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TNF-ALPHA AND SERUM GALECTIN-3 IN NON DIABETIC PATIENTS WITH HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

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Insulin resistance (IR) leads to structural abnormalities in the heart. Purpose of the study is to investigate the levels of serum Gal-3 levels (sGal3), THF-alpha (TNF-a), Nt-proBNP, HOMA index and insulin and their relationships in non-diabetic patients with heart failure with preserved left ventricular ejection fraction (HFpEF). Forty five non-diabetic patients (27 males and 18 females; mean age 60.4.1±9.7 years) with HFpEF were examined. Patients with diabetes mellitus were excluded. The serum sGal3, TNF-alpha, Nt-proBNP and insulin levels measured in serum by ELISA, according to manufacturer's instructions. Homeostasis Model Assessment (HOMA) index was calculated as a measure of IR at fasting state (IR=fasting glucose × fasting insulin/22.5).The echocardiographic parameters were measured with M- and B-mode and calculated following the American Guidelines of Echocardiography Society. Continuous variables are expressed as median (25th, 75th percentile). For nonparametric Spearman's correlation analysis and Mann-Whitney U test were used. All statistical tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

It was found, that IR often occurs in non-diabetic patients with HFpEF. The sGal3, TNF-alpha and insulin are significantly increased in HFpEF patients with IR and without T2DM our study shows an association of the IR, TNF-alpha and sGal3 with echocardiographic parameters in the non diabetic with HFpEF. This fact may indicate the influence of IR on fibrogenesis process and thus facilitate the processes of myocardial remodeling.

KEY WORDS: insulin resistance, tumor necrosis factor alpha, galectin -3, fibrosis, heart failure with preserved ejection function

ФНП-АЛЬФА ТА РІВЕНЬ СИРОВАТКОВОГО ГАЛЕКТИНУ-3 У ХВОРИХ З СЕРЦЕВОЮ НЕДОСТАТНОСТЮ ЗІ ЗБЕРЕЖЕНОЮ СИСТОЛІЧНОЮ ФУНКЦІЄЮ ЛІВОГО ШЛУНОЧКА БЕЗ ЦУКРОВОГО ДІАБЕТУ

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Інсулінорезистентність (ІР) призводить до структурних порушень серця. Мета дослідження: Вивчити рівні сироваткового галектіну-3 (сГал-3), ФНП-альфа, Nt-proBNP, інсуліну та індексу HOMA та їхнього взаємозв'язку у пацієнтів з серцевою недостатністю зі збереженою фракцією викиду (СН-зФВ) без цукрового діабету.

Обстежено 45 пацієнтів (27 чоловіків і 18 жінок, середній вік - 60,4 ± 9,7 року) з СН-зФВ. Пацієнти з цукровим діабетом були виключені. Сироваткові концентрації сГал-3, ФНП-альфа, Nt-proBNP та інсуліну визначалася з використанням набору реактивів «ELISA» відповідно до інструкції виробника. Гомеостатичний індекс ІР (HOMA-IR) розраховували за формулою: HOMA-IR = глюкоза натще (ммоль / л) х інсулін натще (мкЕД / мл) / 22,5). Ехокардіографічні параметри вимірювалися в М- і В-режимах і розраховувалися згідно з рекомендаціями Американського ехокардіографічного товариства. Отримані дані представлені у вигляді медіани і інтерквартільного розмаху (25-й і 75-й процентилі). При порівнянні вибірок використовували непараметричний критерій U тест Манна -Уітні. Для встановлення взаємозв'язку кількісних ознак вибіркових даних застосовували ранговий коефіцієнт кореляції Спірмена (rs). Статистично значущими вважалися відмінності даних і кореляція між даними при $p < 0,05$.

Було встановлено, що ІР досить часто зустрічається у пацієнтів з СН-зФВ навіть без наявності цукрового діабету 2 типу. У ході нашого дослідження виявлено достовірна асоціація ІР, рівнів ФНП-альфа, галектіну-3 і ехокардіографічних параметрів серця у пацієнтів з СН-зФВ без порушень

вуглеводного обміну. Це може свідчити про вплив ІР на процеси фіброгенезу і таким чином сприяти процесам ремоделювання міокарда.

КЛЮЧОВІ СЛОВА: інсулінорезистентність, фактор некрозу пухлин альфа, галектін-3, фіброз, серцева недостатність із збереженою систолічною функцією лівого шлуночка

ФНО-АЛЬФА И УРОВЕНЬ СЫВОРОТОЧНОГО ГАЛЕКТИНА-3 У ПАЦИЕНТОВ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ С СОХРАНЕННОЙ ФРАКЦИЕЙ ВЫБРОСА БЕЗ САХАРНОГО ДИАБЕТА

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Инсулинорезистентность (ИР) приводит к структурным нарушениям сердца. Цель исследования: Изучить уровни сывороточного галектина-3 (сГал-3), ФНО-альфа, Nt-proBNP, инсулина и индекса HOMA и их взаимосвязи у пациентов с сердечной недостаточностью с сохраненной фракцией выброса (СН-СФВ) без сахарного диабета.

Обследовано 45 пациентов (27 мужчины и 18 женщин, средний возраст – 60,4 ± 9,7 года) с СН-СФВ. Пациенты с сахарным диабетом были исключены. Сывороточные концентрации сГал-3, ФНО-альфа, Nt-proBNP и инсулина, определялась с использованием набора реактивов «ELISA» в соответствии с инструкцией производителя. Гомеостатический индекс ИР (HOMA-IR) рассчитывали по формуле: HOMA-IR = глюкоза натощак (ммоль/л) х инсулин натощак (мкЕд/мл) /22,5). Эхокардиографические параметры измерялись в М - и В-режимах и рассчитывались согласно рекомендациям Американского эхокардиографического общества. Полученные данные представлены в виде медианы и интерквартильного размаха (25-й и 75-й процентили). При сравнении выборок использовали непараметрический критерий U тест Манна - Уитни. Для установления взаимосвязи количественных признаков выборочных данных применяли ранговый коэффициент корреляции Спирмена (rs). Статистически значимыми считались различия данных и корреляция между данными при $p < 0,05$.

Установлено, что ИР довольно часто встречается у пациентов с СН-СФВ даже без наличия сахарного диабета 2 типа. В ходе нашего исследования выявлена достоверная ассоциация ИР, уровней ФНО-альфа, галектина-3 и эхокардиографических параметров сердца у пациентов с СН-СФВ без нарушений углеводного обмена. Это может свидетельствовать о влиянии ИР на процессы фиброгенеза и таким образом способствовать процессам ремоделирования миокарда.

КЛЮЧЕВЫЕ СЛОВА: инсулинорезистентность, фактор некроза опухолей альфа, галектин-3, фиброз, сердечная недостаточность с сохраненной систолической функцией левого желудочка

INTRODUCTION

Heart failure (HF) is still a leading cause of both morbidity and mortality in Western society with increasing health care costs. Treatment of these patients requires considerable resources, part of which are spending on hospital care, and given the demographic trend in Ukraine to increase the proportion of the population in older age groups, the issues of the new methods development for prevention of progression, early diagnosis and treatment of heart failure is becoming very important [1]. It is known that diabetes mellitus (DM) aggravates the clinical course and prognosis of heart failure, particularly due to coronary heart disease (CHD). In recent years, the number of diabetic patients, mainly the type 2, in Ukraine has been increased considerably, and number of diabetic patients is about 1.1 million. It is expected that by 2025 the number of these patients reached the level of 5 %, [2], and globally the prevalence of diabetes is likely to increase from 371 million persons in 2013 to 552 million in 2030 [3]. This epidemic mainly refers to type 2 diabetes mellitus (T2DM), which is about 90-95 % of all cases. Modern lifestyle, environment and genetic factors, especially the interaction of the latter two, which influence the development of such an epidemic of diabetes, are closely associated with increased development and prevalence of obesity. Insulin resistance (IR) is a characteristic feature of obesity and type 2 diabetes mellitus and impacts the heart in various ways.

The problem of IR is extremely urgent today. IR is decrease sensitivity or response-veness to metabolic actions of insulin. Impaired insulin-mediated glucose uptake is a uniformly observed characteristic of the heart in these

states, although changes in upstream kinase signaling are variable and dependent on the severity and duration of the associated obesity or diabetes mellitus. The understanding of the physiological and pathophysiological role of insulin resistance in the heart is evolving.

