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QTc INTERVAL DURATION CLASS AND DRUG THERAPY OF PATIENCE IN A FIRST YEAR AFTER PACEMAKER IMPLANTATION

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49 patients (28 female, 21 male) with implanted DDD/DDDR, VVI/VVIR and CRT pacemakers are investigated. Purpose frequency and dose rate of anticoagulants, antiplatelet agents, direct thrombin inhibitors, cardiac glycosides, amiodarone; ivabradine, diuretics, aldosterone antagonists, beta-adrenergic blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), statins were evaluated before, in acute postoperative period (3–5 days), 6 months and 1 year after pacemaker implantation. Patients were divided into classes 1 (normal QTc (320–440 ms)) – 24 (49 %) patients) and 2 (long QTc (> 440 msec)) – 25 (51 %) patients) of QTc interval duration. To process the data using standard statistical procedures using Microsoft Excel. It was more often prescriptions of new anticoagulants, beta-adrenergic blockers, ARBs, statins to patients in the first year after pacemaker implantation. QTc interval duration lengthening was associated with a greater purpose frequency and doses of amiodarone, diuretics, beta-adrenergic blockers, ACE inhibitors, ARBs and statins. Patients with implanted pacemaker need individualized drug therapy according to QTc interval duration, in particular, enhancing antiischemic, antihypertensive, antiarrhythmic therapy and therapy of chronic heart failure in patients with QTc interval duration lengthening.

KEY WORDS: pacemaker, drug therapy, QTc interval duration

КЛАС ТРИВАЛОСТІ ІНТЕРВАЛУ QTc ТА МЕДИКАМЕНТОЗНИЙ МЕНЕДЖМЕНТ ПАЦИЄНТІВ В ПЕРШИЙ РІК ПІСЛЯ ІМПЛАНТАЦІЇ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРУ

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Обстежено 49 пацієнтів (28 жінок, 21 чоловік) з імплантованими електрокардіостимуляторами (ЕКС) в режимах DDD/DDDR, VVI/VVIR і CRT. Оцінювали до, в гострому післяопераційному періоді (3–5 добу), через півроку і 1 рік після імплантації ЕКС частоту призначення і коефіцієнт дози антикоагулянтів, антиагрегантів, прямих інгібіторів тромбіну, серцевих глікозидів, аміодарону; івабрадину, діуретиків, антагоністів альдостерону, блокаторів бета-блокатори, антагоністів кальцію, інгібіторів ангіотензіперетворюючого ферменту (АПФ), блокаторів рецепторів ангіотензину II (БРА), статинів. Пацієнти були розділені на класи 1 (нормального QTc (320–440 мс)) – 24 (49 %) пацієнтів) та 2 (подовженого QTc (> 440 мс)) – 25 (51 %) пацієнтів) тривалості інтервалу QTc. Для обробки даних використовувалися стандартні статистичні процедури за допомогою Microsoft Excel. Пацієнтам в перший рік після імплантації ЕКС більш часто призначаються нові антикоагулянти, блокатори бета-блокатори, БРА, статини. Подовження тривалості інтервалу QTc асоціювалося з більшими частотою призначення і дозами аміодарону, сечогінних препаратів, блокаторів бета-блокатори, інгібітори АПФ, БРА і статинів. Пацієнти з імплантованими ЕКС потребують індивідуалізованого медикаментозного менеджменту з урахуванням тривалості інтервалу QTc, зокрема, посилення антиішемічної, антигіпертензивної, антиаритмічної терапії і терапії хронічної серцевої недостатності (ХСН) у пацієнтів зі збільшенням тривалості інтервалу QTc.

КЛЮЧОВІ СЛОВА: електрокардіостимулятор, медикаментозний менеджмент, тривалість інтервалу QTc

КЛАСС ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QTc И МЕДИКАМЕНТОЗНЫЙ МЕНЕДЖМЕНТ ПАЦИЕНТОВ В ПЕРВЫЙ ГОД ПОСЛЕ ИМПЛАНТАЦИИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРА

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Обследованы 49 пациентов (28 женщин, 21 мужчина) с имплантированными ЭКС в режимах DDD/DDDR, VVI/VVIR и CRT. Оценивали до, в остром послеоперационном периоде (3-5 сутки), через полгода и 1 год после имплантации ЭКС частоту назначения и коэффициент дозы антикоагулянтов, антиагрегантов, прямых ингибиторов тромбина, сердечных гликозидов, амиодарона; ивабрадина, диуретиков, антагонистов альдостерона, блокаторов бета-адренорецепторов, антагонистов кальция, ингибиторов ангиотензипревращающего фермента (АПФ), блокаторов рецепторов ангиотензина II (БРА), статинов. Пациенты были разделены на классы 1 (нормального QTc (320–440 мс)) – 24 (49 %) пациентов) и 2 (удлиненного QTc (> 440 мс)) – 25 (51 %) пациентов) продолжительности интервала QTc. Для обработки данных использовались стандартные статистические процедуры с помощью Microsoft Excel. Пациентам в первый год после имплантации ЭКС более часто назначаются новые антикоагулянты, блокаторы бета-адренорецепторов, БРА, статины. Удлинение продолжительности интервала QTc ассоциировалось с большими частотой назначения и дозами амиодарона, мочегонных препаратов, блокаторов бета-адренорецепторов, ингибиторов АПФ, БРА и статинов. Пациенты с имплантированными ЭКС нуждаются в индивидуализированном медикаментозном менеджменте с учетом продолжительности интервала QTc, в частности, усилении антиишемической, антигипертензивной, антиаритмической терапии и терапии хронической сердечной недостаточности (ХСН) у пациентов с увеличением продолжительности интервала QTc.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимулятор, медикаментозный менеджмент, продолжительность интервала QTc

INTRODUCTION

Cardiac pacing (CP) in different regimes is one of the leading therapies of bradyarrhythmias and chronic heart failure (CHF) [1]. Improving survival and quality of life of patients [1], it is almost always require the concomitant drug treatment as a pacemaker (PM) implantation previous diseases and conditions induced by the PM.

Currently, it is generally accepted the same approach drug therapy of patients with a spontaneous and stimulated rhythm [1–2], however, multi-center studies show that the use of different groups of drugs in patients with a permanent CP should have a number of features.

QTc interval duration lengthening is a poor prognostic indicator as for patients with spontaneous rhythm, as for patients with CP [3–4]. Despite this, especially drug therapy of patients with going of QTc interval duration beyond the normal physiological values after PM implantation has not yet been studied.

OBJECTIVE

The aim of the research is to evaluate drug therapy of patients in the first year after pacemaker implantation in QTc interval duration classes.

MATERIALS AND METHODS

49 patients aged 69 ± 10 ($M \pm sd$) (28 – female, 21 – male) were examined in the department of ultrasound and instrumental diagnostics with miniinvasive interventions of GI «Zaycev V. T. Institute of General and Urgent Surgery of NAMS of Ukraine», 10 among them have an atrial fibrillation (AF). All patients were implanted pacemaker from 2008 to 2014, pacing is carried out in regimes: DDD (10 patients), DDDR (13 patients), VVI (7 patients), VVIR (11 patients), CRT (8 patients).

Patients aged less than 40 years, presence of concomitant stable angina IV functional class (FC), chronic heart failure (CHF) IV FC and/or stage III, the stimulation of the right ventricle (RV) and/or left ventricular (LV) less than 50 % were excluded from the study.

Chronic ischemic heart disease (IHD) was observed in 31 (63 %) patients, including 9 patients – myocardial infarction. Arterial hypertension was observed in 37 (76 %) patients, AF – in 10 (20 %) patients, CHF – in 35 (71 %) patients.

Drug therapy was represented by the following groups of drugs: B01A A anticoagulants (warfarin); B01A C antiplatelet therapy (aspirin, clopidogrel); B01A E direct thrombin inhibitors (dabigatran etexilate), and V01A F direct factor Xa inhibitors (rivaroxaban) (new anticoagulants); C01A cardiac glycosides (digoxin); C01B D01 amiodarone; C01E B17 ivabradine; C03 diuretics (furosemide, torasemide, hydrochlorothiazide); S03D A aldosterone antagonist (spironolactone); C07A beta-adrenergetic blockers (carvedilol, metoprolol, bisoprolol, nebivolol); C08C A calcium channel antagonists (dihydropyridine derivatives – amlodipine, nifedipine and fenilalkilamin derivatives – verapamil); C09A angiotensin converting enzyme (ACE) inhibitors (enalapril, lisinopril, ramipril); C09C angiotensin II receptor blockers (ARBs) (losartan, candesartan); C01A A hydroxymethylglutaryl inhibitors (HMG) coenzyme A (CoA) (statins) (atorvastatin, simvastatin).

Dose coefficient for each group of drugs has been calculated as the average value among the ratios of each drug dose group versus middle therapeutically for this drug, taken as 1.0. It corresponds to the group of anticoagulants warfarin 5 mg; antiplatelet agents – 75 mg of aspirin and 75 mg clopidogrel; 75 mg of dabigatran etexilate and 5 mg rivaroxaban; in the group of cardiac glycosides – 0.00025 mg digoxin; 200 mg amiodarone; 10 mg ivabradine; in the group of diuretics – 40 mg furosemide, 5 mg torasemide, 12.5 mg hydrochlorothiazide, 2.5 mg indapamide; in the group of aldosterone antagonists – 50 mg spironolactone; in the group of beta-adrenergic blockers – 5 mg bisoprolol, 100 mg metoprolol, 12,5 mg carvedilol, 5 mg nebivolol, 5 mg betaxolol, 50 mg atenolol; in the group of calcium channel antagonists – amlodipine 10 mg, nifedipine 90 mg, verapamil 80 mg; in the group of ACE inhibitors – 10 mg enalapril, 10 mg of lisinopril, 5 mg ramipril, 10 mg fosinopril; group ARBs – 50 mg losartan, 8 mg candesartan; in the group of statins – 20 mg atorvastatin, 20 mg simvastatin, 10 mg rosuvastatin.

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: $QTc = QT/(RR \wedge 0,5)$. For patients with AF, QTc was calculated using the formula of Fermingem study for patients with atrial fibrillation: $QTc = QT + 0,154 \times (1000 - RR)$ [5], the measurement accuracy – 0.5 ms.

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 [6].

In class 1 of QTc interval duration 24 (49 %) patients were included, mean age 66 ± 10 years (men – 13, women – 11) and in class 2 – 25 (51 %) patients, mean age 69 ± 9 years (males – 8, female – 17). In the class 3 is not a single patient was registered. Frequency of prescribing groups and dose rate of each of the groups of drugs in relation to the middle therapeutically dose were evaluated before, in the acute postoperative period, after 6 months and 1 year after PM implantation in QTc interval duration classes.

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 $\chi 2$) 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

Before PM implantation it was the most commonly prescribed in the order of ACE inhibitors, antiplatelet agents, statins, beta-adrenergetic blockers, diuretics; and less likely: amiodarone, cardiac glycosides, calcium

channel blockers, aldosterone antagonists, new anticoagulants. In acute postoperative period after PM implantation frequency of appointment of beta-adrenergic blockers was increased, in the rest of drugs the frequency was not significantly changed. By 6 months, and 1 year frequency of appointments of anticoagulants, new anticoagulants, beta-adrenergic blockers, ARBs, statins were consistently increased; of digoxin - decreased; of other groups of drugs – there were no significant changes.

Frequency of appointments and dose ratio groups of drugs in patients in first year after PM implantation in QTc interval duration classes are shown in table.

Table

Frequency of appointments and dose ratio groups of drugs in patients in first year after PM implantation in QTc interval duration classes

Pharmacological drugs		QTc interval duration class							
		Class 1				Class 2			
		Before PM implantation	Acute postoperative period	After 6 months CP	After 6 months CP	Before PM implantation	Acute postoperative period	After 6 months CP	After 6 months CP
B01A A Anticoagulants	Percentage of patients (% ± p)	6 ± 6*	14 ± 9	14 ± 9	20 ± 10	10 ± 7*	18 ± 8	26 ± 9	29 ± 9
	Dose ratio (M ± sd)	1	1	1,1 ± 0,3	1,2 ± 0,4	1	1,5 ± 0,5	1,3 ± 0,7	1,5 ± 0,5
B01A C Antiplatelets	Percentage of patients (% ± p)	38 ± 9	37 ± 13	50 ± 13	56 ± 14	35 ± 11	37 ± 9	45 ± 11	67 ± 16*
	Dose ratio (M ± sd)	1	1	1 ± 0,06	1	1 ± 0,5	1	1	1 ± 0,2
C01A Cardiac glycosides	Percentage of patients (% ± p)	12 ± 10	9 ± 6	7 ± 7	12 ± 10	31 ± 9*,**	23 ± 9	9 ± 6	21 ± 7*,**
	Dose ratio (M ± sd)	1	1	1	1	1	1	1	1
C01B D01 Amiodarone	Percentage of patients (% ± p)	13 ± 11	14 ± 9	21 ± 11	18 ± 9	13 ± 10	18 ± 8	27 ± 9**	32 ± 11**
	Dose ratio (M ± sd)	1 ± 0,4	0,75 ± 0,25	1,2 ± 1,3**	1 ± 0,4	1,2 ± 0,5	1,75 ± 0,4*,**	1 ± 0,3	1,9 ± 0,5*,**
C01E B17 Ivabradin	Percentage of patients (% ± p)	-	-	-	-	-	7 ± 7	7 ± 7	7 ± 7
	Dose ratio (M ± sd)	-	-	-	-	-	1	1	1
C03 Diuretics	Percentage of patients (% ± p)	13 ± 10	14 ± 9	29 ± 12**	26 ± 11**	21 ± 10	23 ± 9	36 ± 10**	39 ± 11*,**
	Dose ratio (M ± sd)	1 ± 0,3	0,75 ± 0,25	1,5 ± 0,75	1,1 ± 0,6	1,2 ± 0,5	1,8 ± 1*	1,9 ± 1	2,1 ± 1*
C03D A Aldosteron antagonists	Percentage of patients (% ± p)	10 ± 5	9 ± 6	16 ± 6*	12 ± 4	8 ± 5	7 ± 7	18 ± 8*	31 ± 13*,**
	Dose ratio (M ± sd)	1 ± 0,4	0,8 ± 0,4	1,2 ± 0,5	1 ± 0,4	0,8 ± 0,3	0,75 ± 0,25	1,3 ± 0,4**	1,6 ± 0,5**

Continuation of the table

C07A Beta-adrenergetic blockers	Percentage of patients (% ± p)	12 ± 7	57 ± 13**	64 ± 13**	69 ± 14**	19 ± 11	45 ± 11	73 ± 10**	82 ± 11**
	Dose ratio (M ± sd)	0,7 ± 0,3	0,9 ± 0,3	1,1 ± 0,4	0,9 ± 0,3	0,8 ± 0,3	0,9 ± 0,3	1,1 ± 0,6	1,5 ± 0,8
C08C A Dihidropiridin calcium channel antagonists	Percentage of patients (% ± p)	11 ± 7	9 ± 6	21 ± 11*,**	17 ± 9*,**	8 ± 5	5 ± 4	9 ± 7	12 ± 6
	Dose ratio (M ± sd)	0,8 ± 0,2	0,5	0,7 ± 0,2	0,5	1 ± 0,3	1,25 ± 0,3	0,8 ± 0,3	1,1 ± 0,3
C08D A01 Fenilalkilamin calcium channel antagonists	Percentage of patients (% ± p)	-	8 ± 6	17 ± 10*,**	14 ± 8	-	5 ± 4	9 ± 7	11 ± 9
	Dose ratio (M ± sd)	-	1,1 ± 0,1	1	1	-	1	1,1 ± 0,7	1,2 ± 0,7
C09A ACE ingibitors	Percentage of patients (% ± p)	39 ± 12	36 ± 13	43 ± 13	40 ± 11	31 ± 8	27 ± 9	45 ± 10**	62 ± 9**
	Dose ratio (M ± sd)	1,2 ± 0,2	1	0,7 ± 0,3	0,8 ± 0,3	1,1 ± 0,4	1 ± 0,3	1,6 ± 0,4**	1,2 ± 0,3
C09C ARBs	Percentage of patients (% ± p)	9 ± 6	9 ± 6	14 ± 9	26 ± 14**	4 ± 5	14 ± 7**	18 ± 8**	21 ± 10**
	Dose ratio (M ± sd)	1	1	1	1,2 ± 0,4	1 ± 0,2	1,3 ± 0,4	1	1,3 ± 0,4
C01A A Statins	Percentage of patients (% ± p)	20 ± 10	21 ± 11	36 ± 13**	30 ± 11**	20 ± 11	18 ± 8	36 ± 10**	49 ± 14*,**
	Dose ratio (M ± sd)	0,6 ± 0,2	0,8 ± 0,2	0,8 ± 0,2	0,6 ± 0,2	0,7 ± 0,2	0,9 ± 0,2	0,9 ± 0,2	1,3 ± 0,3*,**

*Note: M-average value; sd - standard deviation; *p < 0.05 – between values in classes; **p < 0.05 – between values before, in the acute postoperative period, 6 months and 1 year CP.*

Frequency of appointment of anticoagulants, new anticoagulants and antiplatelet agents before and during acute postoperative period after PM implantation did not differ in QTc interval duration classes 1 and 2. By 6 months and 1 year, and it has increased in both classes without significant change drugs doses.

Frequency of digoxin prescription at baseline was greater in QTc interval duration class 2, successively decreasing to 6-month observation period in both classes. By the year it has increased in the class 2 and even more diminished in class 1. The dose of digoxin remained middle therapeutically at all stages of monitoring.

Destination frequency of amiodarone did not differ before and after PM implantation in classes 1 and 2. The dose increase in class 2 to 6 months and a year of observation.

Frequency of appointment and dose ratio of diuretics before PM implantation did not differ in QTc interval duration classes, at 6 months and 1 year consistently increased in both classes 1 and 2. Destination frequency and dose ratio of aldosterone antagonists has also increased to a year, but only in QTc interval duration class 2.

Initially, the same frequency of beta-adrenergic blockers destination, with PM implantation at observation stages consistently increased in both QTc interval duration classes, to a greater degree in the class 2. The dose of beta-adrenergic blockers increased 6 months after PM implantation only in QTc interval duration class 2.

Frequency of appointment of ACE inhibitors and ARBs did not differ before PM implantation in QTc interval duration classes. With implantation to 6 months it has increased

in the class 2 with increasing of ACE inhibitors doses.

Destination frequency of statins before and during acute postoperative period after PM implantation did not differ, however, increased after 6 months in both QTc interval duration classes. Increasing the dose of statins was observed only in the class 2 1 year after PM implantation.

Frequencies of destination and dose ratio of ivabradine, dihydropyridine and fenilalkilamin calcium channel antagonists were the same before and on the stages of follow-up after PM implantation in studied QTc interval duration classes.

We have shown an increase of appointment frequency of anticoagulants, new anticoagulants, beta-adrenergic blockers, ARBs in patients in the first year after PM implantation, that's corresponds to [7–8].

Lack of communication of frequency of appointment increasing for new antiplatelet agents and anticoagulants with QTc interval duration lengthening, shown by us, is consistent with [9] for patients with spontaneous rhythm.

Described in our study the relationship QTc interval duration lengthening and greater frequency of amiodarone destination corresponds to the data [10], diuretics – [11], selective blocker of beta-adrenergic receptors - [12–13] for patients with a spontaneous rhythm without CP. This relationship may be due to the fact of repolarization process violation with the QTc interval duration lengthening is one of the manifestations of myocardial dyssynchrony and, as a consequence, a greater risk of heart failure, and arrhythmias developing [14].

A larger increase in amiodarone, diuretics, and statins dose in patients with QTc interval duration lengthening had shown us, corresponds to the data [10] for patients without a PM. Relation of dose ratio of different groups cardiovascular drugs with QTc interval duration class in patients 1 year after PM implantation has not previously been studied.

CONCLUSIONS

1. Patients in first year after PM implantation more often were prescribed new anticoagulants, beta-adrenergetic blockers, ARBs, statins.
2. QTc interval duration lengthening is associated with a greater frequency of appointments and doses of amiodarone, diuretics, beta-adrenergic blockers, ACE inhibitors, ARBs and statins in patients in first year after PM implantation.
3. Patients with implanted PM need individualized drug management according to QTc interval duration, in particular, enhancing antiischemic, antihypertensive, antiarrhythmic therapy and therapy of CHF in patients with a QTc interval duration lengthening.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to examine the connection of QTc interval duration changes with the appointment frequency and dose ratio of cardiovascular drugs in period more than a year after PM implantation.

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THE ROLE OF A NEW BIOMARKER GROWTH DIFFERENTIATION FACTOR 15 IN PROGNOSIS OF PATIENTS WITH ACUTE CORONARY SYNDROME AND TYPE 2 DIABETES MELLITUS

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Numerous studies confirm worse results in diabetic patients with acute coronary syndrome (ACS) compared with non-diabetic patients. Different mechanisms underlie the adverse outcomes of ACS and diabetes mellitus. In this connection, a special place is occupied by the study of new biomarkers that reflect the complex pathogenic processes in these patients. Purpose: to investigate the role of the biomarker GDF 15 in prognosis of adverse outcomes in type 2 diabetes mellitus (DM2T) patients with ACS. Materials and methods: 73 patients with different forms of ACS were screened. Levels of biomarkers: GDF 15, N-terminal pro brain natriuretic peptide (NT-pro BNP) and C-reactive protein (C-RP) were determined. The follow up period was 1 year. Endpoint was defined as lethal outcome. Results: significant differences in GDF 15 level has been found, prognostic value of GDF 15 was estimated in patients with DM2T, using a ROC-analysis. Threshold level of GDF 15 has been determined as 3894 pg/ml, with sensitivity of 64 % and specificity of 75 %. Conclusion: Patients with ACS and DM2T more often had a history of different cardiovascular diseases and risk factors compared to patients without diabetes. GDF 15 level was significantly higher in patients with ACS who had history of DM2T.

KEY WORDS: biomarkers, GDF 15, diabetes mellitus, acute coronary syndrome, prognosis

РОЛЬ НОВОГО БІОМАРКЕРУ GROWTH DIFFERENTIATION FACTOR 15 У ПРОГНОЗІ ХВОРИХ НА ГОСТРИЙ КОРОНАРНИЙ СИНДРОМ ТА ЦУКРОВИЙ ДІАБЕТ ДРУГОГО ТИПУ

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Численні дослідження підтверджують гірші результати у хворих на цукровий діабет при гострому коронарному синдромі (ГКС) в порівнянні з пацієнтами без діабету. Різні механізми лежать в основі несприятливих наслідків ГКС на фоні цукрового діабету. У зв'язку з цим особливе місце займають дослідження нових біомаркерів, що відображають складні патогенетичні процеси у цих хворих. Мета роботи: вивчити роль нового біомаркери GDF 15 в прогнозуванні перебігу та результатів ОКС на тлі цукрового діабету 2-го типу (ЦД2Т). Матеріали і методи: обстежено 73 хворих з різними формами ГКС. Було визначено рівень біомаркерів: GDF 15, N-terminal pro brain natriuretic peptide (NT-pro BNP) та С-реактивний протеїн (С-РП). Період спостереження склав 1 рік. Кінцева крапка визначена як летальний вихід. Результати: з огляду на виявлені достовірні відмінності рівня GDF 15, була проведена спроба оцінити прогностичну цінність GDF 15 у хворих на ЦД2Т за допомогою ROC-аналізу. Граничним значенням був визначений рівень GDF 15 3894 пг/мл, з чутливістю 64 % і специфічністю 75 %. Висновки. Хворі з ГКС і ЦД2Т частіше мали в анамнезі різні серцево-судинні захворювання та фактори ризику в порівнянні з хворими без ЦД. Рівень GDF 15 був достовірно підвищений у групі хворих на ГКС, які мали в анамнезі ЦД2Т.

КЛЮЧОВІ СЛОВА: біомаркери, GDF 15, цукровий діабет, гострий коронарний синдром, прогноз

РОЛЬ НОВОГО БИОМАРКЕРА GROWTH DIFFERENTIATION FACTOR 15 В ОЦЕНКЕ ПРОГНОЗА У БОЛЬНЫХ ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ И САХАРНЫМ ДИАБЕТОМ ВТОРОГО ТИПА

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Многочисленные исследования подтверждают худшие результаты у больных сахарным диабетом при остром коронарном синдроме (ОКС) по сравнению с недиабетическими пациентами. Различные механизмы лежат в основе неблагоприятных исходов ОКС на фоне сахарного диабета. В связи с этим особое место занимают исследования новых биомаркеров, отражающих сложные патогенетические процессы у этих больных. Цель работы: изучить роль нового биомаркера GDF 15 в прогнозировании течения и исходов ОКС на фоне сахарного диабета 2-го типа (СД2Т). Материалы и методы: обследовано 73 пациента с различными формами ОКС. Был определен уровень биомаркера – GDF 15, N-terminal pro brain natriuretic peptide (NT-pro BNP) и С-реактивній протеин (С-РП). Наблюдательный период составил 1 год. Конечная точка определена как летальный исход. Результаты: учитывая выявленные достоверные отличия уровня GDF 15, была проделана попытка оценить прогностическую значимость ценность GDF 15 у больных СД2Т с помощью ROC-анализа. Пороговым значением был определен уровень GDF 15 3894 пг/мл, с чувствительностью 64 % и специфичности 75 %. Выводы. Больные с ОКС и СД2Т чаще имели в анамнезе различные сердечно-сосудистые заболевания и факторы риска по сравнению с больными без СД. Уровень GDF 15 был достоверно повышен в группе больных ОКС на фоне СД2Т.

КЛЮЧЕВЫЕ СЛОВА: биомаркеры, GDF 15, сахарный диабет, острый коронарный синдром, прогноз

INTRODUCTION

Diabetes mellitus (DM) is significant problem today. According to the WHO data, in 2014 9 % of world population over 18 years has DM. According to the International Diabetes Federation data (Atlas Diabetes, 6th Edition, 2013), number of people with diabetes is 382 million. By 2035 it will increase to 592 million patients.

Type 2 diabetes mellitus (DM2T) is the most common type. The disease is associated with cardiovascular pathology and it significantly impairs patients` survival. Furthermore, DM2T is frequent condition in patients with acute coronary syndrome (ACS). Various international registers have shown that people with DM2T make up 22–34 % of patients with ACS [1–2]. It is known that DM generally and DM2T particularly is closely related to overweight (abdominal obesity), that is confirmed by elevated levels of adipokines such as resistin, leptin, adiponectin, ghrelin [3].

The relationship between levels of Growth differentiation factor 15 (GDF 15) and DM2T is discussed in recent world researches. GDF 15 serum level was increased in women with obesity and DM2T, and it was correlated with body mass index (BMI), level of visceral fat, blood glucose level and C-reactive protein (CRP) [4].

Transforming growth factor β GDF 15 was originally introduced as a marker, that inhibits tumor necrosis factor-α (TNF-α) in Lipopolysaccharide-stimulated macrophages, and thus it was classified as macrophage-inhibitory cytokine-1 (MIC-1) [5].

Today it is known that GDF 15 is an independent predictor of total and cardiovascular mortality. GDF 15 is produced by cardiomyocytes, adipocytes, macrophages, endothelial cells and vascular myocytes, in normal conditions and under stress. But its role as a marker of concomitant pathology has been insufficiently studied.

OBJECTIVE

To investigate the role of the biomarker GDF 15 in prognosis of adverse outcomes in DM2T patients with ACS.

MATERIALS AND METHODS

In Government institution «L. T. Malaya Therapy national institute of the National Academy of Medical Science of Ukraine» 73 patients with different forms of ACS were examined, average age of the studied patients was $61,8 \pm 1,3$ years. Patients with hemodialysis, terminal liver failure, active cancer and also people who refused to sign the informed consent and to comply the study protocol were excluded.

According to the clinical picture, ECG changes and troponin I 18 patients had unstable angina (UA), 14 patients – non Q wave myocardial infarction (non-Q-MI), in 38 patients – Q wave myocardial infarction (Q-IM), 3 patients were excluded from the study because of diagnosis mismatch. As was listed in the medical history 11 patients had DM2T, 60 patients – hypertension, 36 patients – stable angina, 17 patients – myocardial infarction. Blood serum was taken from patients` vein on admission. All patients underwent standard protocol examination. For an acute heart failure diagnosis was used Killip-Kimball classify-cation. Additionally, biomarkers level GDF 15 and N-terminal pro brain natriuretic peptide (NT-pro BNP), C-reactive protein (C-RP) were identified.

Follow up period was 1 year. Endpoint was defined as lethal outcome. After 1 year (± 1 month) patients underwent the six minute walk test (6-MWT) in order to estimate functional class of heart failure according to the New York Heart Association classification. During follow up period 9 people have reached endpoint.

We have received and processed 95 % of information from patients that were included in the study. Statistical data manipulation was carried out using the program «Statistics» (version 10.0). Assessments of significant differences between paired random samples were evaluated by Student's t-test. Continuous variables are presented as M ± SD (SD – standard deviation, mean ± standard error of mean) or Me, depending on distribution type (parametric or non-parametric). Also, assessment of differences between the groups was performed using non-parametric statistics methods: chi-square test, Fisher's exact test. Receiver operating characteristic analysis (ROC-analysis) was used for comparative assessment of parameters influence, characteristic curves tracing was done. For comparison area under curve ratio was used. Considered parameters had a prognostic significance at the borderline of confidence interval area > 0.5 and $p < 0.05$. The larger the area is, the higher the accuracy of the model.

RESULTS AND DISCUSSION

Average glucose level of studied patients was 7,80 ± 0,5 mmol/l. Patients with Q-MI had average blood glucose level of 8.03 ± 0.72 mmol/L, with non-Q-MI – 7.30 ± 0.63 mmol/l, UA – 6,38 ± 0.52 mmol/l; there wasn't a significant difference in blood glucose level in these groups. 11 patients had established diagnosis DM2T on admission to the hospital, glucose level in this group was 9,66 ± 1,40 mmol/l, and differed significantly ($p < 0.05$) compared to the group without DM2T (7,03 ± 0,44 mmol/l).

Family history of coronary artery disease was more frequent in group with DM than group without diabetes (64 % and 49 %, respectively), the same was for patients with myocardial infarction – 36 % and 22 %, respectively.

In detailed assessment of parameters that have been identified during hospitalization in patients with DM2T and without in history, significant differences were identified in the level of high-density lipoproteins (HDL) ($p < 0.05$), C-RP ($p < 0.007$), GDF 15 ($p < 0.01$). There was no significant difference in level of NT-pro BNP. There was no significant difference of BMI parameters in both groups. Detailed characteristic of estimated parameters is presented in table 1.

Considering identified significant differences of GDF 15 level, an attempt has been done to evaluate prognostic value of GDF 15 in patients with DM2T. ROC-analysis was performed to determine threshold level of GDF 15 that allows us to identify DM2T patients with the most sensitivity and specificity. Threshold level of GDF 15 was determined as 3894 pg/ml, with sensitivity of 64 % and specificity of 75 % (95 % Confidence interval (CI) 0.49 – 0.88; Area under curve (AUC) 0.68). Unfortunately, relationship between GDF 15 and diabetes did not reach significant level of ($p = 0.06$), despite significant differences of biomarker in both groups (Fig. 1).

Table 1

Comparative characteristic of parameters in examined groups of patients (M ± sd)

Parameters	n	Without DM2T	N	DM2T	p
Age, years	58	62,17±1,38	11	66,27±2,71	0,2
SBP, mmHg	58	147,9±3,9	11	155,0±7,8	0,46
DBP, mmHg	58	88,34±1,91	11	88,27±3,55	0,98
HR, beats per 1 minute	58	80,05±2,86	11	83,18±8,89	0,68
Creatinine, μmol/l	56	116,5±6,9	11	113,9±13,8	0,87
Cholesterol, mmol/l	55	6,78±1,73	10	4,35±0,47	0,55
HDL, mol/l	55	1,327±0,049	10	1,057±0,081	0,028
Triglycerides, mmol/l	55	1,299±0,089	10	1,223±0,135	0,73
LDL, mmol/l	55	3,16±0,14	10	2,74±0,41	0,27
GDF 15, pg/ml	58	3 565±456	11	7 468±2 073	0,0058
C-RP	34	7,27±1,06	6	20,00±8,96	0,007
Blood glucose, mmol/l	55	7,03±0,44	11	9,66±1,40	0,025
NT-pro BNP, pg/ml	38	825.8±175.9	9	706.5±397.1	0.77

Note: SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – Heart rate, HDL – high-density lipoproteins, LDL – Low density lipoproteins.

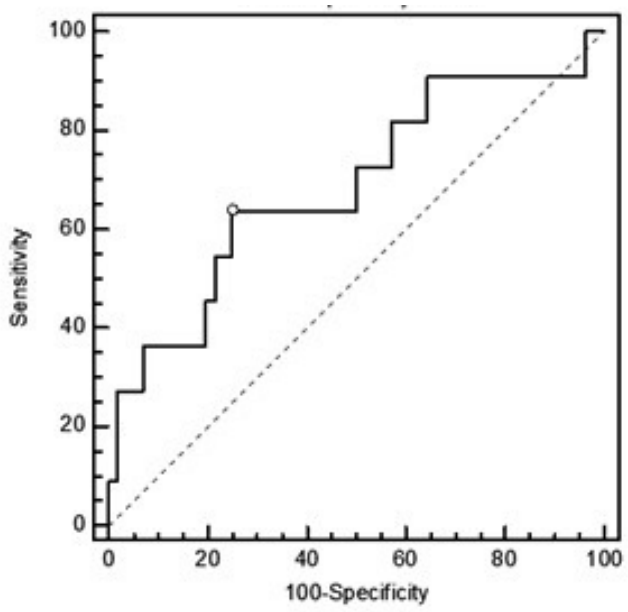

Fig. 1. ROC-curve values GDF 15 from DM2T in patients with ACS history

A significant relationship was identified ($p \leq 0.0001$, sensitivity of 72 % and specificity of 73 %) between GDF 15 biomarker and narcotic drugs prescription frequency in hospital period (95 % CI 0.19 to 0.59; AUC 0.738, level of > 2508 pg/ml) (Fig. 2).

More detailed information about treatment in both groups at the hospital stage, is presented in table 2.

A relationship between the presence of diabetes mellitus and 6-MWT that was conducted one year after coronary events ($p < 0.05$) was found. Significant association was not identified in assessing the relationship between DM2T and class of heart failure by Killip-Kimball. Conversely, elevated level of GDF 15 marker significantly depends on class of heart failure by Killip-Kimball (95 % CI 0.57 – 0.86; AUC 0,714, significant level > 2910 pg/ml), with sensitivity of 80 % and specificity of 65 % ($p \leq 0.005$) (Fig. 3).

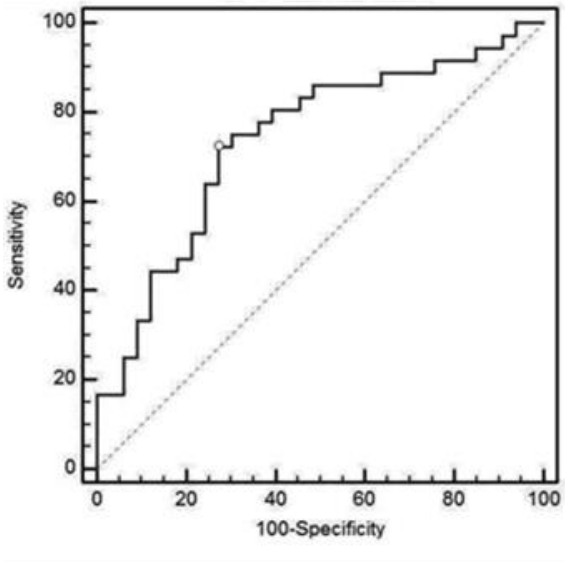

Fig. 2. ROC-curve of GDF 15 and narcotic drugs prescription during hospitalization period

Table 2

Frequency of drugs prescribing in patients with and without DM2T - hospital period (%)

Drugs	DM2T n=11	without DM2T n=59
Acetylsalicylic acid (loading dose)	36	57
Acetylsalicylic acid	91	100
Inhibitors of P2Y12, (clopidogrel, ticagrelor)	100	100
Low molecular weight heparins/pentasaccharides (Enoxaparin/fondaparinux)	91	95
Angiotensin-converting-enzyme inhibitors	64	86
B-blockers	73	85
Narcotic analgesics	73	47
Loading dose of inhibitors of P2Y12	64	73
Nitrates	64	49
Fibrinolytic therapy	9	27
Diuretics	9	20
Statins	91	95

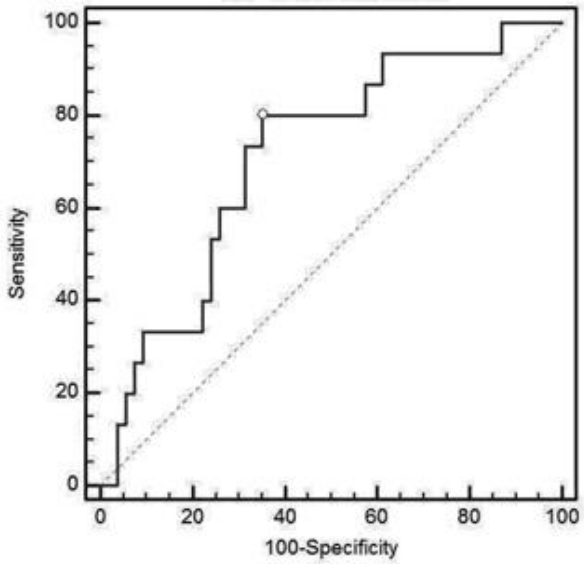

Fig. 3. ROC-curve GDF 15 and class of HF by Killip-Kimball

A significant difference was found in NT-pro BNP among groups of patients with ACS and DM2T who died and survived ($p < 0.05$) and there was no significant difference in GDF 15 (tab. 3).

Table 3

Average values of biomarkers in groups of patients by prognosis (M ± sd)

Parameters	Had reached endpoint	Had not reached endpoint	p
GDF 15, pg/ml	11212,96 ± 4437	6064,15 ± 1157	0,29
NT-pro BNP, pg/ml	1910,6 ± 894	104,5 ± 34,5	0,018

In 2010 T. Kempf et al. [6] have conducted a study where an association between MIC-1 and incident of DM2T was first presented. The level of MIC-1 was significantly increased in the group of patients where DM2T subsequently has developed compared to DM2T-free group. However, there was a borderline significant relationship with modification in gender and age; also this relationship was significantly decreased with modification in indicators such as waist circumference, cardiovascular risk factors, proinflammatory mediators and glycaemia. This study was the first to predict development of DM2T 11 years before manifestation. However, as a result, it was found that an elevated level of MIC-1 was not independently associated with DM2T, although it was significantly increased in the group.

Large number of studies had been conducted to estimate GDF 15 in DM2T patients with concomitant cardiovascular pathology and without it. In XENDOS study, a relationship of obesity and insulin resistance with GDF 15 for patients with pre-diabetes was detected, where the biomarker was an independent predictor. Also, over 4 years follow-up, inadequate glucose control resulted in elevated levels of GDF 15. Besides, only GDF 15 and pre-diabetes, identified initially, were independent predictors of inadequate glucose control over 4-year period [7].

In a study conducted by Greisa Vila et al. [8] a cohort of patients with obesity was examined. All patients were divided into groups based on glucose-tolerance test results: a normal glucose level, with insulin resistance and DM. GDF 15 was significantly increased in all groups compared to control group (healthy population). The main finding was that GDF 15 is related to all parameters that characterize glucose metabolism: it was significantly correlated with glucose, insulin, C-peptide, Hb A_{1C} index and HOMA. GDF 15 level was significantly higher in group of patients with obesity and new onset diabetes mellitus than in group with obesity and normal glucose tolerance.

In 2014, a review about relationship of depending cardiovascular pathology in patients with DM2T and GDF 15 role was published. Level of GDF 15 – 3812 pg/ml was indicated as an independent predictor of patients with diabetic cardiomyopathy (sensitivity of 82.2 %, specificity of 70.2 %) [9].

Although there are a large number of studies of GDF 15 in patients with diabetes, its role in acute coronary pathology is still insufficiently studied.

As noted above, percentage of patients with DM2T and ACS is 20–35 %, but in our study, this figure was 15 %. Patients with DM are initially patients of high risk for ACS complications. In our study adverse outcome was observed in 27 % in the group of patients with DM2T and 10.1 % – in the group of patients without DM2T, and 12.9 % in total group. There was no significant difference in GDF 15 among the group of dead and surviving patients. Probably, this is due to the small number of samples, so this issue needs to be improved by recruiting a larger number of patients.

CONCLUSIONS

GDF 15 levels' was significantly increased in patients with ACS who had DM2T history, but had not reached significant point in the group of patients who died. The final decision about prognostic

value of GDF 15 in patients with ACS and diabetes can be found after we reach the necessary number of patients.

PROSPECTS FOR FUTURE STUDIES

We are going to include more patients with such combined pathology and find the connection between high level of GDF 15 and prognosis for the new algorithm of risk stratification.

The review is a fragment of scientific work «Investigation of new biomarkers for high quality prognosis and treatment of patients with acute coronary syndrome» № 0113U001141.

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OSTEOPONTIN, INTERLEUKIN-15 AND DYSFUNCTION OF LEFT VENTRICULAR MYOCARDIUM IN HYPERTENSIVE PATIENTS WITH CHRONIC HEART FAILURE

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Based on a survey of 108 patients with hypertension complicated by chronic heart failure, studied the connection concentration of osteopontin, interleukin-15 in serum and morpho-functional characteristics of the left ventricle of the heart. In patients with CHF osteopontin levels were significantly higher, it revealed a relationship between adverse LV filling state and knots in serum osteopontin, while the level of IL-15 did not show such a relationship. The results indicate the potential value of osteopontin as a biomarker for the diagnosis of CHF.

