,4 mmol/l.

Antibodies to viral hepatitis B, C: not found.

Coagulogram: clotting time — 11 min., recalcification time — 120 s, prothrombin index — 94,7 %, prothrombin ratio — 1,05, fibrinogen — 3,1 g/g

Chest fluoroscopy (CF): Lungs — without focal lesions. Roots are expanded, sinuses are free. Heart all chambers are increased, but left ventricle is the most. There are signs of mitral regurgitation, hearts sounds and myocardial contractility are significantly reduced.

Electrocardiogram (ECG): irregular rhythm, HR — 83 min., atrial fibrillation, complete left bundle branch block, QRS complex — 188 ms.

Ultrasound (US) of the heart: Aortic atherosclerosis. Fibrosis of the aortic and mitral valves. Dilatation of the cavities. Hypo- and akinesia of interventricular septum. Reduction of left ventricular contractile function (25 %). I degree aortic regurgitation. II degree mitral regurgitation. II degree tricuspid regurgitation.

Clinical diagnosis: Ischemic heart disease: myocardial (unknown date) and and atherosclerotic cardiosclerosis. Permanent atrial fibrillation, eusistolic form. EHRA II. CHF III, III FC (reduced left ventricular systolic function EF — 25 %).

Duodenal ulcer.

Urolithiasis. Chronic pyelonephritis

02.12.2011 — implantation of Medtronic Syncra CRT–P — for cardiac resynchronization therapy with the installation of right ventricular electrode in the interventricular septum (IVS) and left ventricular electrode — on the lateral wall of the left ventricle. The device provides interventricular and intraventricular resynchronization via mode VVDRV (trigger stimulation of the left ventricle (LV) in response to the detection of the right ventricle (RV) with a base frequency of 75 imp/min. Interventricular delay time — 10 ms.

After 2 days after operation the patient noted improvement in general condition: dyspnea reduced; exercise tolerance increased; skin returned to normal color, edema disappeared; rough breath is auscultated over the whole lungs surface with respiratory rate (RR) — 20 times/min; heart sounds are muffled at all points of auscultation; systolic murmur at the apex; HR — 76 beats/min; Ps — 73 times/min; pulse deficiency — 3. BP — 100/70 mm Hg on the right arm, 110/70 mm Hg — on the left arm; soft and painless abdomen in all departments; liver enlarged 4cm under the costal margin, of solid consistency, painless; spleen is not palpable; Pasternatskiy syndrome slightly positive on the both sides; normal stool, urine output.

ECG: pacemaker works on base frequency of ventricular pacing 75 imp/min, atrial fibrillation, QRS 152 ms.

US of the heart: the results before and during the observation stages after implantation of resynchronization device are presented in

Table 1. After installing the pacemaker, improvement is marked in myocardial contractility with a tendency to reduce the dilation of the cavities.

Table 1

Echocardiographic parameters before and during observation stages after implantation of resynchronization device

	28.11. 2011 before surgery	05.12. 2011 after surgery	24.01. 2013 follow-up visit	Normal value
ESV, cm	7,2	6,5	6,2	3,5–4,2
EDV, cm	8,1	7,8	7,5	3,7–5,5
LA, cm	5,2	4,9	4,9	0,95–2,05
RV, cm	3,8	3,6	3,6	1,85–3,3
RA, cm	6,2	6,0	4,6	3,8–4,6
EF, %	25	33	33	More than 55

The patient was discharged in a satisfactory condition with recommendations concerning work and rest, diet number 10, taking carvedilol 3,125 mg 2 times a day, acetylsalicylic acid 75 mg at night, spironolactone 100 mg in the morning, digoxin 0,25 mg 2 times a day, lisinopril 2,5 mg once in the morning, dispensary observation by cardiologist in the place of residence is recomonded.