An important role in the IR syndrome pathogenesis plays cytokines activation [4], and imbalance of these factors (increasing of interleukin (IL) -6, tumour necrosis factor (TNF) -α and decreasing of IL-10, IL-4) are considered as predictor of vascular complications. Proinflammatory cytokines are capable to modify cardiovascular function through a number of mechanisms that result in hypertrophy, dilation of the left ventricle (LV) of the heart, myocardial dysfunction, endothelial dysfunction, cardiomyopathy and fibrosis [5]. Because of this, in recent years, studies of pathophysiological role of cytokines in the pathogenesis of cardiovascular diseases which are not traditionally associated with inflammation, particularly HF various etiologies, are paid great attention [6].

To maintain high energy demands, the heart is capable of using many metabolic substrates. Although insulin signaling may directly regulate cardiac metabolism, its main role is likely the regulation of substrate delivery from the periphery to the heart, excess lipid accumulation in visceral adipose tissue. This actually causes acquisition of diabetogenic properties. In turn, visceral adipose tissue accumulates macrophages that release inflammatory cytokines, which can impair insulin sensitivity.

Thus, TNF-α increases the genes expression involved in the *de novo* synthesis of free fatty acids, which are responsible for insulin resistance and DM further formation [7]. Clinical studies confirm the connection between DM and LV dysfunction, which occurs regardless of hypertension or coronary artery disease presence. This coincides with the conclusions of the authors, who have demonstrated the relationship between the levels of proinflammatory cytokines and the degree of LV remodelling in patients with underlying metabolic disorders, including diabetes. [6].

Thus, changes in the myocardium in heart failure and presence of T2DM are morphologically characterized by hypertrophy of cardiomyocites and myocardial fibrosis due to a large number of extracellular matrixes in the interstitium of ventricular wall [8].

Recently in the literature a large number of myocardial fibrosis markers were described, - but special attention has been paid in patients with heart failure new biomarkers fibrosis - galectin-3. Galectin-3 is a 26 kDa chimaera-type galectin which is unique in that it is the only member of the galectin family [9] with an extended N-terminal domain constituted of tandem repeats of short amino acid segments (about 130 amino acids) linked to a single C-terminal carbohydrate-recognition domain. Whereas the C-terminal domain is responsible for lectin activity, the presence of the N-terminal domain is necessary for the full biological activity of galectin-3 [10, 11].

Galectin-3 is found in a wide range of species and tissues. Similar to other galectins, galectin-3 lacks a secretion signal peptide for classical vesicle-mediated exocytosis, so it is localized primarily in the cytoplasm, in the nucleus and mitochondria. When secreted into the extracellular space (via a non-classical secretory pathway that circumvents the endoplasmic reticulum and Golgi complex. Galectin-3 is involved in numerous pathological processes such as growth, proliferation, endogen inflammation and myocardial fibrosis. [12-14].

OBJECTIVE

Purpose the study is to investigate the levels of serum Gal-3 levels (sGal3), THF-alpha (TNF-a), Nt-proBNP, HOMA index and insulin and their relationships in non-diabetic patients with heart failure with preserved left ventricular ejection fraction (HFpEF).

MATERIALS AND METHODS

Forty five patients (27 males and 18 females; mean age 60.4.1 ± 9.7 years) with HFpEF, I-III NYHA functional classes with EF > 45 % of ischemic genesis without concomitant diabetes mellitus type 2 (T2DM) were examined. All patients were divided into two groups: 32 (71.17 %) patients with HFpEF and IR and 13 (28.9 %) patients with HFpEF and without IR. In control group were included 10 patients without HF, DM and IR (mean age 47.1 ± 9.5 years).

Functional status was determined using the NYHA-FC and the 6 min walk distance. Body weight was recorded in kilograms. Serum concentrations of Gal-3, TNF-alpha, insulin and Nt-proBNP were measured using an enzyme-linked immunosorbent assay with mono- and polyclonal antibodies according to manufacturer's instructions. Optical density measure-

ments were performed on a semiautomatic ELISA analyzer «Immunochem-2100». Serum concentrations of glucose were measured by glucose oxidase test according to manufacturer's instructions. Optical density measurements were performed on a semiautomatic biochemical analyzer CHEM-7. The sGal3 and insulin were measured in serum by ELISA. Homeostasis Model Assessment (HOMA) index was calculated as a measure of IR at fasting state (IR=fasting glucose × fasting insulin/22.5). The upper limit of the HOMA-IR was 2.77 [Wallace, 2004].

The echocardiographic parameters (left ventricular end-diastolic and systolic volume (LVEDV and LVESV), inter ventricular septum fractional thickening (IVSFT), inter ventricular septum fractional thickening (IVSFT), left ventricle posterior wall fraction thickening (LVPWFS), left ventricular ejection fraction (LVEF), E/A ratio) were measured with M- and B-mode echocardiography using Ultrasound's Vivid Three with a 2.5-MHz probe (Japan) and calculated following the American Guidelines of Echocardiography Society.

All of the statistical analyses were performed with the Microsoft Excel 7.0 and SPSS 21.0 Inc. software package. The distribu-tion of variables was analyzed with Kolmogorov-Smirnov test. Nonparametric variables were analyzed with Kruskal-Wallis test. To established the relationship between quantities parametric variables was used one-way analysis of variance (ANOVA) and Spearman's correlation analysis. Other differences were determined by one-way ANOVA. All statistical tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

All enrolled patients provided written informed consent. The exclusion criteria in the study were: heart failure with reduced ejection fraction < 45 %; type 1 and 2 DM, valvular heart disease; recent (up to 10 days) episodes of acute heart failure; acute coronary syndrome within the previous 3 months; inflammatory diseases in the acute stage; increase of thyroid function; cancer. The study protocol was approved by ethical committee of Government Iinstitution «L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine». The baseline clinical characteristics of examined patients are displayed in table 1.

No statistical differences were detected in age, sex, systolic and diastolic blood pressure levels, heart rate, body mass index, 6-Minute walk distance, ejection fraction of LV and index E/A in Performance status scale scores and the distribution of NYHA class between groups (tab. 1).

Table 1

Baseline Demographic and Clinical Characteristics of the Study Population (Me [LQ; UQ]) (n=45)

Index	Group 1 - Patients with HFpEF and without IR (n=13)	Group 2 - patients with HFpEF and IR (n=32)	Control Group (n = 10)
Sex (male / female). n (%)	8 (61.5 %)/5 (38.5 %)	19 (59.4%)/13 (40.6 %)	13 (38.7 %)/18 (58.1 %)
Age. years	64.0 [57.0; 66.0]	60.50 [54.25; 65.0]	50,5 [37,8; 55,3]
Duration of HF. years	4.0 [2.5; 12.5] ♦	5.0 [2.0; 8.5] ■	0
Systolic blood pressure. mm Hg	160.0 [144.0; 170.0] ♦	170.0 [160.0; 179.0] ■	117,5 [110.5; 131,5
Diastolic blood pressure. mm Hg	100.0 [90.0; 100.0] ♦	100.0 [90.0; 100.0] ■	78.0 [71.0; 80.0]
Heart rate. bpm	77.0 [61.0; 82.0]	73.50 [66.50; 84.75]	68.0 [64.3; 71,5]
Body mass index. kg/m2	29.86 [28.91; 31.18] ♦	30.68 [29.14; 34.03] ■	25,8 [24,3; 27,0]
6-Minute walk distance. m	348.0 [272.0; 387.0] ♦	355.00 [298.50; 388.0] ■	582,5 [563,3; 600,3]
Performance status scale. score	2.0 [2.0; 3.0] ♦	3.0 [2.0; 3.0] ■	0 [0; 0]
NYHA class: II III	7 (53.8%) 6 (46.2%)♦	24 (75.0%) 8 (25.0%)■	0 [0;0]
Ejection fraction of LV. %	58.0 [57.0; 60.5] ♦	61.5 [57.25; 63.75] ■	65.5 [64,3; 68.5]
E/A	0.8 [0.8; 0.94] ♦	0.8 [0.8; 0.90] ■	1.6 [1.5; 1.6]

♦ - significant difference between the Group1 and Control Group ($p < 0,01$)
■ - significant difference between the Group2 and Control Group ($p < 0,01$)

IR was diagnosed in 32 (71.17 %) patients with HFpEF patients without a history of diabetes. In the group with HFpEF and IR the level of glucose, sGal3, TNF-alpha and insulin were significantly higher compared to the HFpEF patients without IR and controls ($p < 0.01$, $p < 0.05$, $p < 0.05$ and $p < 0.0001$ respectively) (tab. 2).