KEY WORDS: osteopontin, interleukin-15, hypertension, left ventricular myocardial dysfunction, chronic heart failure

ОСТЕОПОНТІН, ІНТЕРЛЕЙКІН-15 ТА ДИСФУНКЦІЯ МІОКАРДА ЛІВОГО ШЛУНОЧКУ У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ

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На підставі обстеження 108 пацієнтів з гіпертонічною хворобою, ускладненою хронічною серцевою недостатністю, вивчений зв'язок концентрації остеопонтіна, інтерлейкіна-15 в сироватці крові і морфофункціональніх особливостей лівого шлуночку серця. У пацієнтів з ХСН рівень остеопонтіна був достовірно вище, виявлений взаємозв'язок між несприятливим станом наповнення ЛШ та зростанням концентрації остеопонтіна в сироватці крові, в той час, як рівень інтерлейкина-15 не продемонстрував таку залежність. Отримані результати свідчать про потенційну цінність остеопонтіна, як біомаркера діагностики ХСН.

КЛЮЧОВІ СЛОВА: остеопонтін, інтерлейкин-15, гіпертонічна хвороба, дисфункція міокарду ЛШ, хронічна серцева недостатність

ОСТЕОПОНТИН, ИНТЕРЛЕЙКИН-15 И ДИСФУНКЦИЯ МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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На основании обследования 108 пациентов с гипертонической болезнью, осложненной хронической сердечной недостаточностью, изучена связь концентрации остеопонтина, интерлейкина-15 в сыворотке крови и морфо-функциональных особенностей левого желудочка сердца. У пациентов с ХСН уровень остеопонтина был достоверно выше, выявлена взаимосвязь между неблагоприятным состоянием наполнения ЛЖ и нарастанием сывороточной концентрации остеопонтина, в то время как уровень интерлейкина-15 не продемонстрировал такую зависимость. Полученные результаты свидетельствуют о потенциальной ценности остеопонтина, как биомаркера диагностики ХСН.

КЛЮЧЕВЫЕ СЛОВА: остеопонтин, интерлейкин-15, гипертоническая болезнь, дисфункция миокарда ЛЖ, хроническая сердечная недостаточность

INTRODUCTION

Among the causes of death of middle and elderly patients cardiovascular diseases (CVD)

are the first priority. The overall incidence of them also makes a considerable share among the population of Ukraine. Considering, in particular, essential hypertension (EH), in 2015, have been registered in 788214 patients in Ukraine [1]. A serious complication of EH, coming to the risk of cardiovascular events, is chronic heart failure.

CHF occurs as a consequence of the remodeling of the left ventricle (LV). Structural and functional reorganization of the left ventricle is one of the earliest manifestations of systemic EH [2]. Remodeling involves changing the geometrical shape and structure of the heart muscle [3] and leads to myocardial dysfunction.

The main mechanisms of cardiac remodeling in hypertension complicated by heart failure are inflammation and fibrosis. The role of osteopontin, which is a recognized marker of fibrosis, and pro-inflammatory cytokine interleukin-15 (IL-15) has not been studied in the formation of heart failure. Osteopontin is a secretory sialoprotein belonging to the class of matrix protein cells [4]. Proved his involvement in the inflammatory processes with increasing rigidity of the vascular wall, calcification of atheroma [5]. The interrelation level of osteopontin with LV myocardial changes and the development of hypertension in children and adolescents [6]. One of the mechanisms mediating the remodeling of the myocardium is overproduction of cytokines [7]. IL-15 pro-inflammatory cytokine involved in the autoimmune inflammation, proliferation of T-lymphocytes and natural killer cells [8]. His role in the development of structural and functional changes of left ventricular myocardium little studied and is of interest for further research.

PURPOSE OF THE STUDY

The study of the relationship between the concentration of osteopontin, IL-15 serum, remodeling and changes in left ventricular cardiac function in hypertensive patients complicated with chronic heart failure (CHF).

MATERIALS AND METHODS

The study included 108 hypertensive patients complicated with heart failure who have given informed consent to survey and the use of survey data in the publication. The first clinical group consisted of 44 hypertensive patients with concomitant heart failure I stage, the second – 64 hypertensive patients with concomitant heart failure II A-B stage. The control group consisted of 12 healthy people.

Exclusion criteria of patients from the study were: secondary hypertension; heart rhythm disturbances, AB conduction; presence of chronic heart failure stage IIB-III (NY classification); acute myocardial infarction or stroke in history, a sharp left or right heart failure; traumatic lesions of the central nervous system; comorbid psychiatric disorders, alcoholism, drug addiction; decompensated of liver disease (increased AST, ALT more than 3 times); diffuse connective tissue diseases; infectious diseases and cancer.

Verification of the diagnosis, staging and the degree of hypertension, were carried out according to the criteria recommended in 2013 by the European Society of Hypertension (ESH) / and the European Society of Cardiology (ESC). Verification of the diagnosis, determine the degree of heart failure, were performed according to the criteria recommended in 2012 by the Association of Ukrainian specialists in heart failure.

The blood was taken to the biochemical and enzyme immunoassay research is done with the ulnar vein in the morning on an empty stomach is not earlier than after 12-hour fast. Research methods included the collection of complaints and anamnesis, anthropometry (BMI, waist circumference, hip circumference, height).

All patients were determined osteopontin levels (ng/ml) in serum by enzyme immunoassay using a set of «Human Osteopontin Assay Kit -IBL Co., Ltd» Japan, IL-15 (pg/ml) in blood serum using a set «RayBio® Human IL-15 Elisa Kit» USA.

Ultrasound of the heart study was conducted using an ultrasound scanner RADMIR Ultima PA (Ukraine, Kharkov) in a recognized procedure in M-, B- and D- modes echolocation, as recommended by the American Society echocardiographic (Americanssociety of Echocardiography – ASE), with the definition of the following indicators: the mass of the left ventricle (LV MM), g.; myocardial mass index (IMM), g/m2; myocardial mass index on growth ($IMMr^{2,7}$) $g/m^{2,7}$; interventricular septum thickness (IVST) mm; the thickness of the rear wall of the left ventricle (LV CTM) mm; the relative thickness of the left ventricular wall (LV UTS), mm; - End-diastolic dimension (CRA), mm; ejection fraction (EF), %. For the purpose of a detailed

assessment of left ventricular diastolic filling state of patients underwent echocardiography protocol with in-depth study of transmitral flow parameters and motion of the mitral valve fibrous ring tissue Doppler mode: Peak E cm/s; Peak A, cm/s; E/A; Peak E' – cm/s; E/E'.

Statistical processing of the results was performed using standard methods of nonparametric statistics using Statsoft STATISTICA statistical software package v. 10.0 on personal home computers. As the parameters of descriptive statistics used median (Me), the bottom (the LQ) and the upper (UQ's) quartile of the sample. Significant differences between the figures that have been studied, was determined using the Mann - Whitney. To determine the relationship between the studied parameters, carried out a correlation analysis with the calculation of Pearson correlation coefficients of pair.

RESULTS AND DISCUSSION

The study results of osteopontin concentration in serum IL-15 in hypertensive patients complicated with CHF given in tab. 1.

Table 1

The concentration of osteopontin in the blood serum IL-15 in patients with EH complicated by heart failure, Me (LQ; UQ)

Level of serum markers	Clinical patients group		
	Control (n = 12)	Hypertensive patients complicated with heart failure I stage (n = 44)	Hypertensive patients complicated with heart failure IIA-B stage. (n = 64)
Osteopontin, ng/ml	10,0 (7,69;12,8)	14,3 (8,25; 19,1) p > 0,05	15,3 (12,4; 18,5) p > 0,05 p* = 0,002
IL-15, pg/ml	88,6 (57,1; 103,8)	93,1 (79,8; 106,8) p > 0,05	87,7 (82,2;100,4) p > 0,05 p* > 0,05

Note: p – confidence level compared to the control group performance; p – confidence level in comparison with indicators of group 1.*

Osteopontin concentration in serum increased with the accession of CHF and reliably reached the highest values in patients with HF II AB stage, whereas serum IL-15 did not show such a relationship.

The correlation coefficients between the levels of osteopontin and IL-15 in serum and echocardiographic parameters (tab. 2) showed lower strength of correlations osteopontin serum and IL-15 with the linear dimensions of the LV, absolute and relative thickness of its walls, the calculated indices and myocardial mass fraction LV ejection.

Table 2

The correlation coefficients between osteopontin, IL-15 and PV characteristics of LV morphology in hypertensive patients complicated with heart failure

Index	Osteopontin	IL-15
CRA	-0,095	0,250
IVST	-0,065	-0,103
LV TZS	-0,118	-0,096
LV UTS	-0,076	-0,326
MM LV	-0,205	0,001
IMM	-0,164	0,059
IMMr2,7	-0,145	0,128
FW	-0,011	-0,076

In our opinion, this fact can be explained by the fact that in hypertensive patients in the formation of heart failure in the early stages of a typical violation of diastolic function [9]. Previous studies [10–12] show that even in cases where the central hemodynamics has not changed at patients already diagnosed with hypertension heart failure is due to the appearance of diastolic LV myocardial dysfunction. The number of such patients, including patients with hypertension and heart failure is approximately 30–40 % [13].

Reduction of myocardial contractile function, determined by the ejection fraction, joins in the later stages of the disease and is often associated with the manifestations of comorbid pathology, primarily, coronary heart disease [14].

Analysis of the data shown in table 3 shows a lack of significant association between serum IL-15 levels and features of diastolic filling. At the same time, it revealed a negative correlation between the average powers in the serum concentration of osteopontin and peak E '($r = -0,049$), ($p > 0.05$), reflecting a decrease in left ventricular relaxation properties of the myocardium in patients with higher levels of osteopontin. At the same time between the E/E' and osteopontin direct correlation medium strength ($r = 0,500$), ($p > 0.05$), which indicates an increase in stiffness and increase in myocardial LV filling pressure in patients with high levels of osteopontin.

Table 3

The correlation coefficients between osteopontin, IL-15 and functional features of the left ventricle in hypertensive patients complicated with heart failure

Index	Osteopontin	IL-15
Peak E	-0,049	0,059
Peak A	-0,065	0,016
E/A	0,107	0,082
Peak E'	-0,429	-0,036
E/E'	0,500	0,107

The above data confirm the results of earlier studies conducted, during which a direct relationship between the concentration of osteopontin and myocardial stiffness change [14–16] was detected, which leads to the development of left ventricular dysfunction and, as a consequence, CHF.

An analysis of the literature regarding the sources of pro-inflammatory cytokines evidence of their involvement in the LV remodeling [17], but the analysis of data is an IL-15 did not reveal data on the direct interconnection of IL-15 with a clinical picture of heart failure, prognosis of myocardial remodeling. As in this study, the relationship between serum levels of IL-15 and severity of heart failure has not been identified.

Considering the above, it seems appropriate to search for new biomarkers, a change in the level which would have made it possible to predict the development of diastolic dysfunction at the stage prior to its manifestation. Our findings suggest the potential value of osteopontin, which is a proven marker of fibrosis, in predicting the development of myocardial dysfunction.

CONCLUSIONS

1. In hypertensive patients in combination with CHF revealed significantly elevated levels of osteopontin in the blood serum, reaching maximum severity in patients with heart failure stage II. IL-15 level in these patients does not depend on the presence and severity of heart failure.

2. Increased serum levels of osteopontin in hypertensive patients is associated with a relatively unfavorable LV filling state, both in the early and late in diastole, the manifestation of which is the negative correlation with the values of osteopontin peak E, and a positive attitude to the E/E'.

3. The established relationship concentration of osteopontin in the blood serum with functional myocardial changes in hypertensive patients complicated with heart failure, an opportunity to recognize the

important role of this maker of fibrosis in myocardial remodeling and heart failure severity.

PROSPECTS FOR FUTURE STUDIES

In hypertensive patients with levels of osteopontin study established its dependence on the degree of severity of heart failure. Given the correlation between the concentration of serum osteopontin and diastolic myocardial dysfunction, it seems appropriate to consider it as a predictor of functional disorders of the myocardium in hypertensive patients.

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VENTRICULAR RATE AND BLOOD PRESSURE ORTHOSTATIC REACTIONS IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION IN GENERAL CARDIOVASCULAR RISK GROUPS

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Types and prevalence of ventricular rate (VR), systolic (SBP) and diastolic (DBP) blood pressure (BP) orthostatic reactions (OR) in patients with permanent atrial fibrillation (AF) in general cardiovascular risk groups (GCVR) were studied in 137 patients (73 men and 64 women), aged 66.4 ± 9.9 years. VR was measured by the electrocardiography (ECG) on the computer electrocardiograph «CardioLab 2000» and BP – semi-automatic tonometer Microlife BP2BIO. Changes VR, SBP and DBP in the range of ± 5 % were classified as a lack, an increase of 5 % and more – both positive and decreased by 5 % or more – as a negative OR. GCVR calculated in accordance with the scale of SCORE. Patients were classified into groups of GCVR. Statistical evaluation of the results was performed with the parametric estimate of the mean (M) and standard deviation (sd) and non-parametric Student's T-test and Mann-Whitney test methods.

It was found that patients with AF have all three types (positive, absent, negative) OR of VR, SBP and DBP, which are stored in all classes GCVR. Optimizing the management of patients with atrial fibrillation, including with and through modification within the GCVR risk factors should take into account deviations in orthostatic reactions of VR, SBP and DBP.

KEY WORDS: orthostatic reaction, atrial fibrillation, general cardiovascular risk

ОРТОСТАТИЧНІ РЕАКЦІЇ ЧАСТОТИ ШЛУНОЧКОВИХ СКОРОЧЕНЬ ТА АРТЕРІАЛЬНОГО ТИСКУ У ПАЦІЄНТІВ З ПОСТІЙНОЮ ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ У ГРУПАХ ЗАГАЛЬНОГО КАРДІОВАСКУЛЯРНОГО РИЗИКУ

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Вивчено типи і поширеність ортостатичних реакцій (ОР) частоти шлуночкових скорочень (ЧШС), систолічного (САТ) і діастолічного (ДАТ) артеріального тиску (АТ) у пацієнтів з постійною формою фібриляції передсердь (ФП) в групах загального кардіоваскулярного ризику (ЗКВР) на 137 пацієнтах (73 чоловіки і 64 жінки) віком 66,4 ± 9,9 років. ЧШС вимірювали по ЕКГ на комп'ютерному електрокардіографі «CardioLab 2000» та АТ – напівавтоматичним тонометром Microlife BP2BIO. Зміни ЧШС, САТ і ДАТ в діапазоні до ±5 % класифікували як відсутність, збільшення на 5 % і більше - як позитивні і зниження на 5 % і більше – як негативні ОР. ЗКВР розраховували відповідно до шкали SCORE. Пацієнтів класифікували на групи ЗКВР. Статистична оцінка результатів проводилася параметричними з оцінкою середнього (М) і стандартного відхилення (sd) і непараметричними t-критерію Стьюдента та критерію Манна-Уітні методами.

Встановлено, що у пацієнтів з ФП існують всі три типи (позитивні, відсутні, негативні) ортостатичні реакції ЧШС, САТ і ДАТ, які зберігаються у всіх класах ЗКВР. Оптимізація ведення пацієнтів з ФП, в тому числі з урахуванням і через модифікацію входять до ЗКВР факторів ризику повинна здійснюватися з урахуванням ухилень в ортостатичних реакціях ЧШС, САТ і ДАТ.

КЛЮЧОВІ СЛОВА: ортостатична реакція, фібриляція передсердь, загальний кардіоваскулярний ризик

ОРТОСТАТИЧЕСКИЕ РЕАКЦИИ ЧАСТОТЫ ЖЕЛУДОЧКОВЫХ СОКРАЩЕНИЙ И АРТЕРИАЛЬНОГО ДАВЛЕНИЯ У ПАЦИЕНТОВ С ПОСТОЯННОЙ ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ В ГРУППАХ ОБЩЕГО КАРДИОВАСКУЛЯРНОГО РИСКА

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Изучены типы и распространенность ортостатических реакций (ОР) частоты желудочковых сокращений (ЧЖС), систолического (САД) и диастолического (ДАД) артериального давления (АД) у пациентов с постоянной формой фибрилляции предсердий (ФП) в группах общего кардиоваскулярного риска (ОКВР) на 137 пациентах (73 мужчины и 64 женщины) в возрасте 66,4±9,9 лет. ЧЖС измеряли по ЭКГ на компьютерном электрокардиографе «CardioLab 2000» и АД - полуавтоматическим тонометром Microlife BP2BIO. Изменения ЧЖС, САД и ДАД в диапазоне до ±5 % классифицировали как отсутствие, увеличение на 5 % и более – как позитивные и снижение на 5 % и более – как негативные ОР. ОКВР рассчитывали в соответствии со шкалой SCORE. Пациентов классифицировали на группы ОКВР. Статистическая оценка результатов проводилась параметрическими с оценкой среднего (M) и стандартного отклонения (sd) и непараметрическими t-критерия Стьюдента и критерия Манна-Уитни методами.

Установлено, что у пациентов с ФП существуют все три типа (позитивные, отсутствующие, негативные) ортостатические реакции ЧЖС, САД и ДАД, которые сохраняются во всех классах ОКВР. Оптимизация ведения пациентов с ФП, в том числе с учетом и через модификацию входящих в ОКВР факторов риска должна осуществляться с учетом уклонений в ортостатических реакциях ЧЖС, САД и ДАД.

КЛЮЧЕВЫЕ СЛОВА: ортостатическая реакция, фибрилляция предсердий, общий кардиоваскулярный риск

INTRODUCTION

Atrial fibrillation (AF) - the most common type of arrhythmia, which is a serious medical and social problem due to the high rate of complications [1-2] and hospitalizations [3].

Orthostatic reaction (OR) of ventricular contractions rate (VR) and blood pressure (BP) is an objective method for assessing autonomic regulation of the cardiovascular system of the person and have an independent prognostic value for the course and outcomes of various cardiovascular diseases. For example, blood pressure hypotensive OR associated with the risk of acute coronary syndrome [4], izotensive – with a worsening of arterial hypertension [5]. The most favorable are considered hypertensive OR of BP. However, there is evidence of increased risk of «silent» strokes in patients with this type of OR [6–7].

We have not found studies on OR of VR and BP depending on the general cardiovascular risk (GCVR) in patients with AF.

The work was performed as part of research, «Research and development of automatic control of heart rate variability system», the state registration number 0109U000622.

OBJECTIVE

Aim of the research is to study of prevalence of VR and BP OR in patients with permanent AF in GCVR groups for development proposals for increase of the effectiveness of its diagnosis and therapy.

MATERIALS AND METHODS

On the basis of cardiology department of the central hospital «Ukrzaliznytsia» and city polyclinic № 6 137 patients (73 men and 64 women aged 66,4 ± 9,9 years) with permanent AF barred from 1 to 25 years were examined. Arterial hypertension (AH) was diagnosed in 114 patients, coronary artery disease (CAD) – in 67 patients, post-myocardial infarction cardio sclerosis (PICS) – in 15 patients, heart failure (HF) – in 121 patients.

Exclusion criteria were patients with stable exertional angina IV functional class (FC), acute coronary syndrome, valvular disease and heart failure FC IV.

OR of VR evaluated according to its measurement in tilt test on third minute of clinostasis and third minute after switching in orthostasis on the computer electrocardiograph «CardioLab 2000». Changes of VR in the range of ±5 % was classified as a lack, an increase of 5 % or more – as a positive and a decrease of 5 % or more – as a negative VR OR.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the method of Korotkov with semi-automatic tonometer Microlife BP2BIO in tilt test on third minute of clinostasis and third minute after switching in orthostasis. Hypertensive (blood pressure increase of more than 5 %), izotensive (changes in blood pressure to within ± 5 %) and hypotensive (blood pressure reduction by 5 % or more) BP OR were recovered.

GCVR calculated in accordance with the scale SCORE [8]. As a result of the patients were classified into 4 groups GCVR: 1 – low (risk SCORE < 1 %); 2 – moderate (risk SCORE > 1 % and < 5 %); 3 – high (risk SCORE > 5 % and < 10 %) and 4 – very high risk (SCORE > 10 %).

The data is entered into Microsoft Excel database 2010. Statistic evaluation of the results was performed by parametric methods to estimate the mean (M) and standard deviation (sd) and non-parametric Student's T-test and Mann-Whitney test.

RESULTS AND DISCUSSION

Initially VR in all GCVR groups did not differ significantly and conform to tachysistolic AF (Fig. 1). Its value was higher in groups II and III of GCVR (97 and 96 beats/min, respectively) versus groups I and IV GCVR (91 and 90 beats/min, respectively).

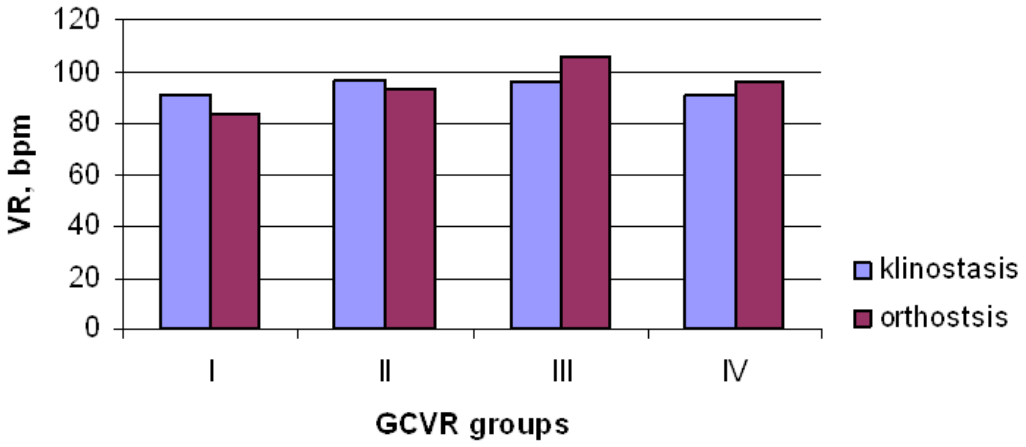

Fig. 1. Ventricular rate orthostatic reactions in patients with permanent AF in GCVR groups

The tilt test in I and II GCVR groups observed moderate nonsignificant VR reduction, more pronounced in the group I (8 % versus 4 %). In III and IV GCVR groups there was a significant ($p \leq 0,05$) VR increase more in group III (10 % vs. 5 %, respectively) in orthostasis.

The initial values of BP and orthostatic changes are shown in Fig. 2. Starting SBD did not differ significantly between the I-III GCVR groups, but was significantly higher in them against values in IV group GCVR ($p \leq 0,01$). In orthostasis in all this GCVR groups is not significantly changed, and only in the group IV significantly decreased by 7 % ($p \leq 0,01$).

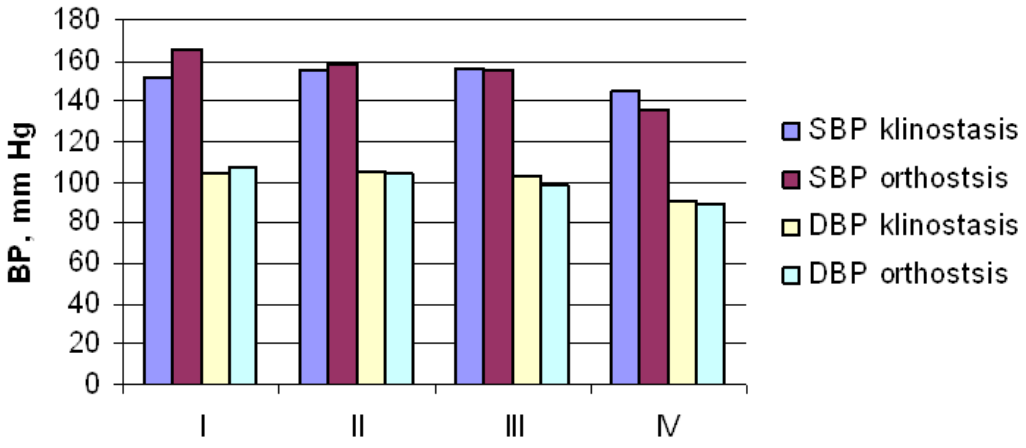

Fig. 2. Systolic and diastolic blood pressure orthostatic reactions in patients with permanent AF in GCVR groups

Initial values of DBP in I-III GCVR groups were almost identical and significantly lower than in group IV ($p \leq 0,01$). In orthostasis occurred nonsignificant increase of DBP in I and IV GCVR groups and slide – in groups II and III.

Table presents the ratio of types of VR and BP OR in GCVR groups. In I GCVR group, the frequency of different types of VR OR distributed equally.

Table

Frequency ratio of blood pressure orthostatic reactions in patients with permanent AF in GCVR groups (%)

Functional values orthostatic reactions		GCVR			
		I	**II**	**III**	**IV**
VR	absent	33,3	39	13	20
	positive	33,3	26	65	64
	negative	33,3	35	22	16
SBP	absent	0	26	17	15
	positive	33	26	61	64
	negative	67	48	22	21
DBP	absent	0	26	43	14
	positive	67	26	39	29
	negative	33	48	18	57

In II GCVR group equally prevailed absent and negative VR OR, in groups III and IV prevailed positive VR OR.

In I and II GCVR groups dominated hypertensive SBP OR. Thus hypotensive SBP OR in I group GCVR was not observed and was similar to izotensive SAD OR frequency in II GCVR group. In III and IV GCVR groups it was the highest frequency of izotensive SBP OR at least the same rate of hypotensive SBP OR and the same intermediate frequency hypertensive SBP OR in both groups.

The frequency distribution of DBP OR corresponds to the frequency allocation of SBP OR only in II GCVR group, where the maximum rate remained hypertensive and were lower and the same frequency of hypotensive and izotensive DBP OR. In the I GCVR group was the maximal frequency izotensive DBP OR and, as in the case of SBP OR, not observed hypotensive DBP OR. In III GCVR group equally predominant frequency of hypo- and izotensive DBP OR with a minimal frequency of hypertensive DBP OR. In IV GCVR group most frequently met hypertensive and least often - hypotensive DBP OR.

The findings not only confirm the existence of patients with AF different types of VR OR, but a SBP and DBP [9-10], which are frequency characteristics are close to those of patients with sinus rhythm [11].

The value of the negative and missing VR OR in adverse outcomes and established the existence of SBP and DBP OR in patients with AF in different frequency ratios in GCVR groups puts the task of studying the possibility of their optimization to improve the quality and duration of life for patients. Such intervention is required in all groups of GCVR.

CONCLUSIONS

In patients with AF, there are three types (positive, absent, negative) VR, SBP and DBP OR, which are stored in all GCVR groups.

Optimizing the management of patients with atrial fibrillation, including with and through GCVR factors modification should take into account deviations in VR, SBP and DBP OR.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study the functional values of cardiovascular system, as well as VR control results in patients with AF in different GCVR groups.

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SIGNIFICANCE OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE DAILY PROFILE TYPES IN CLINICAL EVALUATION OF HYPERTENSIVE PATIENTS

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The characteristics of the arterial hypertension (AH) clinical signs according to the types of diastolic blood pressure (DPB) daily profile in comparison with systolic blood pressure (SBP) daily profile types in 82 patients (33 men and 49 women), mean aged 56 ± 11 years, were studied. Statistical analysis was performed on a PC using the «Microsoft Office Excel 2010» and «STATISTICA» programs. It was found that DPB is as important as SPB hemodynamic parameter in patients with AH, and violation of its circadian rhythm leads to AH potentiating. To higher risk of DBP pathological daily profile types prone females, patients with a short history and the initial stages of AH. Evaluation of DBP daily profile carries additional information about the course of the disease and should be performed in all patients with AH.

KEY WORDS: hypertension, ambulatory blood pressure monitoring, diastolic blood pressure, systolic blood pressure

ЗНАЧЕННЯ ТИПІВ ДОБОВИХ ПРОФІЛЕЙ СИСТОЛІЧНОГО ТА ДІАСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ В КЛІНІЧНІЙ ОЦІНЦІ ПАЦІЄНТІВ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ

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Вивчено частотні характеристики клінічних ознак гіпертонічної хвороби (ГХ) залежно від типів добового профілю діастолічного (ДАТ) в порівнянні з типами добового профілю систолічного артеріального тиску (САТ) у 82 пацієнтів (33 чоловіків і 49 жінок) у віці 56 ± 11 років. Статистична обробка результатів проведена на персональному комп'ютері за допомогою програм «Microsoft Office Excel 2010» та «STATISTICA». Встановлено, що ДАТ є таким же важливим, як і САД, параметром гемодинаміки у пацієнтів з ГХ і порушення його добового ритму призводить до обтяження захворювання. До патологічних типів добового профілю ДАТ більш схильні особи жіночої статі, пацієнти з коротким анамнезом та початковими стадіями ГХ. Оцінка добового профілю ДАТ несе додаткову інформацію про перебіг захворювання і повинна проводитися у всіх пацієнтів з ГХ.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, добове моніторування артеріального тиску, діастолічний артеріальний тиск, систолічний артеріальний тиск

ЗНАЧЕНИЕ ТИПОВ СУТОЧНЫХ ПРОФИЛЕЙ САД И ДАД В КЛИНИЧЕСКОЙ ОЦЕНКЕ ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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Изучены частотные характеристики клинических признаков гипертонической болезни (ГБ) в зависимости от типов суточного профиля диастолического (ДАД) в сравнении с типами суточного профиля систолического артериального давления (САД) у 82 пациентов (33 мужчин и 49 женщин) в возрасте 56 ± 11 лет. Статистическая обработка результатов произведена на персональном компьютере при помощи программ «Microsoft Office Excel 2010» и «STATISTICA». Установлено, что ДАД является таким же важным, как и САД, параметром гемодинамики у пациентов с ГБ и нарушение его суточного ритма приводит к утяжелению заболевания. Более высокому риску патологических типов суточного профиля ДАД подвержены лица женского пола, пациенты с коротким анамнезом и начальными стадиями ГБ. Оценка суточного профиля ДАД несёт дополнительную информацию о течении заболевания и должна проводиться у всех пациентов с ГБ.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, суточное мониторирование артериального давления, диастолическое артериальное давление, систолическое артериальное давление

INTRODUCTION

With the introduction of ambulatory blood pressure monitoring (ABPM) in clinical practice, a number of new parameters came in sight as predictors of cardiovascular (CV) mortality and morbidity, one of which is the type of daily blood pressure (BP) profile [1]. The paradigm shift of diastolic blood pressure (DBP) significance as a CV risk factor in the late 90-ies of the last century led to the fact that at present the vast majority of scientific works are studied diurnal profiles of only systolic blood pressure (SBP) [2–3].

However, the DBP still is an independent risk factor of CV morbidity and mortality, and in patients below 50 years even more strong than SBP and pulse pressure (PP) are [4–5].

Systolic and diastolic hypertension differs in their pathogenesis. The first one is mainly determined by large arteries stiffness, while the second one is associated with arterioles vasoconstriction [6]. It is also important that intensive antihypertensive therapy, directed to achievement SBP target levels, often leads to a significant drop in DBP, which in its turn leads to a decrease in myocardial perfusion and increases the risk of CV morbidity and acute CV events [7].

Taking into account the DBP significance as a CV morbidity and mortality risk factor, assessment of its daily profile, along with SBP daily profile, will allow to determine the degree of CV risk more accurately and to provide an individual approach to each patient with elevated blood pressure [7].

However, there are few data about the role of DBP daily profile violations in patients with arterial hypertension (AH), and we did not find any study in which SBP and DBP profiles were compared.

OBJECTIVE

To study the significance of DBP daily profile types compared with SBP daily profiles in the clinical evaluation of patients with AH.

MATERIALS AND METHODS

On the clinical base of the Kharkov city outpatient clinic № 24 82 patients with AH were examined. The study involved 33 men (40 %) and 49 women (60 %). Average age 56 ± 11 years. The average duration of AH 8 ± 6,7 years.

Exclusion criteria were secondary hypertension, hemodynamically significant valvular heart disease, cardiomyopathy of any genesis, heart failure stage III, FC IV by NYHA, any acute condition (infection, trauma, surgery) within the previous 3 months, chronic diseases in stage of decompensation or exacerbation, cancer, as well as any circumstances that hinder the conduction of ABPM.

Newly diagnosed AH was detected in 9 % of patients. AH of stage I was diagnosed in 13 % of patients, stage II – in 72 %, stage III – 15 %. AH of 1 grade was determined in 54 % of patients, grade 2 – 32 %, grade 3 – 15 %. Heart failure (HF) was diagnosed in 74 % cases: HF stage I – 43 %, HF stage IIA – 57 %, I functional class (FC) of HF was determined in 27 % of patients, II FC – 66 %, III FC – 7 %; coronary heart disease (CHD) – 76 % of cases: stable angina (I–III FC) – 22 %, postinfarction cardiosclerosis (PICS) – 4 %. Obesity was found in 55 % of patients, I degree – 32 %, II degree – 15 %, III degree – 9 %.

SBP profile of «dipper» type was set in 43 % of patients, «nondipper» – 44 %, «night-piker» – 7 %, «overdipper» – 6 %. DBP daily profile of «dipper» type was defined in 35 % of cases, «nondipper»–- 27 %, «night-piker» – 4 %, «overdipper» – 34 %.

Patients were divided into 8 groups – 4 groups according to the type of SBP daily profile and 4 groups in accordance with DBP daily profile type.

All patients underwent such tests: measurement of weight and height, body mass index (BMI) calculation, ABPM.

ABPM was performed using a computer system «Kardiosens» (HAI Medica, Ukraine) with the oscillometric method of blood pressure measurement. The monitoring was performed in the conditions of patient normal working day, the cuff was placed at the non-dominant arm using an appropriately sized cuff. According to Ambulatory Blood Pressure Monitoring International Recommendations 2013 [8], blood pressure was measured every 15 minutes during the day and 30 minutes at

night. Daytime and night-time periods were defined based on a diary, in which participants were asked to record their activities and sleep times during the monitoring session. Editing ABPM, in accordance Ambulatory Blood Pressure Monitoring International Recommendations [8] if any value outside preset limits (see below) was detected during a recording, that measurement was rejected:

– systolic blood pressure (SBP) > 250 or < 70 mm Hg,

– diastolic blood pressure (DBP)> 150 or < 40 mm Hg,

– pulse pressure (PP) > 150 or < 20 mm Hg,

– heart rate (HR) > 200 or < 20 per minute.

Also ABPM data series were considered invalid for analysis in the following cases:

– absence of ≥ 30 % of the scheduled measurements,

– lack of data for > 2 consecutive hourly intervals,

– if patient maintained an irregular rest-activity schedule during consecutive 24-h periods of monitoring,

– if the nighttime sleep span was < 6 h or > 12 h [8].

To define the daily profile the nocturnal BP dip was quantified as the relative decline in mean BP from awake (daytime) to asleep (night-time) periods, and was calculated for SBP, DBP and PP separately using the following equation: ((mean awake BP – mean asleep BP) / mean awake BP)×100 %. Depending on the value of this ration the following types of daily BP profile were defined: «dipper» – physiological decrease in BP during the night – sleep-time relative BP decline 10–20 %; «overdipper» - an excessive fall in BP at night, sleep-time relative BP decline > 20 %; «nondipper» – the lack of BP reduction at night, sleep-time relative BP decline < 10 %; «night-peaker» – night-time BP more than during daily activity, sleep-time relative BP decline < 0 [8].

We determined the frequency ratio of the clinical characteristics of AH – sex, age, BMI, AH stage, grade and duration, the presence of concomitant coronary artery disease, heart failure, acute cardiovascular events in anamnesis, – for each type of daily profile, depending on the selected ABPM index, and compared pairs of SBP and DBP profiles type.

Calculation of ABPM indices was performed using «Kardiosens» program. Data were analyzed with the software «Microsoft Office Excel 2010» and «STATISTICA», with the clinical signs frequency of occurrence assessment in percent (P) ± standard deviation of percent (Sd_P).

RESULTS AND DISCUSSION

In groups of dippers, female patients observed in 1.8 times more frequently in DBP-group, male patients – in two times more frequently in SBP-group. The frequencies of occurrence of patients up to 50 years and of 50–69 y.o. between the groups were not significantly different. Elderly patients were in 3.6 times more common among the SBP-dippers than among DBP-dippers (Tabl. 1a, 1b).

In groups of nondippers incidence of male and female patients did not differ significantly, but women were more common among the SBP-nondippers, men – among the DBP-nondippers. Patients under the age of 50 years met in 2.4 times more frequently among the SBP-nondippers elderly patients and patients of 50–69 y.o. were more common among the DBP-nondippers (Tabl. 1a, 1b).

In groups of night-peakers, female patients were more common among the DBP-night-peakers, male patients – among SBP-night-peakers. All patients in night-peakers groups were 50–69 y.o. (Tabl. 1a, 1b).

Table 1a

Sex and age of patients with AH, depending on the daily profile of SBP, P (%) ± SD_P

		SBP daily profile types			
		Dipper, N = 35	Nondipper, N = 36	Night-piker, N = 6	Overdipper, N = 5
Sex	male	60 ± 49 **	33 ± 47 **	50 ± 50	80 ± 40
	female	40 ± 49 *	67 ± 47 *	50 ± 50	20 ± 40
Age	up to 50 years	26 ± 44	22 ± 42	0	40 ± 49
	50-69 years	63 ± 48 *	67 ± 47 *	100	60 ± 49
	≥ 70 years	11 ± 32	11 ± 31	0	0

*Note: * p < 0,05; ** p < 0,1.*

Table 1b

Sex and age of patients with AH, depending on the daily profile of DBP, P (%) ± SD_P

		DBP daily profile types			
		Dipper, N = 29	Nondipper, N = 22	Night-piker, N = 3	Overdipper, N = 28
Sex	male	28 ± 45	41 ± 49	33 ± 47	54 ± 50 *
	female	72 ± 45 *	59 ± 49 *	67 ± 47	46 ± 50 **
Age	up to 50 years	28 ± 45	9 ± 29	0	32 ± 47 **
	50–69 years	69 ± 46 *	77 ± 42 *	100	54 ± 50 *
	≥ 70 years	3 ± 18	14 ± 34	0	14 ± 35

*Note: * p < 0,05; ** p < 0,1.*

In groups of overdippers female patients occurred in 2.3 times more frequently among DBP-overdippers, male patients – in 1.5 times more frequently among the SBP-overdippers. Patients up to 50 and 50–69 y.o. were more common among the SBP-overdippers, elderly patients in SBP-overdippers group were absent and in DBP-overdippers group constituted 1/7 of all cases (Tabl. 1a, 1b).

In groups of dippers frequencies of occurrence of AH stages and degrees were not significantly different. In SBP-dippers group patients with AH duration up to 5 years and 5–10 years were predominant, while in the group of DBP-dippers patients with 10–5 years and more than 10 years of AH duration dominated (Tabl. 2a, 2b).

In groups of nondippers incidence of AH stage I were not significantly different. The incidence of AH stage II was higher among SBP-nondippers, stage III – among DBP-nondippers. The frequencies of occurrence of AH 1 and 3 degrees were higher in the DBP-nondippers group, AH grade 2 was more common among SBP-nondippers. The frequency of occurrence of AH with duration up to 5 years among the SBP-nondippers was higher by more than 2.5 times, and in group of DBP-nondippers patients with AH duration of 5–10 years and more dominated (Tabl. 2a, 2b)

In groups of night-peakers incidence of AH I stage was higher among DBP-night-peakers, AH III stage – in SBP-night-peakers, AH II stage occurred with equal frequency in both treatment groups. The incidence of AH 1 degree was higher among DBP-night-peakers, AH 3 degree - in the SBP-night-peakers group. AH of 2 degree was absent in these groups. Also, in both groups, there were no patients with newly diagnosed AH. Patients with AH duration up to 5 years were more frequent in DBP-night-peakers group, 5–10 years duration and more – in SBP-night-peakers group (Tabl. 2a, 2b).

Table 2a

AH clinical characteristics frequencies of occurrence depending on the daily profile of SBP, P (%) ± SD_P

		SBP daily profile types			
		Dipper, N = 35	Nondipper, N = 36	Night-piker, N = 6	Overdipper, N = 5
AH stage	I	17 ± 38	8 ± 28	17 ± 37	20 ± 40
	II	74 ± 44 *	81 ± 40 *	33 ± 47	40 ± 49
	III	9 ± 8	11 ± 3	50 ± 50	40 ± 49
AH degree	1	46 ± 50 *	58 ± 49 *	83 ± 37 *	40 ± 49
	2	31 ± 46 **	25 ± 43	0	40 ± 49
	3	23 ± 42	17 ± 37	17 ± 37	20 ± 40
AH duration	newly diagnosed	9 ± 28	8 ± 28	0	20 ± 40
	up to 5 years	31 ± 46 **	25 ± 43 **	17 ± 37	20 ± 40
	5–10 years	37 ± 48 **	28 ± 45 **	50 ± 50	60 ± 49
	more than 10 years	23 ± 42	39 ± 49	33 ± 47	0

*Note: * p < 0,05; ** p < 0,1.*

Table 2b

AH clinical characteristics frequencies of occurrence depending on the daily profile of DBP, P (%) ± SD_P

		DBP daily profile types			
		Dipper, N = 29	Nondipper, N = 22	Night-piker, N = 3	Overdipper, N = 28
AH stage	I	17 ± 38	21 ± 5	33 ± 47	14 ± 35
	II	76 ± 43 *	73 ± 45 *	33 ± 47	71 ± 45 *
	III	7 ± 25	23 ± 42	33 ± 47	14 ± 35
AH degree	1	52 ± 50 *	64 ± 48 *	100	43 ± 49 **
	2	28 ± 45	14 ± 34	0	39 ± 49 **
	3	21 ± 41	23 ± 42	0	18 ± 38
AH duration	newly diagnosed	7 ± 25	9 ± 29	0	11 ± 31
	up to 5 years	28 ± 45	9 ± 29	67 ± 47	36 ± 48 **
	5-10 years	31 ± 46 **	36 ± 48	33 ± 47	39 ± 49 **
	more than 10 years	34 ± 48 **	45 ± 50 **	0	14 ± 35

*Note: * p < 0,05; ** p < 0,1.*

In groups of overdippers AH stage I and III were more frequent in SBP-overdippers group, AH II stage – in DBP-overdippers group. The AH degrees frequencies of occurrence were not significantly different in overdippers groups. Newly diagnosed AH was more common in SBP-overdippers group. Patients with AH duration up to 5 years and more than 10 years were more frequent in DBP-overdippers group, with AH duration of 5–10 years – in SBP-overdippers group (Tabl. 2a, 2b).