In 14 months after the setting of pacemaker patient is in satisfactory condition: have a clear conscience, normal skin color, edema is absent; rough breath is auscultated over the whole lungs surface with RR — 20 min; heart sounds are muffled at all points of auscultation; heart rate — 75 beats/min; pulse — 75 times/ min; pulse deficiency — 0; BP — 110/70 mm Hg on the right arm, 120/70 mm Hg — on the left arm; border of the relative cardiac dullness (right — in intercostal space III up to 1,0 cm laterally from L.parasternalis dextra, upper — in intercostal space III on L. parasternalis sinister, left — intercostal space V up to 1,0 cm outwards from L.clavicularis media); soft, painless abdomen in all departments; liver is enlarged about 2 cm under the costal margin, of firm consistency, painless; spleen is not palpable; Pasternatskiy syndrome is slightly positive on the both sides; stool, urine output normal.

US of the heart: (Table 1) on the background on the continuing decrease in ejection fraction further dilatation of the cavities is observed.

The information obtained from cardiac resynchronization device showed a decrease in the frequency of stimulated ventricular complexes in September 2012, resulting from the ceasing of drugs intake on his pat (Table 2, Fig. 1). During that period, the patient' heart rate had a tendency to increase (Fig. 2). Return to drug therapy helped to return it to the original levels. These results explain the long-term effectiveness of cardiac resynchronization biventricular pacing without destroying the atrioventricular node.

Table 2

Drug therapy and total ventricular pacing (cumulative ventricular pacing, CumVP)

Month	February 2012	September 2012	January 2013
Cumulative ventricular pacing, CumVP	96	73	94
Drugs	Carvedilol Digoxin	None	Carvedilol Digoxin

Recommendations:
medical therapy, additional intake of statins, AB — ablation

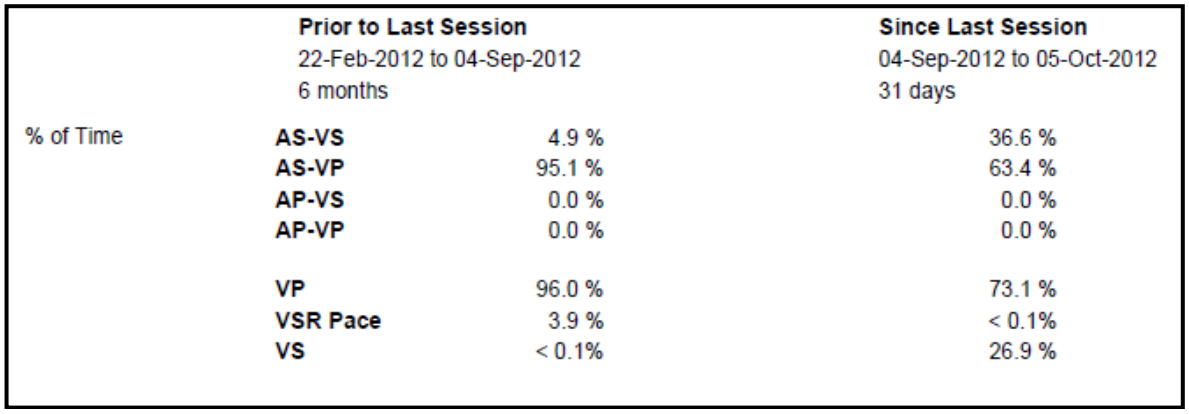

Fig. 1. Effectiveness of cardiac resynchronization therapy in the patient with and without drug therapy

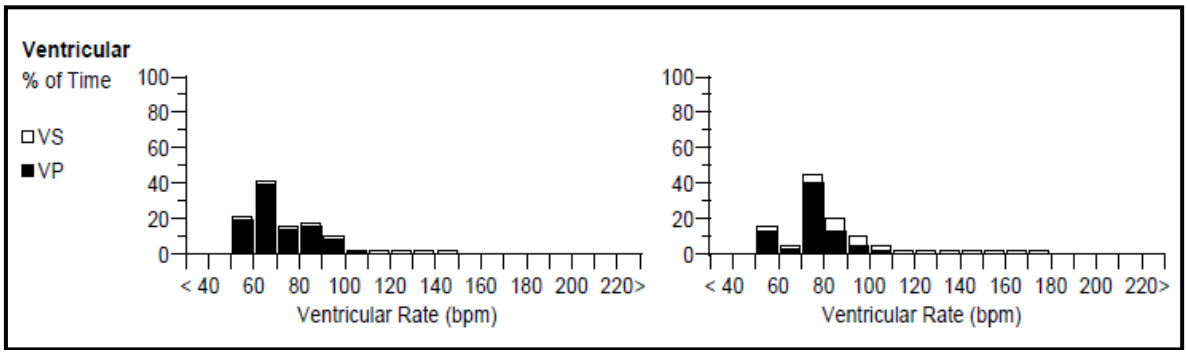

Fig. 2. Histograms of ventricular rate in patients with (left) and without (right) drug therapy