Table 2

Baseline Metabolic Profile of the Study Population (Me [LQ; UQ]) (n=45)

Index	Group 1 - Patients with HFpEF and without IR (n=13)	Group 2 - patients with HFpEF and IR (n=32)	Control Group (n = 10)
Glucose. mmol/l	4.75 [4.08; 5.17]	6.08 [5.37; 7.03] ✸	4,35 [3,66; 4,62] ■
Insulin. μIU/ml	7.99 [6.64; 10.29]	22.41 [15.79; 41.11] ✸	8,3 [5,5; 11.3] ■
HOMA-IR	1.56 [1.49; 2.18]	6.13 [4.07; 11.5] ✸	1,39 [1,05; 2,29] ■
Gal-3. ng/ml	3.04 [2.45; 3.17]	3.32 [2.82; 3.76] ✸	2.38 [2.25; 2.73] ■
TNF-alpha, pg/ml	3.21 [2.78; 4.44]	5.43 [3.69; 6.82] ✸	2,98 [2.46; 3.35] ■
Nt-pro-BNP, pg/ml	207.0 [125.54; 309.76] ♦	125.39 [110.93; 175.15]	125.09 [119,59; 262,82]

✸ - significant difference between the Group1 and Group 2 ($p < 0,05$)
♦ - significant difference between the Group1 and Control Group ($p < 0,01$)
■ - significant difference between the Group2 and Control Group ($p < 0,01$)

Glucose, insulin levels and index HOMA-IR was modestly correlated with left ventricular ejection fraction value ($r=0.371$; $p < 0.05$, $r=0.306$; $p < 0.05$ and $r=0.381$; $p < 0.01$, respectively) (tab. 3). BMI were modestly correlated with left ventricular ejection fraction value and IVSFT measures ($r=0.412$; $p < 0.01$ and $r=0.416$; $p < 0.01$, respectively) (tab. 3), also with serum TNF-alpha levels ($r = 0.345$, $p < 0.05$); (tab. 4) in the general HF-patients population.

Table 3

Correlative relationship in HF-patients (n=45) (I)

Index	SBP	EF LV	IVSFT	LVPWFS	E/A
BMI		$r = 0.412$; $p < 0.01$	$r = 0.416$; $p < 0.01$		
Glucose	-	$r = 0.371$; $p < 0.05$	-	-	-
Insulin	-	$r = 0.306$; $p < 0.05$	-	-	-
Gal-3	$r = 0.359$; $p < 0.01$		-	-	$r = 0.316$; $p < 0.05$
HOMA-IR	-	$r = 0.381$; $p < 0.01$	-	-	-

Table 4

Correlative relationship in HF-patients (n=45) (II)

Index	Glucose	Insulin	HOMA-IR	TNF-alpha
BMI	-	-	-	$r = 0.345$; $p < 0.05$
Glucose	-	$r = 0.446$; $p < 0.05$	$r = 0.649$; $p < 0.0001$	$r = 0.399$; $p < 0.05$
Insulin	$r = 0.446$; $p < 0.05$	-	$r = 0.959$; $p < 0.0001$	-
Gal-3	-	-	-	$r = 0.548$; $p < 0.0001$

Serum galectin-3 levels were inversely correlated with the ratio of peak transmitral flow velocity (E/A) value ($r = -0.316$, $p < 0.05$); a directly correlated with SBP ($r = 0.359$, $p < 0.01$), serum TNF-alpha levels ($r = 0.548$, $p < 0.001$). Conversely, the serum TNF-alpha levels mildly correlated with glucose levels ($r = 0.399$, $p < 0.05$). The increasing of sGal3 levels associated with increasing TNFa levels ($\chi^2 = 7.379$, $p = < 0.05$) (tab. 4).

Among the patients included in the 2nd group (heart failure in combination with insulin resistance) (tab. 5) left ventricular ejection fraction value had a direct correlation with the serum concentration of TNF-alpha ($r = 0.362$, $p < 0.05$), HOMA index ($r = 0.394$, $p < 0, 05$); glucose ($r = 0.401$, $p < 0.05$). As a total group, patients with heart failure and insulin resistance had a direct association between the TNF-alpha level and galectin-3 ($r = 0.522$, $p < 0.01$) (tab. 5).

Table 5

Correlative relationship in HF-patients with IR (n=32)

Index	DBP	EF LV	IVSFT	LVPWFS	Gal-3
BMI			r = 0.523; p < 0.01	r = 0.521; p < 0.01	
Glucose	r = 0.363; p < 0.05	r = 0.401; p < 0.05	-	-	-
HOMA-IR	-	r = 0.394; p < 0.05	-	-	-
TNF-alpha		r = 0.362; p < 0.05			r = 0.552; p < 0.01

In the 1st group of patients (heart failure without insulin resistance) a strong inverse correlation between galectin-3 levels and E/A ratio ($r = -0.899$; $p < 0.0001$) was found. Also elevated insulin levels were associated with higher SBP and DBP values, but galectin-3 levels and index HOMA score had positive correlation with IVSFT ($r = -0.721$; $p < 0.01$) ($r = -0.645$; $p < 0.05$) and LVPWFS ($r = -0.714$; $p < 0.01$) ($r = -0.640$; $p < 0.05$) (tab. 6).

Table 6

Correlative relationship in HF-patients without IR (n=13)

Index	SBP	DBP	IVSFT	LVPWFS	E/A
Insulin	r = 0.601; p < 0.05	r = 0.818; p < 0.05	-	-	-
HOMA-IR	-	-	r = 0.645; p < 0.05	r = 0.640; p < 0.05	-
Gal-3	-	-	r = 0.721; p < 0.01	r = 0.714; p < 0.01	r = 0.899; p < 0.0001

There are some changing in the heart muscle caused by remodelling of morphological and anatomical structures of the heart, and sympathoadrenal and renin-angiotensin-aldosterone systems hyperactivity in HF. In patients with heart failure to meet the increased metabolic demands, which are increased in cardiac output occurs due to stroke output increasing, which leads to the development of left ventricular eccentric hypertrophy.

Myocardial dysfunction due to diffuse, not ischemic fibrosis associated with obesity [15], hypertension [16], aging [17] and diabetes mellitus [18].

At present, there are insignificant data about myocardial energy and humoral supplying, disruption of the mechanisms of their interaction and regulation in heart failure. There are evidences of the relationship of functioning efficiency, coronary heart disease (CHD) and hyperinsulinemia in heart failure patients. The severity of the clinical manifestations in heart failure determined by the insulin sensitivity of the myocardium and peri-

pheral muscle and insulin content in the blood. In our study we demonstrated that increasing the serum glucose, insulin levels and index HOMA-IR was modestly correlated with left ventricular ejection fraction value.

This is consistent with the results of recent meta-analyzes, where association of increasing insulin and glucose levels with increased risk of cardiovascular disease in non-diabetic patients was demonstrated [19, 20]. Moreover, elevated of serum glucose and insulin levels have pro-atherogenic properties [21], which may be the prospect of further research.

Whereas increasing insulin and glucose levels are a direct result of insulin resistance. IR may facilitate to the development of atherosclerosis not only by increasing glucose and insulin levels, but also through mechanisms which include, dyslipidaemia, hypertension, and inflammation [21, 22]. It is known that IRS-1 is the main substrate cytoplasmic enzymatic activity of the insulin receptor [23]. Interaction between TNF-a receptor and IRS-1 probably may inhibit the insulin signal transduction pathway in a cell by decreasing the tyrosine kinase activity of the insulin receptor and phosphorylation of tyrosine. In our study, it was found that the levels of TNF-alpha are progressively increased. At the same in our study the significantly higher TNF-alpha levels were observed in HFpEF and IR patients group compared with those without IR and controls.

Hyperglycaemia, which leads to microangiopathy, reduces the number of capillaries per unit area of the myocardium that leads to ischemia, cardiomyocites apoptosis and activation of fibrogenesis. Wakasaki H et al. demonstrated that increased activity of β-type protein kinase-C (PKC-β), induced by hyperglycaemia, leads to myocyte necrosis and fibrosis, which can be prevented by inhibition of PKC-β [24].

In our study increasing galectin-3 levels (marker of fibrosis) were founded in those patients, whose insulin, TNF-a levels and index HOMA were increased. Moreover, serum galectin-3 levels was inversely correlated with the ratio of peak transmitral flow velocity (E/A) value and had positive correlation with SBP values.

Metabolic factors may also play a role in the development of myocardial dysfunction; hyperinsulinemia and insulin resistance, that can be consequence of proinflammatory cytokine activation, may all contribute to myocardial fibrosis and myocardial dysfunction. Moreover, the deposition of advanced glycation end products (AGEs) may result in increased left ventricular stiffness and consequently to diastolic dysfunction [25].

In addition, modest correlation serum galectin-3 and TNF-a level was found in general population of HF-patients and at the presence of carbohydrate metabolism abnormalities in HF-patients. This dependence increases with the progression of IR. That may be due to increase of fibrosis degree in enhanced inflammation and insulin resistance.