In groups of dippers HF met with the same frequency. In SBP-dippers group incidence of HF stage I was lower than in DBP-dippers group, whereas HF stage IIA was more common among SBP-dippers. The HF of I and II FC frequencies of occurrence were higher in SBP-dippers group, the HF III FC frequency of occurrence was not significantly different between groups (Tabl. 3a, 3b).

In groups of nondippers HF frequency of occurrence was higher among DBP-nondippers. The HF I and IIA clinical stage frequencies of occurrence, as well as frequencies of HF I and III FC significantly between the groups did not differ, while the incidence of HF II FC was higher among SBP-nondippers (Tabl. 3a, 3b).

In groups of night-peakers HF frequency of occurrence was higher among SBP-night-peakers, in this group the incidence of HF stage II A was also higher. HF I clinical stage met with equal frequency in both groups. The incidence of HF I FC was higher among SBP-night-peakers, II FC- among DBP-night-peakers, whereas patients with HF III FC in both groups were absent (Tabl. 3a, 3b).

Table 3a

Heart failure frequency of occurrence depending on the daily profile of SBP, P (%) ± SD_P

		SBP daily profile types			
		Dipper, N = 35	Nondipper, N = 36	Night-piker, N = 6	Overdipper, N = 5
HF	present	69 ± 46 *	81 ± 40 *	83 ± 37 *	60 ± 49
	absent	31 ± 46 **	19 ± 40	17 ± 37	40 ± 49
HF clinical stage	I	37 ± 48 **	50 ± 50 *	33 ± 47	40 ± 49
	II A	31 ± 46 **	50 ± 50 *	50 ± 50	20 ± 40
HF FC	I	26 ± 44	25 ± 43	33 ± 47	40 ± 49
	II	37 ± 48 **	67 ± 47 *	50 ± 50	0
	III	23 ± 6	8 ± 28	0	20 ± 40

*Note: * p < 0,05; ** p < 0,1.*

Table 3b

Heart failure frequency of occurrence depending on the daily profile of DBP, P (%) ± SD_P

		DBP daily profile types			
		Dipper, N = 29	Nondipper, N = 22	Night-piker, N = 3	Overdipper, N = 28
HF	present	69 ± 46 *	91 ± 29 *	67 ± 47	71 ± 45 *
	absent	31 ± 46 **	9 ± 29	33 ± 47	29 ± 45 **
HF clinical stage	I	45 ± 50 **	45 ± 50 **	33 ± 47	43 ± 49 **
	II A	24 ± 43	45 ± 50 **	33 ± 47	29 ± 45
HF FC	I	31 ± 46 **	23 ± 42	0	29 ± 45
	II	31 ± 46 **	59 ± 49 *	67 ± 47	64 ± 48 **
	III	7 ± 25	9 ± 29	0	7 ± 26

*Note: * p < 0,05; ** p < 0,1.*

In groups of overdippers HF frequency of occurrence was higher among DBP-overdippers. The incidence of HF stage I significantly between groups did not differ, IIA stage of HF was more frequent in the group of DBP-overdippers. The frequency of HF I FC significantly did not differ between the groups, while the incidence of HF III FC was higher among SBP-overdippers than in the group of DBP-overdippers in 3 times. Patients with HF II FC in the group of SBP-overdippers were absent and among DBP-overdippers totaled more than half of all cases (Tabl. 3a, 3b).

In groups of dippers CHD met in 1.5 times more frequently among DBP-dippers than among SBP-dippers. Incidence of stable angina did not differ between the groups. In DBP-dippers group patients with I and III FC of angina were absent, the incidence of FC II of angina was higher among DBP-dippers. Acute CV events in anamnesis among SBP-dippers occurred at a low frequency, while in the group of DBP-dippers were absent (Tabl. 4a, 4b).

In groups of nondippers CHD and stable angina occurred with greater frequency in the group of DBP-nondippers in both groups angina of II FC was met more frequently, with the highest frequency among DBP-nondippers. The frequency of acute CV events in anamnesis in group of DBP-nondippers exceeded that one among SBP-nondippers in 3 times (Tabl. 4a, 4b).

In groups of night-peakers incidence of CHD and stable angina was higher among SBP-night-peakers. In DBP-night-peakers group stable angina was not met at all. The incidence of acute CV events in anamnesis was higher in the SBP night-peakers group (Tabl. 4a, 4b).

Table 4a

The incidence of CHD and acute CV events in anamnesis, depending on the daily profile of SBP, P (%) ± SD_P

		SBP daily profile types			
		Dipper, N = 35	Nondipper, N = 36	Night-piker, N = 6	Overdipper, N = 5
CHD		43 ± 49 *	78 ± 42 *	83 ± 37 *	60 ± 49
Stable angina		14 ± 35	25 ± 43	50 ± 50	20 ± 40
FC of angina	I	9 ± 28	3 ± 16	17 ± 37	0
	II	3 ± 17	22 ± 42 *	33 ± 47	20 ± 40
	III	3 ± 17	0	0	0
Acute CV events in anamnesis		3 ± 17	23 ± 6	50 ± 50	40 ± 49

*Note: * p < 0,05; ** p < 0,1.*

Table 4b

The incidence of CHD and acute CV events in anamnesis, depending on the daily profile of DBP, P (%) ± SD_P

		DBP daily profile types			
		Dipper, N = 29	Nondipper, N = 22	Night-piker, N = 3	Overdipper, N = 28
CHD		66 ± 9 *	95 ± 21 *	67 ± 47	71 ± 45 *
Stable angina		14 ± 6	36 ± 48	0	18 ± 38
FC of angina	I	0	9 ± 29	0	11 ± 31
	II	14 ± 6	27 ± 45	0	4 ± 19
	III	0	0	0	4 ± 19
Acute CV events in anamnesis		0	18 ± 39	33 ± 47	11 ± 31

*Note: * p < 0,05; ** p < 0,1.*

In groups of overdippers frequency of CHD was higher among DBP overdippers. The frequencies of occurrence of stable angina significantly between groups did not differ. Angina of I FC was more common among DBP-overdippers, II FC – among SBP-overdippers. Angina of III FC was rarely met in the group of DBP-overdippers and was absent in the group of SBP-overdippers. The frequency of acute CV events in anamnesis was higher among SBP-overdippers (Tabl. 4a, 4b).

In groups of dippers obesity incidence was higher among SBP-dippers, with a predominance of patients with obesity of I degree. The frequency of II and III degree of obesity did not differ significantly between the groups (Tabl. 5a, 5b).

In groups of nondippers the incidence of obesity and its degrees were not significantly different (Tabl. 5a, 5b).

Table 5a

The incidence of obesity, depending on the daily profile of SBP, P (%) ± SD_P

		SBP daily profile types			
		Dipper, N = 35	Nondipper, N = 36	Night-piker, N = 6	Overdipper, N = 5
BMI	Normal weight	9 ± 28	14 ± 35	33 ± 47	0
	Overweight	31 ± 46 **	33 ± 47 **	33 ± 47	40 ± 49
	Obesity, total	57 ± 49 *	53 ± 50 *	33 ± 47	60 ± 49
	Obesity I	43 ± 49 *	25 ± 43	33 ± 47	0
	Obesity II	11 ± 32	14 ± 35	0	60 ± 49
	Obesity III	3 ± 17	14 ± 35	0	0

*Note: * p < 0,05; ** p < 0,1.*

Table 5b

The incidence of obesity, depending on the daily profile of DBP, P (%) ± SD_P

		DBP daily profile types			
		Dipper, N = 29	Nondipper, N = 22	Night-piker, N = 3	Overdipper, N = 28
BMI	Normal weight	14 ± 34	18 ± 39	33 ± 47	4 ± 19
	Overweight	34 ± 48 **	32 ± 47	33 ± 47	32 ± 47 **
	Obesity, total	52 ± 50 *	50 ± 50 **	33 ± 47	64 ± 48 *
	Obesity I	38 ± 49 **	23 ± 42	0	36 ± 48 **
	Obesity II	10 ± 30	14 ± 34	0	21 ± 41
	Obesity III	3 ± 18	14 ± 34	33 ± 47	7 ± 26

*Note: * p < 0,05; ** p < 0,1.*

In groups of night-peakers obesity incidence did not differ between the groups. Among SBP-night-peakers all obese patients had I degree, in DBP-night-peakers group – III degree (Tabl. 5a, 5b).

Among DBP-overdippers obesity incidence was higher than that in SBP-overdippers group. Patients with I and III degree of obesity in SBP-overdippers group were absent, the obesity incidence of II grade was higher among SBP-overdippers (Tabl. 5a, 5b).

Our results concerning to SBP daily profile types correspond to [9–13] and confirm that the infringement of its circadian rhythm leads to a burdening of AH and complications development. The results in reference to DBP daily profile types in comparison with SBP ones are new and show DBP daily profile types independent significance in the assessment of the AH severity.

The fact that female patients prevailed among dippers, night-peakers and overdippers in DBP groups, and male – among dippers, night-peakers and overdippers in SBP groups, suggests that disorders of DBP daily profile more common develop among women, whereas SBP pathological daily patterns more common among men.

The predominance of the initial stages of AH and its first degree among such prognostic unfavorable types of circadian blood pressure profile as overdipper and night-peakers in DBP groups talks about the primary violation of DBP pattern in AH development. This is also confirmed by our findings in relation to AH duration – among overdippers and night-peakers in DBP groups' patients with short history of AH – up to 5 years – dominated.

The prevalence of heart failure and coronary artery disease in DBP groups of nondippers and overdippers may be indicative of a more rapid development of CV disease in patients with pathological types of DBP daily profile.

CONCLUSIONS

1. DBP is as important as the SBP hemodynamic parameter in patients with hypertension
2. Violation of DBP daily rhythm leads to ФР burdening.
3. Evaluation of DBP daily profile carries additional information in AH assessment.
4. Higher risk of DBP daily profile pathological type's development have females, with a short history of AH and its initial stages.
5. Assessment of DBP daily profile, together with SBP daily profile evaluation, should be performed in all patients with hypertension.

PERSPECTIVES OF FURTHER RESEARCH

It seems appropriate to study the value of DBP daily profile monitoring in patients with AH, using antihypertensive drugs of different pharmacological groups.

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PULSE PRESSURE CLASSES AND HEMODYNAMIC PARAMETERS IN PATIENTS AT THE ANNUAL STAGE AFTER CARDIAC RESYNCHRONIZATION AND MEDICAL THERAPY

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The changes of functional blood circulation parameters in 19 patients (13 men and 6 women) at the annual stage after cardiac resynchronization (CRT) and drug therapy in pulse pressure classes (PP: I - very low PP - less than 20 mm Hg; II – low PP – from 20 to 40 mm Hg; III – normal PP – from 40 to 60 mm Hg; IV – high PP – from 60 to 80 mm Hg; V – very high – more than 80 mm Hg) were studied. The probability of differences between groups was determined with a Mann-Whitney U-test. Normalization of diastolic blood pressure (DBP), heart rate (HR) and left ventricular ejection fraction (LV EF) in all PP classes, systolic BP (SBP), end-systolic, end-diastolic volumes (ESV, EDV) in the III PP class patients at the annual stage after CRT and drug therapy were showed. The tendency of normalization of SBP in the IV class, posterior wall thickness of LV (PWLV), myocardial mass of LV (MMLV) and no change in interventricular septum thickness (IVS), left and right atrium (LA and RA), right ventricular (RV) sizes in all PP classes indicated the need for more active monitoring, careful selection of stimulation parameters and medical support correction of patients in IV PP class.

KEY WORDS: cardiac resynchronization therapy, medical therapy, pulse pressure, hemodynamic parameters

КЛАСИ ПУЛЬСОВОГО АРТЕРІАЛЬНОГО ТИСКУ ТА ГЕМОДИНАМІЧНІ ПОКАЗНИКИ У ПАЦІЄНТІВ НА РІЧНОМУ ЕТАПІ ПІСЛЯ КАРДІОРЕСИНХРОНІЗУЮЧОЇ ТА МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ

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Вивчено зміни функціональних показників кровообігу у 19 пацієнтів (13 чоловіків і 6 жінок) на річному етапі спостереження після кардіоресинхронізуючої (КРТ) і медикаментозної терапії в класах пульсового артеріального тиску (ПАТ: I – дуже низький – менше 20 мм. рт. ст., II – низький – більше 20 – менше 40 мм. рт. ст., III – норма – 40–60 мм. рт. ст., IV – високий – понад 60 – менше 80 мм. рт. ст., V – дуже високий – більше 80 мм. рт. ст.). Достовірність відмінностей між групами визначалася за допомогою U-критерію Манна-Уітні. Результати показали, у пацієнтів за весь період спостереження після КРТ і медикаментозної терапії відбувається нормалізація діастолічного АТ (ДАТ), частоти серцевих скорочень (ЧСС) і фракції викиду лівого шлуночка (ФВЛШ) у всіх класах ПАТ, систолічного АТ (САТ), кінцево-систолічного та кінцево-диастолічног об’єму (КСО та КДО) в III класі ПАТ. Тенденція нормалізації САТ в IV класі, товщини задньої стінки ЛШ (ТЗСЛШ) і маси міокарда ЛШ (ММЛШ) і відсутність змін товщини міжшлуночкової перетинки (ТМШП), розмірів лівого та правого передсердя (ЛП та ПП), правого шлуночка (ПШ) у всіх класах ПАТ свідчать про необхідність більш активного моніторингу, ретельного підбору параметрів стимуляції і корекції медикаментозної підтримки пацієнтів у IV класі ПАТ.

КЛЮЧОВІ СЛОВА: кардіоресинхронізуюча терапія, медикаментозна терапія, пульсовий артеріальний тиск, гемодинамічні показники

КЛАССЫ ПУЛЬСОВОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И ГЕМОДИНАМИЧЕСКИЕ ПОКАЗАТЕЛИ У ПАЦИЕНТОВ НА ГОДОВОМ ЭТАПЕ ПОСЛЕ КАРДИОРЕСИНХРОНИЗИРУЮЩЕЙ И МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ

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Изучены изменения функциональных показателей кровообращения у 19 пациентов (13 мужчин и 6 женщин) на годовом этапе наблюдения после кардиоресинхронизирующей (КРТ) и медикаментозной терапии в классах пульсового артериального давления (ПАД: I – очень низкое – менее 20 мм. рт. ст., II – низкое – более 20 – менее 40 мм. рт. ст., III – норма – 40–60 мм. рт. ст., IV – высокое – более 60 – менее 80 мм. рт. ст., V – очень высокое ПАД - более 80 мм. рт. ст.). Достоверность отличий между группами определялась с помощью U-критерия Манна-Уитни. Результаты показали, у пациентов на всем периоде наблюдения после КРТ и медикаментозной терапии происходит нормализация диастолического АД (ДАД), частоты сердечных сокращений (ЧСС) и фракции выброса левого желудочка (ФВЛЖ) во всех классах ПАД, систолического АД (САД), конечно-систолического и конечно-диастолического объема (КСО и КДО) в III классе ПАД. Тенденция нормализации САД в IV классе, толщины задней стенки ЛЖ (ТЗСЛЖ) и массы миокарда ЛЖ (ММЛЖ) и отсутствие изменений толщины межжелудочковой перегородки (ТМЖП), размеров левого и правого предсердий (ЛП и ПП), правого желудочка (ПЖ) во всех классах ПАД свидетельствуют о необходимости более активного мониторинга, тщательного подбора параметров стимуляции и коррекции медикаментозной поддержки пациентов в IV классе ПАД.

КЛЮЧЕВЫЕ СЛОВА: кардиоресинхронизирующая терапия, медикаментозная терапия, пульсовое артериальное давление, гемодинамические показатели

INTRODUCTION

Cardiac resynchronization therapy (CRT) is widely used and has a positive clinical effect in patients with chronic heart failure (CHF), accompanied by cardiac dyssynchrony, however, medical support is not canceled [1].

Reflecting the elastic properties of the great vessels and left ventricular (LV) function [2], pulse pressure (PP) is one of the most important hemodynamic parameters and is an independent predictor of cardiovascular events [3]. Non-physiological PP promotes the dynamic load on the myocardium and the development of hypertrophy with subsequent development of cardiovascular events [4].

By optimizing the heart function, synchronizing heart chambers contraction, CRT improves the pumping function of the heart [2, 5], which is accompanied by LV remodeling [1, 6] and changing in hemodynamic parameters, including PP. However, the functional parameters of blood circulation changing in the PP classes in the long-term follow-up after CRT on background of medical therapy has not yet been studied.

MATERIALS AND METHODS

19 patients, including 13 men and 6 women were examined in the department of ultrasound and instrumental diagnostics with miniinvasive interventions of SI «V. T. Zaytsev Institute of General and Emergency Surgery NAMS of Ukraine». Mean age of the patients was 67 ± 9 years; all of them were implanted CRT in period from 2006 to 2015. Indications for pacemaker implantation were: atrioventricular (AV) block – 21 % patients, bundle branch block – 47 %, sick sinus syndrome (SSS) – 26 % patients, permanent bradysystolic form of atrial fibrillation (AF) – 26 %, dilated cardiomyopathy (DCM) – 21 % patients.

Exclusion criteria were: age less than 40 years, the presence of concomitant angina IV functional class (FC), chronic heart failure (CHF) IV FC, stimulation of the right ventricular (RV) and/or LV lesser than 50 % during the year of observation.

Systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), end-systolic (ESV), end-diastolic volumes (EDV), LV ejection fraction (LV EF), posterior wall thickness of LV (PWLV), interventricular septum thickness (IVS), myocardial mass of LV (MMLV), right atrium (RA), left atrium (LA) and RV sizes were evaluated before the implantation, in the early postoperative period (3–5 days), after 6 months and 1 year after CRT and medication depending on the PP classes.

SBP and DBP were measured by Korotkov's method according to the recommendations of the Association of Cardiologist of Ukraine for the prevention and treatment of hypertension by tonometer Microlife BP AGI-20 after 15 minutes rest. PP was calculated by the formula: PP=SBP-DBP (mm Hg).

Echocardiography study was performed with use of Siemens Cypress and Toshiba Applio 400 machines. LA, RA, RV, PWLV, IVS (measuring accuracy is 0.5 mm), end-systolic (ESS), end-diastolic (EDS) sizes were measured. LV EF was calculated using the formula: EF = (EDV–ESV)/EDV×100 %. The Simpson method was used for calculating EDV and ESV. MMLV was calculated using the Devereux formula:

MMLV=1.04 × ((IVSd+PWLVd+EDS)^3 – EDS^3)–13.6.

Medication support of patients with CRT was provided with: rennin-angiotensin-aldosterone inhibitors (RAAI) (angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARA II)), diuretics, antiarrhythmic drugs (beta-blockers and amiodarone), antithrombotic drugs (antiplatelet agents – acetylsalicylic acid (ASA), oral anticoagulants (AC) – warfarin/dabigatran), statins.

Patients were assigned into five classes according to levels of PP: I - very low - less than 20 mm Hg; II – low – from 20 to 40 mm Hg; III – normal – from 40 to 60 mm Hg; IV – high – from 60 to 80 mm Hg; V – very high PP – more than 80 mm Hg. In each groups of patients at the annual observation point SBP, DBP, HR, ESV, EDV, LVEF, PWLV, IVS, MMLV, RA, LA and RV sizes were determined. Functional parameters of blood circulation in the CRT (P/D) stimulation modes were assessed.

The data were brought into the Microsoft Excel base. For statistical evaluation of the results were used the parametric criteria (M – mean, sd – standard deviation). Significant differences between groups were determined using the Mann-Whitney U-test. Probable results were determined at levels of reliability $p < 0.05$ and $p < 0.01$.

RESULTS AND DISCUSSION

In I, II and V PP classes there are no patients registered, in the III class – 68 %, in the IV class – 32 % of patients.

Table 1 shows SBP, DBP and HR values in patients within one year after CRT and medical support in different PP classes. Initially SBP in III class was in a range of the 1st degree of hypertension (AH) and IV – at the 2nd degree of AH, at the annual stage after CRT and drug therapy has reached physiological range in III and decreased till 1st degree of AH at the IV PP class. DBP was at the physiological level in all groups in the entire observation stage. Initially a low HR in the IV PP class normalized after implantation, in III class – was in the physiological range before and during the year after CRT and drug therapy.

Table 1

SBP, DBP and HR values (M ± sd) in patients within one year after CRT and medical support in different PP classes

Functional values	PP							
	III class				IV class			
	Before CRT	After CRT			Before CRT	After CRT		
		3–5 day	6 month	1 year		3–5 day	6 month	1 year
SBP (mm Hg)	142 ± 8	145 ± 6	135 ± 8	133 ± 6^	162 ± 7*	156 ± 7*	149 ± 8	142 ± 3^
DBP (mm Hg)	84 ± 6	85 ± 9	85 ± 4	84 ± 3	86 ± 8	85 ± 3	85 ± 4	86 ± 8
HR (bpm)	73 ± 19	74 ± 20	68 ± 4	67 ± 5	50 ± 11	62 ± 7	68 ± 6^	67 ± 8^

Note: * $p < 0.05$ – in current values between groups, ^ $p < 0.05$ – certain class of values before and after CRT.

Table 2 shows heart ultrasound values in patients within one year after CRT and medical support in different PP classes. Initially increased ESV and EDV, more pronounced in IV class, were normalized at III and tended to decrease in IV PP class without statistically significant differences between the groups at the annual stage after CRT and drug therapy. Initially reduced LV EF, more pronounced in IV class, came close to normal after 6 months and reached physiological range in a year in all PP classes after CRT and drug therapy. Initially increased PWLV and MMLV, more pronounced in IV class tended to decrease in all PP classes without statistically significant differences between the groups at the annual stage after CRT and drug therapy. Equally increased IVS, LA, RA and RV sizes did not change in all PP classes in the entire period of observation after CRT on the background of medical therapy.

Table 2

Heart ultrasound values (M ± sd) in patients within one year after CRT and medical support in different PP classes

Functional values	PP							
	III class				IV class			
	Before CRT	After CRT			Before CRT	After CRT		
		3–5 day	6 month	1 year		3–5 day	6 month	1 year
ESV	98 ± 12	98 ± 15	70 ± 8	56 ± 11^	134 ± 21*	134 ± 18*	106 ± 18*	81 ± 12^
EDV	174 ± 16	174 ± 9	142 ± 4	126 ± 11^	202 ± 10*	202 ± 11*	188 ± 24*	179 ± 6^
LV EF (%)	43 ± 4	43 ± 6	50 ± 4	63 ± 5^	33 ± 4*	33 ± 7	43 ± 6	55 ± 8^
PWLV (cm)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.35 ± 0.2	1.35 ± 0.2	1.35 ± 0.1	1.3 ± 0.1
IVS (cm)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.1	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.2
MMLV (cm)	354 ± 27	354 ± 31	328 ± 46	302 ± 23	426 ± 37*	426 ± 35*	406 ± 35*	381 ± 28*
RA (cm)	3.6 ± 0.2	3.6 ± 0.2	3.6 ± 0.2	3.6 ± 0.1	3.9 ± 0.2	3.9 ± 0.2	3.9 ± 0.1	3.9 ± 0.1
LA (cm)	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1
RV (cm)	5 ± 0.1	5 ± 0.1	5 ± 0.1	5 ± 0.2	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.2

Note: * $p < 0.05$ – in current values between groups, ^ $p < 0.05$ – certain class of values before and after CRT.

Normalization of DBP, HR, LV EF in all PP classes; SBD, ESV and EDV in III class at the annual stage after CRT and drug therapy that were found is indirectly confirmed by data [6, 7].

Shown in our research decreasing of SBP in IV PP class to the level of the 1st degree of AH, and the downward trend PWLV and MMLV, no change in IVS, LA, RA and RV sizes in all PP classes after CRT and drug therapy is indirectly confirmed by data [8].

Our research has shown that PP is significant in the assessment of hemodynamic parameters in patients after CRT and drug therapy. More favorable changes of functional blood circulation parameters in III, and less – in IV PP classes at the annual observation stage after CRT indicate the need for further medical treatment in a high PP class. The given data are new.

CONCLUSIONS

1. Patients with indications don't have I, II and V PP classes, frequency of occurrence III and IV classes represent 68 % and 32 %, respectively.

2. At the annual stage of CRT and drug therapy in both PP classes DBP, HR and LV EF are fully normalized, in III PP class – SBP, ESV and EDV, and in IV PP class only partially normalization of SBP without achieving a physiological rate.

3. At the annual stage of CRT and drug therapy in both PP classes is a PWLV and MMLV tendency of normalization without statistically significant differences between the groups and no changes in the IVS, LA, RA, RV sizes.

4. More active monitoring, careful selection of stimulation parameters and correction of medical support for patients in IV PP class after CRT is need.

PROSPECTS FOR FUTURE STUDIES

Further investigation of the effect of drug therapy on the optimization of the PP in patients with implanted pacemaker depending on the mode of stimulation in the long pacing period seems to be a perspective direction of researches.

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A COMPARATIVE ASSESSMENT OF THE EFFECT OF MINERALOCORTICOID RECEPTOR ANTAGONISTS ON CHANGES IN GALECTIN-3 AND MMP-1 FIBROSIS MARKERS IN PATIENTS WITH CHRONIC CARDIAC FAILURE COMBINED WITH TYPE 2 DIABETES MELLITUS WITH MANIFESTATIONS OF MYOCARDIUM DYSSYNCHRONY

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A comparative assessment of the effect of mineralocorticoid receptor antagonists on changes in galectin 3 and matrix metalloproteinase 1 fibrosis markers has been carried out on 106 examinations (average age (69 ± 10.37) years) with type 2 DM and CCF of ischemic nature of I-IV FC according to NYHA with retained systolic function of the left ventricle and manifestations of myocardium dyssynchrony.

All the patients were divided into 3 groups depending on the intake of mineralocorticoid receptor antagonists. Myocardium dyssynchrony was assessed according to the generally accepted technique; the volume faction of interstitial collagen was measured using the formula of J. Shirani et al.; galectin-3 and matrix metalloproteinase-1 levels – using the immunoenzyme method according to the manufacturer's manual. The data was processed using the methods of parametric and non-parametric statistics. It was discovered that the myocardium dyssynchrony development percentage in the group of patients not taking mineralocorticoid receptor antagonists was higher than in the group of patients taking spironolactone or eplerenone. An increase in fibrosis marker levels was shown in the spironolactone intake group compared with the group of patients taking eplerenone. Mineralocorticoid receptor antagonist intake requires blood potassium level control and case monitoring of manifestations of dyssynchrony and myocardial fibrosis.

KEY WORDS: interstitial collagen volume faction, chronic cardiac failure, myocardium dyssynchrony, galectin 3, matrix metalloproteinase 1

ПОРІВНЯЛЬНА ОЦІНКА ВПЛИВУ АНТАГОНІСТІВ МІНЕРАЛОКОРТИКОЇДНИХ РЕЦЕПТОРІВ НА ЗМІНИ МАРКЕРІВ ФІБРОЗУ ГАЛЕКТИН-3 І ММП-1 У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ В ПОЄДНАННІ З ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ З ПРОЯВАМИ ДИССИНХРОНІЇ МІОКАРДА

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На 106 обстежуваних (середній вік (69 ± 10,37) років) з ЦД 2-го типу та ХСН ішемічного генезу I–IV ФК за NYHA зі збереженою систолічною функцією лівого шлуночка та проявами диссинхронії міокарда, проведена порівняльна оцінка впливу антагоністів мінералокортикоїдних рецепторів на зміни маркерів фіброзу галектину-3 і матриксної металлопротеінази-1.

Усі пацієнти були розділені на 3 групи в залежності від прийому антагоністів мінералокортикоїдних рецепторів. Диссинхронію міокарда оцінювали за загальноприйнятою методикою, об'ємну фракцію інтерстиціального колагену вимірювали за допомогою формули J. Shirani і співавторів, рівень галектіна-3 і матриксної металлопротеінази 1 за допомогою імуноферментного методу згідно з інструкцією від виробника. Дані обробляли методами параметричної та непараметричної статистики. Виявлено, що в групі хворих, що не приймали антагоністи мінералокортикоїдних рецепторів відсоток розвитку диссинхронії міокарда був вище ніж в групі хворих, що вживали спіроналактон або еплеренон. Показано підвищення рівнів маркерів фіброзу у групі прийому спіроналактону у порівнянні з групою хворих що приймали еплеренон. Прийом антагоністів мінералокортикоїдних рецепторів вимагає контролю рівня калію крові і динамічне спостереження за проявами диссинхронії та міокардіального фіброзу.

КЛЮЧОВІ СЛОВА: об'ємна фракція інтерстиціального колагену, хронічна серцева недостатність, диссинхронія міокарда, галектин-3, матриксна металлопротеіназа-1

СРАВНИТЕЛЬНАЯ ОЦЕНКА ВЛИЯНИЯ АНТАГОНИСТОВ МИНЕРАЛОКОРТИКОИДНЫХ РЕЦЕПТОРОВ НА ИЗМЕНЕНИЯ МАРКЕРОВ ФИБРОЗА ГАЛЕКТИНА-3 И ММП-1 У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ В СОЧЕТАНИИ С САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА С ПРИЗНАКАМИ ДИССИНХРОНИИ МИОКАРДА

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У 106 пациентов, (средний возраст (69 + 10,37) лет) с СД 2-го типа и ХСН ишемического генеза I - IV ФК по NYHA с сохраненной систолической функцией и признаками диссинхронии миокарда, проведена сравнительная оценка влияния антагонистов минералокортикоидных рецепторов на изменения маркеров фиброза, галектина-3 и матриксной металлопротеиназы-1, у больных с хронической сердечной недостаточностью в сочетании с сахарным диабетом 2-го типа с признаками диссинхронии миокарда. Обследуемые разделены на 3 группы в зависимости от приема антагонистов минералокортикоидных рецепторов. Диссинхрония миокарда оценивалась по общепринятой методике, степень выраженности объемной фракции интерстициального коллагена определяли с помощью формулы J. Shirani и соавторов, вровень галектина-3 и матриксной металлопротеиназы-1 с помощью иммуноферментного метода согласно инструкции от производителя. Данные обрабатывали методами параметрической и непараметрической статистики. Выявлено, что в группе больных, не принимавших антагонистов минералокортикоидных рецепторов, процент развития диссинхронии миокарда был выше, чем в группе больных, употребляющих спироналактон или эплеренон. Также показано повышение уровней маркеров фиброза в группе приема спиронолактона в сравнении с группой больных, принимающих эплеренон. Прием антагонистов минералокортикоидных рецепторов требует контроля уровня калия крови и динамическое наблюдение за признаками диссинхронии и миокардиального фиброза.

КЛЮЧЕВЫЕ СЛОВА: объемная фракция интерстициального коллагена, хроническая сердечная недостаточность, диссинхрония миокарда, галектин-3, матриксная металлопротеиназа-1

INTRODUCTION

An increased aldosterone level tends to promote fibrosis development in hypertrophic heart ventricles, decreases myocardial perfusion and it was discovered [1] based on systematic review of the clinical trials carried out by Ezekowitz et al. [2] that the mineralocorticoid receptor antagonists used decrease mortality among patients with chronic cardiac failure (CCF) by 20 %. It is generally recognized that heart remodeling is the main pathogenic sign of left ventricle dysfunction. [3]

Several clinical trials were carried out to study the potential influence of the drugs in question on heart remodeling in patients with CCF, but comprehensive information on the assessment of this influence is not sufficient. Due to this fact, there is a need to continue research aimed at the study of the peculiarities of changes in heart structure and function in patients with left ventricle dysfunction. [4–5]

According to the recommendations of the European Society of Cardiology, mineralocorticoid receptor antagonists are assigned IA recommendation class as first-line drugs for the treatment of CCF of ischemic origin. [6–9] However, the issue of the wide use of these drugs to decrease myocardial fibrosis is still discussed widely; meanwhile, comparative discussions regarding which drug is to be preferred – spironolactone or eplerenone – are held. [4, 10]

There is still no clear information concerning changes in fibrosis marker activity if mineralocorticoid receptor antagonists are used in patients with CCF of ischemic nature accompanied by type 2 diabetes mellitus and manifestations of myocardium dyssynchrony (MD).

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OBJECTIVE

To carry out a comparative assessment of the influence of mineralocorticoid receptor antagonists on changes in galectin 3 and matrix metalloproteinase 1 fibrosis markers in patients with chronic cardiac failure combined with

type 2 diabetes mellitus with manifestations of myocardium dyssynchrony.

MATERIALS AND METHODS

For the study to be completed, 106 patients with type 2 DM and CCF of ischemic genesis of I–IV FC under NYHA with retained systolic function and manifestations of myocardium dyssynchrony were examined. The average age of all the examinees was (67.45 ± 10.32) years. 43 men (41 %), aged (65 ± 10.62) on average, and 63 women (59 %), aged (69 ± 10.37) on average, were examined in the group. Fibrosis marker activity in the blood serum was determined for 72 examinees.

The criteria of inclusion in the study were as follows: having type 2 DM and CCF of I–IV FC under NYHA. Patients were excluded from analysis if they had an acute coronary distress or chronic kidney failure.

Type 2 DM was diagnosed according to the recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) concerning type 2 DM diagnosing criteria.

Myocardial fibrosis was assessed with the content of galectin 3 and matrix metallo-proteinase (MMP) 1 in the blood serum determined using the immunoenzyme method; galectin 3 based on the Human Galectin-3 kit (Platinum ELISA; eBioscience, Bender MedSystems, Austria) and MMP-1 content based on the Human MM3-1 kit (ELISA; Abfrontier Biotechnology supplier, South Korea). The degree of interstitial collagen volume fraction was calculated from the formula of J. Shirani et al. [11]: ICVF (%) = $(1\text{-}1{,}3*\frac{totalQRS(mm)\,x\,height\,(m)}{LVMM\,(g)})*100$,

wherein the normal level of ICVF was set within the range of 1 % and 2 %.

Myocardium dyssynchrony was assessed using echocardiography synchronized with electrocardiography according to the generally accepted method of determining myocardium dyssynchrony, where the following was determined: the septal to posterior wall motion delay (SPWMD), the aortic (APEI) and pulmonary (PPEI) pre-ejection interval, the interventricular mechanical delay (IVMD), the left ventricular filling time (LVFT), the registration time of E and A waves, the left ventricular ejection time (LVET), the isovolumic relaxation time (IVRT), the early ventricular filling flow deceleration time (DT), the time from the start of the QRS complex to the start of the peak systolic velocity, the time to the peak systolic velocity (Ts), the root-mean-square time deviation to the peak LV systolic velocity (Ts-SD).

To complete the task set, the examinees (n = 106) were divided into 3 groups. Group 1, (n = 40) people – 38 % of the examinees, did not take any mineralocorticoid receptor antagonists. Group 2, (n = 34) people – 32 % of the examinees, took 50 mg of spironolactone daily. Group 3, (n = 32) people – 30 % of the examinees, took 50 mg of eplerenone daily.

The data were processed after the base was formed using Microsoft Excel and Statistical software. Parametric (M, SD) and non-parametric (absolute and relative (percentages (p, %) and criterion $\chi 2$) of units)) criteria were used for the statistical assessment of results. The probability of differences between the groups was determined using the Mann-Whitney U-test. The expected result was determined by the confidence level of $p < 0.05$.

RESULTS AND DISCUSSION

The results obtained were analyzed in view of whether there is any dyssynchrony in the groups. Mechanical myocardium dyssynchrony was discovered in 83 (78 %) individuals. Among them, the isolated myocardium dyssynchrony type was diagnosed in 52 individuals (49 %): intraventricular myocar-dium dyssynchrony in 49 individuals (46 %), atrioventricular one in 2 individuals (1.8 %), interventricular one in 1 individual (0.94 %), and the combined type in 31 individual (29 %). 8 examinees (20 %) in group 1 had no signs of myocardium dyssynchrony; interventricular MD was observed in 1 individual (2.5 %); 20 individuals (50 %) had intraventricular MD; 11 individuals (27.5 %) had combined type MD. In group 2, 9 (26 %) of the examinees had no signs of myocardium dyssynchrony; intraventricular MD was noted in 12 individuals (35 %); 13 individuals (38 %) had combined type MD. In group 3, 7 examinees (22 %) had no signs of myocardium dyssynchrony; 2 individuals (6 %) had atrioventricular dyssynchrony; 16 individuals (50 %) had intraventricular MD; combined type MD was noted in 7 examinees (22 %).

The highest average values of Gal-3 and MMP-1 were noted in the 2nd group of examinees taking spironolactone. For instance, Gal-3 (9.03 ± 1.06) ng/ml, the lowest Gal-3 in

the group not taking the drugs is (6.68 ± 0.64) ng/ml. MMP-1 in group 1 not taking the drugs was lowest, (0.27 ± 0.05) ng/ml; in group 2 of the examinees taking spironolactone, MMP-1 was (0.72 ± 0.36) ng/ml (Tab). VICF in the 1st group of examinees not taking the drugs was lowest, (6.92 ± 0.47) %. The VICF values did not differ significantly between groups 2 (patients taking spironolactone) and group 3 (patients taking eplerenone) (tab.).

Table

Fibrosis marker activity in patients with type 2 DM and CCF of ischemic nature with manifestations of MD depending on the intake of mineralocorticoid receptor antagonists – spironolactone and eplerenone (M ± m)

Indicator	Group 1 (n=40)	Group 2 (n=34)	Group 3 (n=32)
Gal-3, ng/ml	6.68±0.64	9.03±1.06	7.07±0.93
MMP-1, ng/ml	0.27±0.05	0.72±0.36*	0.64±0.36
VICF, %	6.92±0.47	7.26±0.46	7.55±0.49

Notes: – the degree of probability of differences in group 2 compared with group 1 ($p \leq 0.05$).

Thus, the lowest percentage of combined forms of myocardium dyssynchrony, which aggravate CCF manifestations the most, was noted in the group of the examinees taking eplerenone. Increased MMP-1 levels in patients taking mineralocorticoid receptor antagonists evidence that collagen degradation processes are launched. Increase in myocardium fibrosis increases electric non-homogeneity by strengthening leading heart system dysfunction. In [12–14] early use of spironolactone and eplerenone hinders further development of myocardium fibrosis by improving noradrenaline consumption by the myocardium and increases the pumping function productivity of the myocardium, hindering left ventricle remodeling in patients with CCF. [15–16] For a clearer notion of myocardial fibrosis against the background of spironolactone and eplerenone intake, it is expedient to study galectin 3 and MMP 1 markers in real time for several months more from the start of the treatment.

CONCLUSIONS

Fibrosis marker activity is more expressed in the examinees on spironolactone than in the patients taking eplerenone. Higher myocardium dyssynchrony values and a higher percentage of combined forms of myocardium dyssynchrony are observed in the examinees who have not been taking any mineralocorticoid receptor antagonists than in the examinees taking spironolactone or eplerenone. For a clearer notion of the dynamics of change in myocardial fibrosis against the background of spironolactone and eplerenone intake, it is expedient to study galectin 3 and MMP 1 markers for several months more from the start of the treatment, monitoring the blood potassium level and manifestations of myocardium dyssynchrony against the background of type 2 DM with CCF of ischemic nature.

PROSPECTS FOR FUTURE STUDIES

Further study of the peculiarities of changes in interstitial collagen values depending on the use of therapy aimed towards decrease in myocardial fibrosis and myocardium dyssynchrony phenomena by titrating the daily doses of the drugs remains topical.

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DEPENDENCE OF NEUROPSYCHOLOGICAL DEVELOPMENT OF EARLY AGE CHILDREN FROM THE FUNCTIONAL ACTIVITY OF SEROTONERGIC AND PITUITARY-THYROID SYSTEMS

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The high frequency of neurological disorders in children deprived of parental care was demonstrated (94.1 ± 2.2 %). The most commonly the syndrome of statokinetic, mental and pre-speaking retardation was diagnosed (49,2 ± 4,7 %, $p < 0,001$). High frequency disturbances of mental development and neurological status are accompanied by a reduction in the functional activity of the pituitary-thyroid system and the activation of serotonin. Between levels of thyrotropin and serotonin in the blood serum there is a moderate direct correlation ($\rho = 0,56$), which may indicate the adaptive increasing of the serotonin system activity, designed to compensate the lack of thyroid effects.

KEY WORDS: neurologic status; psychological development, pituitary-thyroid system; serotonin, young children

ЗАЛЕЖНІСТЬ НЕРВОВО-ПСИХІЧНОГО РОЗВИТКУ ДІТЕЙ РАННЬОГО ВІКУ ВІД ФУНКЦІОНАЛЬНОЇ АКТИВНОСТІ СЕРОТОНІНЕРГІЧНОЇ ТА ГІПОФІЗАРНО-ТИРЕОЇДНОЇ СИСТЕМ

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У статті продемонстрована висока частота клінічних проявів перинатальних уражень нервової системи серед дітей раннього віку, позбавлених батьківського піклування (94,1±2,2 %). Встановлено, що в структурі неврологічних порушень домінує синдром затримки стато-кінетичного, психічного і предмовленнєвого розвитку (49,2 ± 4,7 %, $p < 0,001$). Висока частота порушень нервово-психічного розвитку та неврологічного статусу супроводжується зниженням функціональної активності гіпофізарно-тиреоїдної системи та активізацією серотонінергічної. Між рівнями тиреотропіну та серотоніну в сироватці крові існує прямий кореляційний зв'язок помірного ступеню ($\rho = 0,56$), що може вказувати на адаптаційний характер підвищення активності серотонінергічної системи, спрямований на компенсацію недостатності тиреоїдних впливів.