The clinical case illustrates the effectiveness of long-term biventricular pacing without destroying the atrio-ventricular node in the patient with severe heart failure and atrial fibrillation. The history of the disease makes it easy to understood that the results would have been much better if the surgery had been performed just after patient' first visit to the cardiology department (2008).

Biventricular pacing in patients with severe heart failure and atrial fibrillation with significant atrial size with theoretical and practical impossibility switch to a long persistent atrial fibrillation serves as a reasonable alternative to atrio-ventricular pacing.

Despite the fact that the destruction of the atrio-ventricular node can be delayed for a long period of time it should be done at the earliest opportunity.

Pacemaker implantation does not substitute medical therapy which should be in line with the biventricular pacing.

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Review

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COMPLICATIONS AND FACTORS OF REACTIVATION OF VZV-INFECTION IN CHILDREN AND ADULTS

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Data of our country and foreign data concerning complications of VZV-infection in children and adults are summarized in this article. The presented data confirm the urgency of VZV-infection complications in adults regarding its prevalence within able-bodied population and high possibility of lingering disability.

KEY WORDS: VZV-infection, varicella (chickenpox), herpes zoster (shingles), complications of VZV-infection

ХАРАКТЕР УСКЛАДНЕНЬ ТА ФАКТОРИ РЕАКТИВАЦІЇ VZV-ІНФЕКЦІЇ У ДІТЕЙ ТА ДОРОСЛИХ

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В статті підсумовані дані вітчизняної та закордонної літератури щодо характеру ускладнень у дітей та дорослих при VZV-інфекції. Наведені данні, підтверджуючі актуальність проблеми ускладнень VZV-інфекції у дорослих в зв'язку з високою частотою їх виникнення у працездатного населення та вірогідністю тривалої втрати працездатності та інвалідізації.

КЛЮЧОВІ СЛОВА: VZV-інфекція, вітряна віспа, оперізуючий лишай, ускладнення VZV-інфекції

ХАРАКТЕР ОСЛОЖНЕНИЙ И ФАКТОРЫ РЕАКТИВАЦИИ VZV-ИНФЕКЦИИ У ДЕТЕЙ И ВЗРОСЛЫХ

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В статье суммированы данные отечественной и зарубежной литературы о характере осложнений у детей и взрослых при VZV-инфекции. Приведены данные, подтверждающие актуальность проблемы осложнений VZV-инфекции у взрослых в связи с высокой частотой их возникновения у трудоспособного населения и вероятностью длительной утраты трудоспособности и инвалидизации.

КЛЮЧЕВЫЕ СЛОВА: VZV-инфекция, ветряная оспа, опоясывающий лишай, осложнения VZV-инфекции

The significant frequency of severe and complicated forms of varicella (chickenpox) is associated with high rate of disability among adults, especially within young ones, tells about the urgency of VZV-infection [1–3]. Nearly 150 000 cases of varicella within children population are registered annually in Ukraine [4]. The mortality rate of VZV-infection in children aged 1-14 years is 2 cases out of 100 000; at the same time its morbidity rate is less than common cold rate only [5, 6]. The morbidity rate among Ukrainian soldiers significantly exceeds the same rate in civil population [1]. The amount of patients with acute forms of VZV-infection that need specific therapy, have doubled during the last two decades; nearly 70 % out of them are older 60 years with appreciable prevalence of women [7, 8]. Annually 80–90 million cases are registered worldwide in accordance to the WHO information; 90–98 % of Earth population is infected by VZV [9]. The final conclusion says

that virus carrying may be met in 90 % of population, but the frequency of its clinical manifestation is significantly less and makes up 10–25 % [11].