CONCLUSIONS

1. IR was diagnosed in 71.1 % HFpEF patients without a history of diabetes.
2. Serum galectin-3, TNF-alpha and insulin are significantly increased in HFpEF patients with IR and without T2DM.
3. Serum galectin-3 levels were directly correlated with SBP, and inversely correlated with diastolic left ventricular dysfunction. With increasing serum galectin-3 levels increases diastolic dysfunction of the left ventricular severity.
4. Our study shows an association of the IR, TNF-alpha and sGal3 with echocardiographic parameters in the non diabetic with HFpEF. This fact may indicate the influence of IR on fibrogenesis process and thus influence the processes of myocardial remodeling in HFpEF patients.

PROSPECTS FOR FUTURE STUDIES

The study and analysis of the relationships between changes in levels of immunological inflammation, galectin-3, an index of insulin resistance, parameters of intracardiac hemodynamics in patients with heart failure of different etiologies are promising.

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Clinical researches

UDC 616-06

ANALYZE OF DEATH IN PATIENTS WITH CARDIAC PACING

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This study included 30 cases of death among patients at the age of 47 to 83 years who underwent permanent pacing. The estimated factors considered patients' sex (male, female), age, cause of death, clinical diagnosis, indications, type, the frequency and duration of pacing. Depending on the length of pacing, these deaths were divided into I) acute (from 1 to 7 days), II) sharp (7 to 30 days), III) postimplantation (30 days to 5 years) and IV) remote postimplantation (more than 5 years) periods. The obtained results reveal the fact that more than 2/3 of the deaths occurred in acute and postimplantation periods. The number of deaths pertaining these periods was approximately equal. The rest of the lethal cases, which includes 1/3 of the deaths, falls on the acute and remote postimplantation periods. The number of deaths happened in the acute period was two times less than in the remote postimplantation period. In 2/3 cases the death was caused by the acute heart failure, happening in the acute and sharp periods, correspondently. 1/3 of deaths can be qualified as caused by comorbid pathology, happened in postimplantation and remote postimplantation periods. Patients, who had heart failure in their life-time, have the least favorable prognosis for recovery.

KEY WORDS: pacemaker, mortality, heart failure

АНАЛІЗ ЛЕТАЛЬНИХ ВИПАДКІВ У ПАЦІЄНТІВ З ІМПЛАНТОВАНИМ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРОМ

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Проведено аналіз летальних випадків 30 померлих у віці від 47 до 83 років, які при житті піддалися постійної електрокардіостимуляції (ЕКС). Оцінювали: вік, стать, причину смерті, клінічний діагноз, показання, тип, частоту та тривалість стимуляції ЕКС. Летальні випадки, в залежності від тривалості ЕКС, були розділені на: I) найгостріший (від 1 до 7 днів), II) гострий (від 7 до 30 днів), III) постімплантанційний (від 30 днів до 5 років) та IV) віддалений постімплантанційний (більше 5 років) періоди. З отриманих результатів маємо: більше 2/3 летальних випадків були в найгострішому та постімплантаційному періодах, де по частоті вони були приблизно однакові, з залишившойся 1/3, їх частота в гострому періоді була майже в 2 рази менше, ніж у віддаленому постімплантаційному періоді. У 2/3 випадках причиною смерті була гостра серцева недостатність (СН), переважно, в найгострішому та гострому, та у 1/3 – коморбідна патологія, переважно, у постімплантаційному та віддаленому постімплантаційному періодах. Пацієнти, які в анамнезі життя мали СН, мають більш несприятливий прогноз для одужання.

КЛЮЧОВІ СЛОВА: електрокардіостимулятор, смертність, серцева недостатність

АНАЛИЗ ЛЕТАЛЬНЫХ ИСХОДОВ У ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРОМ

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Проведен анализ летальных исходов 30 умерших в возрасте от 47 до 83 лет с имплантированным при жизни постоянным электрокардиостимулятором (ЭКС). Учитывались возраст; пол, причина

смерти, клинический диагноз, показания, тип, частота и продолжительность ЭКС. Летальные исходы в зависимости от продолжительности ЭКС были разделены на I – острейший (от 1 до 7 дней), II – острый (от 7 до 30 дней), III – постимплантационный (от 30 дней до 5 лет) и IV) отдаленный постимплантационный (более 5 лет) периоды. Результаты показали, что более 2/3 летальных исходов приходилось на острейший и постимплантационный периоды, где по частоте они были примерно одинаковы, из оставшейся 1/3 их частота в остром периоде была почти в два раза меньше, чем в отдаленном постимплантационном. В ⅔ случаях причиной смерти являлась острая сердечная недостаточность (СН), преимущественно, в острейшем и в остром, и в ⅓ - коморбидная патология, преимущественно, в постимплантационном и отдаленном постимплантационном периодах. Пациенты, имеющие СН в анамнезе, имеют более неблагоприятный прогноз для выздоровления.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимулятор, смертность, сердечная недостаточность

INTRODUCTION

The implantation of a permanent pacemaker (ECS) is the leading treatment of bradysystiolic arrhythmia and chronic heart failure (CHF) resistant to medical treatment. [1-4]. Pacing prevents syncope recurrence and improves patients' life expectancy [5]. Despite the wide range of indications for pacemaker implantation and positive results, part of patients died not only in the long term, but in the first days after surgery, and to improve its results requires an analyze of mortality. [5-6]. There are publications related to mortality in patients only with single-chamber ventricular pacing.

OBJECTIVE

The aim of this work is to analyze mortality in patients with permanent pacemakers.

MATERIALS AND METHODS

On the basis of the mortuary of SI «Zaytsev V.T. Institute of General and Urgent Surgery NAMS of Ukraine» and Regional Hospital of Kharkiv, there were examined protocols of autopsy of 30 dead patients (15 men and 15 women) at the age of 47 to 83 (average 70,9 ± 8,3) There were estimated sex (male, female), age, duration of stimulation and cause of death. From the available archival histories of disease of 19 dead patients were additionally estimated the clinical diagnosis, indications for stimulation, type and frequency of stimulation of pacemaker. We managed to determine the type of pacemaker stimulation in patients with identified history of illness: in 5 % - DDD and in 95 % cases VVI.

There were 4 periods isolated: I) acute (from 1 to 7 days), II) a sharp (7 to 30 days), III) postimplantation (30 days to 5 years) and IV) remote postimplantation (more than 5 years) periods.

In all patients and dedicated periods ECS for the age, the frequency and duration of stimulation, there were found the arithmetic mean and standard deviation.

The frequency of causes of death and indications for pacing were evaluated in percentage.

The results obtained were processed after forming the database. Statistical evaluation was performed using Microsoft Excel 2007.

RESULTS AND DISCUSSION

More than 2/3 cases of deaths occurred in I and III periods, where the frequency was about the same, the remaining 1/3 cases of their frequency in the II period was almost two times less than in the IV period (Fig. 1).

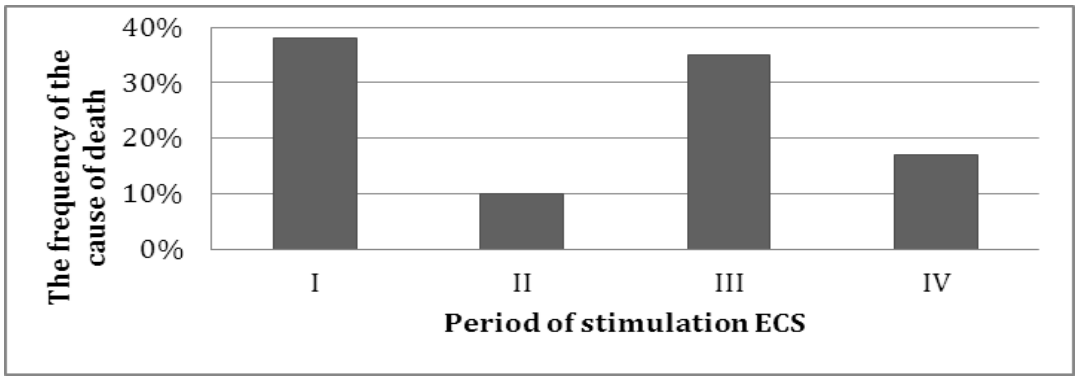

Fig. 1 The frequency of deaths in periods ECS (in %)

In ⅔ cases the cause of death was caused by heart failure, and in the remaining ⅓ - comorbid pathology (tab. 1)

Table 1

The frequency of the cause of death among patients with implanted pacemaker in the periods of ECS (in %)

	AHF	PE	Stroke	Cancer intoxication	Acute bleeding
I	75	16	8	----------	----------
II	100	----------	----------	----------	----------
III	56	----------	33	----------	11
IV	60	----------	20	20	----------

Abbreviations: AHF - acute heart failure,
PE- pulmonary embolism,
stroke - acute cerebrovascular accident.