КЛЮЧОВІ СЛОВА: неврологічний статус; нервово-психічний розвиток; гіпофізарно-тиреоїдна система; серотонін, діти раннього віку

ЗАВИСИМОСТЬ НЕРВНО-ПСИХИЧЕСКОГО РАЗВИТИЯ ДЕТЕЙ РАННЕГО ВОЗРАСТА ОТ ФУНКЦИОНАЛЬНОЙ АКТИВНОСТИ СЕРОТОНИНЕРГИЧЕСКОЙ И ГИПОФИЗАРНО-ТИРЕОИДНОЙ СИСТЕМ

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В статье продемонстрирована высокая частота клинических проявлений перинатальных поражений нервной системы среди детей раннего возраста, лишенных родительской опеки (94,1 ± 2,2 %). Установлено, что в структуре неврологических нарушений доминирует синдром задержки стато-кинетического, психического и предречевого развития (49,2 ± 4,7 %, $p < 0,001$). Высокая частота нарушений нервно-психического развития и неврологического статуса сопровождается снижением функциональной активности гипофизарно-тиреоидной системы и активизацией серотонинергической. Между уровнями тиреотропина и серотонина в сыворотке крови существует прямая корреляционная связь умеренной степени ($\rho = 0,56$), что может указывать на адаптационный характер повышения активности серотонинергической системы, направленный на компенсацию недостаточности тиреоидных воздействий.

КЛЮЧЕВЫЕ СЛОВА: неврологический статус; нервно-психическое развитие; гипофизарно-тиреоидная система; серотонин, дети раннего возраста

INTRODUCTION

Neuropsychological development and neurological status of the young child depends on many factors that affect the nervous tissue both in utero and after birth. One of the main conditions for corrects formation of the structures of the central nervous system (CNS) and provides their functional activity is an adequate level of thyroid hormones. It is believed that thyroid hormones (TH) play role of a kind «timer», which provides a clear sequence in the formation, maturation and functioning of the nervous system. The most critical is a violation of thyroid homeostasis during the antenatal period and the first years of life. In the embryonic period of development TH affect the processes of neurogenesis, neuronal migration, maturation of axons and participate in the growth of dendrites [1–2]. Adequate levels of these hormones after birth is required for ensure timely myelination and the formation of a sufficient number of synaptic connections, a high level of functional activity of the brain [3–4].

Significant place in the regulation of the formation and functioning of the CNS also belongs to biogenic amines, particularly serotonin. Serotonin (5-hidroksitryptamin) is formed in the body as a result of conversion of the amino acid L-tryptophan in various organs and tissues. In the embryonic period, like thyroid hormones, it affects glia proliferation, differentiation of neurons, myelination of axons and accelerates the maturation of the nervous system. With it participation in the early neonatal period occurs branching of neurons. In addition, at any age serotonin acts as a neurotransmitter of synaptic transmission of nerve impulses. Mediator the role of it was first proved by V. V. Brodie and P. A. Shore (1957). Serotonin which is synthesized by specific system of neurons, moves on axons, reaching its terminals and by releasing interacts with serotonergic receptors of other neurons. The basic amount of neurons that synthesize serotonin located in nine-seam cores (nuclei raphe) and placed in the center of the middle and medulla oblongata. These neurons and their axons are regarded as specific serotonergic system of the brain. The two main serotonergic ways are described: mesolimbic and mesostrial. Serotonergic system of the brain is involved in regulating the overall activity level of CNS, cycles of sleep and vivacity, outdoor activity, emotional behavior, learning and memory processes.

Functioning of serotoninergic and pituitary-thyroid system (PTS) is in close relationship. Back in the 60s of last century it was suggested the important role of mastocyted serotonin in the synthesis of TH. During conducted studies it was found that tissue basophils of TG not synthesize serotonin but by it holding regulates the level of bioamines in an environment of follicles. The nature of serotoninergic regulation of thyroid function depends on the actions of a mediator. It has been demonstrated that the presence of serotonin in the incubation environment provides similar to thyroid-stimulating hormone (TSH) direct stimulatory effect on thyrocytes and increases it sensitivity to TSH. In addition, it was shown that serotonin stimulates proliferation of thyrocytes by activation of anabolic processes through guanylate cyclase mechanisms of cellular regulation. In its turn, the exchange of bioamines in the brain is sensitive to changes in thyroid status: in hyperthyroidism content of serotonin in the brain tissue is usually increased, while hypothyroidism contrary - is reduced. Thus, neurotransmitters are modified of thyroidin production, on the other hand - the synthesis of neurotransmitters is controlled by TG. [5–6].

The prevalence of neuropsychological disorders and perinatal CNS dysfunction in young children has increased significantly in recent years. Group of special risk are children who arrive for life to baby home because mostly born from pregnancies that were unwanted, against the background of insufficient and/or poor nutrition, alcohol abuse, mothers smoking, without necessary medical supervision. These children often have congenital malformations, lagging in physical and neuro-psychological development. In addition, at the time of admission for the life to baby home is usually impossible to set completely anamnesis and identify specific factors of nervous system damaging. This necessitates to the study of neurohormonal disorders that affect the functional activity of CNS in young children for rationale and

develop new and improve existing rehabilitation.

OBJECTIVE

The research goal is to examine functional activity of serotoninergic and pituitary-thyroid system and analyze its impact on neuro-mental development and neurological status of young children.

MATERIALS AND METHODS

During the study were examined 123 children aged between 2 and 3.5 months, which came for life to the baby house as children deprived of parental care (continuous pooled sample). The study was carried out after obtaining the views of Ethics Committee, the consent of the local authorities and fiduciary. After excluding children with congenital anomalies of development (5/123, 4,1 ± 1,7 %) under the supervision was remained 118 children: 56 girls (47,5 ± 4,6 %) and 62 boys (52,5 ± 4,6 %). The amount of primary research has been standardized for each child and includes: review and objective examination of children for signs of violations of the functioning of the endocrine and nervous systems and adaptive processes; assess their neuropsychological development; studying the functional level of the pituitary-thyroid and stress limits systems.

Evaluation of physical and psychomotor development of children was held in dynamics according to clinical protocols of medical care for a healthy child under 3 years approved by the Ministry of Health of Ukraine from 20.03.2008 № 149.

Evaluation of neurological status was performed based on neurological examination according to the classification of lesions of the nervous system in children and adolescents (Martynyuk V. Y.). Prevailing of clinical syndromes of the nervous system, such as the syndrome of increased neuro-reflex excitability, syndrome of statokinetic and psycho-speaking delay and syndrome of movement disorders were taken into account.

In order to examine characteristics of the functional state of the pituitary-thyroid system and its relationship with the state of stress limits system for all children was conducted in-depth research on the biochemical definition of thyrotropin (TSH).

TSH level was determined by competitive solid phase chemiluminescent enzyme immunoassay using test kits «Immulite 1000 Rapid TSN», «Immulite 1000 Total T3» on automatic analyzer («Diagnostic Products Corporation», Los Angeles, USA).

Under the optimal functional state of the pituitary-thyroid system was considered TSH level within 0,4–2,0 mU/L with normal level of thyroxine. Increased TSH within 2,0-4,0 mU/L with normal rate of free T4 was used the term minimal thyroid dysfunction. If the TSH level was higher than 4,0 mU/L with reduction of free T4 to the lower border of norm (12,0 pmol/L) was noted the status of subclinical hypothyroidism. If level of TSH was reduced to 0,3 mU/L with higher level of thyroxine above 22,0 pmol/L was set state of hyperthyroidism [7].

The concentration of serotonin in the blood serum was determined by competitive solid phase chemiluminescent enzyme immunoassay using a set of test systems Serotonin ELISA («IBL Hamburg», Germany).

Mathematical processing was performed by variation statistics (statistical hypothesis testing, variance and correlation analysis) by which was defined qualitative and quantitative relationship between parameters of study.

Averages of arithmetic mean (M), median (Me), mode (Mo), standard error of mean values (m), standard deviation (σ) and confidence intervals (CI) were calculated.

Before comparing averages and reliability assessment of differences between them was behaved verify compliance with normal Gaussian distribution. Then control of variances data was performed by Fisher criterion - in the case of normal distribution, by criterion Siegel-Tukey – in the case of abnormal distribution. In the normal distribution average data was presented in the form of M ± m (CI 95), where the CI – confidence interval, and in the distribution, different from normal, in the form of Me [QR], where QR – interquartile range.

If the variance were equal was used t-Student test for equal variances – for normal distribution of data, the criterion of Mann–Whitney–Wilcoxon – on abnormal distribution. If the variance were unequal was used t-Student test for unequal variances – in the case of normal distribution data and Mann–Whitney two-tailed test – in the case of abnormal distribution.

In conducting the statistical analysis of qualitative variables for comparing equity parts (proportions P) was used z-criterion and

criterion $\chi 2$ for contingency table with correction for continuity by Yates. The standard error of the difference and its 95-th confidence interval were determined.

To investigate the relationship between quantitative traits was used mated Pearson correlation coefficient (r) in normal distribution of values and Spearman coefficient (ρ) – in distribution of values different from normal.

Under significance level (α) during comparing statistical hypotheses was taken likelihood of rejecting the null hypothesis when it accuracy is 5 % ($\alpha = 0,05$). In comparing of two values the difference between its was considered reliable at the achieved level of $p < 0,05$. In processing the results of the study was a used standard tool of Microsoft Excel 2007 and application package Statistica 7.0.

RESULTS AND DISCUSSION

According to the results of the clinical neurological examination 94,1 ± 2,2 % (111/118) of children had symptoms of perinatal lesions of the nervous system. According to the data from medical staff of baby home 45,7 ± 4,5 % (54/118) children had a bad dream. On examination in 19,5 ± 3,6 % (23/118) of persons was observed muscular dystonia, 21,2 ± 3,7 % (25/118) had an increased muscle tone, at 4,2 ± 1,7 % (5/118) was occurred muscular hypotonia. Marbling of skin at the examination was observed in 22,8 ± 3,8 % (27/118), recurrent spitting up in 16,1 ± 3,3 % (19/118), positive symptom of Graefe in 10,2 ± 2,7 % (12/118), spontaneous reflex of Moro 16,1 ± 3,3 % (19/118), tremor in limbs and chin in 58,5 ± 4,5 % (69/118), convergent strabismus in 16,1 ± 3, 3 % (19/118), nystagmus in 3,4 ± 1,6 % (4/118). Increased of tendon reflexes were observed in 45,7 ± 4,5 % (54/118), reduction of tendon reflexes was in 24,6 ± 3,9 % (29/118) of children, reduced the amount of active and passive movements was observed in 11,0 ± 2,8 % (13/118), an increased amount of active and passive movements were in 10,2 ± 2,7 % (12/118) inmates of baby home (Fig.1.).

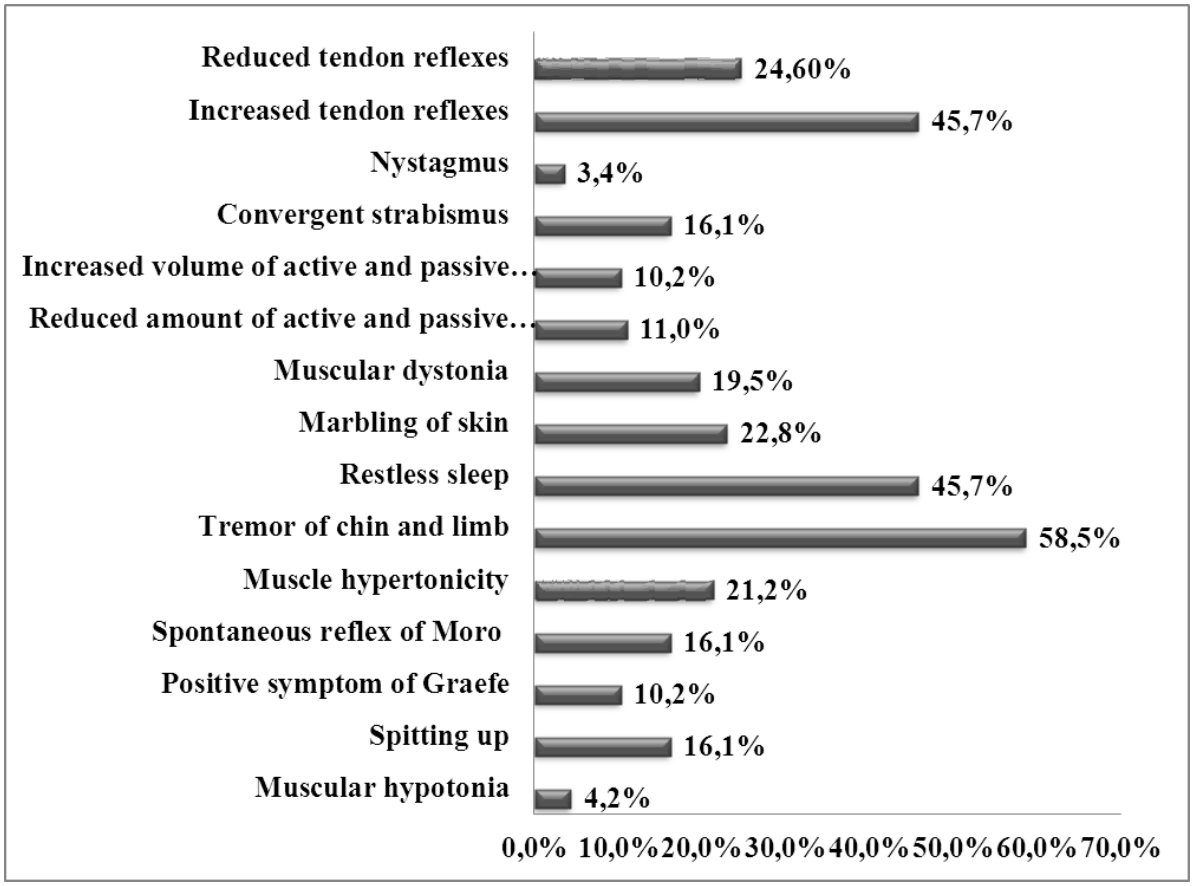

Fig. 1. The nature and frequency of the nervous system lesions in young children

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In the structure of neurological disorders of the recovery period syndrome of statokinetic, mental and speaking delay was dominated. Its features were found in 49,2 ± 4,7 % (58/118) of surveyed children. The syndrome of motor disorders occurred in 26,3 ± 4,1 % (31/118, p < 0,001) children. Manifestations of the syndrome of increased neuro-reflex excitability observed in 18,6 ± 3,6 % (22/118) of cases (p < 0,001). No violations of CNS was found only in 5,9 ± 2,2 % (7/118) of surveyed children in baby home (Fig. 2).

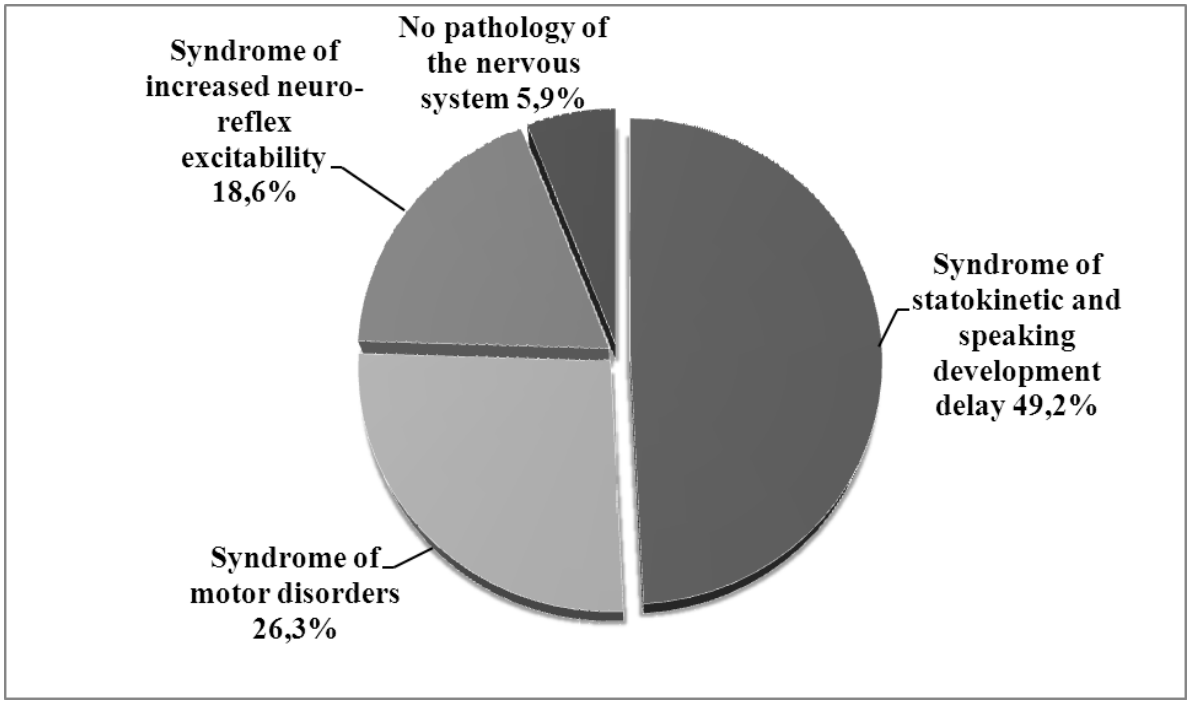

Fig. 2. Structure of neurological disorders of inmates of baby home

Exploring of the functional state of the pituitary-thyroid axis in surveyed children allowed to establish that TSH level in blood serum, optimal range for formation of structures of CNS is 0,3–2,0 mU/L, was determined only in 28,8 ± 4,1 % (34/118) of cases. The most common indicators of TSH were in the range of 2,0–4,0 mU/L in 44,1 ± 4,5 % (52/118) of patients. The level of thyrotropin in blood serum was exaggerated more than 4,0 mU/L in 27,1 ± 4,1 % (32/118) of children. No cases of congenital or transient hypothyroidism (TSH more than 20 mU/L) were found.

Increased of TSH more than 4,0 mU/L statistically more frequently observed in children with clinical manifestations of the syndrome of statokinetic and speaking development delayed - in 39,6 ± 6,3 % of cases (23/58) against 19,3 ± 7,1 % (6/31) of persons with signs of syndrome of motor disorders (p = 0,087) and 13,5 ± 7,2 % (3/22) – in children with symptoms of the syndrome of increased neuro-reflex excitability (p = 0,051). In the group of children with the syndrome of statokinetic and speaking delay the thyrotropin median was 3,5 mU/L [QR: 2,6; 4,7] versus 3,1 mU/L [QR: 1,9; 3,9] in children with the syndrome of motor disorders (p = 0,076), 2,8 mU/L [QR: 1,8; 3,7] – in patients with a syndrome of increased neuro-reflex excitability (p = 0,697) and 2,1 mU/L [QR 1,8; 3,1] – in children with no signs of disorders of the nervous system functioning (p = 0,637) (Fig. 3).

Clinically in children with levels of TSH more than 4,0 mU/L significantly more frequently than in inmates with indices of thyrotropin within 0,3–2,0 mU/L and TSH within 2,0–4,0 mU/L were observed changing of motor features: in 59,3 ± 8,6 % (19/32) of cases versus 5,8 ± 4,0 % (2/34, p < 0,001) and 13,5 ± 4,6 % (7/52, p < 0.001), respectively. Facial expression and fine motor skills was

broken in children with high TSH values in 43,7 ± 8,6 % (14/32) of cases compared with patients with optimal values of thyrotropin (8,7 ± 4,7 %, 3/34, p = 0,003) and normal high levels of TSH (9,5 ± 4,0 %, 5/52, p = 0,001). The frequency of disturbances in emotional and volitional spheres had no difference statistically.

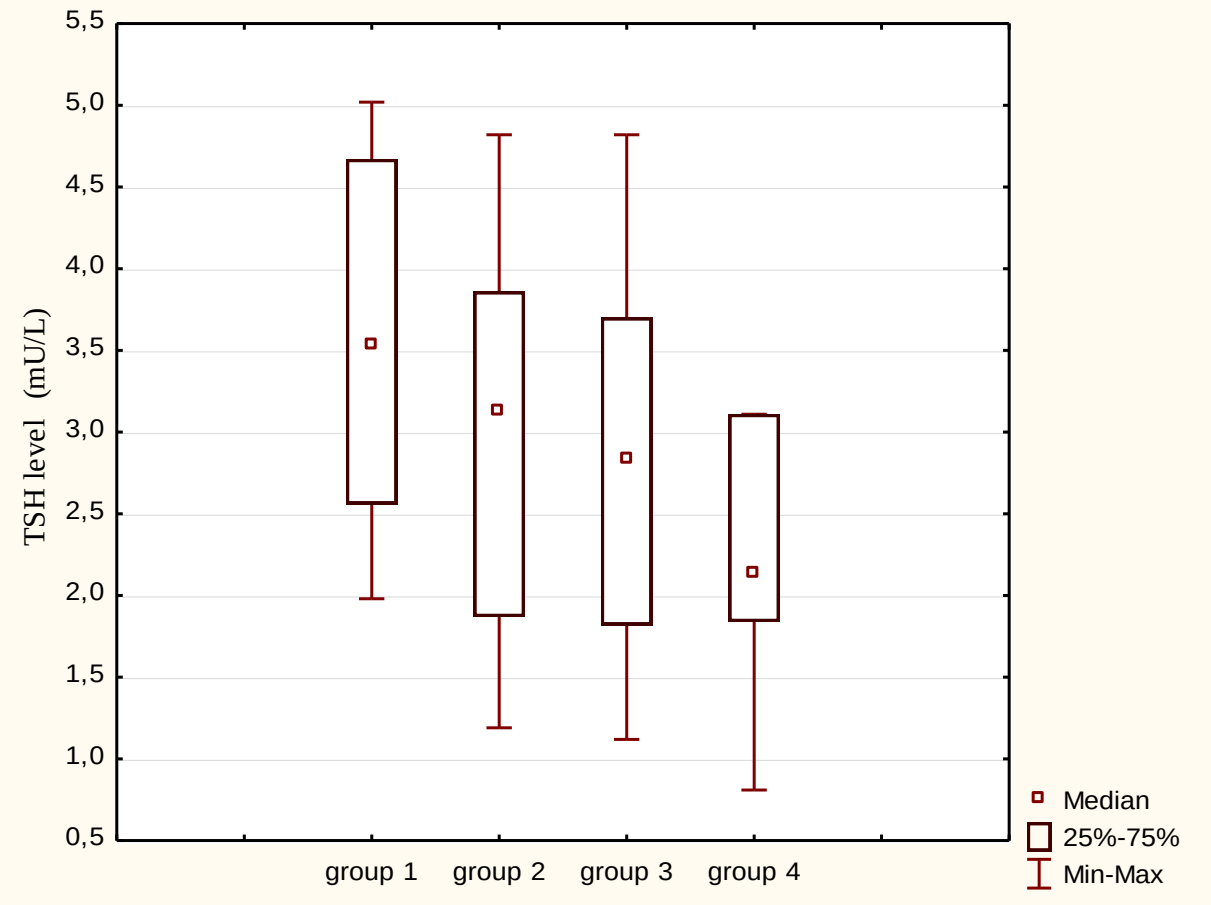

Fig. 3. TSH level in children of early age depending on the nature of the clinical manifestations of the nervous system lesions (mU/L)

Notes: group 1 - children with the syndrome of statokinetic and speaking development delay; group 2 - children with the syndrome of motor disorders; group 3 - children with the syndrome of increased neuro-reflex excitability; group 4 - children without neurological disorders.

The level of serotonin in the blood serum of children with impaired functioning of the nervous system was higher than in healthy children. In the group of children with the syndrome of statokinetic and speaking delay median of serotonin was 202,2 nmol/ml [QR: 194,8; 207,3] versus 198,6 nmol/ml [QR: 185,9; 202,5] in children with the syndrome of motor disorders (p = 0,025), 197,7 nmol/ml [QR: 188,6; 198,9] in patients with the syndrome of increased neuro-reflex excitability (p = 0,004) and 184,9 nmol/ml [QR 175,8; 198,4] – in children without signs of CNS lesions (p = 0,049) (Fig. 4).

During carrying out of Spearman analysis correlation between TSH level and level of serotonin in blood serum was found moderately expressed direct correlation (p = 0,56, p < 0,001) (Fig. 5).

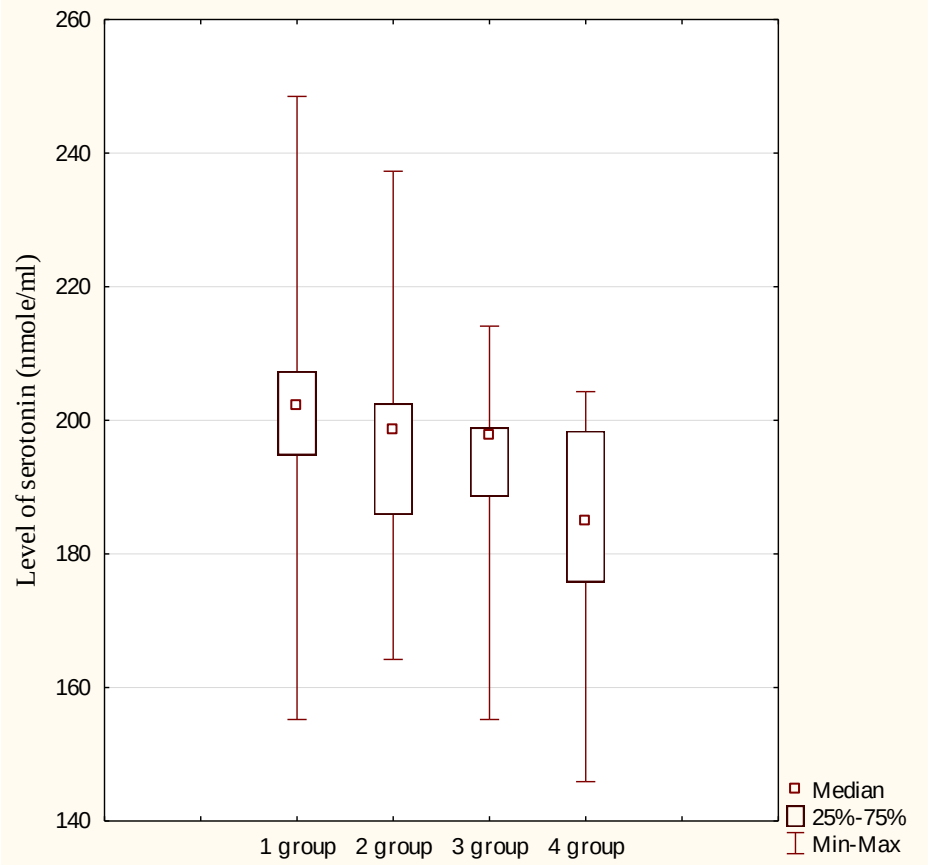

Fig. 4. The level of serotonin in children of early age depending on the nature of clinical manifestations of nervous system lesions

Notes: group 1 – children with the syndrome of statokinetic and speaking development delay; group 2 – children with the syndrome of motor disorders; group 3 – children with the syndrome of increased neuro-reflex excitability; group 4 – children without neurological disorders.

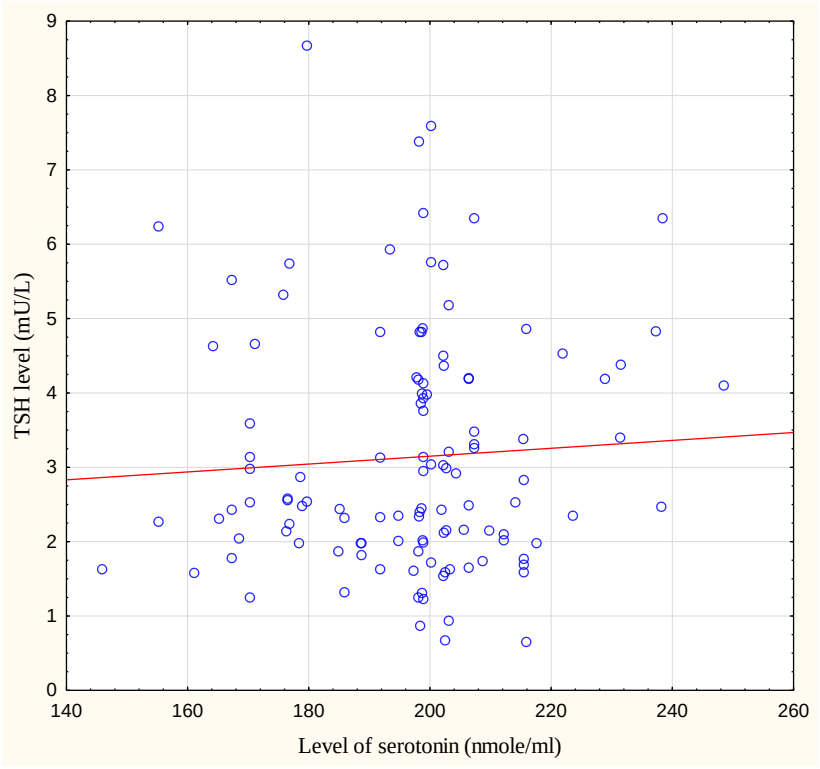

Fig. 5. Correlation between TSH level and level of serotonin

Therefore in the studies were detected unidirectional upward changes of TSH and serotonin in children of early age with impaired neurological status and neuropsychological development. An increased level of TSH reflects the intense functional state of the pituitary-thyroid system and, as it's known, are the results of hypothyroid periods [8–10]. The latter may be a consequence of insufficient activity of the thyroid gland, hypothalamus and pituitary gland and special requirements for thyroid hormones production that, in conditions of iodine insufficiency, debilitating thyroid gland. Hypothyreosis, in the opinion of many researchers, should be considered as one of the main factors of forming disturbances of the nervous system structures [11].

Increasing the concentration of serotonin in the blood serum of children with clinical manifestations of perinatal nervous system indicates activation of adaptive systems, aimed at launching of dendritic branching, activation of synapse formation and continuing formation of neuronal connections. Perhaps that way the child's body tries to compensate for the lack of thyroid regulation of these processes. In favor of this opinion was shown that a serotonin level in children with impaired neurological status is higher than that of children without signs of thyroid disease.

CONCLUSIONS

In the baby home inmates there is a high frequency of decrease of functional activity of the pituitary-thyroid system and serotoninergic activation that is accompanied by neuro-psychological development and neurological status lesions. Between levels of serotonin and thyrotropin in blood serum there is a moderate degree direct correlation ($\rho = 0{,}56$), which may indicate the adaptive nature of increased activity of serotoninergic systems because of thyroid deficiency.

PROSPECTS FOR FUTURE STUDIES

It is necessary to continue further study of this problem for the development of new, more advanced methods of rehabilitation and treatment of neuropsychiatric disorders of children of early age by correction of thyroid regulation based on the study of functional features of stress limits and pituitary-thyroid system.

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UDC [616.379-008.64+616.12.331.1]-078:57.083.185'175.8

ROLE OF NESFATIN-1 IN MAINTAINING CARBOHYDRATE HOMEOSTASIS IN HYPERTENSIVE PATIENTS

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The aim of this study is to analyze changes in the nesfatin-1 level in hypertensive patients depending on the carbohydrate profile parameters. 83 hypertensive patients aged 33 to 77 years were examined. Nesfatin-1 levels were determined by enzyme immunoassay method. Hypertensive patients have significantly higher levels of adipocytokine than healthy people. Results of data analyses may indicate a possible antihyperglycemic and insulinotropic effect of nesfatin-1 in hypertensive patients with normoglycemia or prediabetes. Confirmation of these processes requires a special study.

KEY WORDS: nesfatin-1, insulin, hypertension, prediabetes, polymorbidity

РОЛЬ НЕСФАТИНУ-1 У ПІДТРИМЦІ ВУГЛЕВОДНОГО ГОМЕОСТАЗУ У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ

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Метою даного дослідження є аналіз змін рівня несфатину-1 у хворих на гіпертонічну хворобу в залежності від параметрів вуглеводного профілю. Обстежено 83 пацієнта з гіпертонічною хворобою у віці від 33 до 77 років. Рівень несфатину-1 визначали методом імуноферментного аналізу. Хворі на гіпертонічну хворобу мають достовірно вищі рівні адипоцитокіну, ніж здорові люди. Результати аналізу даних можуть вказувати на антигіперглікемічний і інсулінотропний ефект несфатину-1 у хворих на гіпертонічну хворобу з нормоглікемією або прediабетом. Підтвердження цих процесів вимагає окремого дослідження.

КЛЮЧОВІ СЛОВА: несфатин-1, інсулін, гіпертонічна хвороба, прediабет, поліморбідність

РОЛЬ НЕСФАТИНА-1 В ПОДДЕРЖАНИИ УГЛЕВОДНОГО ГОМЕОСТАЗА У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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Целью данного исследования является анализ изменений уровня несфатина-1 у больных гипертонической болезнью в зависимости от параметров углеводного профиля. Обследовано 83 пациента с гипертонической болезнью в возрасте от 33 до 77 лет. Уровень несфатина-1 определяли методом иммуноферментного анализа. Больные гипертонической болезнью имеют достоверно более высокие уровни адипоцитокина, чем здоровые люди. Результаты анализа данных могут указывать на антигипергликемический и инсулинотропный эффект несфатина-1 у больных гипертонической болезнью с нормогликемией или предиабетом. Подтверждение этих процессов требует отдельного исследования.

КЛЮЧЕВЫЕ СЛОВА: несфатин-1, инсулин, гипертоническая болезнь, предиабет, полиморбидность

INTRODUCTION

Cardiovascular diseases remain the leading position in the structure of Ukraine's population mortality for many years. According to the data of the last decade, the proportion of mortality from cardiovascular diseases increased from 62.5 % (2005) to 68.0 % (2015), and mortality rose from 28.9 to 31.8 % respectively among working age people [1]. Hypertension is the most common worldwide factor in the development of cardiovascular events.

Obesity contributes to development of a number of pathological conditions, including essential hypertension (EH), hypercholesterolemia, insulin resistance, and others. The link between these abnormalities exists at the level of etiological factors and pathogenetic mechanisms [2]. The association of hypertension, obesity and metabolic disorders greatly increases the risk of coronary heart disease, type 2 diabetes mellitus (T2DM) and its complications, which directly affects the morbidity and mortality rates. The development of T2DM usually follows a phase of impaired glucose metabolism which is manifested by insulin resistance, elevated fasting glucose and impaired glucose tolerance. Correction of these conditions is complicated partly because of incomplete understanding of the mechanisms by which glucose homeostasis is ensured. Therefore, detection of early predictors of metabolic disorders has important medical and social importance.

Nesfatin-1 was found by Oh-I and his colleagues in 2006 [3]. They showed that nesfatin-1 is released by neurons of nuclei of the hypothalamus responsible for appetite control, and identified it as a satiety molecule. Some studies have found that nesfatin-1 is secreted by peripheral tissues such as adipose tissue, the mucosa of the stomach, testis, and others in addition to some structures of the central nervous system [4]. In experimental studies nesfatin-1 production was found in beta-cells of the pancreatic islets. It was shown that nesfatin-1 potentiates glucose-induced insulin secretion by activating the transmembrane transport of Ca^{2+} ions through L-type calcium channels [5]. Unlike anorexigenic effect with CNS-mediated mechanism, peripheral nesfatin-1 improves glucose metabolism (shown in rodents, both non-obese and obese) by direct action on insulin targeted organs: skeletal muscle, liver and adipose tissue [6].

During 10 years studying by different authors, it has been identified both positive and negative properties of nesfatin-1. For example, due to its anorectic effect, the administration of nesfatin-1 is regarded as a potential method of obesity correction [7]. The increase in insulin secretion by nesfatin-1 administration gives hope for the possible using of it for the correction of hyperglycemia in patients with diabetes [5]. At the same time, other researchers identified some adverse effects of increasing its level. Tanida et al. showed that intracerebroventricular injection of nesfatin-1 stimulates the activity of the sympathetic nervous system, and the blood pressure rises significantly through the central melanocortin system [8]. Recently nesfatin-1 was presented as a factor regulating thyroid function in patients with T2DM and the aging process, due to its significant role in energy balance and glucose metabolism [9, 10].

Given the ambiguity of the clinical manifestations of nesfatin-1 plasma level changes, it is required further study of its relationship with the development of comorbid metabolic disorders in humans.

OBJECTIVE

The aim of this study is to analyze changes in the nesfatin-1 level in hypertensive patients depending on the carbohydrate profile parameters.

MATERIALS AND METHODS

83 hypertensive patients aged 33 to 77 years were examined. All patients were divided into 3 groups by clinical characteristics: Group 1 – 50 (60 %) patients with hypertension and normoglycemia, Group 2 – 15 (18 %) patients with hypertension and prediabetes, Group 3 – 18 (22 %) patients with hypertension and T2DM. The control group consisted of 12 healthy individuals.

Patients with next pathology were excluded from the study: secondary hypertension; heart rhythm or AV conduction disturbances; presence of chronic heart failure stage IIB-III (NYHA classification); acute myocardial infarction or stroke in the past, acute left- or right ventricular failure; traumatic lesions of the central nervous system; comorbid psychiatric disorders, alcoholism; decompensated liver disease (increased AST, ALT more than 3 times); diffuse connective tissue diseases; infectious diseases or cancer.

Blood pressure was measured in the sitting position of the patient after 5 min of rest. EH verification was based on the revision of the European Society of Hypertension recommendations (ESH, 2013). T2DM has been verified on the basis of recommendations of the American Diabetes Association (ADA, 2014).

The blood sample for the biochemical and enzyme immunoassay researches was taken from the ulnar vein in the morning after 6–12-hours starvation. Anthropometric measurements included height (cm), weight (kg), waist

circumference (WC, cm) and hips circumference (HC, cm). It was followed by calculation of body mass index (BMI, kg/m^2) according to the formula BMI = body weight / height^2 as well as calculation of the waist to hip ratio (WHR).

Fasting glucose of serum was taken and determined by the glucose oxidase method for the control of carbohydrate metabolism. In case of the diabetes absence and with patient's agreement the glucose tolerance test was conducted: during 5 minutes after taking of fasting blood sample, patient drinks a glass of warm water with glucose solution (75 g), followed by blood sampling in 2 hours. According to the ADA recommendations (2014), prediabetes has been established in patients with impaired fasting glucose (5.6–6.9 mmol/l) and postprandial hyperglycemia (7.8–11.0 mmol/L).

Insulin levels (mkIE/ml) were determined by enzyme immunoassay method using «DRG Instruments GmbH» kit of reagents (Germany). Insulin resistance (IR) was assessed using HOMA-IR (Homeostasis Model Assessment Insulin Resistance) = concentration of insulin (mkIE/ml) × fasting glucose (mmol/L) / 22.5. Caro indexes were calculated additionally as a ratio of fasting glucose to insulin levels. Nesfatin-1 levels (ng/ml) were determined by enzyme immunoassay method using Kono Biotech® Human Nesfatin-1 ELISA Kit reagents.

Analysis of the data was carried out by methods of nonparametric statistics. In samples with the non-parametric data distribution the results are presented as Me (Q25–Q75), where Me – median (the 50th percentile), Q25 and Q75 – the 25th and 75th percentiles respectively (the upper and lower quartiles). The Mann-Whitney test, ANOVA rank Kruskal-Wallis test, the median test were used for comparison of the results between groups. Spearman's rank correlation coefficient was used for estimation of the relationship between two variables. The null hypothesis is excluded at the level of $p < 0.05$ significance.

RESULTS AND DISCUSSION

The data of patients groups are shown in Table.

The analysis of these parameters showed that insulin levels were significantly higher in all hypertensive patients compared with control subjects. First of all, this may be due to the fact that most of the patients have varying degrees of obesity, which is often characterized by insulin resistance. In hypertensive non-obese patients peripheral insulin resistance manifests in more than half of the cases [11, 12]. Insulin levels in Groups 2 and 3 were significantly higher than in Group 1. However, difference wasn't established in comparison of the levels of insulin in prediabetes and T2DM patients.

HOMA-IR index in hypertensive patients with dysglycemia was also higher than in Group 1 or control group. Differences between HOMA-IR indexes in prediabetes and T2DM patients were not significant.

Caro index among all patients was significantly lower in Groups 1 and 2. In hypertensive patients with T2DM, this parameter is somewhat higher, that is probably due to higher levels of fasting blood glucose.

Nesfatin-1 levels in all patients (7.63 (6.91–8.43) ng/ml) were significantly higher than in the control group, regardless of the carbohydrate status. It can indicate possible prohypertensive effect of this adipocytokine. According to some studies, intracerebro-ventricular injection of nesfatin-1 increased blood pressure in rats due to stimulation the sympathetic nervous system by acting on the central melanocortin receptors [13]. It has also been shown that intravenous injections of nesfatin-1 to rats cause vasoconstriction by inhibiting the synthesis of nitric oxide, thereby increasing blood pressure [14].

No significant differences have been identified in comparing of nesfatin-1 levels of the groups. This was probably due to the fact, that some of patients in each group had concomitant obesity, which can be accompanied by changes in adipocytokine level. So, given the fact that initially nesfatin-1 has been identified as a satiety molecule, scientists have shown its ability to reduce the consumption of food by rodents [7]. It is also necessary to consider that the production of nesfatin-1 by adipose tissue is increasing in obesity and varies depending on the type of food [15].