More than 3 million cases of varicella are registered annually in the USA, 90 % out of them are children aged from 1 to 14 years; and more than 300 000 cases of herpes zoster are registered mainly within elderly [10, 14, 15]. Specific antibodies against VZV (varicella-zoster virus) can be found in 95 % of adults. These people are under the high risk of herpes zoster development [14]. The annual rate of mortality because of different varicella complications is 105 cases in the USA [16].

The typical biological features of all human herpesviruses, including VZV, are tissue tropism, lifelong persistence and latency in an infected human body [17, 20].

VZV is the type III herpesvirus of human Herpesvirus family. It is neuro- and dermatotropic and affects cells of central and peripheral neurological system. The virion is oval-shaped and 120–200 nm in size. The virus invades intravertebral ganglions and posterior spinal roots, and stays there for a long time in the latent stage of its lifecycle. In the contemporary classification 5 principal taxons of VZV are marked out [104]. Genotyping, epidemiologic evidence and mathematical simulation showed all-round distribution of different VZV genotypes [105–111].

VZV is a unique virus, it is able to develop two different human diseases: varicella (a.k.a. chickenpox) and herpes zoster (a.k.a. shingles).

The source of VZV-infection is a person that suffers from varicella, who is dangerous for others from 10^{th} day of incubation till 5^{th} day after the last rash elements appearance [21]. Sometimes people with herpes zoster can be the source of infection (until the vesicles drying up). The transmission of infection realizes through droplet pathway. It could not be excluded the intrauterine infection [21]. The susceptibility to the infection is total.

The source of herpes zoster is the person with herpes zoster or varicella. The disease is transmitted through droplet pathway and contagion. The placental transmission may not be denied [21]. There is no seasonal prevalence. The disease is mainly sporadic.

Complications of VZV-infection. The main problem of VZV-infection concerning able-bodied population is its complications followed by disability and lethal cases. From the economical point of view the cost of treatment of patients with postherpetic neuralgia (PHN) per se is a significant financial problem. For instance, in the UK the cost of PHN treatment reaches 18 million pounds per year. In the USA the only antiviral therapy costs nearly 1200 dollars for one patient [14]. In Germany the financial loss caused by varicella morbidity is 188 million euro, 82 % out of them (154 million) are payments for parents' disability, and remained 34 million are medical care costs, mainly for children older 12 years [22]. In Ukraine the cost of antiviral therapy has not been estimated yet.

For the current moment there are no exact recommendations regarding early diagnostic and treatment of VZV-infection, that is the one of cause of increased number of patients with PHN and other complications and gives a reason for detailed investigation of this not only «children's» infection [14].

Within the complications of VZV-infections the followed prevail over the rest: CNS alteration, pyoderma and pneumonia [4, 23]. Encephalitis after varicella makes up 90 % of all neural system injuries.

The literature data overview reveals 0,1–0,2 % frequency rate of neural system injuries; accounting this the frequency of acute cerebral ataxy is 1 per 4 000 cases [25]. In rare cases the ataxy develops before exanthema appearance, but more often from 5^{th} till 10^{th} days from the onset of rash.

The VZV-mediated injuries of neural system develop as encephalitis or encephalomyelitis mainly in children aged less 2 years [23, 28, 29]. The frequency of encephalitis is 1 case per 4 000. VZV-mediated encephalitis in immunocompromised patients has been described in plenty publications in recent years. Authors point that the number of VZV-mediated encephalitis cases meaningly rose in era of HIV/AIDS and other immunodeficiency states [31, 34].

The literature data of author's country says that activation of VZV-infection is followed by viral ganglionitis development with damage of spinal ganglia (including posterior roots) or ganglia of cranial nerves [14, 17, 39]. In severe cases the anterior and middle horns, white substance, and cerebrum are involved into pathological process, causing meningoencephalitis [13, 32, 33, 35, 36]. It was established that there is no dependence between the severity of varicella course, onset and course of neuro-

logical complications; the last ones may arise in the time of very severe as well as in the time of mild cases of infection [25].