Causes of death in the I period were the following: AHF, pulmonary embolism, stroke, in the II period - AHF, in the III and IV periods - AHF, stroke, tumor diseases and acute bleeding.

The frequency of clinical entities and clinical syndromes before the death of patients with implanted ECS are shown in the fig 2.

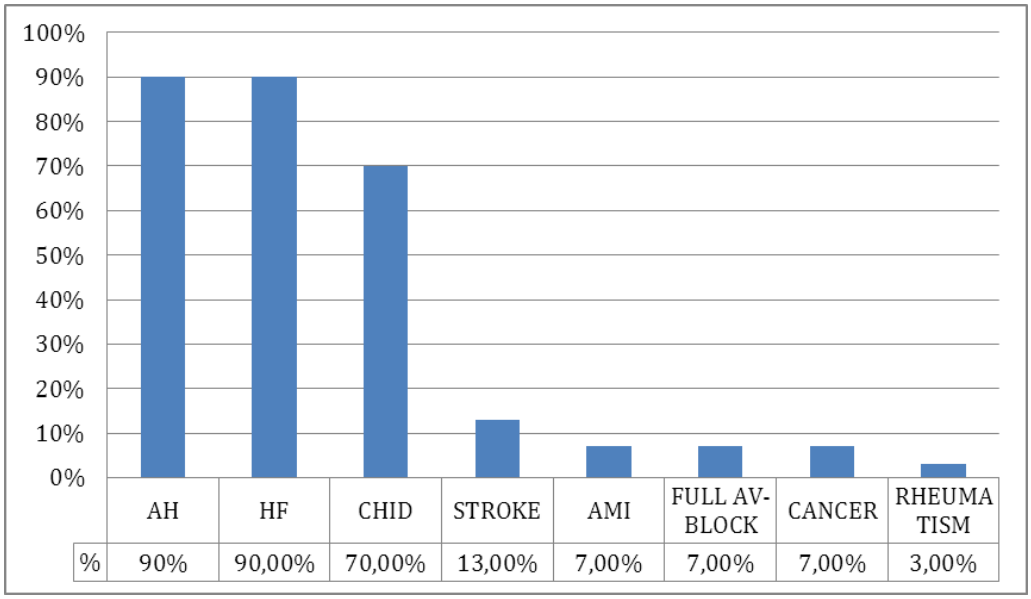

Fig.2 The frequency of clinical entities and clinical syndromes before the death of patients with implanted ECS in decreasing order (in %)

Abbreviations: AH – atrial hypertension,
HF - heart failure,
AMI - acute myocardial infarction,
CIHD - chronic ischemic heart disease.

The majority of patients had the combination of AH, CHID, seldom - stroke and AMI, and more seldom - other states.

The predominant indication for pacemaker implantation was AV block, which in two cases was combined with a permanent form of atrial fibrillation, among other indications - ventricular dyssynchrony and Sick sinus syndrome (SSS) (Fig. 3).

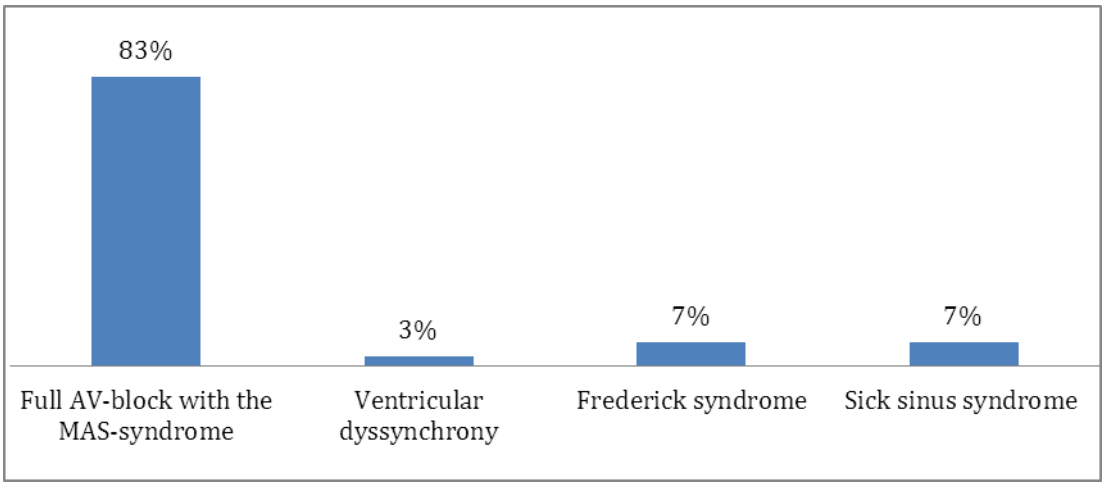

Fig. 3 Frequency of indications for pacemaker implantation in the studied group (in %)

In the studied group the rate of frequency of pacemaker stimulation during the life-time ranged from 60 to 80 beats / min (67 ± 6,78 beats / min at VVI pacing and 70 beats / min during DDD pacing)

AHF as most frequent cause of death in patients with implanted pacemaker was confirmed [6-7]. Publications with a detailed analyze of deaths especially that concerns the periods of ECS, weren't found in the literature and are the new ones.

CONCLUSIONS

1. More than 2/3 of the deaths were in the acute and postimplantation periods, where their frequency was about the same, the remaining 1/3 of their frequency falling on the acute period was almost two times less, than in the remote postimplantation period.
2. In 2/3 cases the death was caused by the acute heart failure, happening in the acute and sharp periods, correspondently. 1/3 of deaths can be qualified as caused by comorbid pathology, happened in postimplantation and remote postimplantation periods
3. Patients, who had heart failure in their life-time, have the least favorable prognosis for recovery.

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FUNCTIONAL PARAMETERS OF BLOOD CIRCULATION IN PATIENTS DURING FIRST SIX MONTHS OF RIGHT VENTRICULAR PACING IN QTc INTERVAL DURATION CLASSES

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37 patients (22 men and 15 women) with implanted pacemakers (PM) in DDD/DDDR and VVI/VVIR modes were investigated. Systolic blood pressure (SBP) and diastolic blood pressure, QTc interval duration, QRS complex duration, heart rate, end-systolic and end-diastolic volume, left ventricular ejection fraction , the thickness of the posterior wall of the left ventricle and interventricular septum, left ventricular myocardial mass, anterior-posterior size of the left atrium, right atrium and right ventricular were evaluated before, during acute postoperative period (3-5 days) and six months after pacemaker implantation. Patients were divided into classes 1 (normal QTc (320-440 ms)) - 17 (46 %) of the patients) and class 2 (long QTc (> 440 ms)) - 20 (54 %) patients) of QTc interval duration. For data processing were used standard statistical procedures by Microsoft Excel. PM implantation, increasing to a greater extent initially normal and less - an elongated QTc interval duration, to 6 months period leads them to the same level of values in both QTc interval duration classes. Increase of SBP and QRS complex duration in the class 2 demonstrates the need for more intensive monitoring and drug management in these patients.

KEY WORDS: cardiac pacing, right ventricular pacing, electrocardiography, QTc interval, echocardiography

КЛАС ТРИВАЛОСТІ ІНТЕРВАЛУ QTc І ФУНКЦІОНАЛЬНІ ПОКАЗНИКИ КРОВООБІГУ У ПАЦІЄНТІВ З ПРАВОШЛУНОЧКОВОЮ СТИМУЛЯЦІЄЮ У ПЕРШІ ПІВРОКУ ПІСЛЯ ІМПЛАНТАЦІЇ ЕКС

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Обстежені 37 пацієнтів (22 чоловіки та 15 жінок) з імплантованими одно- і двокамерними електрокардіостимуляторами (ЕКС) в режимах DDD/DDDR і VVI/VVIR. Оцінювали до, в гострому післяопераційному періоді (3-5 добу) і через півроку після імплантації ЕКС рівень систолічного артеріального тиску (САТ) і діастолічного артеріального тиску, тривалість інтервалу QTc, комплексу QRS, частоту серцевих скорочень; кінцево-систолічний і кінцево-дістоліческого об'єму, фракцію викиду лівого шлуночка, товщину задньої стінки лівого шлуночка і міжшлуночкової перегородки, масу міокарда лівого шлуночка, передньо-задній розмір лівого передсердя, правого передсердя і правого шлуночка. Пацієнти були розділені на класи 1 (нормального QTc (320-440 мс)) - 17 (46 %) пацієнтів) і 2 (подовженого QTc (> 440 мс)) - 20 (54 %) пацієнтів) тривалості інтервалу QTc. Для обробки даних використовувалися стандартні статистичні процедури за допомогою Microsoft Excel. Імплантація ЕКС, збільшуючи більшою мірою початково нормальну і в меншій - подовжену тривалість інтервалу QTc, приводила її до піврічного періоду до одного рівня значень в обох класах тривалості інтервалу QTc. Збільшення САТ і тривалості комплексу QRS в класі 2 свідчить про необхідність більш інтенсивного спостереження та медикаментозного менеджменту у цих пацієнтів.