Table

Clinical characteristics, anthropometric and laboratory indicators of patients

Index	Index value, Me (Q25-Q75)			
	Group 1	**Group 2**	**Group 3**	**Control group**
Age, years	60.5 (52.0–64.0) $p_2 > 0.05$ $p_3 > 0.05$ $p_0=0.05$	61.0 (55.0–66.0) $p_1 > 0.05$ $p_3 > 0.05$ $p_0=0.05$	65.0 (58.0–69.0) $p_1 > 0.05$ $p_2 > 0.05$ $p_0=0.05$	53.0 (49.5–55.0)
Height, cm	165.0 (160.0–172.0) $p_2 > 0.05$ $p_3 > 0.05$ $p_0 > 0.05$	168.0 (159.0–175.0) $p_1 > 0.05$ $p_3 > 0.05$ $p_0 > 0.05$	165.0 (160.0–170.0) $p_1 > 0.05$ $p_2 > 0.05$ $p_0 > 0.05$	170.0 (164.0–177.0)
Weight, kg	88.0 (80.0–98.0) **$p_2 < 0.001$** $p_3 > 0.05$ **$p_0 < 0.001$**	103.0 (91.0–118.0) **$p_1 < 0.001$** **$p_3 < 0.05$** **$p_0 < 0.001$**	89.0 (75.0–112.0) $p_1 > 0.05$ **$p_2 < 0.05$** **$p_0 < 0.001$**	63.5 (59.0–70.5)
BMI, kg/m^2	32.36 (28.84-36.84) **$p_2 < 0.001$** $p_3 > 0.05$ **$p_0 < 0.001$**	38.83 (33.57-44.58) **$p_1 < 0.001$** **$p_3 < 0.05$** **$p_0 < 0.001$**	31.92 (28.35-40.90) $p_1 > 0.05$ **$p_2 < 0.05$** **$p_0 < 0.001$**	22.47 (21.47–23.09)
WC, cm	104,0 (94,0–116,0) **$p_2 < 0,001$** $p_3 > 0,05$ **$p_0 < 0,001$**	120.0 (111.0–130.0) **$p_1 < 0.001$** **$p_3 < 0.05$** **$p_0 < 0.001$**	102.0 (94.0–125.0) $p_1 > 0.05$ **$p_2 < 0.05$** **$p_0 < 0.001$**	73.5 (71.0–80.0)
HC, cm	117.0 (103.0-122.0) **$p_2 < 0.01$** $p_3 > 0.05$ **$p_0 < 0.001$**	128.0 (111.0-139.0) **$p_1 < 0.01$** $p_3 > 0.05$ **$p_0 < 0.001$**	115.5 (102.0-139.0) $p_1 > 0.05$ $p_2 > 0.05$ **$p_0 < 0.001$**	95.0 (94.0–98.0)
WHR	0.90 (0.87-0.95) **$p_2 < 0.01$** $p_3 > 0.05$ **$p_0 < 0.001$**	0.94 (0.88-0.98) **$p_1 < 0.01$** **$p_3 < 0.01$** **$p_0 < 0.001$**	0.91 (0.83-0.94) $p_1 > 0.05$ **$p_2 < 0.01$** **$p_0 < 0.001$**	0.76 (0.74–0.85)
Fasting glucose, mmol/L	4.52 (4.18–5.00) **$p_2 < 0.001$** **$p_3 < 0.001$** $p_0 > 0.05$	6.63 (5.91–6.78) **$p_1 < 0.001$** $p_3 > 0.05$ **$p_0 < 0.001$**	7.45 (5.00–8.23) **$p_1 < 0.001$** $p_2 > 0.05$ **$p_0 < 0.001$**	4.62 (4.30-4.93)
Postprandial glucose, mmol/L	5.09 (3.63–6.88) **$p_2 < 0.001$**	8.52 (7.79–9.22) **$p_1 < 0.001$**	-	-
Insulin, mkIE/ml	29.90 (20.93–39.24) **$p_2 < 0.001$** **$p_3 < 0.05$** **$p_0 < 0.001$**	38.58 (27.16–58.62) **$p_1 < 0.001$** $p_3 > 0.05$ **$p_0 < 0.001$**	40.57 (20.03–48.80) **$p_1 < 0.05$** $p_2 > 0.05$ **$p_0 < 0.001$**	13.15 (11.26–15.01)
HOMA-IR	5.54 (4.04–8.33) **$p_2 < 0.001$** **$p_3 < 0.001$** **$p_0 < 0.001$**	11.42 (7.25–18.05) **$p_1 < 0.001$** $p_3 > 0.05$ **$p_0 < 0.001$**	9.22 (7.30–14.97) **$p_1 < 0.001$** $p_2 > 0.05$ **$p_0 < 0.001$**	2.61 (2.30–3.13)
Caro index	0.15 (0.120.21) $p_2 > 0.05$ **$p_3 < 0.05$** **$p_0 < 0.001$**	0.16 (0.12–0.22) $p_1 > 0.05$ **$p_3 < 0.05$** **$p_0 < 0.001$**	0.19 (0.13–0.33) **$p_1 < 0.05$** **$p_2 < 0.05$** **$p_0 < 0.01$**	0.34 (0.29–0.41)
Nesfatin-1, ng/ml	7.62 (6.94–8.43) $p_2 > 0.05$ $p_3 > 0.05$ **$p_0 < 0.001$**	7.21 (6.79–8.27) $p_1 > 0.05$ $p_3 > 0.05$ **$p_0 < 0.001$**	7.76 (6.60–8.47) $p_1 > 0.05$ $p_2 > 0.05$ **$p_0 < 0.001$**	4.53 (4.23–4.87)

where p_1 - confidence level in comparison with parameters of Group 1, p_2 - confidence level in comparison with parameters of Group 2, p_3 - confidence level in comparison with parameters of Group 3, p_0 - confidence level in comparison with parameters of the control group.

A negative correlation of nesfatin-1 levels with BMI ($r = -0.164$, $p < 0.05$) in hypertensive patients with normoglycemia could be evidence of its anorexigenic effect [3, 7], preventing the development of obesity. Positive correlations of nesfatin-1 levels were detected with the levels of fasting glucose ($r = 0{,}198$, $p < 0{,}05$), insulin ($r = 0{,}180$, $p < 0{,}05$) and HOMA-IR index ($r = 0{,}205$, $p < 0{,}05$). These data may be a confirmation of previous studies, which have shown glucose-induced insulinotropic action of nesfatin-1 [5].

Nesfatin-1 levels were positively correlated with WHR ($r = 0.529$, $p < 0.001$) in the group of patients with hypertension and diagnosed prediabetes. By detailed examination of the characteristics of Group 2 it become apparent significantly higher levels of body weight, BMI, WC, HC, WHR in comparison with other groups. This can be explained by the fact that patients with obesity (especially abdominal) have higher risk of insulin resistance or T2DM development. At the same time, adipose tissue that is increased in obesity can play a role of nesfatin-1 producing organ [4]. Furthermore, a negative correlation was found between levels of nesfatin-1 and postprandial glucose ($r = -0.430$, $p < 0.05$) in Group 2. As was already stated earlier, according to some studies, nesfatin-1 is also produced by pancreatic β-cells in addition to other organs, increasing insulin secretion and the sensitivity of skeletal muscle, liver and adipose tissues to insulin [6]. As a result of these mechanisms, rising of nesfatin-1 concentration may lead to reduction of blood glucose levels.

Patients of Group 3 were characterized by similar anthropometric data with patients of Group 1. There were negative correlations of nesfatin-1 level with body weight ($r = -0.318$, $p < 0.05$), BMI ($r = -0.285$, $p < 0.05$) and WC ($r = -0.271$, $p < 0.05$) in this group. No significant correlations between nesfatin-1 level and parameters of the carbohydrate metabolism have been identified that may be due to the influence of hypoglycemic drugs.

Thus, hypertensive patients had significantly increased nesfatin-1 levels. It can be assumed possible antihyperglycemic and insulinotropic effect of this adipocytokine in hypertensive patients with normoglycemia or prediabetes. These data may indicate a role of nesfatin-1 in the mechanism of metabolic disorders formation in hypertensive patients.

CONCLUSIONS

1. Nesfatin-1 levels in hypertensive patients (7.63 ng/ml) were significantly higher than in the control group (4.53 ng/ml). No significant differences were found between nesfatin-1 levels in hypertensive patients with normoglycemia, prediabetes or T2DM (7.62, 7.21 and 7.76 ng/ml respectively). However patients of Group 2 had significantly higher BMI.
2. Nesfatin-1 levels positively correlate with the fasting glucose levels in patients with hypertension and without disturbances of carbohydrate profile. Increasing of nesfatin-1 level in blood is accompanied by increased secretion of insulin. These links are not observed among parameters of hypertensive patients with dysglycemia.
3. Determination of nesfatin-1 level in hypertensive patients with normoglycemia in combination with the carbohydrate metabolism parameters may have important diagnostic value in the assessment of glucose tolerance.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to investigate the role of nesfatin-1 on the carbohydrate metabolism in isolated pathology (in patients without EH and with normal weight), given the diversity of its effects in polymorbidity.

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Clinical case

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AMIODARONE-INDUCED THYROID DYSFUNCTION: CLINICAL CASE WITH LITERATURE REVIEW

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The article addresses the problem of amiodarone-induced thyroid dysfunction based in the clinical case. The literature data on the pathogenesis, diagnosis of this disease, as well as management tactics for different variants of amiodarone-associated thyroid dysfunction are shown.

KEY WORDS: amiodarone, thyroid dysfunction, diagnosis, treatment

АМІОДАРОН-ІНДУКОВАНА ДИСФУНКЦІЯ ЩИТОПОДІБНОЇ ЗАЛОЗИ: КЛІНІЧНИЙ ВИПАДОК З ОГЛЯДОМ ЛІТЕРАТУРИ

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На приладі клінічного випадка розглядається проблема дисфункції щитоподібної залози, що обумовлена прийомом аміодарону. Наведені дані літератури щодо патогенезу, діагностики цієї патології, а також щодо тактиці ведення хворих при різних варіантах аміодарон-індукованої дисфункції щитоподібної залози.

КЛЮЧОВІ СЛОВА: аміодарон, щитоподібна залоза, діагноз. лікування

АМИОДАРОН-ИНДУЦИРОВАННАЯ ДИСФУНКЦИЯ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: КЛИНИЧЕСКИЙ СЛУЧАЙ С ОБЗОРОМ ЛИТЕРАТУРЫ

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На примере клинического случая рассматривается проблема дисфункции щитовидной железы, обусловленная приемом амиодарона. Приведены данные литературы по патогенез, диагностике этой патологии, а также по тактике ведения больных при различных вариантах амиодарон-индуцированной дисфункцией щитовидной железы.

КЛЮЧЕВЫЕ СЛОВА: амиодарон, щитовидная железа, диагностика, лечение

INTRODUCTION

Currently, the amiodarone has got the status the most commonly used antiarrhythmic drug in the world's clinical practice. In addition to its principle class III (potassium channel blockade) antiarrhythmic effects, amiodarone has class I (sodium channel blockade), class II (noncompetitive α- and β-blocking) and class IV (calcium channel activity) related actions [1].

Amiodarone's unique properties make it highly effective in the management of recurrent ventricular dysrhythmias, paroxysmal supraventricular dysrhythmias, including atrial fibrillation and flutter, and in the maintenance of sinus rhythm after electrical cardioversion of atrial fibrillation. Moreover, it has the added benefit of being well tolerated in patients with normal as well as impaired left ventricular systolic function [2].

Despite amiodarone's potent antidysrhythmic actions, its use is associated with numerous adverse effects on various organs, which are becoming more prevalent given the increasing incidence of dysrhythmias and wider amiodarone use. The common side effects include the thyroid gland dysfunction

(both hypo- and hyperfunction), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid gland [2].

In this article clinical case demonstrates diagnostic and treatment approaches to amiodarone-induced hypothyroidism on background of literature review.

CASE PRESENTATION

A 72-year-old man with a past medical history of non-Q-wave myocardial infarction, dyslipidemia and atrial fibrillation, but without previous history of thyroid gland disease has been followed-up in our clinic for 2 years. A year and a half ago patient developed episodes of atrial fibrillation confirmed on ECG Holter monitoring and amiodarone was initiated.

BACKGROUND

Amiodarone is a benzofuran derivative containing two atoms of iodine per molecule. A normal daily maintenance dose of amiodarone (200–400 mg) generates about 6–12 mg of free iodine per day. This results in an iodine load that far exceeds the World Health Organisation's recommended optimal iodine intake of 0.15–0.3 mg per day. In patients treated with amiodarone, urinary and plasma levels of inorganic iodide are found to increase up to 40-fold, whereas thyroidal iodide uptake and clearance decrease significantly [3–4] Amiodarone’s effects on the thyroid gland are numerous and complex and occur via a number of differing mechanisms. These can be divided into iodine-induced effects and those due to the intrinsic properties of amiodarone [5]

Intrinsic amiodarone-related drug effects. Inhibition of monodeiodination (5-deiodinase activity) of T4 by amiodarone leads to a decrease in the generation of T3 from T4, a decrease in the clearance of reverse T3 (rT3) and consequently increased rT3 accumulation [6-7]. Amiodarone can lead to inhibition of T4 and T3 entry into the peripheral tissues. Both amiodarone and its principle metabolite desethylamiodarone (DEA) may have direct cytotoxic effects on the thyroid follicular cells, leading to a destructive thyroiditis [6, 8]. Furthermore, DEA is a noncompetitive inhibitor of the binding of thyroid hormone (T3) to the β1-thyroid hormone receptor (T3R) [6, 9].

Iodine-related effects of amiodarone on thyroid function. The normal autoregulation of iodine prevents normal individuals from becoming hyperthyroid after exposure to an iodine load. When intrathyroidal iodine concentrations reach a critical high level, iodine transport and thyroid hormone synthesis are transiently inhibited until intrathyroidal iodine stores return to normal levels (the Wolff-Chaikoff effect). Patients with underlying thyroid disease, however, have defects in autoregulation of iodine. This tends to occur in patients with underlying Hashimoto's disease [10]. In addition there may be iodine-related potentiation of thyroid autoimmunity and unregulated thyroid hormone synthesis in patients with underlying Graves' disease (Jod–Basedow effect) [10–11]. The risk of amiodarone-induced thyroid dysfunction depends on the presence of underlying thyroid disease. Thus, hypothyroidism develops more often in patients with underlying autoimmune thyroid disease, most likely as a result of the inability to escape from the Wolff-Chaikoff effect. Patients with multinodular goiter or subclinical Graves’ disease tend to develop hyperthyroidism during treatment with amiodarone as a result of increased synthesis of thyroid hormones due to excess iodine from the amiodarone [12].

CASE PRESENTATION

Given the higher risk of developing amiodarone-induced thyroid dysfunction in the presence of underlying disorders our patient’s thyroid function was evaluated prior to initiation of amiodarone therapy. Patient complaints were negative for dysfunction of thyroid gland. He denied muscle weakness, nervousness, any problems with defecation, difficulty sleeping or somnolence, body weigh changes, heat or cold intolerance, dysphagia and neck pain.

On physical examination the blood pressure was 112/78 mm Hg, heart rate=pulse=62 bpm, regular. Ocular reflexes were negative. Palpation revealed smooth, elastic, mobile, nontender thyroid gland of usual size. There were no discrete nodules appreciated and no bruits auscultated. There was no tremor. Lungs, heart, abdomen were unremarkable.

Thyroid function tests drawn before initiation of amiodarone treatment confirmed euthyroid patient’s status: a thyroid stimulating hormone (TSH) was 2, 2 mIU/L (normal. 0,27–4,2 mIU/L), free thyroxin (T4) was 1.2 ng/dL (normal, 0,93–1,7 ng/dL), and

free triiodothyronine (T3) was 3,5 pg/mL (normal, 2,5–4,3 pg/mL), antithyroperoxidase (anti-TPO) and thyroglobulin antibody titers were low.

BACKGROUND

In iodine-sufficient areas, amiodarone-induced hypothyroidism is more common than hyperthyroidism, and may occur in up to 20 percent of patients treated with amiodarone [7]. In contrast, amiodarone-induced hyperthyroidism is more common than hypothyroidism in iodine-deficient regions [13]. The reported incidence of amiodarone-induced hypothyroidism varies widely, ranging from 6 % in countries with low iodine intake to 13 % in countries with a high dietary iodine intake. The risk of developing hypothyroidism is independent of the daily or cumulative dose of amiodarone [3]. The clinical manifestations and diagnosis of amiodarone-associated hypothyroidism are similar to those of hypothyroidism from any cause. Fatigue, lethargy, intolerance of cold, mental sluggishness and dry skin are commonly reported; goiter is uncommon.

Hypothyroidism and hypothyroid symptoms may develop as soon as two weeks or as late as 39 months after the initiation of amiodarone therapy [14]. Patients should have thyroid function assessed several weeks after starting amiodarone and every few months thereafter for the development of overt hypothyroidism, especially those with evidence for autoimmunity prior to initiating amiodarone [10, 15]. In general, patients should be monitored at 6 weeks and then every 3 months [3]. If equivocal biochemical results are obtained in clinically euthyroid patients, suggestive of subclinical hypothyroidism, then further testing in six weeks is recommended [16].

Hypothyroidism should be diagnosed on the basis of a screening serum TSH value before the patient has symptoms. Since small increases in serum TSH concentrations (10 to 20 mU/L) are seen in euthyroid patients for the first three to six months after amiodarone therapy is initiated, amiodarone-induced hypothyroidism should only be diagnosed when serum T4 concentrations are low-normal or low, or mild TSH elevation persists.

The alterations in thyroid function tests are usually divided into acute (≤ 3 months) and chronic (> 3 months) phases following the initiation of amiodarone therapy (see table) [17].

Table

Effects of amiodarone on thyroid function tests in euthyroid patients [17]

Thyroid hormone	Acute effects (≤ 3 months)	Chronic effects (> 3 months)
Total and free T4	↑ 50 %	Remains ↑ 20 – 40 % of baseline
T3	↓15 – 20 %, remains in low-normal range	Remains ↓20 %, remains in low-normal range
Reverse T3	↑ 200 %	Remains ↑150 %
TSH	↑20 – 50 %, transient, generally remains < 20 mU/L	Normal

CASE PRESENTATION

The patient was assigned a follow-up visit in 6 weeks of initiation of amiodarone therapy to assess its efficacy and safety. On follow-up visit patients still denied any complaints typical for hypo- or hyperfunction of thyroid gland. The laboratory tests showed signs of subclinical hypofunction of thyroid gland: TSH was 9, 7 mIU/L (0,27–4,2 mIU/L), free thyroxin (T4) was 1.22 ng/dL (0,93–-1,7 ng/dL), antithyroperoxidase (anti-TPO) and thyroglobulin antibody titers were still low.

BACKGROUND

There are two approaches to the treatment of autoimmune thyroiditisю. The first one means the discontinuation of amiodarone with replacing it with another antiarrhythmic drug. The second approach comprises normalization of thyroid function by replacement with T4 while amiodarone is continued. Discontinuation of amiodarone may not be feasible because of its highly effective anti-arrhythmic properties, especially in the treatment of life-threatening ventricular tachyarrhythmias.

That is why, a safer and more reliable option is to institute thyroid hormone replacement therapy, starting with 25–50 μg levothyroxine daily and increasing at intervals of 4–6 weeks until the symptoms have resolved and the target serum T4 level is achieved [3]. The goal of treatment is to restore the serum TSH concentration to normal and to bring serum thyroxine levels to the upper end of the normal range, as often seen in euthyroid patients who are receiving amiodarone [7]. It should take into account that a larger than usual dose may be required because of the likely effects of amiodarone on intrapituitary T4 metabolism and T3 production, and possibly thyroid hormone action [7]. It may be difficult to recognize the dysfunction because many changes in thyroid function test results occur in euthyroid patients who are receiving amiodarone and patients on amiodarone can have mildly elevated serum TSH levels despite adequate thyroid hormone replacement. Permanent hypothyroidism requiring T4 replacement is more common in patients with thyroid antibodies [18]. In such patients if TSH is raised, treatment with T4 should be started without delay [19].

On the other hand, overtreatment with levothyroxine may nullify the anti-arrhythmic effects of amiodarone, believed to be mediated via an intracellular state of hypothyroidism within the cardiac tissues [3].

The third opportunity to treat amiodarone-induced hypothyroidism is to restore the thyroid function with perchlorate. This approach was investigated in small studies, in which such treatment has been shown to restore normal thyroid function rapidly [20–21].

The drug relieves iodine-induced inhibition of thyroid hormone synthesis by its ability to discharge inorganic iodine and to block further entry of iodide into the thyroid [22]. But nowadays this approach cannot be generally recommended because of perchlorate toxicity which can result from either prolonged use or high dosages (> 1 g daily) and because hypothyroiddism can be easily and safely treated with thyroid hormone replacement [3].

In the absence of hypothyroid symptoms or thyroid antibodies, patients with moderately raised serum TSH (< 20 mU/l) but high-normal or raised serum free T4 concentrations may reflect amiodarone-induced alteration in thyroid function parameters or subclinical hypothyroidism [17].Close monitoring may be all that is necessary in these subjects [3].

Amiodarone is usually not discontinued unless it fails to control the underlying arrhythmia. However, if amiodarone is stopped, hypothyroidism in patients with no apparent preexisting thyroid disease often resolves. In contrast, hypothyroidism may persist after withdrawal of amiodarone in patients who have underlying chronic autoimmune thyroiditis with high titers of anti-TPO antibodies and goiter, and they therefore require permanent T4 therapy [17, 23].

CASE PRESENTATION

As our patient had no clinical symptoms of hypothyroidism and laboratory tests showed only moderately increased serum TSH and normal T4 level, the patient status was regarded as euthyroid and we decided to continue amiodarone therapy under close follow-up. Another argument in favor of expectant management tactics was the absence of thyroid antibodies before and during treatment with amiodarone. Patient was instructed to visit our clinic in 6 weeks for clinical check-up and laboratory tests evaluation. The follow-up confirmed the absence of clinical signs of thyroid gland dysfunction, laboratory tests showed the tendency of normalization of TSH, it was 6, 9 mIU/L versus 9, 7 mIU/L on previous visit (normal limits are 0,27–4,2 mIU/L). Three months later TSN returned to norm (4,1 mIU/L). Currently, the patient continues to receive amiodarone, and results of clinical and laboratory thyroid function tests remain normal.

CONCLUSIONS

Transient changes in thyroid function tests often occur in euthyroid individuals treated with amiodarone. Amiodarone causes predictable changes of tests that characterize the function of the thyroid gland, explicable in terms of physiological effects, caused by an iodine excess and its inhibition of deiodinase activity. Identify euthyroid hypothyroxinemia should not be considered as an indication for the abolition of amiodarone. While patients with pre-existing autoimmune thyroid disease (subclinical Hashimoto's thyroiditis or positive antithyroid antibodies) are at increased risk of developing amiodarone-induced hypothyroiddism, most patients remain euthyroid during amiodarone therapy. Since small increases in

serum TSH concentrations (10 to 20 mU/L) are seen in euthyroid patients for the first three to six months after amiodarone therapy is initiated, amiodarone-induced hypothyroidism should only be diagnosed when serum T4 concentrations are low-normal or low, or mild TSH elevation persists.

In most patients who develop amiodarone-induced hypothyroidism amiodarone therapy may be continued and euthyroidism should be restored by replacement with thyroid hormone in doses often larger than normal.

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MANAGEMENT OF A PATIENT WITH ATHEROSCLEROSIS AND ARTERIAL HYPERTENSION COMORBID WITH AN ASYMPTOMATIC PANCREATIC PSEUDOCYST ON THE EXAMPLE OF CLINICAL CASE

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Management of patients in therapeutic practice is becoming serious difficulties in view of the large prevalence of comorbidity pathologies of various organs and systems, especially atherosclerosis and arterial hypertension since these diseases is epidemic in recent years. Pancreatic pseudocyst is a localized fluid collection that is rich in amylase and other pancreatic enzymes and it presentation can be ranged from asymptomatic process to major abdominal catastrophe due to complications like infections, hemorrhages, obstruction and rupture. The main difficulty in the management of patients with pancreatic pseudocysts is a lack of effective medical and surgical treatment. Success can only be achieved with an individual approach to the patient with the joint cooperation of doctors of various profiles, as shown by our clinical case.

KEY WORDS: arterial hypertension, atherosclerosis, pancreatic pseudocyst, management

ВЕДЕННЯ ПАЦІЄНТА З АТЕРОСКЛЕРОЗОМ І АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ КОМОРБІДНИМИ З БЕЗСИМПТОМНОЮ КІСТОЮ ПІДШЛУНКОВОЇ ЗАЛОЗИ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Лікування хворих в терапевтичній практиці має серйозні труднощі через велику поширеність коморбідної патології різних органів і систем, особливо атеросклерозу і артеріальної гіпертензії, бо ці захворювання мають характер епідемії в останні роки. Кіста підшлункової залози представляє собою локалізований збір рідини, багатої на амілазу та інші панкреатичні ферменти, а клінічна картина може змінюватись в діапазоні від безсимптомного процесу до великої абдомінальної катастрофи через такі ускладнення, як інфекції, кровотечі, непрохідність і розриви. Основні труднощі в лікуванні пацієнтів з панкреатичною псевдокистою полягають у відсутності ефективного медичного та хірургічного лікування. Успіх може бути досягнутий тільки при індивідуальному підході до пацієнта при спільній співпраці лікарів різних профілів, як показано на нашому клінічному випадку.

КЛЮЧОВІ СЛОВА: артеріальна гіпертонія, атеросклероз, кіста підшлункової залози, ведення

ВЕДЕНИЕ ПАЦИЕНТА С АТЕРОСКЛЕРОЗОМ И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ КОМОРБИДНЫМИ С БЕССИМПТОМНОЙ КИСТОЙ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Лечение пациентов в терапевтической практике имеет серьезные трудности из-за большой распространенности коморбидной патологии различных органов и систем, особенно атеросклероза и артериальной гипертензии, потому как эти заболевания имеют характер эпидемии в последние годы. Киста поджелудочной железы представляет собой локализованный сбор жидкости, богатой амилазой и другими панкреатическими ферментами, а клиническая картина может меняться в диапазоне от бессимптомного процесса до большой абдоминальной катастрофы из-за таких осложнений, как

инфекции, кровотечения, непроходимость и разрывы. Основные трудности в лечении пациентов с панкреатической псевдокистой заключаются в отсутствии эффективного медицинского и хирургического лечения. Успех может быть достигнут только при индивидуальном подходе к пациенту при совместном сотрудничестве врачей разных профилей, что и показано в нашем клиническом случае.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертония, атеросклероз, киста поджелудочной железы, ведения

INTRODUCTION

Management of patients in therapeutic practice is becoming serious difficulties in view of the large prevalence of comorbidity pathologies of various organs and systems. This question is particularly relevant for patients with atherosclerosis and arterial hypertension since these diseases is epidemic in recent years [1–2].

Pancreatic pseudocyst is a localized fluid collection that is rich in amylase and other pancreatic enzymes and is surrounded by a wall of fibrous tissue that is not lined by epithelium [3].

Clinical presentation of this condition can be ranged from asymptomatic process [4] to major abdominal catastrophe due to complications like infections, hemorrhages, obstruction and rupture [5–7].

The main difficulty in the management of patients with pancreatic pseudocysts is a lack of effective medical and surgical treatment [8]. Success can only be achieved with an individual approach to the patient considering comorbidity with the joint cooperation of doctors of various profiles, as shown by our clinical case [9–10].

OUR CASE

Passport data: Male, 75 years old, retired.

Complaints: Transient rise of blood pressure to 170/90 mm Hg without any clinical manifestations. Shortness of breath during climbing to the 4th floor. Edema of the legs, prominently in the right.

History of the disease: Arterial hypertension since 1976 with the highest figure of blood pressure 240/120 mm Hg, the usual blood pressure is 150–160/80–90 mm Hg. Since 2000 were registered atherosclerotic lesions of cardiac valves on ultrasound investigation of the heart. Repeatedly treated in outpatient and inpatient clinic, last hospitalization in 2012. The present deterioration occurred during several months. At the moment took amlodipine.

History of the life: Peptic ulcer disease since 1995, twice history of gastrointestinal bleeding, last in December 2010. Diabetes mellitus, tuberculosis and infectious disease are denied. The patient smoked earlier for 20 years, has not smoked since 1972. Denied any allergies.

Somatic status: active position. Skin in usual characteristics. Peripheral lymph nodes were not enlarged. The thyroid gland is not clearly determined. Muscular-skeletal system without special features. Vesicular sounds during lung percussion. On lung auscultation is vesicular breathing. Rhythmic activity of the heart. Heart tones are muted. Pulse 65 min. Blood pressure on both arms on the background of antihypertensive therapy is 150/90 mm Hg. Abdomen: normal size, soft, painless. In the left iliac region a dense painless formation with a diameter of about 10 cm was palpated, localized practically below the left hypochondria, it descends into minor pelvis (swollen bowel loops? formation?). Liver is at the edge of the costal arch, painless. Physiological functions without special features. A sign of costovertebral angle tenderness is negative on both sides. Swelling of the right lower leg, no edema on the left.

Plan of survey: full blood count, urinalysis, biochemical test of blood (common cholesterol, bilirubin, AlAT, AsAT, fasting plasma glucose, creatinine, urea, potassium, sodium), chest X-ray, ECG, ultrasound of the heart, 24-hours daily monitoring of ECG and blood pressure, ultrasound and/or computer tomography of the abdomen, ultrasound of lower extremities vessels, test with dosed physical activity, interdisciplinary consultation with other specialist doctors when it needs.

RESULTS OF THE SURVEY

Full blood count: All figures are in the normal range.

Urinalysis: All figures are in the normal range.

Biochemical test of blood: Hypercholesterolemia due to LDL.

Chest X-ray: Focal and infiltrative changes of the lungs are not detected. The roots are structural, not expanded. The sinuses are free. Aperture clearly delineated. Pleuropericardial left cord was extended, calcification of the valve. Aortic sclerosis. Determined expansion of the upper mediastinum.

ECG: Sinus rhythm, right, heart rate 52 beats/min. Left ventricle hypertrophy.

Ultrasound of the heart: Sclerotic changes of the aorta wall, leaflets of aortic and mitral valves. Left ventricle hypertrophy. Ejection fraction is 60 %.

24-hours daily monitoring of ECG and blood pressure: During all observation time on the background of sinus rhythm with a mean heart rate 67 beats/min single supraventricular and ventricular premature beats was registered. Ischemic ECG changes were not recorded. Figures of systolic and diastolic blood pressure during the entire period of observation were characterized by normotension.

Test with dosed physical activity: Presence of formation of the abdominal cavity with unknown etiology is a relative contraindication for this test, so the procedure was not performed.

Ultrasound of lower extremities vessels: Deep vein at the current studies without evidence of thrombosis, phlebitis and valvular insufficiency. Varicose of saphenous veins of right leg. Incompetency of perforating vein of the right shin. Moderate expansion of veins on both calves.

Vascular surgeon: Primary varicose veins of right lower limb, chronic venous insufficiency of stage 2, recommended surgical treatment.

Ultrasound of the abdomen: Diffuse changes in the liver parenchyma, diffuse changes in pancreas parenchyma, diffusive degenerative changes in both kidneys, cysts of both kidneys. Pathological formation of abdomen with heterogeneous liquid volume of about 2 liters. (pseudocyst? cyst? formation? megacolon?).

Computer tomography of the abdomen: CT features are more typical for the pseudocyst of pancreas tail.

Interdisciplinary consultation with other specialist doctors: The patient was examined by therapists, abdominally surgeon, oncologist, gastroenterologist, endocrinologist and doctor of functional diagnostics together. Given the results of the physical examination and imaging studies, the patient was set with diagnosis giant pseudocyst of the tail of the pancreas. Given the high risk of complications, it was decided to perform drainage of the cavity of the pseudocyst with

CLINICAL DIAGNOSIS

Atherosclerosis of aorta. Arterial hypertension 3 degree. Heart failure 1 functional class by NYHA. Moderate additional cardiovascular risk. Peptic ulcer disease in remission phase. Primary varicose veins of right lower limb, chronic venous insufficiency 2 stage. Giant pseudocyst of the pancreas (?).

RECOMMENDATIONS

– Modification of lifestyle (diet, regular physical activity);

– Amlodipine 5 mg in the morning under the control of BP;

– Lisinopril 10 mg in the evening under the control of BP;

– Atorvastatin 20 mg in the evening under the control of lipid profile and AlAT;

–Hospitalization to the surgical department for operative treatment.

OPERATIVE TREATMENT

One week later patient was admitted to the surgical department for planned surgical treatment of supposed pancreatic pseudocyst.

Considering location of the pseudocysts in the abdomen cavity, the patient's age, concomitant diseases of other organs and systems, it was decided to perform laparoscopic surgery with followed drainage.

Clinical diagnosis after surgical treatment: Giant pseudocyst of pancreas. Drainage of pseudocyst cavity. Residual fluid volume – 25 ml. Atherosclerosis of aorta. Arterial hypertension 3 degree. Heart failure 1 functional class by NYHA. Moderate additional cardiovascular risk. Peptic ulcer disease in remission phase. Primary varicose veins of right lower limb, chronic venous insufficiency 2 stage.

FOLLOW-UP IN 1 MONTH AFTER SURGERY

Complaints: none.

Somatic status: active position. Skin in usual characteristics. Peripheral lymph nodes were not enlarged. The thyroid gland is not clearly determined. Muscular-skeletal system without special features. Vesicular sounds during lung percussion. On lung auscultation is

vesicular breathing. Rhythmic activity of the heart. Heart tones are muted. Pulse 67 per min. Blood pressure on both arms on the background of antihypertensive therapy is 125/75 mm Hg. Abdomen: normal size, soft, painless. In the left iliac region a dense painless formation with a diameter of about 7 cm is palpated, localized practically below the left hypochondria. Liver is at the edge of the costal arch, painless. Physiological functions without special features. A sign of costovertebral angle tenderness is negative on both sides. Swelling of the right lower leg, no edema on the left.

Plan of survey: ultrasound of the abdomen, interdisciplinary consultation with other specialist doctors when it needs.

RESULTS OF THE SURVEY

Ultrasound of the abdomen: Diffuse changes in the liver parenchyma, diffuse changes in pancreas parenchyma, diffusive degenerative changes in both kidneys, cysts of both kidneys. Giant pseudocyst of pancreas with liquid volume of about 2 liters.

Interdisciplinary consultation with other specialist doctors: The patient was examined by therapists, abdominally surgeon, oncologist, gastroenterologist, endocrinologist and doctor of functional diagnostics together. Considering relapsing course of pancreatic pseudocyst with an absolute absence of symptoms, it was decided to choose expectant management. It was recommended to perform of computer tomography of the abdomen every 6 months in the absence of symptoms of the abdominal cavity and immediately get medical attention in case of any discomfort in the abdomen.

CLINICAL DIAGNOSIS

Atherosclerosis of aorta. Arterial hypertension 3 degree. Heart failure 1 functional class by NYHA. Very high additional cardiovascular risk. Peptic ulcer disease in remission phase. Primary varicose veins of right lower limb, chronic venous insufficiency 2 stage. Giant pseudocyst of pancreas, drainage of pseudocyst cavity, residual fluid volume – 25 ml. Relapse of giant pseudocyst of pancreas.

RECOMMENDATIONS

– Lifestyle modification and drug therapy in accordance with previous recommendations;

– Perform of computer tomography of the abdomen every 6 months in the absence of symptoms of the abdominal cavity;

– Immediately get medical attention in case of any discomfort in the abdomen.

CONCLUSIONS

Management of patients with comorbid a disorder has not yet been standardized and is interdisciplinary problem at the junction of various medical specialties.

Our patient belongs to the very high additional cardiovascular risk in mind the presence of hypertension and atherosclerosis, which can greatly complicated during anestesiological procedures and carrying out abdominal surgery for pancreatic pseudocyst [1–2, 8].

We have taken a wait and see tactics, and apparently made no mistake. Within 2 years we are committed telephone and ambulatory visits with CT control of pseudocyst state every six months, the negative dynamics is still not fixed, any subjective symptoms are also still missing.

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DYNAMIC CHANGES IN SPECTRAL HEART RATE VARIABILITY PARAMETERS IN PACED BREATHING TEST IN PATIENT WITH UNCONTROLLED ARTERIAL HYPERTENSION AND POLYMORBIDITY

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A clinical case of a patient with uncontrolled hypertension and polymorbidity. The paced breathing test was made, was found prevalence of low frequency influences at the initial stage and its intensification at the resting stage, growth of the total power of heart rate variability spectrum (TP) with respiratory modulation. The course of the disease worsened the appearance of new-onset atrial fibrillation (registered paroxysm on Holter monitoring); the general deterioration of the patient's state reflected HRV changes on sinus rhythm tracing - significantly reduced TP growth in response to paced breathing, an increase in LF/HF (ratio of low frequency to high frequency waves), as well as switching to the neurohormonal level of heart rate regulation at the resting stage. After the treatment the growth of TP in response to the test has increased and LF/HF level has decreased.

KEY WORDS: arterial hypertension, heart rate variability, paced breathing

ДИНАМІЧНІ ЗМІНИ ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ПРОБІ З МЕТРОНОМІЗОВАННИМ ДИХАННЯМ У ПАЦІЄНТА З НЕКОНТРОЛЬОВАНОЮ ГІПЕРТЕНЗІЄЮ І ПОЛІМОРБІДНІСТЮ

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Описано клінічний випадок пацієнта з неконтрольованою артеріальною гіпертензією та поліморбідністю. Проведена проба з метрономізованим диханням, виявлено превалювання низькохвильових впливів на етапі фонового запису і посилення їх на етапі відпочинку, приріст загальної потужності спектру варіабельності серцевого ритму (ТР) при модуляції дихання. Перебіг захворювання погіршила поява вперше виявленої фібриляції передсердь (зареєстрований пароксизм при холтерівському моніторуванні), загальне погіршення стану пацієнта відбили зміни ВСР при запису з синусовим ритмом - значне зниження приросту ТР у відповідь на метрономізоване дихання, підвищення LF/HF (відношення хвиль низької частоти до високочастотним), а також перемикання регуляції серцевого ритму на стадії відпочинку на нейрогормональний рівень. Після проведеної терапії збільшився приріст ТР у відповідь на пробу, знизився рівень LF/HF.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, варіабельність серцевого ритму, метрономізіроване дихання

ДИНАМИЧЕСКИЕ ИЗМЕНЕНИЯ ПАРАМЕТРОВ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА В ПРОБЕ С МЕТРОНОМИЗИРОВАННЫМ ДЫХАНИЕМ У ПАЦИЕНТА С НЕКОНТРОЛИРУЕМОЙ ГИПЕРТЕНЗИЕЙ И ПОЛИМОРБИДНОСТЬЮ

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Описан клинический случай пациента с неконтролируемой артериальной гипертензией и полиморбидностью. Проведена проба с метрономизированным дыханием, выявлено превалирование низковолновых влияний на этапе фоновой записи и усиление их на этапе отдыха, прирост общей мощности спектра вариабельности сердечного ритма (ТР) при модуляции дыхания. Течение заболевания усугубило появление впервые выявленной фибрилляции предсердий (зарегистрирован пароксизм при холтеровском мониторировании), общее ухудшение состояния пациента отразили изменения ВСР при записи с синусовым ритмом – значительное снижение прироста ТР в ответ на

метрономизированное дыхание, повышение LF/HF (отношение волн низкой частоты к высокочастотным), а также переключение регуляции сердечного ритма на стадии отдыха на нейрогормональный уровень. После проведенной терапии увеличился прирост TP в ответ на пробу, снизился уровень LF/HF.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, вариабельность сердечного ритма, метрономизированное дыхание

INTRODUCTION

Essential hypertension is one of the most widespread diseases [1–2], dangerous, primarily for its complications [1–3], the risk of which increases significantly especially in the case of uncontrolled hypertension that may be associated with inadequate antihypertensive therapy or with its non-systematic use [3–4]. The presence of comorbidities, that exacerbate hypertension, significantly worsens the prognosis of these patients [5].

Heart rate variability (HRV) is not only noninvasive, but also a convenient method of evaluating the functional state of the cardiovascular system. A test with paced breathing is considered to be one of the most effective components of the HRV evaluation, which gives wide opportunities for the dynamic analysis of the effectiveness of antihypertensive therapy, changes in the autonomous regulation of heart rate, both at rest and during respiratory modulation and provides possibilities for an individual approach to each patient [6–7].

Heart rate variability spectral analysis allows to estimate the ratio of the distribution of the main components of HRV spectrum: high frequency waves (HF), reflecting the sympathetic and in some extent parasympathetic influences; very low frequency waves (VLF) that characterize the neurohormonal regulation of the heart rate, the low frequency waves (LF), responsible for the vagal control of HRV, and LF/HF – ratio of the low frequency waves to high frequency waves. Also important role in HRV analysis plays TP – the total power of heart rate variability spectrum [8].

CASE STUDY

A 53-year old woman presented with complaints on periodically appearing headaches, mostly in occipital area, «feeling of heaviness in the head» provoked by physical overload or stress, palpitations, poorly controlled blood pressure.

Patient also complained on inability to decrease and control her excessive weight.

Patient was first diagnosed with arterial hypertension near 5 years ago; since 2013 she tried to treat herself with occasional intake (once in several weeks) of amiodarone as a «some doctor had advised», but she didn't notice significant improvement of her state. In Jan 2014 she was examined in National Institute of Therapy named by L.T. Malaya, where the diagnosis was made: essential arterial hypertension II grade 2 stage, high risk, the left ventricle hypertrophy, aortic stenosis I st., heart failure IIa st. with presserved systolic function, II functional class, impaired fasting glucose. Bisoprolol 5 mg per day, enalapril 10 mg per day was prescribed. The patient took prescribed medications occasionally, non-systematically.

The patient has been working as a cook at the market during last 10 years. She denies smoking, drug abuse, drinks alcohol occasionally; denies chronic cardiovascular diseases and acute cardiovascular events (including sudden cardiac death) in close relatives. Had no operations, traumas in the past; in 2014 was diagnosed with single-nodular goiter, subclinical hypothyroidism.