The one of the widely-distributed complications of VZV-infection, mainly herpes zoster, is PHN that follows hemorrhagic necrosis and fibrosis of sensory spinal ganglia and is characterized by hard pain along nerves and leads to temporary or permanent disability [12, 13, 18, 19, 24, 26, 27].

The Ukrainian literature data point that 10–20 % patients with VZV become ill with PHN immediately after acute manifestation of herpes zoster. PHN develops in 60 % patients, 80 % out of them are people older 65 years [41]. The risk of PHN development in old patients may reach 50 % [43]. In typical cases the pain in the injured nerve region becomes extinct during 2–3 months in 50 % of patients; during 1 year in 80 % of patients and it may last for years in 10–20 % of patients [8, 17, 25, 44].

The less frequent, but mentioned in the literature neurological complications in adults are ganglionitis of Gasser's ganglion, osteonecrosis and spontaneous falling out of teeth in the case of middle and inferior trigeminal nerve branches involvement into VZV-infection course; oculomotor nerve injury (III, VI and IV cranial nerves in accordance to the frequency of their alteration), Hunt's syndrome (in the case of geniculate ganglion and tympanichord injury followed by vestibular, trifacial, facial and sublingual nerves involvement), affection of jugular sympathetic ganglia, herpetic ganglionitis of bottom part of jugular and top part of thoracic and lumbosacral vertebral regions, myelitis with pyramidal paraparesis with sensory and sphincter disorders, granulomatous arteritis (encephalitis with great and minute vessels affection) (lethality rate is about 25 %), ventriculitis and meningitis, meningoencephalitis [14, 25, 26, 28, 37, 38, 40, 42, 46–48, 51, 53–56, 59, 93–95, 100]. The majority of neurological states during VZV reactivation are connected to single or multiple infarctions due to vasculopathy development because of virus replication in the walls of great and minute cerebral arteries [60]. From 7 to 31 % of ischemic strokes in children were evoked by acute form of VZV-vasculopathy, and 44 % of children suffered from periodic ischemic attacks following varicella [45, 49, 61–63]. In childhood 1 out of 15 000 cases of varicella are complicated by stroke.

Shingles is rarely complicated by acute inflammatory demyelinating radiculoneuropathy — Guillain-Barre syndrome [23, 25, 28, 51, 64]. This heterogenic immunologically mediated disease includes primary demyelinating and primary axonal variants. Autoantibodies against membrane components gangliosides GM2 play the main role in the disease development. VZV infection is associated with disseminated sclerosis development [98, 99].

It is known that VZV is able to affect autonomic ganglia causing visceral disfunction [7, 14, 17, 21, 48, 65]. Affection of urino-genital system caused by varicella is presented usually as cystitis and characterizes by vesicle rash on mucus, followed by hematuria and leucocyteuria as well as neurogenic urinary bladder with urinary retention. The urinary retention and constipation arise against the background of viral alteration of sacral nerves [66, 96].

Another complication VZV-infection is eye involvement which occurs provided a 1st branch of trigeminus involvement [13, 26, 30]. Without antiviral therapy 50 % of patients with VZV-infection develop ophthalmological complications (episcleritis, iridocyclitis, keratitis). In some cases glaucoma may emerge. Such lesions were registered in about 45 % of patients with shingles as reported E. P. Dekonenko et al. (1999).

Visceral complications of VZV-infection regarding some authors' data are the followed: pericarditis, myocarditis, endocarditis, fulminant hepatitis, splenic infarction, acute appendicitis [50, 52, 57, 58]. In addition to that hematological and vascular complications may occur: sickle-cell disease, purpura fulminans, disseminated intravascular clotting [67, 72, 74, 79, 85, 91, 92].

Along with neurological complications there were registered bacterial complications of VZV-infection, causative agent of which in most cases was *S. pyogenes* [4, 48, 97]. In accordance to examining of 119 patients in 1996 authors revealed the followed bacterial complications caused by S. pyogenes: pyoderma (26,0 %), pyoarthrosis (4,2 %), osteomyelitis (3,3 %), necrotizing fasciitis (2,5 %), orbital cellulitis (1,6 %), pneumonia (0,8 %).