КЛЮЧОВІ СЛОВА: електрокардіостимуляція, правошлуночкова стимуляція, електрокардіографія, інтервал QTc, ехокардіографія

КЛАСС ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QTc И ФУНКЦИОНАЛЬНЫЕ ПОКАЗАТЕЛИ КРОВООБРАЩЕНИЯ У ПАЦИЕНТОВ С ПРАВОЖЕЛУДОЧКОВОЙ СТИМУЛЯЦИЕЙ В ПЕРВЫЕ ПОЛГОДА ПОСЛЕ ИМПЛАНТАЦИИ ЭКС

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Обследованы 37 пациентов (22 мужчины и 15 женщин) с имплантированными одно- и двухкамерными электрокардиостимуляторами (ЭКС) в режимах DDD/DDDR и VVI/VVIR. Оценивали до, в остром послеоперационном периоде (3-5 сутки) и через полгода после имплантации ЭКС уровень систолического артериального давления (САД) и диастолического артериального давления, продолжительность интервала QTc, комплекса QRS, частоту сердечных сокращений; конечно-систолический и конечно-диастолический объемы, фракцию выброса левого желудочка, толщину задней стенки левого желудочка и межжелудочковой перегородки, массу миокарда левого желудочка, передне-задний размер левого предсердия, правого предсердия и правого желудочка. Пациенты были разделены на классы 1 (нормального QTc (320-440 мс)) - 17 (46 %) пациентов) и 2 (удлиненного QTc (> 440 мс)) – 20 (54 %) пациентов) продолжительности интервала QTc. Для обработки данных использовались стандартные статистические процедуры с помощью Microsoft Excel. Имплантация ЭКС, увеличивая в большей степени исходно нормальную и в меньшей - удлиненную продолжительность интервала QTc, приводила ее в полугодовом периоде к одному уровню значений в обоих классах продолжительности интервала QTc. Увеличение САД и продолжительности комплекса QRS в классе 2 свидетельствует о необходимости более интенсивного наблюдения и медикаментозного менеджмента у этих пациентов.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимуляция, правожелудочковая стимуляция, электрокардиография, интервал QTc, эхокардиография

INTRODUCTION

Right ventricular (RV) pacing is one of the leading treatment methods for bradyarrhythmias [1]. Blood circulation functional parameters monitoring allows control the pacemaker and accompanying medical treatment [1-3].

Output of corrected QT interval duration (QTc) values beyond physiological scope is a poor prognostic sign, not only in patients with spontaneous rhythm, but also with the pacemaker (PM) [4]. Despite this, functional parameters of blood circulation in QTc interval duration classes of stimulated complexes in patients with PM have not previously been studied.

OBJECTIVE

The purpose of this study is to evaluate functional parameters of blood circulation in patients during first six months of right ventricular pacing in QTc interval duration classes.

MATERIALS AND METHODS

37 patients aged 68 ± 9 (M ± sd) (15 – female, 22 – 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», among them – 9 patients have atrial fibrillation (AF). All patients were underwent permanent pacing therapy from 2006 to 2013 in modes: DDD (8 patients) and DDDR (14 patients), VVI (8 patients), VVIR (7 patients). RV pacing more than 50 % was observed in 35 (78 %) patients. Mainly atrial pacing (AP) (90 %) during DDD/DDDR pacing was observed in 8 patients (18 %) with sick sinus node syndrome (SSNS).

Functional parameters of blood circulation were evaluated before, in acute postoperative period (3-5 hours) and six months after PM implantation: systolic blood pressure (SBP) and diastolic blood pressure (DBP); ECG parameters: QTc interval duration, QRS complex duration, heart rate (HR); echocardiography (EchoCG) parameters: end-systolic volume (ESV) and end-diastolic volume (EDV), ejection fraction (EF) of the left ventricle (LV), the thickness of the left ventricle posterior wall (LVPW), the thickness of the interventricular septum (IVS) left ventricular myocardial mass (LVMM), antero-posterior dimension of the left atrium (LA), right atrium (RA) and right ventricular (RV).

To measure the duration of the QT interval and heart rate of the patients before and after pacemaker implantation (3-5 days after surgery) were recorded on a computer ECG electrocardiograph «Cardiolab +» (HAI-Medica). The stimulated QTc interval duration was measured after the removal of the stimulus artifact in three consecutive complexes of the Q wave to the beginning of the descending segment of the return of the T wave in leads to the contour II, V5, and V6 with choosing of a maximum value. The corrected QT interval duration (QTc) of the patients with spontaneous rhythm and pacing was calculated by the Bazett formula: QTc = QT / (RR ^ 0,5). For patients with AF, QTc was calculated using the formula QTc = QT + 0,154 × (1000 - RR) Fermingem study for patients with atrial fibrillation [5], the measurement accuracy - 0.5 ms.

Echocardiography was conducted by the ultrasound machine Siemens Cypress and Toshiba Applio 400. RA, LA, RV sizes, end-systolic size (ESS), end-diastolic size (EDS) and LVPW, IVS thickness was measured. EDV and ESV were calculated by the method of Simpson. Left ventricular mass (LVM) was calculated according to the formula Devereux: LVM = 1.04*((AP LV+ IVS+ESS)^3-ESS^3) - 13.6 [6]. The measurement accuracy was 0.5 mm. For the calculation of EF using the formula EF = SV / EDV (SV-stroke volume) [6]. SBP and DBP were measured by tonometer Microlife BP AG1-20 by Korotkov method, the measurement accuracy - 1 mm Hg.

The patients with pacemakers were divided into 3 classes of QTc interval duration of stimulated complexes (further classes): Class 1 - normal (in the physiological range of values) - 320-439 ms, Class 2 - (qualified) an elongated QTc interval- > 440 ms, and Class 3 - (qualified) shortened QTc interval - < 320 ms [7].

There are a 17 (46 %) patients aged 65 ± 11 in class 1 (male - 9 female - 8, in the stimulation mode DDD/DDDR - 9 patients (53 %), VVI/VVIR - 8 patients (47 %)) and 20 (54 %) patients aged 71 ± 8 in class 2 (male - 13 female - 7, in the stimulation mode DDD/DDDR - 13 patients (65 %), VVI/VVIR - 7 patients (35 %)). In class 3, there was not a single patient. Values were estimated in the classes of QTc interval duration in groups of DDD/DDDR and VVI/VVIR stimulation modes.

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 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

QTc interval duration during first six months of right ventricular pacing in different modes of stimulation in classes 1 and 2 is shown in fig. 1.

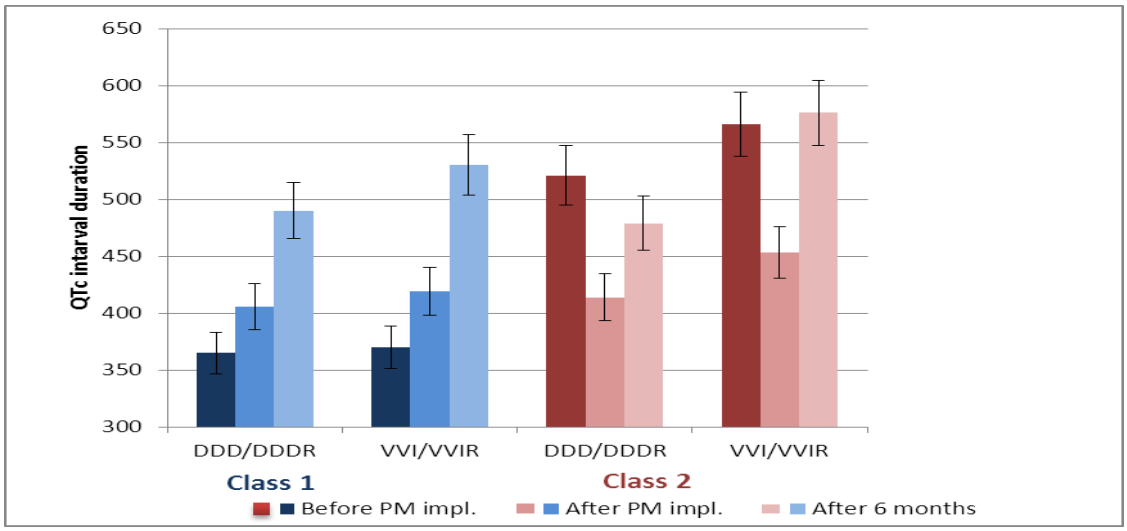

Fig. 1. QTc interval duration during first six months of right ventricular pacing in different modes of stimulation in classes 1 and 2.