On objective examination: The general status of the patient is satisfactory, clear consciousness, posture is active. Height is 162 cm, weight – 120 kg, BMI = 45 kg/m^2. Skin: pale-pink, with preserved moistness and elasticity; visual mucous membranes are pink, moist, undamaged; fat tissue is developed excessively, distributed symmetrically. Peripheral edemas are absent. Thyroid gland: by palpation both lobes of thyroid gland are diffusely enlarged, painless; there is a mass near 1cm in diameter in the right lobe. Lungs: resonance percussion sound, vesicular breathing over the lungs fields, RR 19 pm. Heart borders are extended to the left on 1 cm, heart activity is rhythmic with HR 72 bpm. Heart tones are rhythmic, with mid-systolic ejection murmur of moderate intensity in the II and V points of auscultation.

Blood pressure *sin* 144/100 mm Hg, *dext* 146/102 mm Hg, radial pulse is synchronous, rhythmic at 72 bpm.

Abdomen: abdominal girth – 133,5 cm, abdomen is painless on superficial and deep palpation in all regions. Liver at the costal margin, painless; spleen is not palpable. Absence of vascular sounds during abdomen auscultation. Pasternatskiy sign is negative on both sides. Urination is free, painless.

The results of current patient's investigations were: clinical full blood count, urinalysis, creatinine, urea, blood electrolytes, ALT, AST, within the normal range; fasting plasma glucose FPG – 6,5 mmol/l (N – 3,3–5,5 mmol/l); lipid profile – very low density lipoprotein cholesterol VLDL-C-1,52 mmol/l (N – < 1,05 mmol/l), low density lipoprotein cholesterol LDL – C (N – < 2,59 mmol/l) – 5,1 mmol/l, high density lipoprotein cholesterol HDL-C – 1,4 mmol/l (N – 1, 04–1,55 mmol/l), triglycerides – 3,35 mmol/l (N – < 2,3 mmol/l), total cholesterol – 8,2 mmol/l (N – < 5,2 mmol/l), atherogenic coefficient – 4,85 U (N – < 3U).

ECG: sinus rhythm, heart rate – 71/min, complete right bundle brunch block; echocardiography– increased stiffness of aorta and leaflets of aortic valve with their fibrotic changes, signs of moderate aortic stenosis (opening restricted to 1,2 cm, pressure gradient on aortic valve – 20 mm Hg), left ventricle hypertrophy, diastolic dysfunction of left ventricle, EF – 63 %.

HRV paced breathing test – showed imbalance of autonomous nervous system with prevalent very low frequency and decreased high frequency components of HRV spectrum, low TP in the initial stage; paced breathing showed positive growth of TP and parasympathetic response with increased high frequency involvement, resting stage demonstrated non-significant growth of TP in comparison with initial stage and intensification of low frequency influences (see table).

Diagnosis: essential hypertension stage II, grade 2, high risk. Left ventricular hypertrophy. Atherosclerosis of the aorta and its valve with aortic stenosis 2 st. Heart failure IIA with preserved ejection fraction, II functional class. Obesity grade 3. Dyslipidemia. Impaired fasting plasma glucose. Single-nodular goiter 1st stage with unspecified function.

Prescriptions of the patient were: life style modifications, lisinopril 5 mg per day, atorvastatin 20 mg per day, aspirin – 75 mg daily. After 2 weeks of therapy the general status of the patient has been improved, her blood pressure was running on values 130–132/85–90. Next visit was recommended after 3 month but the patient didn't come.

After 8 month the patient came with complaints on periodically appearing (once or twice in a month) attacks of extreme weakness, palpitations, dizziness and burning chest pain with irradiation into the interscapulum space; such episodes developed usually «without any obvious reasons»; relieved by prolonged rest and intake of corvalol. Several times attacks were so severe that patient fainted.

Patient first started to notice such attacks for about 4 months ago; first they were rare and insignificant but then their intensity and frequency began to increase. Near 5 months ago she stopped antihypertensive therapy by herself but the last week she began to take lisinopril 5 mg per day again.

On objective examination – there are edemas of the lower thirds of sheens; blood pressure *sin* 160/100 mm Hg, *dext* 164/106 mm Hg, other physical signs without significant changes.

On laboratory and instrumental investigations: lipid profile – VLDL – 1.2 mmol/l, LDL – 5,1 mmol/l, HDL – 1,3 mmol/l, triglycerides – 2.27 mmol/l, total cholesterol – 7,26 mmol/l, atherogenic coefficient – 4,84 U; FPG – 5.0 mmol/l; ultrasonography of thyroid gland: diffuse changes of thyroid gland with enlargement of both lobes of thyroid gland; there are nodules in both lobes; thyroid function test: free thyroxin FT4 – 0,993 ng/dl (N – 0,93–1,7 ng/dl), free triiodothyronine FT3 – 3,02 pg/dl (N – 2,0–4,4 pg/dl), serum thyrotropin TSH – 1,45 μIU/mL (N – 0,27–4,2 μIU/mL), thyroid peroxidase antibodies TPO – 16,13 IU/mL (N – < 34,0 IU/mL). Echocardiography – signs of aortosclerosis, moderate aortic stenosis (pressure gradient on aortic valve – 30 mm Hg), moderate dilation of the left atrium, concentric hypertrophy of left ventricle, diastolic dysfunction of left ventricle, EF – 61 %.

Holter monitoring – 20.10.2015 reported episode of atrial fibrillation with ventricular rate 90–160, lasting 54 minutes, during which

observed following complaints – weakness, burning sensation behind the sternum and interscapulum region, the feeling of impending syncope. Also during the period of observation were registered 7 supraventricular extrasystoles.

HRV paced breathing test (PBT) sinus rhythm tracing – characterized by decreased heart functional state with extremely low TP, prevalence of low frequency components of HRV spectrum with significantly increased LF/HF ratio and high level of very low frequency waves; the reaction on paced breathing was positive with increased parasympathetic activity, although TP showed poor growth; in resting stage occurred intensification of neurohormonal impact on heart rate regulation (see table).

Diagnosis: essential hypertension stage II, grade 2, high risk. First diagnosed atrial fibrillation, tachy form (20.10.2015 registered episode of atrial fibrillation with duration of 54 minutes). Left ventricular hypertrophy. Atherosclerosis of the aorta and its valve with aortic stenosis 2 st. Heart failure IIA with preserved ejection fraction, II FC. Obesity grade 3. Dyslipidemia. Nodular goiter 1st stage. Euthyreosis.

Prescriptions for the patient were: sotalol 40 mg twice daily with control of ECG QT interval in 3 days, if QT remain normal, dosage should be increased up to 80 mg twice a day with QT interval control in 3 days, furosemide 40 mg a day every 3-rd day, under control of plasma electrolytes balance), lisinopril 5 mg daily, atorvastatin 20 mg once daily, aspirin 100 mg daily.

After 7 months of treatment, the patient's general condition improved significantly, attacks of atrial fibrillation were almost ceased, blood pressure stabilized at the level of 125–130/80–85. On Holter's monitoring episodes of atrial fibrillation were not detected.

Paced breathing test (sinus rhythm tracing) demonstrated sympatotonia with increased neurohormonal contribution to the HRV spectrum in initial stage, paced breathing stage was characterized with increase of vagal parameters, and in initial stage was observed significant shift to neurohormonal influences (see table).

RESULTS AND DISCUSSION

Dynamic changes in spectral parameters of HRV in the patient are shown in table.

Table

Dynamic changes of the HRV spectral components in paced breathing test (sinus rhythm tracings)

Spectral HRV parameters	06.02.15, 1st visit	13.10.15, 2nd visit	13.06.16, 3rd visit
Initial stage			
VLF, %	52	43	40
LF, %	32	46	46
HF, %	16	11	14
LF/HF	2,09	4,01	3,25
TP, ms^2	254	142	239
Paced breathing			
VLF, %	33	23	37
LF, %	13	31	20
HF, %	54	46	43
LF/HF	0,23	0,68	0,47
TP, ms^2	1819	264	861
Resting stage			
VLF, %	49	69	63
LF, %	43	27	30
HF, %	9	4	7
LF/HF	4,84	7,23	4,44
TP, ms^2	351	189	580

Note: VLF - very low frequency waves, LF - low frequency waves, HF – high frequency waves, LF/HF - ratio of the low-frequency waves to high-frequency waves, TP – total power of HRV spectrum.

Dynamic changes in spectral indices quite clearly reflected the functional state of the heart rhythm regulation, depending on the course of the disease. Changes of LF/HF ratio showed increase in low frequency influences on the 2nd visit, compared with the 1st one,

which were especially pronounced in the resting stage, where LF/HF reached the value of 7, 23. The deterioration of vagal response to paced breathing on the 2nd visit compared with 1st one was also apparent. However on the 3rd visit, was noted decline in the LF/HF ratio at all stages of the breathing test, thus demonstrating the improvement of the patient's condition in connection with the effectiveness of the therapy and systematic intake of drugs.

Dynamic changes in LF / HF index are illustrated in Figure 1.

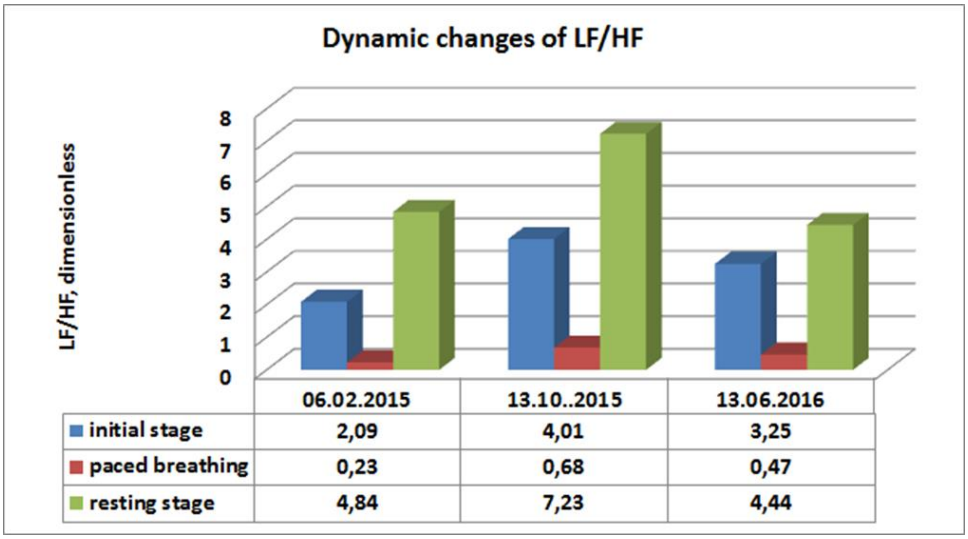

Fig. 1. Dynamic changes of index LF / HF in paced breathing test.

Dynamic changes in the total power TP showed lower values of this parameter at the initial stage of the paced breathing test at all visits, but on the 1st visit a marked TP growth was noted as response to paced breathing, while in the 2nd visit increase of TP was very insignificant, illustrating reduced functionnality of heart rate regulation in connection with the deterioration of the patient's condition. The 3rd visit showed improvement of TP growth in response to respiratory modulation in comparison with the 2nd visit, as well as a more pronounced increase of this index in resting stage.

Dynamic changes in the total power spectrum TP are reflected in the Figure 2.

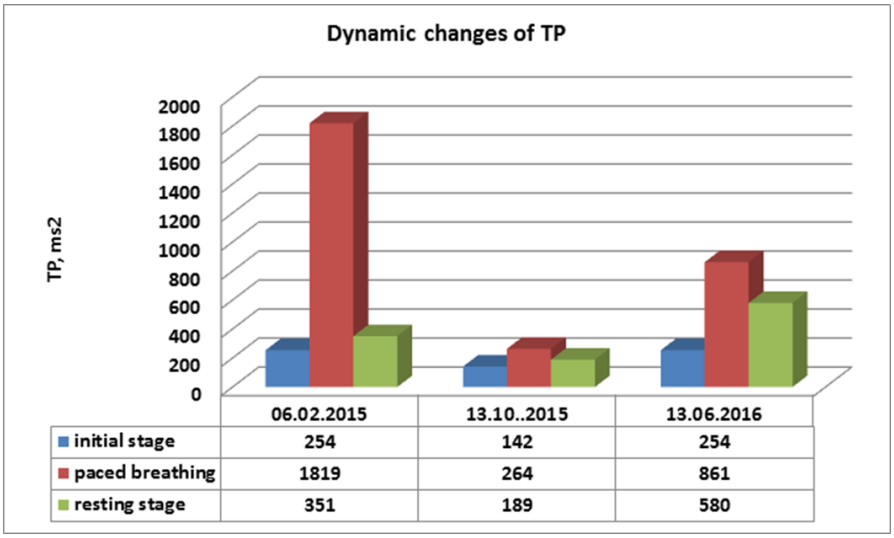

Fig. 2. Dynamic changes in the total power spectrum TP in paced breathing test.

Influence of neurohormonal HRV components in the initial stage was most pronounced on the 1st visit, and prevailed over low-frequency index in paced breathing stage. In the 2nd and 3rd visit was observed a significant increase in LF component

compared to the VLF, but at the resting stage was noted a shift towards to increase in neurohormonal effects, by means of reducing low-frequency and high-frequency waves.

Thus the deterioration of the patient's condition that manifested with the registered episode of atrial fibrillation due to uncontrolled hypertension, non-systematic approach to drug intake and due to existing concomitant diseases was reflected by the aggravation of imbalance of the heart rate regulation related to the reduced regulatory capacity of the autonomous nervous system characterized by the decrease of the total power of the HRV spectrum and intensification of sympathetic and especially neurohormonal influences. On the other hand, after effective application of therapeutic regimens reverse changes in the spectral parameters of HRV occurred.

CONCLUSIONS

Assessment of heart rate variability by means of paced breathing test is a useful tool for dynamic monitoring of the patient's condition that allows to improve evaluation of treatment efficacy and to individualize therapy.

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THE IMPORTANCE OF THE COMPLIANCE TO A MEDICAL TREATMENT OF A PATIENT WITH A VERY HIGH CARDIOVASCULAR RISK AND COMORBIDITY: ARTERIAL HYPERTENSION, ATRIAL FIBRILLATION AND DIABETES MELLITUS

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The ultimate goal of any prescribed medical therapy is to achieve certain desired results in the patients concerned. Compliance to medical recommendations not only includes patient compliance with medication but also with diet, exercise, or lifestyle changes. Considered a clinical example of the patient of a very high cardiovascular risk with comorbid pathology: arterial hypertension, atrial fibrillation and diabetes mellitus. We have shown with this case as in comorbid patients with high cardiovascular risk could be organized medical treatment without polypharmacy.

KEY WORDS: compliance, cardiovascular risk, hypertension, heart failure, atrial fibrillation, diabetes mellitus

ВАЖЛИВІСТЬ ПРИХИЛЬНОСТІ ДО МЕДИЧНОГО ПРИЗНАЧЕННЯ ПАЦІЄНТА ВИСОКОГО КАРДІОВАСКУЛЯРНОГО РИЗИКУ ТА КОМОРБІДНОЮ ПАТОЛОГІЄЮ: АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ, ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ ТА ЦУКРОВИМ ДІАБЕТОМ

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Кінцева мета будь-якої призначеної медичної терапії - досягнення певних бажаних результатів у зацікавлених пацієнтів. Дотримання лікарських рекомендацій включає в себе не тільки дотримання пацієнтом медикаментозної терапії, а й зміна дієти, фізичних вправ, або способу життя. Розглянуто клінічний приклад пацієнта високого кардіоваскулярного ризику та коморбідною патологією: артеріальною гіпертензією, фібриляцією передсердь та цукровим діабетом. Ми показали цим випадком як при коморбідності у пацієнта з високим кардіоваскулярним ризиком можна організувати медикаментозну терапію минаючи поліпрагмазію.

КЛЮЧОВІ СЛОВА: прихильність, кардіоваскулярний ризик, гіпертензія, серцева недостатність, фібриляція передсердь, цукровий діабет

ВАЖНОСТЬ ПРИВЕРЖЕННОСТИ МЕДИЦИНСКИМ НАЗНАЧЕНИЯМ ПАЦИЕНТА ВЫСОКОГО КАРДИОВАСКУЛЯРНОГО РИСКА И КОМОРБИДНОЙ ПАТОЛОГИЕЙ: АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ, ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ И САХАРНЫМ ДИАБЕТОМ

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Конечная цель любой назначенной медицинской терапии - достижение определенных желаемых результатов у заинтересованных пациентов. Соблюдение врачебных рекомендаций включает в себя не только соблюдение пациентом медикаментозной терапии, но и изменение диеты, физических упражнений, или образа жизни. Рассмотрен клинический пример пациента высокого кардиоваскулярного риска и коморбидной патологией: артериальной гипертензией, фибрилляцией

предсердий и сахарным диабетом. Мы показали этим случаем как при коморбидности у пациента высокого кардиоваскулярного риска можно организовать медикаментозную терапию уйдя от полипрагмазии.

КЛЮЧЕВЫЕ СЛОВА: приверженность, кардиоваскулярный риск, гипертензия, сердечная недостаточность, фибрилляция предсердий, сахарный диабет

INTRODUCTION

Compliance with medical recommendations, especially with drug therapy, has been recognized to represent a complex challenge since its first mentioning by Hippocrates about 2400 years ago. An in-depth scientific approach towards this problem, however, can only be traced over the past three decades with a strong increase in published studies over this period of time [1].

Major barriers to compliance are thought to include the complexity of modern medication regimens, poor «health literacy» and lack of comprehension of treatment benefits, the occurrence of undiscussed side effects, the cost of prescription medicine, and poor communication or lack of trust between the patient and his or her health-care provider. Efforts to improve compliance have been aimed at simplifying medication packaging, providing effective medication reminders, improving patient education, and limiting the number of medications prescribed simultaneously [2–3].

Estimation of total CV risk is easy in particular subgroups of patients, such as those with antecedents of established cardiovascular disease (CVD), diabetes, coronary heart disease (CHD) or with severely elevated single risk factors [4].

Compliance to medical recommendations is important for patients with comorbidity because of high one-year- mortality in this group of patients especially without adequate treatment [5].

We represent a clinical example of the patient of a very high cardiovascular risk with comorbid pathology: arterial hypertension, atrial fibrillation and diabetes mellitus without previous compliance to medical recommendations.

CLINICAL CASE

The patient L., a man born in 1949, was admitted to the Kharkiv Railway Clinical Hospital № 1 of Brence of «HC» JSC «Ukrzaliznytsia» cardiology department in October, 2015 with complaints of disruptions of the heart beats and heart palpitations which are not related to physical activity (appeared at rest, night and during every day physical activity); shortness of breath when walking (observed during usual physical exertion), disappearing after the rest; unstable blood pressure (increasing of BP despite taking hypotensive drugs – Lisinopril, amlodipine); additional: dry mouth, intermittent numbness in the toes.

HISTORY OF DISEASE

Essential hypertension was diagnosed more than 30 years with the maximum blood pressure (BP) over 200/140 mm Hg. The usual BP is about 140/90 mm Hg (antihypertensive drugs – Lisinopril 10 mg, amlodipine 5 mg but sometimes he misses the dosage). Since 2012 reports the attacks of palpitations (heart rate over 130 beats/min).

Since 2012, is hospitalized 1-2 times a year for a planned examination and treatment to the cardiology department (Diagnosis: Arterial hypertension stage II, 3 grade. Persistent Atrial Fibrillation. HF II-A stage, FC III). Intakes warfarin 5 mg per day. Does not check INR regularly. Last admission in November 2014.

Current worsening from 27.10.2015 when the aggravation of the complaints has been happening, that's why he was hospitalized to the second cardiological department of CCH UZ for examination and correction of the treatment.

ANAMNESIS VITAE

He denies tuberculosis, malaria, viral hepatitis, sexually transmitted diseases and AIDS intake; denies allergic reactions to drugs. Diabetes mellitus since 2010 year, intakes metformin 500 mg twice a day. Hasn't been controlling his glucose level.

Previous smoker. Denies smoking for over 20 past years; denies alcohol consumption.

Sedentary life style. Hasn't been following recommended low-carb diet; hasn't checked his lipid profile over 6 months. Hereditary (father-essential hypertension).

PHYSICAL EXAMINATION

General condition is satisfactory, consciousness is clear, emotionally stable,

optimistic mood. Height = 178 cm, Weight = 95 kg, BMI = 30 kg/m^2, waist-to-hip ratio 1,15.

Skin is normal colored, without any scars. Peripheral lymph nodes, the thyroid gland are not palpable.

Pulmonary percussion–resonant sound, auscultation – weakened vesicular breathing, no adventitious sounds. Heart borders extended to the left on 1,5 cm of midclavicular line, HR =72 bpm irregular. Ps= 72 bpm. No pulse deficiency.

Auscultation of the heart - heart sounds are muted, accent of the II tone above the aorta. Systolic murmur above the aorta. BP dextr = BP sin= 170/100 mm Hg (on the background of antihypertensive therapy).

Abdomen is soft, painless, symmetrical, no discrepancies of the abdominal muscles. No visible peristalsis. Liver edge is smooth, painless, palpated 1.5 cm below the costal arch. Spleen and pancreas are not palpable. Symmetrical mild shin pitting edema.

REFERRAL DIAGNOSIS

Essential arterial hypertension. Atrial fibrillation. Heart failure. Diabetes mellitus. Obesity.

RESULTS OF LABORATORY AND INSTRUMENTAL DIAGNOSIS

Complete blood count (29/10/15): hyperhemoglobinemia, erythrocytosis, hemoconcentration.

Urinalysis (29/10/2015): glycosuria (174.5 mmol/l (23 g/l)).

Biochemical analysis (29/10/2015): hyperglycemia (17.27 mmol/l): patient reported that he ate a big cake the day before the test and he didn't remember if he took a metformin in the evening; decreased kidney function (GFR by Cockcroft -Golt 66 ml/min/1.73 m2)

Fasting glucose test (30/10/15): hyperglycemia (13.1 mmol/l).

Blood lipid spectrum (29/10/15): II b type of dyslipidemia.

INR (29/10/15) – 1.04; (02/11/15) – 1.52; (05/11/15) – 2.47.

Electrocardiography (ECG) (28/10/15): atrial fibrillation with ventricular contraction rate 72 bpm. Premature left ventricle contraction. Deviation of the heart electrical axis to the left.

Echocardiography (29/10/15): sclerotic changes of aortic walls, aortic and mitral valves. Dilation of the ascending aorta. The aortic stenosis (atherosclerotic). Dilatation of both atriums. Left ventricular hypertrophy. Signs of increasing diastolic stiffness of the left ventricular wall.

Ultrasonography of the abdomen (29/10/15): hepatomegaly, liver steatosis. Diffuse parenchymal changes of the liver. Stagnation of the bile in the gallbladder. Gallbladder cholesterosis. Diffuse changes of the pancreas parenchyma without increasing of its size. Microstones in the kidney.

Consultation endocrinologist (01/11/15): Diabetes mellitus type 2, moderate severity, decompensation. Prescription: increase the dosage of metformin to 1000 mg twice a day.

RECOMMENDATIONS FOR FURTHER EXAMINATION

24 hour ambulatory ECG monitoring.

Daily glycemic profile, glucose tolerance test, HbA1C.

Creatinine after 2 weeks to exclude kidney disease.

Ophthalmologist, neurologist consultation.

TREDMIL-TEST to exclude silent myocardial ischemia.

ECHO for evaluation of diastolic function of LV.

Lipid profile (LDL), ALT (liver) +/- CK (rhabdomyolysis) – control of efficacy and safety of rosuvastatin.

Blood electrolytes (K, Na, BUN) [6–7].

CLINICAL SYNDROMES

Atherosclerosis (sclerotic changes of aortic valve, mild atherosclerotic aortic stenosis);

Arterial hypertension *;

Arrhythmias (permanent (constant) AF);

Heart failure;

Dyslipidemia*;

Hypertensive heart (LVH, atrial enlargement, increased diastolic stiffness);

Hepatomegaly, liver steatosis;

Erythrocytosis, hemoconcentration;

Hyperglycemia / glycosuria syndrome*;

Obesity: BMI = 30 kg/m2, waist-to-hip ratio 1,15*.

– features of metabolic syndrome.

CLINICAL DIAGNOSIS

Main:

Systemic atherosclerosis (atherosclerosis of the aorta, mild aortic stenosis);

Arterial hypertension stage II, 3 grade. Hypertensive heart (LVH);

Permanent atrial fibrillation, normosystolic type;

EHRA IIa class. CHA2-DS2-VASC-4. HAS-BLED-2;

Heart failure with preserved left ventricle systolic function, II FC, stage B. Dyslipidemia II B type (after Fredrickson);

Very high added total CV risk.

Comorbidity:

Diabetes mellitus type II, moderate severity, subcompensation;

Obesity I degree;

Nonalcoholic fatty liver disease [4, 6–8];

CASE MANAGEMENT IN THE HOSPITAL

Drug therapy:

Bisoprolol 5 mg in the morning;

Torasemide 2,5 mg in the morning;

Perindopril 5 mg in the morning;

Amlodipine 5 mg in the morning;

Warfarin according to the scheme (starting dosage -5 mg per day at 5 p.m.);

Metformin 1000 mg 2 times a day.

IV therapy:

Thiotriazoline 2. 0 + NaCl 0. 9 % 10.0 N10;

«Asparcam» (Mg+K) 10,0 + NaCl 0.9 % 200.0 N10.

OUR RECOMMENDED TREATMENT ACCORDING LAST GUIDELINES

Lifestyle modification.

1. Reduce weight by 5 % to 10 %.
2. Regular physical activity.
3. Diet: eat regular meals and snacks; avoid fasting to lose weight; consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants); understand Nutrition Facts Label information; use mild cooking techniques instead of high-heat cooking.
4. Follow to doctor's appointments [6-7].

Drug treatment

1. Angiotensin-converting enzyme (ACE) inhibitor-PERINDOPRIL 8 mg in the evening (target BP – 130/85 mm Hg).
2. Diuretic – TORASEMIDE 10 mg in the morning.
3. B- blocker – BISOPROLOL 5 mg in the morning (target HR – 60 b/m).
4. Statin - ROSUVASTATIN 10 mg in the evening.
5. Anticoagulant – WARFARIN according to the scheme 17:00; better – the new oral anticoagulants (NOAC – Dabigatran – 110 mg 2 times daily or Rivaroxaban – 15 mg p/day).
6. Oral hypoglycemic agents-METFORMIN 1000 mg 2 times a day.
7. Control of compliance to medical recommendations [4, 6–8].

PROGNOSIS

Prognosis for life – non-compliance to doctor's appointments – non-satisfactory. The prognosis for recovery – an unfavorable.

CONCLUSIONS

Compliance to a prescribed medication showed a positive effect in different researches. Patients with a high adherence to medication had improved the quality of life (QOL). These results in importance not only in developing intervention programs for patients but also in improving their QOL through sustainable health promotion [1, 9]. Avoiding of polypharmacy another main condition which increases the compliance of comorbid patients with high cardiovascular risk to medical recommendations. Making sure patients understand the drug dosing regimen could also improve compliance.

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Review

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MODERN ASPECTS OF COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH DIABETES MELLITUS

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Clinical importance of the community-acquired pneumonia clinical course and treatment in patients with diabetes mellitus is discussed in this review. Clinical characteristics, immunological parameters, possible drugs regimen, depending on community-acquired pneumonia severity, and the ability to optimize therapy with antibacterial drugs are considered. The features of the appointment of antibacterial drugs in the step-down antibacterial therapy, peculiarities of pneumonia in patients with diabetes mellitus.

KEY WORDS: diabetes mellitus, pneumonia, outcomes, antibacterial treatment

СУЧАСНІ АСПЕКТИ НЕГОСПІТАЛЬНОЇ ПНЕВМОНІЇ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ

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Клінічну значимість перебігу негоспітальної пневмонії та її лікування у пацієнтів із цукровим діабетом було обговорено у даному огляді. Клінічні характеристики, імунологічні показники, можливі режими антибактеріальних препаратів, в залежності від тяжкості течії негоспітальної пневмонії, а також можливість оптимізації терапії антибактеріальними препаратами були обговорені. Розглянуто особливості призначення антибактеріальних препаратів під час ступінчастої антибактеріальної терапії, особливості перебігу пневмонії у пацієнтів з цукровим діабетом.

КЛЮЧОВІ СЛОВА: цукровий діабет, пневмонія, результати, антибактеріальна терапія

СОВРЕМЕННЫЕ АСПЕКТЫ ВНУТРИБОЛЬНИЧНОЙ ПНЕВМОНИИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ

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Клиническая значимость течения внебольничной пневмонии и ее лечения у пациентов с сахарным диабетом была обсуждена в данном обзоре. Клинические характеристики, иммунологические показатели, возможные режимы антибактериальных препаратов, в зависимости от тяжести течения внебольничной пневмонии, а также возможность оптимизации терапии антибактериальными препаратами были обсуждены. Рассмотрены особенности назначения антибактериальных препаратов при ступенчатой антибактериальной терапии, особенности течения пневмонии у пациентов с сахарным диабетом.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет, пневмония, исходы, антибактериальная терапия

INTRODUCTION

In the northern hemisphere the annual incidence of community-acquired pneumonia (CAP) is about 12 cases per 1,000 people, the biggest part of CAP cases occur during the wintertime [1]. Total number of adult patients with CAP in five biggest European countries (Britain, France, Italy, Germany, Spain) exceeds around 3 million people [2]. In Ukraine annual CAP morbidity is 3-11 cases per 1000 adults and the highest ranges usually observed among older patients [3]. CAP clinical course as one of the most common infectious diseases have certain characteristics associated with patient age, presence

concomitant diseases, drug interactions between medication for the basic treatment of concomitant diseases and antibacterial therapy of CAP, which can cause an additional risks and change the prognosis of patients [4–8]. Older age and concomitant diseases such as diabetes (DM), heart failure, chronic obstructive pulmonary disease, chronic renal failure, liver disease, immunodeficiency, increase the risk of CAP incidence and disease outcomes in that case will be worse [9]. Since 2006, each year in the USA with a diagnosis diabetes mellitus are hospitalized around 6 million of patients. 8–12 % of them - because of various infectious diseases. Patients with diabetes in 2 times more often hospitalized because infectious diseases diagnosis than patients without it. Since 2006, about 10 million of diabetic patients were hospitalized in the ICU. Infectious diseases such as premium cause of hospitalization observed in 10 % of cases of annual diabetes mellitus patient's hospitalization [10].

IMMUNE SYSTEM CHANGES IN PATIENTS WITH DIABETES MELLITUS AS A CAUSE OF HIGH RISK OF INFECTIOUS DISORDERS

Increased susceptibility and increased mortality from CAP in patients with diabetes mellitus could be explained by specific changes in these patients' immunity and response to infections. The main pathophysiologic mechanisms which are responsible for altered immunity function are: increased virulence of some pathogens because of hyperglycemia; glycosuria, decreased production of interleukins during infection response; reducing of chemotaxis and phagocytic abilities, polymorph nuclear leukocytes immobilization; gastrointestinal and urinary dysmotility [11–14]. For example, decreased secretion of interleukin-1 and interleukin-6 by mononuclear cells and monocytes in response to stimulation by lipopolysaccharides [11, 15]. Hyperglycemia reported as the cause of decreased mobilization of polymorph nuclear leukocytes, chemotaxis, and phagocytic activity [16–18]. Also high level of glucose in DM patients lead to block of the inhibiting glucose-6-phosphate dehydrogenase (G6PD), increased apoptosis of polymorph nuclear leukocytes, and reducing their transmigration through the endothelium and as result of it - decreased leukocytes antimicrobial function [15]. Some studies reveal that the biological function of the antibodies becomes impaired with increasing of glycated hemoglobin levels [19]. Experimental animal models of inflammation and in humans confirm the compromised immune response in patients with diabetes: increased pro-inflammatory [20–21], and antyfibrinolitic pro-coagulating activity, increased expression of cell surface receptors, which can recognize foreign agents [22]. Cytokines may increase blood glucose levels by stimulating gluconeogenesis and increasing insulin resistance in peripheral tissues and in the liver [23-24]. In pneumonia patients with concomitant diabetes hyperglycemia were significantly higher compared with patients with diabetes alone (level of HbA1c 8, 2 % and 7, 2 % respectively, $p < 0.01$). Worse hyperglycemia control leads to the increased incidence of pneumococcal pneumonia in patients with diabetes, but high levels of hyperglycemia during hospitalization did not lead to increasing of disease severity [25]. For patients with diabetes, taking in account that more than two-thirds of them have two or more comorbidities [26], respiratory infections has long been considered as inflammation precipitators. In this situation the challenge is the complicity of the diagnosis making based only on clinical and radiological findings. But some of clinical studies showed absolutely opposite results. For example, The GenIMS Study confirmed that serum concentrations of biomarkers of inflammation (Tumor Necrosis Factor - α, interleukin – 6 and interleukin – 10), coagulation (antithrombin, factor IX) and fibrinolysis (PAI-1 and D-dimers) are similar among patients with diabetes and non-diabetes patients when measured during the first week of the treatment. In a large number of patients serum cytokine levels were within the normal range [27] and diabetes did not affect the concentration of other biomarkers [23, 28]. The degree of increased releasing of primary inflammation mediators is closely connected with the clinical variant of the disease [29].

ETIOLOGICAL CAUSES OF CAP IN PATIENTS WITH DM: STREPTOCOCCUS PNEUMONIAE? ACINETOBACTER? OR NOTHING SPECIAL?

In the case of patients with diabetes, in the global scientific medical literature there is no sufficient information regarding the clinical characteristics and microbiological factors of CAP [30]. In patients with diabetes, there are

two important microbiological points of view of the peculiarities of pneumonia. First is the increased importance of specific etiologic pathogens (S. aureus, gram-negative strains) in CAP development. Second is an identified susceptibility to more severe and complicated course of pneumonia, caused by S. pneumoniae, with frequent bacteremia appearance. Another distinction of respiratory infections in these patients is a frequent occurrence of bacterial superinfection and ketoacidosis during the influenza season [31]. Saibal M.A.A. et al. [32] compered in their study total 47 diabetic and 43 non-diabetic adult hospitalized patients with CAP and in 7 (20.0 %) cases more than one organism was isolated from sputum samples. Klebsiella pneumoniae was the most commonly isolated organism from sputum sample and its level was higher in the group of DM patients than in non-DM group (19,1 vs 4,7 % respectively). But Streptococcus pneumoniae incidence in sputum species were higher in the non-DM group (0,0 vs 20,7 % respectively). Also in the group of DM patients were found 2 (4,3 %) E. Coli, 2 (4,3 %) Pseudomonas aeruginosa and 1(2.9 %) Acinetobacter grows, that weren't present in sputum samples of non-DM patients. These findings were similar to the previous international investigations data, such significantly increased risk of Acinetobacter spp. as a possible causative agent of CAP in patients with concomitant diabetes in Ljubic S. et al. investigation made in Croatia. Infections caused by Acinetobacter spp. usually are difficult to treat because of its rapidly developed antibacterial resistance and more than 60 % mortality from pneumonia in this case [33–34]. The main pathogens that were the cause of CAP has developed in hospitalized patients with type 2, according to Russian researchers are S. pneumoniae (32,9 %), S. aureus (16,5 %), H. influenza (15,2 %), K. pneumoniae (13,9 %) and M. pneumoniae (12,7 %) [35]. Patients suffering from diabetes, often die from invasive pneumococcal pneumonia comparing to those without diabetes. Moreover, in patients with diabetes are often prevalent unfavorable prognostic factors of pneumococcal bacteremia such as advanced age and presence of comorbidities [36]. In patients with diabetes due to esophagus paresis episodes of esophageal contents micro aspiration from oropharynx or stomach are prevalent compering with non-DM patients. According to some authors [37–38], because of this phenomenon in diabetic patient's aspiration pneumonia most likely pathogens can be aerobic bacteria (S. pneumoniae, S. aureus and K. pneumoniae).

FEATURES OF CAP CLINICAL COURSE IN DM: WHY THESE PATIENTS ARE SO SPECIAL?

By the presence of all those factors written above could be explained more severe and complicated pneumonia clinical course reported in the global scientific medical literature. One of the latest investigations were made in Portugal 2016 year [39], as this country presents one of the highest rates of DM in Europe. Clinical cases of CAP with DM were compared with CAP without DM in age and gender subgroups, hospitalization time and mortality rate, across age groups and over the 2009–2012 periods. Compared to patients with CAP without DM (61.9 %) average length of stay in CAP with DM cases was significantly longer ($p < 0.0001$), with an average length of stay was 12.0 ± 10.5 vs 11.2 ± 10.1 days respectively. Also, in-hospital mortality (20–79 years), adjusted for sex and age, was significantly higher in patients with CAP who have DM as compared to patients with CAP without DM (15.2 % vs 13.5 %, $p = 0.002$). Interesting is the fact that, when cohort was analyzing by age group, increased mortality of patients with DM was only observed in the youngest age group. These findings can be explained by presence of the prevalence type 1 diabetes cases represented in the youngest age group (20–39 years; 26.8 %) with more severe DM clinical course, frequent pneumonia complication as pleurisy and presence of ketoacidosis episodes during the treatment period. In a meta-analysis, which included 33,148 patients with CAP, were demonstrated increased mortality among patients with diabetes (odds ratio 1.3; 95 % confidence interval (CI) 1,1–1,5) [40]. However, this study was based on high levels of glucose in patients without confirmed diagnosis of diabetes. However, modern clinical reports provide strong evidence of increased vulnerability to infections in diabetic patients, who are not only at increased risk for severe and current infections but rather infections are the most common cause of destabilization of diabetes and in 20–25 % of cases is the first DM manifestation [31]. For example, in a population cohort study that included 29.900

patients [41] was studied whether DM increases the risk of death and complications from pneumonia. According to the data, the adjusted risk of mortality at 30 and 90 days was 1.2 (95 % CI 1.1–1.3) and 1.10 (95 % CI 1,02–1,18) for patients with diabetes. But the difference between the groups of patients with diabetes and without regarding the number of episodes of pulmonary complications or bacteremia was not found. High levels of blood glucose during hospitalization was associated with an increase in deaths rate of patients (adjusted risk of 30-day mortality for high blood glucose levels equal to 1.46 (95 % CI 1,01–2,12)). It is important that after the reduction and normalization of blood glucose levels after admission to the hospital, diabetes was no longer associated with increased levels of mortality (risk of death in diabetic patients with blood glucose within 6,1–11,0 mmol/l was 0,96 (95 % CI 0,69–1,35)). Since hyperglycemia is an essential feature of diabetes, conceptually difficult to separate the impact of blood glucose levels from the effects of diabetes only. In a large study, which covered 623,718 patients aged ≥ 65 years with the level of mortality 10.6 %, was confirmed adverse relationship between total in-hospital mortality and diabetes (OD 1.27; 95 % CI 1,23-1,31) in patients with pneumonia [42-43]. According to the order № 128 of Ministry of Health of Ukraine from 19.03.2007, patients with pneumonia and concomitant DM referred to the group with risk factors of high deaths risk and adverse disease outcome [44]. Summarizing all written above could be named features of CAP in patients with DM. They are: Diabetes increases the risk of hospitalization of patients with CAP; Community-acquired episodes of pneumonia in patients with diabetes require a longer hospital stay; Diabetes affects mortality hospitalized patients with CAP (increases).

WHERE TO TREAT CAP PATIENTS WITH CONCOMITANT DM: AMBULATORY, HOSPITAL WARD OR ICU?

There are two important issues that are widely discussed in medical society in the context of CAP treatment: where and how to treat these patients? To determine the appropriate place of treatment and the range of appropriate diagnostic procedures is very important to determine the severity of the disease. According to the order № 128 of Ministry of Health of Ukraine from 19.03.2007 patients with pneumonia and concomitant DM as II clinical group of CAP (mild clinical CAP course in patients with concomitant diseases) could be treated or ambulatory either as III clinical group (CAP with moderate clinical course) can be hospitalized to the hospital due to clinical judgment of physician or inability to take medicine, receive appropriate care during pneumonia treatment. If patient with DM has severe CAP, this group of patients should be treated in ICU units [44]. How physician can define the clinical course severity of CAP in patients with DM? Leading international and national guidelines for CAP treatment [45–46] recommend basing the choice of antibacterial treatment and the place of CAP treatment on specific instruments that allow determining the severity of the disease when diagnosis was made. Such as prognostic model Pneumonia Severity Index (PSI) or scales CURB-65/CRB-65 (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater) [47–48] which usually supplemented with physician determination of subjective factors as the ability to safely and reliably take oral-parenteral medication and the availability of outpatient support resources [49–50]. Ambulatory patients who have a CRB-65 score of 0 are at low risk of death and do not normally require hospitalization for clinical reasons; patients who have a CRB-65 score of 1 or 2 are at increased risk of death, particularly with a score of 2, and hospital referral and assessment should be considered; patients who have a CRB-65 score of 3 or more are at high risk of death and require urgent hospital admission. If measurement of urea level could be provided, CURB-65 should be used for determination of CAP severity [44, 50–51]. In Hai-yan Li et al. (2016) study were found that CURB-65 score could be simplified by removing low blood pressure because CUR-65 score of ≥ 2 for prediction of mortality was better than that of a CURB-65 score of ≥ 3 and it might be a more valuable cutoff value for severe CAP [51]. PSI is most commonly used prognostic model in the world named also PORT (according to the study Pneumonia Patient Outcomes Research Team), in which provides the definition of 20 main pneumonia clinical parameters. Evaluation of these parameters as patients age, presence/absences of the main comorbidities, level of heart rate or blood pressure etc., allows determine pneumonia severity index data,

predict the risk of lethal outcome and provide recommendations for treatment and places of empirical CAP antibacterial treatment [44, 50–52]. Mazen S. Bader et al. (2016) in late research found that appearance of CAP complications in patients with DM were associated with the first antibiotic dose prescribed > 8 hours after hospitalization (odds ratio = 3.16; 95 % CI: 1.58–6.32; p = 0.001) and with index PORT scale (PSI) > 90 (odds ratio = 3.52; 95 % CI: 1.45–8.53; p = 0.005). An increasing the length of stay in hospital was associated with: the first antibiotic dose > 8 hours with hospitalization [HR] = 0.56, p = 0.01 and with index scale PORT (PSI) > 90 (HR = 0.62, p = 0.01), CAP symptoms duration before hospitalization (HR = 0.96, p = 0.04) and CAP pre-hospital antibacterial therapy (HR = 0.90, p ≤ 0.0001) [53, 54].