Necrotic phlegmon caused by *S. aureus* was reported as VZV-infection complication [68]. Mikaeloff Y. et al. consider that nonsteroidal anti-inflammatory drugs and paracetamol increase a risk of skin bacterial infection development in patients with chickenpox, espe-

cially in children [103]. Retrospective assessment of 680 case reports of children (56,3 % out of them were boys and 43,7 % were girls) aged from 3 weeks till 19 years old (average age 6,2 ± 4,6 years) with varicella was led. The population involved into the study was treated since 2001 till 2011 in the hospital of children's infectious diseases department of O. Bogomoltsa National medical university [39]. The first place among complications of varicella took bacterial infection (12,1 % out of all patients and 49,1 % out of all complications). Among bacterial complications in all age groups till 15 years were found out the listed below diseases: pyoderma (25,7 %), pneumonia (23,2 %), stomatitis (23,2 %), skin abscess (12,2 %), acute gastroenteritis (7,3 %), bronchitis (2,4 %), purulent otitis media (2,4 %), mucousopurulent conjunctivitis (2,4 %), infection of urinary tracts (1,2 %).

Rarely the varicella is complicated by viral pneumonia, lethality of which may reach 10–30 % especially among adults with immunodeficiency and pregnant women [69, 70].

Factors of VZV reactivation. The state-of-the-art of infectious diseases and their complications development lies mainly in their immunopathogenesis, notably in relationship between macro- and microorganism, immunoreactivity decrease, features of microorganism, including their ability to hide from immune control by antigenic mimicry as well as modify human immune response [71].

Latent infection activates because of reduced immunological resistance connected to concomitant diseases, organ function impairment, immunosuppressive medications administration, old age [7, 14, 17]. In an age group 60–69 years morbidity of zoster makes up 6,9 out of 1 000; in an age group of people older 80 years it is already 10,9 out of 1 000 [73]. Other not less important risk factors are: belonging to the white race, psychological stress and physical trauma. In accordance to the assessment of patients from risk groups which were stressed (during the space flight) it is possible to develop inapparent infection followed by virus distribution with saliva [75]. Family predisposition is accounted as a risk factor of VZV reactivation too [76].

VZV reactivation followed by zoster development may be explained by cell-mediated immunity malfunction [77, 78].

VZV reactivation against the background of immunosuppression may lead to virus dissemination that can end lethally [10, 13, 17, 43, 80–84, 86, 87]. The most severe forms of zoster are observed in patients with leukemia, lymphogranulomatosis, malignant tumors, HIV infection and in people treated by corticosteroids and X-ray therapy [7, 14, 17, 21, 28, 43, 88].

VZV-infection reactivation can be observed in 25 % of patients with AIDS and may arise during any stage of this infection. It was established that HIV-positive people are 10 times more inclined to zoster development than seronegative patients independently from their social and financial status and sexual behavior [14, 43]. Some authors reported that people who suffered from varicella during 1st year of life are more susceptible to zoster development at the age after 60 years.

Prevention of VZV-infection. Vaccination is called to reduce the severity of complications and VZV-reactivation frequency. Cohort immunization against varicella was included into vaccination calendar in 1997 in the USA. Children are vaccinated at the age of 12–18 months with followed booster dose at 12 years of age. Administration of attenuated vaccine against VZV in the USA favoured decrease of morbidity rate 76–87 % down in the period from 1995 till 2000 years and led to lethality rate reduction from 50–100 to 10 cases annually [89, 90].

The European branch of WHO recommends by all means vaccinating selectively patients with leukaemia during remission and patients from transplantation waiting list which do not have varicella in their history.

The Ukrainian national calendar of vaccination is regulated by Ukrainian Health Department instruction of prophylactic vaccination (Instruction № 48 from 03.02.2006). The vaccination against VZV was included as recommended manipulation for healthy children older than 15 months old; for children before entrance the school and for health workers which are under the high risk to be infected and which do not have varicella in their history. The data exist which show the absence of efficacy of human immunoglobulin administration for varicella prevention without previous assessment of specific antibodies rate [89].

Hereby the urgency of immune reactivity problem during VZV-infection is obvious that is confirmed by worldwide tendency of active immunization against VZV infection and consequently its complications development prevention in adults and children.

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