In class 1 the QTc interval duration after PM implantation naturally increased, peaking to half-year period of observation in both DDD/DDDR, and in VVI/VVIR modes. The degree of QTc interval duration increase was greater in the VVI/VVIR mode than in the DDD/DDDR mode. In class 2 after almost twofold reduction in the acute postoperative period after PM implantation it increased again six months later, approaching the value set before the operation. The degree of this increase was greater in the VVI/VVIR mode of than in the DDD/DDDR mode.

Functional parameters blood circulations in patients with right ventricular pacing in different modes in first six months after pacemaker implantation in QTc interval duration classes are shown in tab. 1.

Table 1

Functional parameters blood circulations in patients with right ventricular pacing in different modes in first six months after pacemaker implantation in QTc interval duration classes

Functional parameters		Pacing mode	QTc interval duration					
			Normal			Elongated		
			Before PM	After PM implantation (3-5	After 6 months	Before PM	After PM implantation (3-5	After 6 months
Arterial pressure (M±sd, mm Hg)	SBP	DDD/DDDR	130±18	125±8	122±11	146±17*	124±12	140±19*
		VVI/VVIR	143±15	130±6	134±9	142±17*	130±11	149±12*
	DBP	DDD/DDDR	79±12	79±5	75±7	84±10	86±7	90±11
		VVI/VVIR	84±9	84±5	82±8	81±9	82±6	82±7
ECG parameters	QRS (M±sd, ms)	DDD/DDDR	90±15	118±27	126±21**	115±27	141±24*, **	148±30*, **
		VVI/VVIR	102±21	132±20	149±22**	124±28	138±21	159±37
	HR (M±sd, 1/min)	DDD/DDDR	48±15	67±6	66±8	54±14	71±10	68±11
		VVI/VVIR	53±8	65±7	62±8	62±17	72±7	70±12
EchoCG parameters	ESV (M±sd, ml)	DDD/DDDR	77±34**	40±23	48±19	94±52**	61±41	79±38
		VVI/VVIR	66±25	48±18	51±15	75±43	77±36	76±29
	EDV (M±sd, ml)	DDD/DDDR	188±34**	159±29	160±31	175±55	146±49	154±48
		VVI/VVIR	139±32	132±28	140±33	195±49*, **	151±43	164±40
	EF (M±sd, %)	DDD/DDDR	52±7	53±6	50±8	52±12	54±10	51±12
		VVI/VVIR	54±9	56±7	50±11	53±13	54±10	50±9
	LVPW (M±sd, sm)	DDD/DDDR	1±0,1	1±0,1	1±0,1	1±0,1	1±0,1	1±0,1
		VVI/VVIR	1±0,1	1±0,1	1±0,2	1±0,2	1±0,1	1±0,1
	IVS (M±sd, sm)	DDD/DDDR	1±0,2	1±0,1	1±0,1	1±0,2	1±0,1	1±0,1
		VVI/VVIR	1±0,1	1±0,1	1±0,2	1±0,2	1±0,2	1±0,2
	LVMM (M±sd, g)	DDD/DDDR	369±81	369±81	371±72	319±77	320±77	351±65
		VVI/VVIR	320±64	317±61	330±47	331±90	326±86	390±79
	LA (M±sd, sm)	DDD/DDDR	4±0,4	4±0,5	4±0,4	4±0,7	4±0,6	4±0,5
		VVI/VVIR	4±0,5	4±0,5	4±0,5	4±0,7	4±0,6	4±0,6
	RA (M±sd, sm)	DDD/DDDR	5±0,5	5±0,4	4,9±0,5	4±0,4	4±0,4	4±0,4
		VVI/VVIR	4±0,4	4±0,4	4,3±0,5	5±0,5	5±0,6	5,2±0,6
	RV (M±sd, sm)	DDD/DDDR	5±0,6	5±0,6	5±0,5	5±0,6	5±0,6	5±0,6
		VVI/VVIR	4±0,5	4±0,4	4,5±0,5	5±0,7	5±0,6	5,2±0,6

Notes:

* $p < 0,05$ – between values in classes;

** $p < 0,05$ – between values in class before and after PM implantation

SBP in class 1 was not significantly changed with pacemaker implantation in both DDD/DDDR and VVI/VVIR modes, and in the class 2 it decreased in acute postoperative period, returning after six months to baseline values. The degree of increase was greater in the VVI/VVIR mode, than in the DDD/DDDR mode. Pacemaker implantation had no effect on DBP in classes 1 and 2 in both modes of stimulation.

The duration of the QRS complex in class 1 did not change with pacemaker implantation in the acute postoperative period, but significantly increased after six months in both modes of stimulation. The degree of increase was greater in the VVI/VVIR mode. In class 2 the duration of QRS complex increased in the acute postoperative period and remained so six months after pacemaker implantation. Increase was observed only in the DDD/DDDR. Changes in HR after pacemaker implantation in classes 1 and 2 of QTc interval duration in both modes of stimulation was not observed.

ESV and EDV in class 1 of QTc interval duration decreased with pacemaker implantation in acute postoperative period only in the DDD/DDDR mode and did not change significantly after six months in both modes of stimulation. In class 2 reduction ESV with pacemaker implantation was observed in the DDD/DDDR mode, and EDV - both in the DDD/DDDR and in the VVI/VVIR modes. Six months later, CSR and CSR changes were observed in both modes of stimulation.

PM implantation had no effect on EF, thickness of IVS, LVPW, antero-posterior dimension of RA, LA, RV in DDD/DDDR and VVI/VVIR modes in classes of QTc interval duration.

QTc interval prolongation during RV stimulation, which we found six months after PM implantation, corresponds to the data [8, 9] for its initially normal and the data [10, 11] - an extended duration.

In contrast to [12], who showed no reaction SBP and DBP in patients after PM implantation, we received an increase of SBP in the class of increased QTc interval duration, which can be associated both with increased duration of electrical systole and insufficient antihypertensive therapy in this class.

QRS complex prolongation in the class of increased QTc interval duration, which we found in patients with DDD/DDDR and VVI/VVIR cardiac pacing, differed from the data [13, 14] described it only in patients with biventricular stimulation and has not been studied in the classes of the QTc interval duration.

In contrast to the data [15], showed a decrease of ESV and EDV only in patients with biventricular PM, we discovered it in DDD/DDDR and VVI/VVIR modes of cardiac pacing, which can be explained more physiological impulse conduction due to the right ventricular electrode implantation in interventricular septum in our study, against its implantation in apex. Reduction of ESV and EDV happened is statistically significant changes in the PV modes DDD / DDDR and VVI / VVIR pacemaker, which corresponds to the data [9, 15].

Changes in functional parameters of blood circulation in patients in the first six months of right ventricular pacing after PM implantation are determined in generally, among other factors, by QTc interval duration class. There more often changes in patients with prolonged QTc interval duration indicate that they require more intensive PM monitoring and therapeutic management, in particular strengthening of antihypertensive therapy.

CONCLUSIONS

1. DDD/DDDR and VVI/VVIR pacemaker implantation, increasing to a greater extent initially normal and less - an elongated QTc interval duration, to 6 months period leads them to the same level of values in both QTc interval duration classes.

2. Increased QTc interval duration associated with higher SBP and longer QRS complex duration in DDD/DDDR mode, normal - with greater reduction ESV and EDV in DDD/DDDR and VVI/VVIR modes.

3. Patients with increased QTc interval duration after right ventricular PM implant-tation require more intensive monitoring and enhancing medication.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to investigate the relationship between QTc interval duration after right ventricular PM implantation and changes in functional parameters of blood circulation after correction of drug therapy in the class of prolonged QTc interval duration in late postoperative period.