HOW TO TREAT CAP PATIENTS WITH CONCOMITANT DM: DOES ANY SPECIFIC RECOMMENDATION EXIST?

American College of Family Physicians not revealed any specific recommendations for the treatment of respiratory infections in patients with diabetes. In Europe, these patients are usually treated in outpatient medical departments. In Ukraine specific guidelines for treatment of CAP in patients with DM weren't created and this category of patients can be referred to II, III or IV clinical groups of patients depending of the severity of CAP [44]. International experts offer three strategies for duration of CAP treatment: 1) based on the current clinical course of CAP; 2) based on the etiological reason – treatment is continuing in accordance with specified pathogen; and 3) the duration of treatment is determined according to an antibacterial drug that has been selected for treatment [44, 49–50]. Before prescription an antibacterial treatment of CAP in patients with DM should be considered: interactions of antimicrobial drugs with glucose-lowering drugs; probable reduced medication absorption during intramuscular and oral drugs administration in patients with diabetes due to the development of diabetic microangiopathy; probability of serious complications such as ketoacidosis and multiple infections; careful control of blood glucose levels in a patient not depending of the cause of hospitalization. When the first dosage of antibacterial drug should be prescribed for diabetes patients with CAP? According to the latest guidelines all patients should receive antibacterial treatment since the diagnosis CAP was made, but not later than 4 hours after hospitalization in a medical institution. In case of severe CAP, first dosage of antibacterial drug can be assigned by a family doctor prior to hospitalization [50]. Prescription of the antibacterial therapy more than 4 hours from the time of diagnosis CAP was made increases the level of in-hospital mortality in patients with diabetes (OR 6.5, 95 % CI 2.2 – 18.8, p = 0.001) [53]. Summarizing guidelines for CAP treatment: for patients with mild (low) severity CAP should be prescribed oral monotherapy by amoxicillin or if its needed parenteral injections of amoxicillin or benzyl penicillin, or clarithromycin [53], in Ukraine preferable drugs are monotherapy with amoxicillin/sulbactam or cefuroxime or their combination with macrolides [44]. Patients with CAP moderate severity should be treated with monotherapy of amoxicillin or macrolide if patients have failed to respond to an adequate course of amoxicillin before admission. In case if parenteral rout of prescription is needed, combination of amoxicillin or benzyl penicillin, together with clarithromycin is preferable [53]. Ukrainian recommendations suggest using combinations of β-lactam (parenteral) with macrolide (per os) and respiratory fluoroquinolones as drugs of other choice [44]. Patients with CAP high severity should receive a parenteral combination of a broad-spectrum β-lactamase stable antibiotic together with a macrolide or a second-generation (e.g., cefuroxime) – third-generation (e.g., cefotaxime or ceftriaxone) cephalosporin can be used instead of broad-spectrum β-lactamase stable antibiotic, together with macrolide [53]. Ukrainian recommendations suggest prescribing of combinations of β-lactam (parenteral amoxicillin/clavulonate or cephalosporin's III generation) with macrolide and respiratory fluoroquinolones as drugs of another choice [44]. How long antibiotics should be given for CAP patients? In patients with moderate clinical course of CAP antibacterial treatment could be discontinued in 3–5 days after normal ranges of body temperature will be stabilizing. For those with high severity microbiologically - undefined pneumonia, 7–10 days of treatment is proposed. This length of treatment could be extended to 14 or 21 days according to clinical judgement of physician [44, 53]. When should the intravenous route be switched to oral? Step –

down antibacterial treatment provides a two – phase's antibiotics prescription: when parenteral route of drugs administration in early treatment phases could be switched to oral immediately after stabilization of the clinical state of the patient. The advantages of step - down therapy is the reducing of the duration of parenteral treatment, which provides a significant reduction in the cost of treatment and the patient's length of stay in hospital with maintaining high clinical efficiency [55–57]. In this type of drugs prescription preferred is the usage of antimicrobial drugs with two dosage forms – both for parenteral administration and for application per os. Selected drug must also has a high bioavailability, doesn't interact with other drugs, being are well tolerated, have a long half-life and provide optimal cost of treatment [56, 58]. Patients treated initially with parenteral antibiotics should be transferred to an oral regimen as soon as clinical improvement occurs and the temperature has been normal for 24 h, providing there is no contraindication to the oral route. The antibiotic choices for the switch from intravenous to oral are onward where there are effective and equivalent oral and parenteral formulations. For example in the case of initial parenteral cephalosporin's prescription, the oral switch could be made to amoxicillin/clavulonate 625 mg three times daily rather than to oral cephalosporin with low per oral bioavailability. Or if patient was initially treated with combination of benzyl penicillin + levofloxacin in case of severe CAP, after stabilization of the patients state this therapy could be switched to oral levofloxacin with or without oral amoxicillin 500 mg–1.0 g three times daily [53, 58].

CONCLUSION

Despite absence of specific guidelines for CAP treatment in patients with concomitant DM, this patients should be treated carefully because of: increased risk of infectious pathology, presence of the macro and micro complications of DM which can affect antibacterial drugs bioavailability and both diseases clinical course; pathological changes in immunity of DM patients with decreasing of immune reactivity to infectious agents; specific medication interactions between antibacterial drugs and glucose lowering agents as respiratory fluoroquinolones interactions with glucose lowering agents could lead to severe hypoglycemia; high risk of DM and CAP complication.

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THE EFFECTIVENESS OF BIOFEEDBACK IN THE TREATMENT OF DIFFICULT-TO-CONTROL ARTERIAL HYPERTENSION

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Review is devoted to difficult-to-control arterial hypertension and possibilities of biofeedback as additional method to standard antihypertensive therapy. Reasons and current approaches to therapy of difficult-to-control arterial hypertension are discussed. Particularities of biofeedback therapy and variants of the technical implementation of the different loops are described. Recent publications that contain data of the effectiveness of biofeedback among hypertensive patients are given. Relevance of this problem among patients with difficult-to-control arterial hypertension is proved.

KEY WORDS: difficult-to-control arterial hypertension, biofeedback, heart rate variability

ЕФФЕКТИВНІСТЬ ЗАСТОСУВАННЯ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ В ТЕРАПІІ ВАЖКОКОНТРОЛЬОВАНОІ АРТЕРІАЛЬНОІ ГІПЕРТЕНЗІІ

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Огляд присвячений проблемі важкоконтрольованої артеріальної гіпертензії та можливості застосування біологічного зворотного зв'язку в якості доповнення до стандартної антигіпертензивної терапії. Розглянуто причини виникнення важкоконтрольованої артеріальної гіпертензії, сучасні напрямки терапії. Викладено особливості біологічного зворотного зв'язку і варіанти реалізації контурів. Наведено публікації останніх років, присвячені оцінці ефективності біологічного зворотного зв'язку у пацієнтів з артеріальною гіпертензією. Доводиться актуальність досліджуваної проблеми щодо важкоконтрольованої гіпертензії.

КЛЮЧОВІ СЛОВА: важкоконтрольована артеріальна гіпертензія, біологічний зворотний зв'язок, варіабельність серцевого ритму

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В ТЕРАПИИ ТРУДНОКОНТРОЛИРУЕМОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Обзор посвящен проблеме трудноконтролируемой артериальной гипертензии и возможности применения биологической обратной связи в качестве дополнения к стандартной антигипертензивной терапии. Рассмотрены причины возникновения трудноконтролируемой артериальной гипертензии, современные подходы к терапии. Изложены особенности биологической обратной связи и варианты реализации контуров. Приведены публикации последних лет, посвященные оценке эффективности биологической обратной связи у пациентов с артериальной гипертензией. Доказывается актуальность изучаемой проблемы в отношении трудноконтролируемой гипертензии.

КЛЮЧЕВЫЕ СЛОВА: трудноконтролируемая артериальная гипертензия, биологическая обратная связь, вариабельность сердечного ритма

INTRODUCTION

Arterial hypertension (HT) is one of the most common cardiovascular diseases. According to the World Health Organization, the prevalence of high blood pressure (BP) in the population over 25 years old is about 40 %. This prevalence of HT is irregular among the different ethnic groups and gender [1–2].

Due to the extensive development of the pharmaceutical industry, antihypertensive drugs may be selected for patients considering their

individual characteristics, stage and severity of the disease, and also the presence of comorbidities. However, some individuals have difficulties in achieving the target values of BP even if they use combined drug treatment [3]. Clinical researches show that approximately 20 % of patients needs three or more antihypertensive drugs for successful correction of BP [4].

There are circa 30,4–31,8 % of patients with an inadequate response to therapy [5], among them 10 % of cases is resistant HT [6]. This indicates that, despite the obvious success of drug therapy, the problem of difficult-to-control HT has not lost its value.

DIFFICULT-TO-CONTROL AND REFRACTORY HT – DEFINITION AND ETIOLOGY

The target level of BP during therapy should be less than 140/90 mm Hg. Inability to achieve this level by a combination of antihypertensive drugs indicates the presence of difficult-to-control or refractory HT. An additional criterion of difficult-to-control HT is the lack of reduction of BP at night, i.e. «non-dipper» type [7]. The terms «difficult-to-control» and «refractory (resistant)» HT should not be considered as fully equivalent.

The clear term of difficult-to-control HT is not provided in the scientific literature. For practical aim it has been proposed to use in clinical cases in which control of BP cannot be achieved by using two antihypertensive drugs in adequate fixed dose. That is, the term «difficult-to-control HT» means a broader concept, which includes of true refractory and pseudo-resistant HT [5].

The frequency of difficult-to-control HT correlates with age. This pathology occurs more frequently among the elderly patients. The high prevalence of the disease among black individuals is also noted [8]. According to data of population studies 12 % of patients receiving antihypertensive drugs have resistance to treatment [9].

Difficult-to-control HT is diffuse due to the presence of undiagnosed secondary HT, isolated systolic HT, severe course of essential or secondary HT (renovascular, endocrine) [10]. The prevalence of secondary HT among patients with difficult-to-control type is 20 %. Among the total population of people with HT the secondary forms occupy about 5–6 % [11]. The most common reasons of all types of secondary HT are renovascular and renal parenchymal diseases (20 % of all cases of difficult-to-control HT), rarely HT occurs as a consequence of pheochromocytoma (0,1–0,6 % in the general population of individuals with HT, but there are no data about individuals with difficult-to-control HT), hyperaldosteronism (20 % among patients with the resistant HT), Cushing's disease or syndrome, thyroid disease [10].

Difficult-to-control HT is frequently observed among patients with diabetes type 2 and metabolic syndrome. This is due to the fact that in diabetes as a result of direct effects on vascular endothelial cells is broken processes of endothelium-dependent vasodilation [12]. As a consequence, it was shown increasing of BP.

It is known that difficult-to-control HT is associated with obstructive sleep apnea. [3] It is believed that the periodic hypoxemia observed during sleep apnea leads to a permanent increase in the activity of sympathetic system. The elements of the pathogenesis not only predispose to persistent increase of BP, but also help stimulate the production of mediators of vasoconstriction, which reduces the effectiveness of drug therapy [13].

There is evidence of genetic predisposition of difficult-to-control HT [14]. The prevalence of mutations in the beta and gamma subunits of the sodium channel glomerular renal epithelium was higher for patients with difficult-to-control HT than in those with normal BP. Patients with genotype 3 786SSNOS have a higher risk of developing difficult-to-control HT. This is due to the fact that this genotype is associated with reduced nitric oxide synthase activity [15].

Specific antibodies play important role in pathogenesis of difficult-to-control HT. In 44 % of patients with severe HT have been discovered agonist antibodies to alpha 1-adre-noceptors [16]. The role of antibodies to angiotensin II receptor first type (AT1) is also known in the development of HT [17].

Overweight is one of the reasons for the difficulties in controlling the blood pressure. The prevalence of obesity in the population leads to an increasing the cases of difficult-to-control HT [6]. Every 10 % of excess weight accompanied by increasing in systolic BP by 6,5 mm Hg. However, in people with a body mass index over 30 kg/m^2, which corresponds to the first degree of obesity, the likelihood of developing difficult-to-control HT is higher than in those with the normal body weight [18].

The term «resistant HT» was firstly proposed in 1988 for describing cases in which the use of antihypertensive drugs in combination with lifestyle modification (restriction of salt intake, exercise stress) does not lead to the normalization of BP levels [19].

Currently resistant HT involves cases when it is impossible to achieve target level of BP by using three or more antihypertensive drugs including diuretics [20]. The American Heart Association suggests using the term resistant HT even in cases when treatment with 3 drugs in combination with a diuretic helps achieve target BP. In this case, the patient should take a triple therapy for more than one month. Daugherty study showed that more than half of patients with suspected difficult-to-control HT, had controlled BP after prescribing of such therapy during a year [21].

Low loyalty of patients to treatment leads to the development pseudo refractory HT. Only 50 % of people with HT continue to regularly take antihypertensive drugs during for 12 months after their prescription [22]. Therefore, the exact prevalence of true refractory HT is not known. This data varies from 5 % to 50 % in the different populations [23].

There are many reasons for the development of difficult-to-control HT. However, it is believed that most of the presented pseudo-resistant HT cases [24]. The reasons of pseudo-resistant form may include the following factors: errors in the measurement of BP (including «white coat» HT and a violation of the measurement technique); poor patient loyalty to drug therapy; failure to comply by patient recommendations for lifestyle changes; irrational mode of appointment of prescription of antihypertensive drugs (including an inadequate combination of drugs, insufficient dosage and the multiplicity of taking drugs).

According to the European Association of Cardiology, to pseudo resistant HT should also include the volume overload and taking medications that increase BP (non-steroidal and steroidal anti-inflammatory drugs, ampheta-mine, nicotine, caffeine, sympathomimetic, oral contraceptives, tricyclic antidepressants, monoamine oxidase inhibitors) [25].

DIFFICULT-TO-CONTROL HT AND THE RISK OF COMPLICATIONS

Lowering BP during antihypertensive therapy is accompanied by a reduction in cardiovascular mortality and disability [26]. Inability to achieve BP control on the recommended target level, i.e. the presence of difficult-to-control HT leads to a significant increase in the risk of complications from cardiovascular system [27]. Hypertrophy of the left ventricle develops faster among patients with difficult-to-control HT. Increase in myocardial mass leads to increased risk of ischemia, heart failure, sudden cardiac death. ALLHAT study confirms the rapid progression of organ damage in difficult-to-control HT [28].

Patients with uncontrolled BP have a higher risk of developing cognitive impairment than those with controlled HT [29].

The average 10-year risk of developing coronary heart disease and stroke, according to Framingham scale was higher among people with difficult-to-control HT. The risk of renal failure is also increase [30].

Monitoring more than 50,000 patients with HT showed that the risk of cardiovascular events increases more significantly in the population of patients with difficult-to-control HT [31].

There is a significant positive correlation between the level of BP and total mortality. The increase in BP leads to an increase in risk [32]. Given that difficult-to-control HT is often accompanied by the presence of diabetes, obesity and other metabolic disorders, there is an increase of cardio-vascular risk in 2–6 times [33].

CURRENT APPROACHES TO THE TREATMENT OF DIFFICULT-TO-CONTROL HT

Lifestyle plays an important role in the development of HT [34]. Therefore, treatment of HT, including difficult-to-control, should start with lifestyle modifications activities [1].

Patients with overweight should be recommended to decrease body weight. Weight loss in individuals with obese helps reduce BP levels. Target body mass index must be from 18 to 25 kg/m2, the recommended waist circumference should be less than 102 cm for men and less than 88 cm in women [3]. The loss of one kilogram can reduce the level of systolic BP by 0,13 mmHg and diastolic by 0,07 mm Hg [35].

An important element of lifestyle modification is to reduce salt intake. Excessive salt intake is considered one of the factors in the pathogenesis of HT resistant to medical therapy [36]. The current recommendations to reduce

salt intake look this way – daily consumption of salt should not exceed 5–6 g. As a result it can reduce SBP by 5,39 mm Hg and diastolic BP by 2,82 mm Hg. For difficult-to-control form of HT the reduction of salt intake less than 3 grams per day has a more pronounced effect [37]. Restriction of salt intake, combined with the DASH-diet causes a decrease in systolic BP by 11,5 mm Hg [38].

There is a linear relationship with the use of alcohol. Increased consumption of alcohol causes increase in BP and moderate drinking may not have such an effect. Daily use of ethanol for men should not exceed 35 ml and for women no more than 17 ml [39].

Smoking has a negative effect on the cardiovascular system. Tobacco addiction leads to the development of endothelial dysfunction as a result, production of vasodilators decreases, vascular stiffness increases [40].

Within 15 minutes after smoking one cigarette SBP may raise in 10-30 mmHg and DBP in 5–10 mm Hg. This is due to the activation of the sympathetic system [41]. Smoking cessation may decrease BP to 4,6 mm Hg [42].

Regular physical activity should be one of the obligatory components of therapy of difficult-to-control HT [4]. Sedentary lifestyle, especially when it combined with an unbalanced diet, contributes to the development of metabolic syndrome, which is often accompanied by difficult-to-control HT [43].

There is decrease in systolic BP by 6,9 mmHg and diastolic pressure by 4,9 mm Hg during regular exercise. 30 minutes of aerobic exercise per day help keep target BP even after reduction of dose of one of the drugs [44].

Difficult-to-control HT requires efforts to identify the causes and elimination of reasons of pseudo resistance. It is necessary to exclude or confirm the etiology of the secondary HT [45]. If it is possible to identify the cause, the treatment of the main disease should be prescribed [1].

It is important to review the previously received therapy before the start of drug treatment of HT. Some drugs can raise BP [20]. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (SCS) may reduce the effectiveness of antihypertensive therapy and contribute to development of difficult-to-control HT [46]. The use of NSAIDs among patients with HT is characterized by 1,32-times increased risk of CKD, as a result it contributes to the deterioration of the control of BP [47].

Antihypertensive drugs are an integral part of the treatment of HT. Usually it is impossible to reach the target level of BP without a drug therapies. This is especially true for patients with difficult-to-control HT [48].

Currently there is little evidence from clinical studies about the treatment of difficult-to-control HT. Thus, there are no recommendations about the best combinations of drugs, or the benefits of any strategy in this variant of HT [20].

The effectiveness of the antihypertensive therapy combinations was evaluated only in a few large clinical trials. There are FEVER, ADVANCE and ACCOMPLISH. In all these studies, there was no group of patients with difficult-to-control HT. Therefore the results can only be extrapolated as recommendations for the prevention of mortality and cardiovascular events in this group of patients.

Due to the absence of randomized clinical trials, the selection of therapy for people with difficult-to-control HT occurs empirically, given the national guidelines for the treatment of essential HT [1]. The best treatment strategy in this case is to select a combination of antihypertensive drugs, which will affect the various links in the pathogenesis and development of physiological mechanisms of HT, as well as to take into account the individual patient comorbidities. The most popular combinations of antihypertensive drugs used for the treatment of difficult-to-control HT are: ACE inhibitor/RAAS blocker + CCB + thiazide/thiazide-like diuretics; ACE inhibitor/RAAS blocker + CCB + loop diuretic; ACE inhibitor/RAAS blocker + CCB + diuretic + mineralocorticoid antagonist; ACE inhibitor/RAAS blocker + CCB + diuretic + beta-blocker; ACE inhibitor/RAAS blocker + CCB + diuretic + alpha-blocker; ACE inhibitor/RAAS blocker + CCB + diuretic + vasodilator.

1. The combination of an ACE inhibitor/RAAS blocker + CCB + thiazide/thiazide-like diuretic

The most appropriate combination of antihypertensive drugs in the treatment of difficult-to-control HT includes angiotensin-converting enzyme (ACE) inhibitor or blocker of the renin-angiotensin-aldosterone system (RAAS), dihydropyridine calcium channel blockers (CCB) and a thiazide/thiazide-like

diuretic [49]. Before prescribing the treatment, individual characteristics of the patient and his comorbidities should be considered. For example, if there are signs of congestive heart failure calcium antagonists should be avoided. It is necessary to avoid an ACE inhibitor in the presence of bilateral renal artery stenosis [20].

This combination is considered as the most effective treatment of difficult-to-control HT. This drug affects various mechanisms of the pathogenesis of HT. It helps achieve the best results of treatment [50].

Triple antihypertensive therapy in the case of difficult-to-control form of HT reduces risk of cardiovascular complications [51]. The risk of cardiovascular events among patients receiving the combination of an ACE inhibitor, a diuretic and a CCB, was reduced by 12 % [52].

The optimal dose of an ACE inhibitor for the treatment of difficult-to-control HT should be at least 50 % from the maximum recommended. It is 5 mg for ramipril and 4 mg for perindopril. Required dosage for RAAS blockers is 50 mg for losartan and 80 mg for valsartan [53].

Among CCBs is recommended using amlodipine, nifedipin with long term action [54]. BP control was achieved in 62,5 % of patients with difficult-to-control HT during using of amlodipine (10 mg) and olmesartan (40 mg). In the placebo group, BP control was only in 18,4 % of individuals [55]. The usefulness of the BPC as a component of antihypertensive therapy was shown in the study FEVER, which studied the effect of felodipine in addition to diuretics on the prognosis of patients with HT and a high risk of cardiovascular events. Patients treated with a combination of felodipine had greater BP reduction compared to the placebo group (mean BP was 137,3/82 mm Hg versus 142,5/85 mm Hg). And the risk of stroke decreased by 28 % [56].

Study ACCOMPLISH shows the necessity of adding an ACE inhibitor to CCB. It has been demonstrated that the combination of CCB (amlodipine) with ACE inhibitor (benazepril) is preferable than the combination of ACE inhibitor and diuretic (hydrochlorothiazide) in terms of prediction of cardiovascular events. The combination of an ACE inhibitor + CCB reduces the risk of cardiovascular death by 22 %. However, significant differences in the reduction of BP weren't observed. 75,4 % of patients achieved BP control with the combination of ACE inhibitor + CCB, and 72.4 % of patients who used ACE inhibitor + diuretic [57].

Patients with difficult-to-control HT often have the presence of hidden fluid retention. Therefore, diuretics are an important part of an effective antihypertensive therapy in this group of individuals [58].

A meta-analysis of studies has demonstrated that diuretics lead to a significant decrease in SBP. This is especially important in the treatment of patients with difficult-to-control HT [59]. Diuretics can potentiate the effect of other antihypertensive drugs [60].

For most patients with difficult-to-control HT are recommended to prescribe hydrochlorothiazide or chlorthalidone. [3] Daily use of these drugs improves BP control among patients with difficult-to-control form of HT.

Clinical studies have demonstrated greater efficacy of chlorthalidone as a component of antihypertensive therapy among patients with difficult-to-control HT [61]. It is recommended starting treatment with a dose of 12,5 mg of chlorthalidone per day, then, if it is necessary, it can be increased to 25 mg.

Chlorthalidone has a longer duration of action than hydrochlorothiazide. Some authors recommend replace hydrochlorothiazide to chlorthalidone in the treatment of patients with resistant and refractory HT because of more pronounced antihypertensive effect [20]. Clinical data suggest that chlorthalidone leads to more reduction in cardiovascular morbidity and risk of complications than hydrochlorothiazide [62]. However, the European Society of Cardiology guidelines do not indicate the benefits of this drug.

Due to long half-life chlorthalidone can cause hypokalemia and renal failure in predisposed individuals [63]. In elderly people or patients with a combination of difficult-to-control HT and renal failure chlorthalidone can be replaced by indapamide. Use of indapamide leads to a significant decrease in SBP (-22,2 mm Hg) compared with the combination with hydrochlorothiazide (-17,27 mm Hg) [64]. The effective starting dose of indapamide is 1,5 mg per day.

2. The combination of an ACE inhibitor/RAAS blocker + CCB + loop diuretics

Given that difficult-to-control HT is often combined with diabetes type 2 or impaired

glucose tolerance, the use of thiazides in this group of patients is limited [65]. Loop diuretics are recommended in addition to an ACE inhibitor/RAAS blocker and CCB among patients with metabolism disorders, gout, and hypokalemia [66].

Loop diuretics are also recommended among patients with concomitant nephropathy and with glomerular filtration rate less than 30 mL/min [24]. The dose of loop diuretic (furosemide, torasemide) is dependent on the severity of renal dysfunction. Given the short-term activity of furosemide and torasemide, drugs should be taken twice per day. This not only helps better control of BP, but also helps prevent increase in activity of RAAS [67]. Torasemide has a longer duration of action than furosemide, therefore it may be used once per day.

3. Antagonist of mineralocorticoid (spironolactone) in the treatment of difficult-to-control HT

Spironolactone and other potassium-sparing diuretics are used as a supplement to the basic combination of drugs among patients with difficult-to-control HT [10]. Compared with placebo, use of low daily doses of spironolactone (25 mg per day) among patients with difficult-to-control HT leads to significant decrease in SBP (13 mm Hg) and diastolic BP (6 mm Hg) [68]. Contraindication for antagonist of mineralocorticoid is level of potassium in the blood more than 5 mmol/l.

Effectiveness of spironolactone as an additional drug to the combination of an ACE inhibitor, a CCB and a diuretic is associated with a significant reduction in BP. This combination is more effective than combination with beta or alpha-adrenergic receptor blockers [69].

Despite the fact that spironolactone is the most effective drug in HT caused by primary aldosteronism, the use of high therapeutic doses among patients with difficult-to-control HT demonstrated decrease in SBP by 14–32,2 mmHg and DBP by 7–12,5 mm Hg. Apparently, it is due to the development of secondary hyperaldosteronism in these patients [70].

Achieving BP control during use of spironolactone in addition to triple combination is observed more frequently (58 %) than using the combination with doxazosin (42 %) or bisoprolol (43 %) [71]. The decrease in SBP and DBP among patients receiving combination with spironolactone is suitably – 32 mm Hg and – 12 mm Hg. Use of doxazosin as a fourth component of the treatment is reduced SBP by 16 mm Hg and DBP by 7 mm Hg [72].

4. The beta adrenergic receptor antagonists in the treatment of difficult-to-control HT

Beta adrenergic receptor antagonists (Beta-blockers or BB) belong to the second-line drugs in treatment of difficult-to-control HT. BBs are recommended for patients with HT and coronary heart disease or heart failure, with severe sympathicotony [20]. They are not recommended as first-line drug in case of the absence of such indications, as their role in the prevention of cardiovascular events is less significant than using ACE inhibitors or RAAS blockers and CCBs [7]. ASCOT study shows that the combination with the BB has worse dynamics of BP as compared to the combination of an ACE inhibitor and CCB [73].

If difficult-to-control HT is not accompanied with organic disorders of the heart, beta-blockers are recommended to prescribe as the fifth drug in case of inefficiency of the four drugs therapy (diuretic + ACE inhibitor/RAAS blocker + CCB + antagonist of mineralo-corticoid) [74].

5. Alpha-adrenergic receptor blockers in the treatment of difficult-to-control HT

Alpha adrenergic blockers are also recommended as the second-line drugs in treatment of difficult-to-control HT. In 42 % of difficult-to-control HT cases BP control is achieved by using doxazosin in addition to the main combination [75]. During taking doxazosin as the fourth component of the treatment SBP is reduced by 16 mm Hg and DBP by 7 mm Hg [70].

Alpha-blockers do not have the impact on the prognosis of complications among patients with difficult-to-control HT, so their use is limited [74].

6. Vasodilators in the treatment of difficult-to-control HT

Among the vasodilators only the use of minoxidil has been studied among patients with difficult-to-control HT. This drug, in addition to first-line agents, helps achieve the control of BP [75]. Using a combination with minoxidil was associated with a reduction in BP from 162,4 ± 15,1/83,2 ± 12,7 mm Hg to 135,8 ± 12,2/72,8 ± 6,9 [71]. The results confirmed that minoxidil has indications for use in the subgroup of patients with difficult-to-control HT and with chronic kidney disease [76].

The combination and dosage of antihypertensive drugs is chosen based on the individual needs of patient, presence of concomitant diseases. Use of small doses of several drugs with different mechanisms of action is more effective than monotherapy with high doses [77]. However, due to the absence of large randomized clinical trial, there is no evidence of the benefits of a particular combination of drugs among patients with difficult-to-control HT [20].

7. Invasive treatment

Ineffectiveness of pharmacological therapy in combination with lifestyle modification leads to necessities to use invasive methods as an additional treatment of difficult-to-control HT [78]. There are some invasive methods in order to achieve BP control methods: sympathetic denervation of the renal arteries; electrical stimulation of the carotid sinus baroreceptors; neurovascular decompression; formation of arteriovenous anastomoses.

According to the recommendations of the European Society of Cardiology the presence of a true refractory HT with the level of office BP over 160/110 mm Hg, and high blood pressure during daily monitoring are indications for invasive intervention [20]. Invasive methods are considered an additional method for the treatment of HT.

Electrical stimulation of baroreceptors located in the carotid sinus leads to a decrease in SBP and DBP. The receptors are located in the area of the carotid bifurcation. They are able to respond to changes in pressure inside the vessel and can regulate sympathetic tone in the opposite direction [79]. Surgery includes the implantation of special devices, new of its provide unilateral stimulation. It is safer for patients as compared to the bilateral devices [80]. As a result of this treatment in 43 % of patients with uncontrolled BP it is possible to reduce SBP to less than 140 mm Hg. In a year in 81 % of patients maintained a stable decline of SBP over 10 mm Hg, and in 63 % of cases target BP is achieved [81].

Denervation of the renal arteries is percutaneous intervention for ablation of the sympathetic nerves. Normally, the sympathetic innervation activates renin secretion and constriction of vessels of the kidneys, resulting in increased reabsorption of sodium and increased BP. Denervation excludes the influence of the sympathetic nerves and thus, it is possible to achieve control of BP [82]. However SYMPLICITY HTN-3 study showed that the benefits from the renal denervation compared with optimal medical therapy is not significant, the difference in the degree of reduction in BP also was not significant [83]. After renal denervation ambulatory SBP decreased by 6,8 mm Hg and in the control group by 4,8 mm Hg [84].

Microvascular decompression is indicated among patients with refractory to the treatment HT due to neurogenic causes. The technique is based on the effects of arterial compression of the brain stem on the regulation of the cardiovascular system [85]. The studies show that after decompression 14 of 28 patients with difficult-to-control HT achieved normalization of BP without medication. For rest of them is needed medical support to achieve the target level. However, long-term results of the intervention are a cause for discussion [86]. Arteriovenous anastomosis is a device similar to a stent. Its implantation provides the connection of the external iliac vein and the same artery. Constant lumen of device and blood flow pressure is maintained due to the property of shape memory. Reduction in blood pressure is due to increased pliability of the artery walls and reduces their resistance [87]. Arteriovenous anastomosis causes a significant decrease in blood pressure, and decreases the risk of complications. After the intervention there is decrease SBP to 20 mm Hg and DBP to 14,7 mm Hg. In the control group, there is no statistically significant reduction in BP. This method may be useful for the treatment of patients with HT refractory to medical correction [88].

BIOFEEDBACK – PHYSIOLOGICAL ASPECTS

The difficulty in achieving target level of BP leads to searching of additional non-pharmacological treatments for HT. One of such methods is biofeedback (BFB).

Biofeedback is a noninvasive method for assessing the functioning of the regulatory systems of the body. The level of human health and the ability to monitor the condition of the body in a variety of adverse conditions depends on the quality of regulatory systems [89]. In addition, biofeedback is a method of treatment. It helps to involve patient in the process of treatment [90].

The process of self-control learning requires special equipment to convert physiological

signals into visual and auditory. Using a computer monitor, patients receive feedback that helps them develop control over physiological processes. The processes occurring in the body are illustrated on the monitor. That serves as a guide for the use of feedback for the purpose of controlling and monitoring [91]. Patients become active members of the therapeutic process. They may learn self-regulation without feedback displays in front of them and it will be possible to perform biofeedback sessions at home. Availability of personal computers, smart phones and mobile devices, simplifies the implementation of procedures and provides controlled results [92].

Due to biofeedback patient may self-assess and manage health. Changes in the activity of the autonomic nervous system due to chronic stress represent one of the most important factors for a large group of diseases. These diseases are known as psychosomatic disorders. All regulatory systems are divided into three parts: sensor, integrative (central) and effector [93]. Sensor part is represented by the sense organs and receptors. Through them, the information comes into integrative part, which includes the structure of the central nervous system, the highest vegetative centers. After the analysis of the incoming information the transfer of solutions aimed at optimizing the regulatory systems on the effector unit occurs [94].

The effectiveness of biofeedback is associated with the formation of neural connections and the possibility of further direct access to them. Biofeedback is aimed at combating stress through relaxation techniques. The method appears to be most effective for conditions that are heavily influenced by stress [95].

Methods (contours) of biofeedback can be realized through physiological parameters which available to measure [96]. The most common of them are temperature biofeedback, galvanic skin response training, electro-myography (EMG) biofeedback, circuit electroencephalography, respiratory biofeed-back, heart rate variability (HRV), combination of HRV and respiration.

Temperature biofeedback

Changes in temperature of the skin reflect the diameter of the arterioles. Their dilatation can cause stimulation of beta-adrenergic receptors. As the result the skin surface temperature increases [97]. Narrowing causes stimulation of alpha-adrenergic receptors, resulting the temperature will decrease [98].

Implementation of the cutaneous thermometry biofeedback requires a device which consists of a plate capable to change its resistance in response to the level of oscillation in body temperature. Device sensors are attached to the fingers. Indicator can convert changes to degrees. It is used to make diagram that provide feedback [99].

Method can be used as additional therapy of chronic pain [100], headache [101], anxiety disorders, Raynaud's disease [102].

Galvanic skin response (GSR)

Evaluation is carried out using biofeedback measuring bioelectric properties of skin depending on the activity of the sweat glands. Stress increases the activity of the sweat glands, accordingly, there are observed changes in the properties of the skin surface [103]. Negative emotions reduce the electrical resistance of the skin. Relaxation exercises leads to an increase in electrical resistance [104].

Biofeedback technique with loop galvanic skin response involves using skin electrodes that measure electrical resistance of the skin during the training. For better control it is useful to combine GSR with measuring skin temperature [105].

Method is used in the treatment of epilepsy [106], Tourette's syndrome [107], headache [108].

Contour with electroencephalography (EEG), or neurofeedback.

Electroencephalograph determines bioelectric activity of the brain. Waves of different frequencies reflect its condition. Stress, trauma and somatic pathology can change the normal characteristics of these waves. It is reflects the irregular brain regulation [109].

Sensors located on the skin of the patient's head record biopotentials of the brain. This biopotentials are recorded by computer software as an electroencephalogram. Efficien-cy of biofeedback is improved by using not only visual but also audible signals representative of cerebral activity [110].

In practice, the method is used in the treatment of anxiety and depressive disorders [111], stress, epilepsy [112], migraine [113], disorders of concentration and hyperactivity [114].

Respiration biofeedback

The correct depth and rhythm of breathing helps achieve physical and mental relaxation. It involves meditation principles [115].

Sound amplifiers are used for control biofeedback. It helps more clearly hear the breathing. Device for graphic recording of frequency and amplitude of respiratory movements are also used [116].

Method can be used in pulmonology as additional therapy of asthma [117], obstructive sleep apnea [118]. It is used in anxiety disorders [119], panic attacks [120], chronic pain syndrome [121], stress [122].

Electromyography (EMG)

Biofeedback with EMG is based on the appearance of bioelectric potentials in skeletal muscle during their tension [123].

On certain muscle groups applied electrodes. The evidence of the degree of muscle tension is demonstrated on the monitor. The task of the patient is to achieve muscle relaxation using biofeedback. [124].

Therapy is effective in the presence of muscle spasm [125], pain [126] as well as during rehabilitation after injury, stroke [127].

Heart rate variability (HRV)

HRV is a measure of the stability of psychological and behavioral flexibility that reflects a person's ability to effectively adapt to the changing circumstances of the environment and the internal homeostasis [128].

Clinical significance of HRV was noted in 1965, when it was found that fetal distress preceded by changes in the HRV before any changes of heart rate [129]. Subsequently, HRV analysis showed that reduced potential of regulatory systems can contribute to the development of depression, anxiety, functional gastrointestinal disorders, diseases of the cardiovascular system, including the tendency to increase blood pressure [130]. Low HRV is considered to be an independent predictor of future health problems. It is correlated with all causes of mortality [131].

Estimation of HRV is based on measuring the time intervals between the RR intervals on ECG [132]. Method allows you to assess the condition of mechanisms of regulation of physiological functions of the body, the activity of neurohumoral component of the regulatory function and the relationship between the activity of the sympathetic and parasympathetic autonomic nervous system [133].

The combination of HRV and respiratory biofeedback

The functioning of the cardiovascular system is controlled by neurohumoral regulatory systems. There are various methods that can be used to influence them [134]. One of the most effective is with biofeedback of HRV and paced breathing. This method of implementation of HRV is one of perspective directions in treatment of hypertension, heart failure (HF), coronary heart disease (CHD) [135].

Biofeedback of HRV and paced breathing is based on teaching of the patients slow, deep breathing. Anatomical proximity of the respiratory center and nucleus of the vagus nerve leads to high efficiency. Thus, it is possible to influence the HRV parameters due to stimulating activity of the respiratory center [136]. The regulation of BP is carried out by a complex network of pressure sensitive of mechanosensitive baroreceptors or neurons which are located in the heart and the aortic arch. Factors that change BP are also affected by oscillation in the heart rate, which confirms their relationship [137].

During biofeedback training heart rate may change due to a certain frequency and amplitude of respiratory movements and the influence of the vagus nerve [138]. Changing the frequency and depth of breathing leads to increased sympathetic or parasympathetic influence on the heart [139]. Potentials induced palpitations, can be used to determine the influence of afferent pathways of the heart to the brain and effects on them. The HRV may reflect the interaction between the heart and the brain [136].

Parasympathetic component of HRV can be increased during pacing breath. It demonstrates good results as the additional therapy of arterial hypertension [140]. Deep, slow breathing improves baroreflex sensitivity, as the result there is an antihypertensive effect [130].

The vagus nerve is the main channel through which the afferent signals from the heart and other internal organs are transmitted to the brain, including the baroreflex signals [131]. In case of increase in BP baroreceptors generate action potentials more often. The more its stretch, the more action potentials is produced and transmitted to the brain structure [90]. Increased in their activation inhibits vascular center and stimulates the nucleus of the vagus nerve. The end result is the inhibition of activation of the sympathetic and parasym-

pathetic nervous system. Thus, the regulation of blood pressure is carried out [132].

The effect of impulses on the vagus nerve especially pronounced when the respiratory rate is less than 8,5 breaths per minute, or during deep breaths. It is believed that this breathing version of «trains» baroreflex [93], in the future it has an effect on blood pressure reduction.

CLINICAL APPLICATIONS IN BIOFEEDBACK THERAPY

Biofeedback involves complex of therapeutic and preventive measures that allow learning the skills of self-control and optimizing the performance of regulatory systems [127]. Simple exercises aimed at relaxation, help learn to control various functions of the body, including to regulate blood pressure [136].

The method is widely implemented in various branches of medicine. [133] at present the biofeedback is one of the important directions of scientific research and is used as an auxiliary therapy in the following areas:

- Cardiology – treatment of HT [126], arrhythmias [134], heart failure [140], coronary heart disease [141].
- Pulmonology – treatment of obstructive sleep apnea [115], asthma [116].
- Gastroenterology – chronic constipation [133], irritable bowel syndrome [134].
- Rheumatology – Raynaud's disease [101].
- Urology – erectile dysfunction [142].
- Neurology – headaches [112], chronic pain syndrome [99], post-traumatic stress, anxiety disorders [143], depressive disorders [110].
- Pediatrics – hyperactivity disorder and disturbance of concentration in children [113].

Biofeedback in cardiology

Biofeedback has a great therapeutic potential in treatment of cardiovascular diseases, because many of them are associated with dysregulation of the autonomic nervous system [144]. HRV is an informative method for detecting the activity of the predominance of one of the parts of the autonomic nervous system. It is useful in determining therapeutic tactics and choice of antihypertensive agent among patients with HT [145].

Biofeedback therapy is used to reduce the activation of the sympathetic-adrenal system in case of heart failure (HF). It helps to slow down the progression of disease [131]. The use of a combination of biofeedback therapy with standard medical therapy leads to increased exercise tolerance among patients with left ventricular ejection fraction more than 31 % [146].

Among patients with coronary heart disease biofeedback training helps to normalize autonomic regulation. And the use of techniques aimed at relaxation helps improve the quality of life [147]. Biofeedback is increasingly being used as a part of cardiac rehabilitation programs [148].

Experience in the use and effectiveness of biofeedback for arterial hypertension

One of the key mechanisms of hypertension is an imbalance of the regulatory systems of the body, so it makes sense to combine standard pharmacological treatment and biofeedback therapy [149].

Data from clinical studies and their meta-analysis demonstrate the effectiveness of biofeedback of HRV and paced breathing for the treatment of patients with hypertension and prehypertension [150]. In a three-month observation biofeedback sessions significantly improved the sympathetic-vagal regulation with tendency to normalization of blood pressure in individuals with prehypertension [151]. Among patients with prehypertension therapy trainings help to prevent further progression of the disease [152]

Biofeedback training includes abdominal type of slow breathing. It helps effectively control of BP among patients with a tendency to hypertension [153]. Standard short record (5 minutes) of biofeedback in contour of HRV can be considered as a method of estimation of functioning vagal regulation of the cardiovascular system among patients with high BP [154].

Regular biofeedback training in hospital helped in reducing SBP by 7,5 mm Hg and DBP by 4 mm Hg. Indicators of changes in blood pressure in the control group were less pronounced. There was reducing SBP by 2,9 mm Hg, DBP by 1,5 mm Hg [155]. Duration of study was 9 weeks. Longer training may significantly reduce BP after the completion of a course of training [156]. Ambulatory monitoring of patients shown that biofeedback training can reduce the SBP in rest by 9,5 mm Hg. The hypotensive effect is persists for 8 weeks after the completion of a course of training [157].

Evaluation of biochemical parameters of blood among patients with hypertension who have sessions of biofeedback shows a decrease of cortisol and aldosterone. There is also decrease in psycho-emotional stress, which indirectly affects the function of the adrenal cortex and production of vasopressors [158].

Studies of the Department of Internal Medicine KhNU Karazin show that after 10 sessions of biofeedback with standard medical therapy background, positive dynamics of the main indicators of HRV is observed. In comparison with the isolated anti-hypertensive therapy, additional biofeedback therapy among patients with controlled HT make possible to reach target levels of SBP and DBP [159]. Standard drug therapy reduces SBP by 26,6 %, and with the addition of biofeedback training SBP is improved by 32,3 % [160].

The results of observations show that treatment, including systematic biofeedback sessions with paced breathing and medical therapy background leads to significant improvement in the quality of patient's life with controlled hypertension [161]. The use of biofeedback of HRV and paced breathing in hypertensive patients can achieve better control of BP, heart rate and HRV parameters [162].

The results showed BQI positive dynamics in the biofeedback group. It shows the optimization of the functioning of regulatory systems. This indicates the existence of the regulation system «training» effect as a result of biofeedback. Therefore, the method can be used as additional therapy [162].

Studies confirm the effectiveness of therapy with biofeedback of HRV and paced breathing among patients with controlled hypertension. This demonstrates the possibility of its use in addition to standard medical support for these patients. However, the technique continues to be studied. In particular, there is no data on the use of biofeedback therapy in difficult-to-control HT, which makes the problem relevant.

CONCLUSION

The prevalence of difficult-to-control HT is 30,4–31,8 %. Inability to achieve BP control with standard antihypertensive therapy background is a reason for the study of new drugs, the introduction of invasive methods to treat HT and finding additional non-pharmacological therapies. One of such promising areas is the study of biofeedback. Regular sessions of biofeedback in addition to lifestyle modifications and standard medical therapy among patients with controlled hypertension allow optimizing treatment. However, there are no data on the effectiveness of biofeedback among patients with difficult-to-control HT. Therefore, the widespread introduction of biofeedback therapy in clinical practice requires further scientific clinical studies.

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Lecture

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MANAGEMENT OF PATIENTS WITH ACUTE KIDNEY INJURY

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Presented lecture is about management of a serious condition – acute kidney injury (AKI). It is intended for students, general practitioners, family physicians, therapists and those who may face with manifestations of AKI, and on which depends its timely diagnosis and the success of therapy. Definition, epidemiology, risk factors, causes, pathogenesis, classification, symptoms, diagnosis and differential diagnosis, treatment, complications, prognosis and prevention of AKI are described.

KEY WORDS: acute kidney injury, management, nephrology

МЕНЕДЖМЕНТ ПАЦІЄНТІВ ІЗ ГОСТРОЮ НИРКОВОЮ НЕДОСТАТНІСТЮ

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Представлена лекція про ведення пацієнтів із важким захворюванням – гострою нирковою недостатністю (ГНН). Вона призначена для студентів, лікарів загальної практики, сімейних лікарів, терапевтів та тих, хто може зіткнутися з проявами ГНН і від яких залежить її своєчасна діагностика та успішність терапії. Зазначені визначення, епідеміологія, фактори ризику, причини, патогенез, класифікація, симптоми, ускладнення, діагностика та диференціальна діагностика, лікування, прогноз і профілактика ГНН.

КЛЮЧОВІ СЛОВА: гостра ниркова недостатність, ведення, нефрологія

МЕНЕДЖМЕНТ ПАЦИЕНТОВ С ОСТРОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Представлена лекция о ведении пациентов с тяжелым заболеванием – острой почечной недостаточностью (ОПН). Она предназначена для студентов, врачей общей практики, семейных врачей, терапевтов и тех, кто может столкнуться с проявлениями ОПН и от которых зависит ее своевременная диагностика и успешное лечение. Обсуждаются определение, эпидемиология, факторы риска, причины, патогенез, симптомы, осложнения, диагностика и дифференциальная диагностика, лечение, прогноз и профилактика ОПН.

КЛЮЧЕВЫЕ СЛОВА: острая почечная недостаточность, ведения, нефрология

DEFINITION

Acute kidney injury (AKI), also known as acute renal failure, is defined as a sudden decrease in kidney function, resulting in an inability to maintain acid-base, fluid and electrolyte balance and to excrete nitrogenous wastes [1]. AKI is a designation for a heterogeneous group of conditions that share common diagnostic features: an increase in the blood urea nitrogen concentration; an increase in the plasma or serum creatinine (SCr) concentration, often associated with a reduction in urine output (UO) [1].

EPIDEMIOLOGY

There is lack of studies which evaluating AKI in the community setting, as well as a lack of comparisons between intensive care unit (ICU) patients and non-ICU patients.

According to a recently published meta-analysis the pooled incidence and mortality of AKI in patients is circa 30 % worldwide [2]. The incidence of AKI in critically ill patients

has increased over the years, mostly because of dialysis-requiring AKI, especially among the elderly, the male gender, and the black population.

The incidence of AKI in hospitalized patients has also increased from 4,9 % to 20 % during last 10 years [3]. This may partly be due to the definitions of AKI becoming more time sensitive and may reflect an increase in detection rather than an overall increase in incidence in disease.

RISK FACTORS [4]

Patient-related risk factors: advanced age, arterial hypertension, atherosclerosis, biliary surgery/jaundice, cardiogenic shock, chronic obstructive pulmonary disease, chronic renal disease, cirrhosis of the liver, congestive heart failure, diabetes, female gender, left main coronary disease, left ventricular ejection fraction < 35 %, major vascular surgery, myeloma, nephrotoxic drugs, peripheral vascular disease, pre-eclampsia/eclampsia, renal insufficiency, sepsis.

Procedure-related risk factors: blood loss, cross-clamp time, diarrhea/bowel preparation, diuretic therapy, gastric aspiration/vomiting, hemodilution, hemolysis, hypovolemia (oliguria), hypoxia, ileus obstruction, inflamemation, length of cardiopulmonary bypass, major burns, massive blood transfusions and transfusion reactions, muscle breakdown, nonpulsatile flow, off-pump versus on-pump coronary artery bypass graft surgery, pancreatitis, peritonitis, polytrauma, preoperative starvation, prolonged tissue exposure, surgical edema.

CAUSES

Causes of AKI due to decreased kidney perfusion (prerenal) [5]:

Decreased intravascular fluid volume: extracellular fluid loss (burns, diarrhea, vomiting, diuretics, salt-wasting renal disease, primary adrenal insufficiency, gastrointestinal hemorrhage), extracellular fluid sequestration (pancreatitis, burns, crush, injury, nephrotic syndrome, malnutrition, advanced liver disease).

Decreased cardiac output: myocardial dysfunction (myocardial infarction, arrhythmias, ischemic heart disease, cardiomyopathies, valvular disease, hypertensive disease, severe cor pulmonale, etc.).

Peripheral vasodilation: drugs (antihypertensive agents), sepsis, miscellaneous (adrenal cortical insufficiency, hypomagnesemia, hypercapnia, hypoxia, etc.).

Severe renal vasoconstriction: sepsis, drugs (nonsteroidal anti-inflammatory agents, ß-adrenergic agonists), hepatorenal syndrome.

Mechanical occlusion of renal arteries: thrombotic occlusion, miscellaneous (emboli, trauma, etc.).

Causes of AKI due to parenchymal or vascular diseases (renal) [5]:

Renal vascular disorders: vasculitis, malignant hypertension, scleroderma, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, mechanical renal artery occlusion (surgery, emboli, thrombotic occlusion), renal vein thrombosis.

Glomerulonephritis: postinfectious, membranoproliferative, rapidly progressive glomerulonephritis (idiopathic, polyarteritis nodosa, systemic lupus erythematosus, Wegener's syndrome, microscopic polyarteritis, Goodpasture's syndrome, Henoch-Schonlein purpura, drugs.

Interstitial nephritis: drugs (penicillin, sulfonamide, rifampin, ciprofloxacin, phenindiones, cimetidine, proton pump inhibitors, azathioprine, phenytoin, captopril, thiazides, furosemide, bumetanide, allopurinol, nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, 5-aminosalicylates), hypercalcemia.

Infections: nonspecific due to frank septicemia or systemic anti-inflammatory response syndrome, specific organisms (legionella, leptospira, rickettsia, Hantavirus, candida, malaria), specific organ involvement (bacterial endocarditis, visceral abscess, pyelonephritis).

Infiltration: sarcoid, lymphoma, leukemia.

Connective-tissue disease.

Tubular necrosis: renal ischemia (prolonged prerenal), nephrotoxins (aminoglycosides, radiocontrast agents, heavy metals, organic solvents, other antimicrobials), pigmenturia, (myoglobinuria, hemoglobinuria), miscellaneous.

Intratubular: crystal deposition (uric acid, oxalic acid), methotrexate, acyclovir, triamterene, sulfonamides, indinavir, tenofovtransplant rejection, protein deposition (light chains, myoglobin, hemoglobin).

Causes of AKI due to urinary tract obstruction (postrenal) [6-7]:

Extrarenal: ureteral/pelvic intrinsic obstruction (tumor, stone, clot, pus, fungal ball, papilla), extrinsic obstruction (retroperitoneal and pelvic malignancy, fibrosis, ligation, abdominal aortic aneurysm).

Bladder: prostate hypertrophy/malignancy, stones, clots, tumor, neurogenic, medication.

Urethral: stricture, phimosis.

PATHOGENESIS

Renal blood flow is 25 % of cardiac output but some areas are particularly sensitive to ischemic damage. Most of the blood flow supplies the cortex, which contains the glomeruli and convoluted tubules, areas that require good perfusion to achieve filtration and reabsorption, the latter with high energy demands. The outer medulla is comparatively starved of oxygen, its blood supply first traversing the glomerular capillary bed, and losing hydrostatic pressure (in essence, a portal circulation), and then on entering the medulla, losing oxygen by countercurrent exchange with the venous vasa recta. These features are essential to maintain the osmotic gradients within the medulla and thus generate concentrated urine, but render the outer medulla very susceptible to variations in blood flow. This area contains the thick ascending limb of the loop of Henle and S3 segment of the proximal tubule, both with high oxygen requirements. Impaired tubular sodium reabsorption attributable to reduced perfusion causes constriction of the afferent arteriole and a further reduction in glomerular filtration rate (GFR). This compensatory mechanism (tubuloglomerular feedback), designed to protect the downstream nephron, may cause injury if prolonged, or if normal regulation of the arterial tone is blocked (for example, by non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs)). Reduced blood flow in the peritubular capillaries produces ischemic damage in vascular endothelial cells, resulting in cell swelling and the expression of cell adhesion molecules – reducing flow further and leading to leucocyte activation. Adherent leucocytes further impede blood flow and produce cytokines and reactive oxygen species that damage endothelial and tubular epithelial cells. Tubular cells swell, lose their brush border, and develop cytoskeletal abnormalities with abnormal localization of cell membrane components (for example, Na+/K+−ATPase), changes in cellular polarity, and loss of cell-cell and cell-basement membrane attachment. These swollen, detached cells obstruct the tubular lumen, and back leak of filtrate occurs through the damaged basement membrane. In the classic histological appearance of acute tubular necrosis (ATN), tubules are surrounded by flattened, denuded epithelium, and the lumen filled by cell debris, with congested peritubular capillaries and an extensive inflammatory cell infiltrate. Cell death occurs predominantly by necrosis, although apoptosis also contributes – especially in the thick ascending limb and late in the process (Fig.).

A remarkable feature of the kidney is its ability to regain normal structure and function after such injury. Once renal perfusion and oxygen supply are normalized, viable cells still adherent to the tubular basement membrane can spread to cover denuded areas, and then differentiate to reproduce normal tubular architecture, and function. The return of glomerular filtration aids clearance of tubular debris and relief of obstruction. A period may exist where glomerular filtration has normalized, but tubular function remains deranged, hence the polyuric phase of ATN, where urine output is often excessive without normal homoeostasis.

The anuric phase of ATN classically lasts 7–21 days, and recovery to pre-insult levels of renal function can be expected, although some impairment of function may persist, particularly if there is a background of chronic renal insufficiency [8].

CLASSIFICATION

The RIFLE classification is presented in table 1 [9]. The Acute Dialysis Quality Initiative (ADQI) group for the study of AKI was published in May 2004 the consensual RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification. It accomplished the following criteria: easy clinical applicability, sensitivity and specificity, consider baseline SCr variations and also consider the «acute-on-chronic» phenomenon (which means the occurrence of an acute insult over a chronically injured renal function causing its deterioration). This definition classify AKI according to its severity (mild versus severe) and its timing of

occurrence (precocious versus late AKI). By fulfilling these criteria, this classification allow to detect of patients whose kidney function was slightly affected (high sensitivity but low specificity) as well as patients with severe kidney function deterioration (high specificity with diminishing sensitivity).

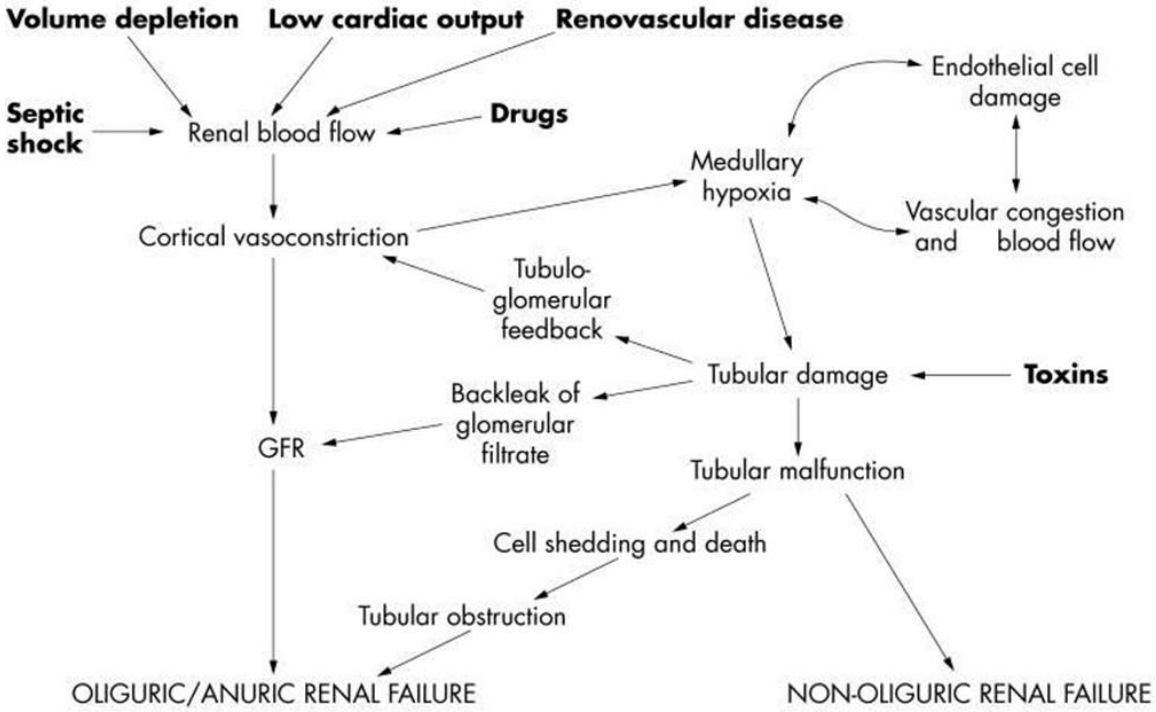

Fig. Mechanisms of acute tubular necrosis by A. Fry and K. Farrington [2]

Table 1

The RIFLE classification of AKI

Class	Glomerular filtration rate	UO
Risk	↑ SCr 1,5 times or ↓ GFR for more than 25 %	less than 0,5 mL/kg/h during 6 hours
Injury	↑ SCr 2 times or↓ GFR for more than 50 %	less than 0,5 mL/kg/h during 12 hours
Failure	↑ SCr 3 times or ↓ GFR for more than 75 % or if baseline SCr ≥353,6 mmol/L (4 mg/dL), ↑ SCr for more than 44,2 mmol/L (0,5 mg/dL)	less than 0,3 mL/kg/h during 24 hours or anuria during 12 hours
Loss of kidney function	Complete loss of kidney function > 4 weeks	
End-stage kidney disease	Complete loss of kidney function > 3 months	

If baseline SCr is unknown and if there is no history of chronic kidney disease (CKD), baseline SCr should be calculated using the Modification of Diet in Renal Disease (MDRD) equation, assuming a baseline GFR of 75 mL/min/1,73m^2.

Limitations of the RIFLE classification [9]. Determination of renal function using RIFLE classification has several limitations: the endogenous production and serum release of Cr are variable, and it is influenced by multiple factors, namely age, gender, diet, and muscle mass; from 10 to 40 % of Cr elimination is performed by tubular secretion and this mechanism is amplified as the GFR diminishes, thus, overestimating renal function in AKI patients; many medications inhibit tubular secretion of Cr, causing a temporary increase in SCr; various factors can interfere with SCr determination, causing a false elevation in SCr; Cr is a marker of renal function, and not of renal lesion; sensitivity and specificity of UO can be significantly changed by the use of diuretics and in diabetes insipidus, et al.; UO can only be determined in patients with a bladder catheter in place, which is not frequent in hospitalized patients; it is possible that the predictive ability of UO could be inferior to that of SCr; etiology of AKI are not considered; classification does not provide any information regarding the origin of the renal lesion (i.e. cellular or subcellular levels), as opposed to several biomarkers of AKI recently identified and studied.

The Acute Kidney Injury Network (AKIN) classification is presented in table 2 [9]. In 2007 a new classification of AKI was proposed by the Acute Kidney Injury Network (AKIN) working group. They modify RIFLE classification in some points: the diagnosis of AKI is only considered after achieving an adequate status of hydration and after excluding urinary obstruction; the AKIN classification only relies on SCr and not on GFR changes; baseline SCr is not necessary in the AKIN classification, and it requires at least two values of SCr obtained within a period of 48 h.

Table 2

AKIN classification of AKI

Stage	SCr	UO
1	↑ SCr more than 26,5 mmol/L (0,3 mg/dL) or ↑ SCr for more than 150-200 % (in 1,5-2 times)	less than 0,5 mL/kg/h during more than 6 hours
2	↑ SCr for more than 200-300 % (in 2-3 times)	less than 0,5 mL/kg/h during more than 12 hours
3*	↑ SCr for more than 300 % (in 3 times and more) or if baseline SCr more than 353,6 mmol/L (4 mg/dL), ↑ SCr more than 44,2 mmol/L (0,5 mg/dL)	less than 0,3 mL/kg/h during 24 hours or anuria during 12 hours

** stage 3 also includes patients requiring, initiating or at the moment on renal replacement therapy (RRT).*

Limitations of the AKIN classification [9]. AKIN classification also have some limitations: it does not allow the identification of AKI when SCr elevation occurs in a time frame higher than 48 hours; stage 3 of the AKIN classification includes three diagnostic criteria and the extreme variability in the beginning and cessation of RRT as well as in RRT modality used and in the dose of dialysis among different physicians, hospitals and countries could significantly limit the prognostic acuity of this classification, particularly of stage 3.

SYMPTOMS

Symptoms of acute kidney failure may include any of the following [10–11]: bloody stools, breath odor and metallic taste in the mouth, bruising easily, changes in mental status or mood, decreased appetite, decreased sensation, especially in the hands or feet, fatigue or slow sluggish movements, flank pain between the ribs and hips, hand tremor, heart murmur, high blood pressure, nausea or vomiting, may last for days, nosebleeds, persistent hiccups, prolonged bleeding, seizures, shortness of breath, swelling due to the body keeping in fluid (may be seen in the legs, ankles, and feet), urination changes, such as little or no urine, excessive urination at night, or urination that stops completely.

During physical examination possible to find [10–11] asterixis and myoclonus, pericardial or pleural rub, peripheral edema (if volume overload is present), pulmonary rales (if volume

overload is present), elevated right atrial pressure (if volume overload is present).

COMPLICATIONS

The most common complication of AKI is an infection of the urinary tract with the further development of chronic pyelonephritis and outcome in CKD [12].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A patient history and physical examination, with an emphasis on assessing the patient's volume status, are crucial for determining the cause of acute kidney injury (table 3, 4) [10, 13–14].

The history should identify use of nephrotoxic medications or systemic illnesses that might cause poor renal perfusion or directly impair renal function. Physical examination should assess intravascular volume status and any skin rashes indicative of systemic illness.

Patients with AKI may suffer from excessive bleeding, because of uremia induced platelet dysfunction and coagulopathies (for example, sepsis associated disseminated intravascular coagulation).

AKI is associated with numerous metabolic disturbances but energy expenditure is not increased significantly.

Table 3

Historical and physical examination findings in patients with different types of AKI [1]

Type of AKI	History findings	Physical examination findings
Prerenal	Volume loss (e.g., history of vomiting, diarrhea, diuretic overuse, hemorrhage, burns)	Weight loss, orthostatic hypotension and tachycardia
	Thirst and reduced fluid intake	Poor skin turgor
	Cardiac disease	Dilated neck veins, S_3 heart sound, pulmonary rales, peripheral edema
	Liver disease	Ascites, caput medusa, spider angiomas
Intrinsic renal		
Acute tubular necrosis	History of receiving nephrotoxic medications (including over-the-counter, illicit, and herbal), hypotension, trauma or myalgias suggesting rhabdomyolysis, recent exposure to radiographic contrast agents	Muscle tenderness, compartment syndrome, assessment of volume status
Glomerular	Lupus, systemic sclerosis, rash, arthritis, uveitis, weight loss, fatigue, hepatitis C virus infection, human immunodeficiency virus infection, hematuria, foamy urine, cough, sinusitis, hemoptysis	Periorbital, sacral, and lower-extremity edema; rash; oral/nasal ulcers
Interstitial	Medication use (e.g., antibiotics, proton pump inhibitors), rash, arthralgias, fever, infectious illness	Fever, drug-related rash
Vascular	Nephrotic syndrome, trauma, flank pain, anticoagulation (atheroembolic disease), vessel catheterization or vascular surgery	Livedo reticularis, funduscopic examination (showing malignant hypertension), abdominal bruits
Postrenal	Urinary urgency or hesitancy, gross hematuria, polyuria, stones, medications, cancer	Bladder distention, pelvic mass, prostate enlargement

Table 4

Probable etiologies of AKI based on the physical examination [1]

Physical examination	Probable causes of acute renal failure
Temperature	Possible infection
Blood pressure	Hypertension: nephrotic syndrome or malignant hypertension
	Hypotension: volume depletion or sepsis
Weight loss or gain	Hypovolemia or hypervolemia
Mouth	Dehydration
Jugular veins and axillae (perspiration)	Hypovolemia or hypervolemia
Pulmonary system	Signs of congestive heart failure
Heart	New murmur of endocarditis or signs of congestive heart failure
Abdomen	Bladder distention suggesting urethral obstruction
Pelvis	Pelvic mass
Rectum	Prostate enlargement
Skin	Rash of interstitial nephritis, purpura of microvascular disease, livedo reticularis suggestive of atheroembolic disease, or splinter hemorrhages or Osler's nodes of endocarditis

The initial laboratory evaluation should include [1–2, 4] urinalysis, complete blood count, and measurement of SCr level and fractional excretion of sodium (FE_{Na}) (table 5). Imaging studies can help rule out obstruction.

SCr level. It is important to compare the patient's current SCr level with previous levels to determine the duration and acuity of the disease. The definition of acute kidney injury indicates that a rise in creatinine has occurred within 48 hours, although in the outpatient setting, it may be hard to ascertain when the rise actually happened. A high SCr level in a patient with a previously normal documented level suggests an acute process, whereas a rise over weeks to months represents a subacute or chronic process.

Urinalysis. Urinalysis is the most important noninvasive test in the initial workup of acute kidney injury. Findings on urinalysis guide the differential diagnosis and direct further workup.

Complete blood count. The presence of acute hemolytic anemia with the peripheral smear showing schistocytes in the setting of acute kidney injury should raise the possibility of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

Urine electrolytes. In patients with oliguria, measurement of FE_{Na} is helpful in distinguishing prerenal from intrinsic renal causes of acute kidney injury. FE_{Na} is defined by formula

$$FE_{Na} = 100 \times \frac{urinary\ sodium \times serum\ creatinine}{serum\ sodium \times urinary\ creatinine}.$$

A value less than 1 percent indicates a prerenal cause of acute kidney injury, whereas a value greater than 2 percent indicates an intrinsic renal cause. In patients on diuretic therapy, however, a FE_{Na} higher than 1 percent may be caused by natriuresis induced by the diuretic, and is a less reliable measure of a prerenal state. In such cases, fractional excretion of urea may be helpful, with values less than 35 percent indicating a prerenal cause. FE_{Na} values less than 1 percent are not specific for prerenal causes of acute kidney injury because these values can occur in other conditions, such as contrast nephropathy, rhabdomyolysis, acute glomerulonephritis, and urinary tract obstruction.

Imaging studies. Renal ultrasonography should be performed in most patients with acute kidney injury, particularly in older men, to rule out obstruction (i.e., a postrenal cause). The presence of postvoid residual urine greater than 100 mL (determined by a bladder scan or via urethral catheterization if bladder scan is unavailable) suggests postrenal acute kidney injury and requires renal ultrasonography to detect hydronephrosis or outlet obstruction. To diagnose extrarenal causes of obstruction (e.g., pelvic tumors), other imaging modalities, such as computed tomography or magnetic resonance imaging, may be required.

Renal biopsy. Renal biopsy is reserved for patients in whom prerenal and postrenal causes of acute kidney injury have been excluded and the cause of intrinsic renal injury is unclear. Renal biopsy is particularly important when clinical assessment and laboratory investigations suggest a diagnosis that requires confirmation before disease-specific therapy (e.g., immunosuppressive medications) is instituted. Renal biopsy may need to be performed urgently in patients with oliguria who have rapidly worsening acute kidney injury, hematuria, and red blood cell casts. In this setting, in addition to indicating a diagnosis that requires immunosuppressive therapy, the biopsy may support the initiation of special therapies, such as plasmapheresis if Goodpasture's syndrome is present.

Table 5

Diagnostic test results and corresponding diseases in patients with AKI [1]

Test result	When to order	Associated diseases/conditions
Elevated antineutrophil cytoplasmic antibody, antiglomerular basement membrane antibody	Suspected acute glomerulonephritis, pulmonary renal syndromes	Vasculitis, Goodpasture's syndrome
Elevated antistreptolysin O titer	Recent infection and clinical picture of acute glomerulonephritis	Poststreptococcal glomerulonephritis
Elevated creatine kinase level, elevated myoglobin level, dipstick positive for blood but negative for red blood cells	Recent trauma, muscle injury	Rhabdomyolysis
Elevated prostate-specific antigen level	Older men with symptoms suggestive of urinary obstruction	Prostate hypertrophy, prostate cancer
Elevated uric acid level	History of rapidly proliferating tumors, recent chemotherapy	Malignancy, tumor lysis syndrome
Eosinophiluria	Fever, rash	Allergic interstitial nephritis
Evidence of hemolysis (schistocytes on peripheral smear, decreased haptoglobin level, elevated indirect bilirubin level, elevated lactate dehydrogenase level)	Fever, anemia, thrombocytopenia, neurologic signs	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, other autoimmune diseases
Hydronephrosis on renal ultrasonography	Suspected obstruction	Malignancy, prostate hypertrophy, uterine fibroids, nephrolithiasis, ureterolithiasis
Increased anion gap with increased osmolar gap*	Suspected poisoning, unresponsive patient	Ethylene glycol or methanol poisoning
Low complement level	Suspected acute glomerulonephritis	Systemic lupus erythematosus, endocarditis, postinfectious glomerulonephritis
Monoclonal spike on serum protein electrophoresis	Anemia, proteinuria, acute kidney injury in older patients	Multiple myeloma
Positive antinuclear antibody, double-stranded DNA antibody	Proteinuria, skin rash, arthritis	Autoimmune diseases, systemic lupus erythematosus
Positive blood cultures	Intravenous drug use, recent infection, new cardiac murmur	Endocarditis
Positive HIV test	Risk factors for HIV infection	HIV nephropathy

Differentials to consider in AKI include abdominal aneurysm, alcohol toxicity, alcoholic ketoacidosis, chronic renal failure, dehydration, diabetic ketoacidosis, gastrointestinal (GI) bleeding, heart failure, metabolic acidosis, obstructive uropathy, protein overloading, renal

calculi, sickle cell anemia, steroid use, urinary obstruction, urinary tract infection.

Changes in UO generally correlate poorly with changes in the GFR. The identification of anuria, oliguria, and nonoliguria may be useful in the differential diagnosis of AKI, as follows:

- anuria (UO less than 100 mL/day) – urinary tract obstruction, renal artery obstruction, rapidly progressive glomerulonephritis, bilateral diffuse renal cortical necrosis;
- oliguria (UO from 100 to 400 mL/day) – prerenal failure, hepatorenal syndrome;
- nonoliguria (UO more than 400 mL/day) – acute interstitial nephritis, acute glomerulonephritis, partial obstructive nephropathy, nephrotoxic and ischemic ATN, radiocontrast-induced AKI, and rhabdomyolysis.

TREATMENT

Lifestyle [1–2]. Patients with acute kidney injury generally should be hospitalized unless the condition is mild and clearly resulting from an easily reversible cause.

All medications that may potentially affect renal function by direct toxicity or by hemodynamic mechanisms should be discontinued, if possible. For example, metformin should not be given to patients with diabetes mellitus who develop acute kidney injury. Dietary intake of potassium should be restricted.

Risk Assessment [1–2]. All patients, both on admission and during their hospital stay should be assessed regularly for their risk of developing AKI.

Patients with CKD [8]. Patients in the community with CKD (eGFR < 60 mL/min/1,73m2) and patients with normal renal function who are treated with ACEi or ARB are at increased risk of AKI if they develop an illness associated with hypovolemia and hypertension. This provides instructions for temporary cessation of certain medications, which may in this setting, induce, exacerbate and complicate AKI (diuretics, ACEi/ARBs, metformin, NSAIDs). Patients with high BP are advised to follow a DASH (Dietary Approaches to Stop Hypertension) diet, which has proven efficacy. Modification of a DASH diet will be required in CKD patients because of its high potassium and phosphate contents.

Medication [15–18]. Optimal management of acute kidney injury requires close collaboration among primary care physicians, nephrologists, hospitalists, and other subspecialists participating in the care of the patient. After acute kidney injury is established, management is primarily supportive.

Optimise intra-vascular fluid volume. Volume status should be carefully assessed and an attempt should be made to categories the patient into one of three states: hypovolemic, euvolaemic or hypervolaemic. Hartmann's solution or 0.9 % sodium chloride solution should be used. Hartmann's solution contains a small amount of potassium (5 mmol/L) and should be avoided in patients with significant hyperkalemia (potassium ≥ 6 mmol/L). Large volumes of 0.9 % sodium chloride can provoke a hyperchloraemic metabolic acidosis.

The physiologic goals are: 1) return of mean arterial blood pressure (MAP) to ≥ 65 mm Hg (MAP is derived from a patient's systolic blood pressure (SBP) and diastolic blood pressure (DBP); since MAP is a product of cardiac output (CO) and systemic vascular resistance (SVR): [MAP = CO × SVR]. Another way to calculate MAP: double the diastolic blood pressure and add the sum to the systolic blood pressure, then divide by 3); 2) central venous pressure between 8–12 mm Hg; 3) improvement in blood lactate levels; 4) central venous oxygen saturation (ScvO2) > 70 %; and 5) a urine output of ≥ 0,5 ml/kg/h.

Failure of the patient to maintain an effective blood pressure following this regime should raise the possibility of underlying sepsis or significant ongoing losses.

Reduction in plasma potassium concentration. Treatment with calcium is a temporizing measure «buying time» while measures are started to reduce the serum potassium through increasing cellular uptake. Various options exist:

Insulin with glucose. Insulin acts rapidly to indirectly activate the cell membrane Na+/K+−ATPase and thus increase cellular potassium uptake, probably via activation of Na+/H+ channels and an increase in intracellular [Na+]. The addition of glucose to the insulin bolus is necessary to prevent hypoglycemia. Ten units of fast acting soluble insulin should be added to 50 ml of 50 % dextrose and infused over 10–20 minutes. A reduction in $[K+]_p$ is seen after 20–30 minutes. Insulin alone can be given to hyperglycemic patients (blood glucose > 14 mmol/l) as the infusion of further glucose can worsen

hyperkalemia secondary to its osmotic effect. This, plus the need for rapidly attained supraphysiological insulin levels to produce a hypokalemic effect, explains the inadequacy of glucose infusion alone as treatment for hyperkalemia in non-diabetic patients. Whether insulin and dextrose, or insulin alone, is used, the blood glucose should be monitored carefully for at least six hours. Hypoglycemia occurred in up to 75 % of patients in some studies, and was generally associated with higher insulin or lower glucose doses.

β_2 adrenergic agonists. Salbutamol binds to β_2 receptors and through cytosolic second messengers activates the Na+/K+−ATPase, thus promoting cellular potassium uptake. Nebulized and intravenous salbutamol produce a similar effect to insulin, but at higher doses than used for bronchospasm (10–20 mg via nebulizer, or 0.5 mg intravenously). Up to 40 % of patients do not respond. Tachycardia is common especially after intravenous administration. The method should not be used in patients taking β blockers or in those with a high risk of cardiac side effects. For these reasons, insulin is the agent of choice to reduce $[K+]_p$, but salbutamol may be preferably in certain circumstances, especially pediatric patients, and combined therapy with insulin and dextrose plus salbutamol may be more effective than either treatment alone.

Sodium bicarbonate. The infusion of sodium bicarbonate has little immediate effect on hyperkalemia, but may be used to correct acidosis (see later).

Dopamine. The use of low dose (1–3 μg/kg/min) dopamine has been advocated to increase renal perfusion in critically ill patients. Recent studies, including a large randomized controlled trial, have shown it to lack efficacy on renal outcome or overall mortality. Use of dopamine may also reduce splanchnic perfusion, depress respiration, suppress anterior pituitary hormone release and function, and worsen renal function in hypovolemic or normovolaemic patients. Its routine use in AKI is not currently justifiable.

Diuretics. There is a theoretical rationale for the use of loop diuretics in AKI – inhibition of the Na+/K+/2Cl − pump in the thick ascending limb of the loop of Henle, with subsequent decrease in Na+/K+−ATPase activity, should reduce the oxygen requirements of these cells, and thus their susceptibility to ischemic damage. There are scarce clinical data to support this, and recent studies have either correlated the use of diuretics with increased mortality, or shown no benefit. It seems reasonable to use diuretics only in adequately resuscitated – but oliguric – patients, at a dose suitable to the degree of renal impairment (250 mg furosemide intravenously over one hour is a standard regimen), and to stop diuretic treatment if oliguria persists. Converting oliguric to no oliguric renal failure may help with fluid and electrolyte management, but does not seem to affect eventual need for dialysis or overall mortality, and should not delay the start of renal replacement therapy when otherwise indicated. There are no data to support the use of mannitol.

Additional supportive therapy due to the cause of AKI. Supportive therapies (e.g., antibiotics, mechanical ventilation, glycemic control, anemia management) should be pursued based on standard management practices. In patients with rapidly progressive glomerulonephritis, treatment with pulse steroids, cytotoxic therapy, or a combination may be considered, often after confirmation of the diagnosis by kidney biopsy. In some patients, the metabolic consequences of acute kidney injury cannot be adequately controlled with conservative management, and renal replacement therapy will be required.

Relief of obstruction. It is important to relieve urinary tract obstruction promptly. Bladder outflow obstruction can be relieved by passage of a urethral catheter – which should be considered in all patients with AKI to accurately measure urine output – but relief of upper tract obstruction may require either antegrade (percutaneous nephrostomy) or retrograde (cystoscopy and retrograde ureteral catheterization) approaches. Urethral catheterization can be performed immediately, but other techniques require planning. Close collaboration between nephrological, urological, and radiological services is required, and in many cases renal replacement therapy may be necessary before relief of obstruction can be achieved.

A significant diuresis can complicate relief of complete urinary tract obstruction, through both appropriate (excretion of retained solute and water) and inappropriate mechanisms (tubular concentrating dysfunction). Severe polyuria is rare and requires careful management to prevent volume depletion and possible pre-renal impairment, or overzealous

fluid resuscitation and a further drive to diuresis.

Complications of treatment [19–20]. The treatment of urinary obstruction is associated with a variety of complications.

Gross hematuria (a large amount of bloody urine) can occur when the catheter is placed in patients who have bladder outlet obstruction. This happens because the sudden decrease in pressure causes the bladder veins to bleed. Unfortunately, slow decompression of the bladder does not prevent hematuria.

Reflex hypotension (low blood pressure) is a rare complication that can occur if a patient experiences sudden stimulation of the vagus nerve during catheter insertion.

Postobstructive diuresis is high urine output that may, initially, exceed 500 to 1000 milliliters per hour. This frequently occurs after an obstruction is removed. The renal tubules typically cannot reabsorb water and electrolytes in a normal manner after having been obstructed for a period of time. Rarely, a person suffers severe dehydration and requires large amounts of intravenous fluids.

Obstruction may result in an impaired distal tubular response to aldosterone, resulting in a paradoxical hyperkalemic acidosis when relieved. This usually resolves spontaneously. A small number will have permanent tubular damage and a persistent salt wasting nephropathy.

Renal replacement therapy (RRT) [21–23]. The initiation of RRT in patients with AKI prevents uremia and immediate death from the adverse complications of renal failure.

Multiple modalities of RRT are currently available. These include intermittent hemodialysis (IHD), continuous renal replacement therapies (CRRT), and hybrid therapies, such as sustained low-efficiency dialysis (SLED).

Indications for dialysis in AKI are refractory fluid overload; hyperkalemia (plasma potassium concentration > 6,5 me/l) or rapidly rising potassium levels; metabolic acidosis (pH less than 7,1); signs of uremia e.g. pericarditis and decline in mental state; certain alcohol and drug intoxications.

Timing of initiation of dialysis. Studies published during the 1960s and 1970s suggested that improved outcomes were associated with the initiation of hemodialysis when bun reached exceeded 150 to 200 mg/dl. More recent studies have evaluated the relationship between the timing of RRT initiation and clinical outcomes. Several non-randomized studies have reported that improved outcomes, including survival, are associated with early versus late initiation of RRT. It has been suggested that initiation of RRT dialysis prior to the development of overt symptoms and signs of renal failure due to AKI improves the outcome.

Discontinuation of RRT therapy. RRT is usually continued until the patient manifests evidence of recovery of kidney function: increase in urine output; a progressive decline in serum creatinine concentration after initial attainment of stable values (assessed daily during CRRT or predialysis in patients managed with IHD) despite a constant dose of renal support; measurement of creatinine clearance e.g. on six-hour timed urine collections obtained when the urine output exceeded 30 ml/hour based on an average serum creatinine at the beginning and end of the timed collection.

PROGNOSIS

Patients with acute kidney injury are more likely to develop chronic kidney disease in the future. They are also at higher risk of end-stage renal disease and premature death. Patients who have an episode of acute kidney injury should be monitored for the development or worsening of chronic kidney disease [1–2].

PREVENTION

Because of the morbidity and mortality associated with AKI, it is important to identify patients who are at high risk of developing this type of injury and to implement preventive strategies (table 6) [1–2]. Those at highest risk include adults older than 75 years; persons with diabetes or preexisting CKD; persons with medical problems such as cardiac failure, liver failure, or sepsis; and those who are exposed to contrast agents or who are undergoing cardiac surgery.

Table 6

Risk factors of AKI and preventive strategies [1]

Risk factors	Preventive strategies
Cancer chemotherapy with risk of tumor lysis syndrome	Hydration and allopurinol administration a few days before chemotherapy initiation in patients at high risk of tumor lysis syndrome to prevent uric acid nephropathy
Exposure to nephrotoxic medications	Avoid nephrotoxic medications if possible
	Measure and follow drug levels if available
	Use appropriate dosing, intervals, and duration of therapy
Exposure to radiographic contrast agents	Avoid use of intravenous contrast media when risks outweigh benefits
	If use of contrast media is essential, use isoosmolar or lowosmolar contrast agent with lowest volume possible
	Optimize volume status before administration of contrast media; use of isotonic normal saline or sodium bicarbonate may be considered in high-risk patients who are not at risk of volume overload
	Use of N-acetylcysteine may be considered
Hemodynamic instability	Optimal fluid resuscitation; although there is no consensus, MAP goal of > 65 mm Hg is widely used; isotonic solutions (e.g., normal saline) are preferred over hyperoncotic solutions (e.g., albumin)
	Vasopressors are recommended for persistent hypotension (MAP < 65 mm Hg) despite fluid resuscitation; choice of vasoactive agent should be tailored to patients' needs
	Dopamine is not recommended
Hepatic failure	Avoid hypotension and gastrointestinal bleeding
	Early recognition and treatment of spontaneous bacterial peritonitis; use albumin, 1,5 g per kg at diagnosis and 1 g per kg at 48 hours
	Early recognition and management of ascites
	Albumin infusion during large volume paracentesis
	Avoid nephrotoxic medications
Rhabdomyolysis	Maintain adequate hydration
	Alkalization of the urine with intravenous sodium bicarbonate in select patients (normal calcium, bicarbonate less than 30 mEq per L or 30 mmol per l, and arterial pH less than 7,5)
Undergoing surgery	Adequate volume resuscitation/prevention of hypotension, sepsis, optimizing cardiac function Consider holding renin-angiotensin system antagonists preoperatively

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