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EFFECTIVENESS OF BIOFEEDBACK IN THE CLOSED LOOP OF HEART RATE VARIABILITY AND PACED BREATHING IN THE PATIENTS WITH SOMATOFORM AUTONOMIC DYSFUNCTION

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To study the effectiveness of biofeedback (BFB) in the closed loop of heart rate variability (HRV) and paced breathing in patients with somatoform autonomic dysfunction (SAD) 20 patients with SAD (14 women and 6 men, mean age 19,53 ± 1,55) were examined. All probationers were divided into two groups comparable for sex and age: 1 - BFB group (15 patients), in which 7 sessions was held and 2 - the comparison group (5 patients), where only two sessions were completed -at the first and seventh day of the study. Additionally, all patients in both groups received diet food (Table № 10 by Pevzner), mebicar, glycine, tiotriazolin. Effectiveness of biofeedback was evaluated by comparing of parameters optimality (O), sensitivity (S), the efficiency (E) and the integral index BQI in both groups. It was determined that biofeedback in the closed loop of HRV and paced breathing allows to optimize the state of the regulatory systems of the body in patients with SAD, moreover the combination of biofeedback sessions in the test loop and medical treatment are significantly better than isolated pharmacological therapy. High effectiveness of biofeedback in closed loop of HRV and paced breathing in patients with SAD allows us to recommend it as independent method of treatment, and as a component of combined therapy of this disease.

KEY WORDS: somatoform autonomic dysfunction, biofeedback, heart rate variability, paced breathing

ЕФЕКТИВНІСТЬ БІОЛОГІЧНОГО ЗВОРОТНЬОГО ЗВ'ЯЗКУ В ЗАМКНУТОМУ КОНТУРІ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І МЕТРОНОМІЗОВАНОГО ДИХАННЯ У ПАЦІЄНТІВ ІЗ СОМАТОФОРМНОЮ ВЕГЕТАТИВНОЮ ДИСФУНКЦІЄЮ

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Для вивчення ефективності біологічного зворотного зв'язку (БЗЗ) в замкнутому контурі варіабельності серцевого ритму (ВСР) і метрономізованого дихання у пацієнтів з соматоформною вегетативною дисфункцією (СВД) було обстежено 20 пацієнтів із СВД (14 жінок і 6 чоловіків, середній вік 19,53 ± 1,55 років). Всіх випробуваних розділили на 2 групи, відповідні за статтю та віком: 1 – група БОС (15 пацієнтів), в якій було проведено 7 сеансів, і 2 - група порівняння (5 пацієнтів), де було виконано тільки два сеанси – у перший та сьомий день дослідження. Крім того, всі пацієнти обох груп отримували дієтичне харчування (стіл № 10 по Певзнеру), мебікар, гліцин, тіотриазолін. Ефективність біологічного зворотного зв'язку оцінювали шляхом порівняння значень показників оптимальності (О), чутливості (S), ефективності (Е) та інтегрального індексу BQI в обох групах пацієнтів. Встановлено, що БОС у замкнутому контурі ВСР і метрономізованого дыхання дозволяє оптимізувати стан регуляторних систем організму у пацієнтів з СВД, більш того комбінація сеансів БОС у досліджуваному контурі і медикаментозного лікування значно перевершує по ефективності ізольовану медикаментозну терапію. Висока ефективність БОС у замкнутому контурі ВСР і метрономізованого дихання у пацієнтів з СВД дозволяє рекомендувати її і як самостійний засіб лікування, і як компонент комплексної терапії при даному захворюванні.

КЛЮЧОВІ СЛОВА: соматоформна вегетативна дисфункція, біологічний зворотний зв'язок, варіабельність серцевого ритму, метрономізоване дихання

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В ЗАМКНУТОМ КОНТУРЕ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА И МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ У ПАЦИЕНТОВ С СОМАТОФОРМНОЙ ВЕГЕТАТИВНОЙ ДИСФУНКЦИЕЙ

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Для изучения эффективности биологической обратной связи (БОС) в замкнутом контуре вариабельности сердечного ритма (ВСР) и метрономизированного дыхания у больных с соматоформной вегетативной дисфункцией (СВД) было обследовано 20 пациентов с СВД (14 женщин и 6 мужчин, средний возраст 19,53 ± 1,55). Всех испытуемых разделили на 2 группы, сопоставимые по полу и возрасту: 1 – группа БОС (15 пациентов), в которой было проведено 7 сеансов и 2 - группа сравнения (5 пациентов), где выполнено только два сеанса – в первый и седьмой день исследования. Кроме того, все пациенты обеих групп получали диетическое питание (стол № 10 по Певзнеру), мебикар, глицин, тиотриазолин. Эффективность биологической обратной связи оценивали путем сравнения значений показателей оптимальности (О), чувствительности (S), эффективности (Е) и интегрального индекса BQI в обеих группах пациентов. Установлено, что БОС в замкнутом контуре ВСР и метрономизированного дыхания позволяет оптимизировать состояние регуляторных систем организма у пациентов с СВД, более того комбинация сеансов БОС в исследуемом контуре и медикаментозного лечения значительно превосходит по эффективности изолированную фармакологическую терапию. Высокая эффективность БОС в замкнутом контуре ВСР и метрономизированного дыхания у пациентов с СВД позволяет рекомендовать ее и как самостоятельное средство лечения, и как компонент комплексной терапии при данном заболевании.

КЛЮЧЕВЫЕ СЛОВА: соматоформная вегетативная дисфункция, биологическая обратная связь, вариабельность сердечного ритма, метрономизированное дыхание

INTRODUCTION

According to the results of studies in recent years, wide spread, especially in young and middle-aged persons, have received various functional disorders of the cardiovascular system [1, 2]. In 32-50 % of cases they are implemented in the form of somatoform autonomic dysfunction (SAD), which today is characterized as a polietiologic functional disease of the cardiovascular system with neurogenic nature, based on the failure of adaptation of the regulatory systems of the body, which is manifested by a variety of clinical syndromes (neurologic, cerebrovascular, cardiac, respiratory, peripheral vascular), and their combinations [3, 4].

The main therapeutic measures in this disease is the use of various programs of autogenic therapy (construction of visual imagery, positive thinking) [5, 6] and relaxation (diaphragmatic breathing, muscle relaxation) [6, 7], aimed at restoring the balance of regulation, sometimes complemented by drug therapy [7].

A perspective treatment for patients with SAD can be biofeedback (BFB) in the closed loop of heart rate variability (HRV) and paced breath with the start from free breathing, which has established itself as an effective mean of restoring the balance of regulatory systems of the body in healthy people [8, 9] and patients with arterial hypertension [10].

Since there is no data in the literature about the effectiveness of the proposed method of biofeedback in patients with SAD, and the question of treatment of this disease is still relevant [11, 12], we decided to perform this work.

The study was performed as a part of research KNU «Development and research of system of automatic control heart rate variability», № registration 0109U000622.

OBJECTIVE

The purpose of this study is to evaluate the effectiveness of biofeedback sessions in the closed loop of HRV and paced breathing with the start from free breathing in patients with SAD.

MATERIALS AND METHODS

The study involved 20 patients with SAD (14 women and 6 men, average age 19,53 ± 1,55). Inclusion criteria according to patients' complaints are false angina, anxiety, labile blood pressure, tachycardia, hyperaemia or skin cover pallor, palpitations, dissatisfaction breath, weakness, fatigue, headache, cold extremities in the absence of confirmed organic reasons of their causes, matching the results of laboratory and instrumental study age norm.

According to the objective of the study all patients were divided into 2 groups: 1 - BFB group (15 patients), 2 - the comparison group (5 patients). In group 1 seven daily sessions of BFB in the closed loop of HRV and paced breathing with the start from free breathing were held, in group 2 only two sessions in the first and seventh day of treatment were held.

Additionally, all patients in both groups received diet food (Table № 10 by Pevzner),

mebicar 300 mg three times a day, glycine 100 mg three times a day and tiotriazolini 4 ml once a day.

BFB sessions were held on a computer diagnostic complex «CardioLab 2009» («HAI-Medica») containing a special module «Biofeedback», consisting of software-related visual and sound metronome of breathing and the algorithm for determining the parameters of HRV.

HRV parameters were determined in the sliding buffer for a period of 1 minute by the dynamic spectral decomposition through the fast Fourier transform of lengths sequence of RR-intervals of monitor ECG records in the first standard lead with a sampling rate of 1000 Hz signal. All calculations was made in real time scale within the 7 minute session. Among HRV parameters powers of low frequency (V, 0.05 Hz), medium frequency (L, 0,05-0,15 Hz) and high frequency (H, 0,15-0,40 Hz) were evaluated, which then were converted into two-dimensional coordinate plane with axes L/H and V/(L + H), by corresponding powers of sympathovagal and neurohumoral regulation links [13].

In the first two minutes the adaptation algorithm initialization of module «Bio-feedback» was took place, research subjects were breathing in the familiar for them rhythm, then for each subsequent minute specific frequency of paced breathing by visual and sound metronome frequency tuning was set. Adaptation algorithm was consisted of the automatic search for such a breaching frequency at which the current values of L/H and V/(L + H) was approached as close as possible to the optimum zone [14].

Efficiency of BFB use was evaluated on the basis of proposed in [9] parameters of optimality (O), sensitivity (S), efficiency (E) and integral index BQI, which was calculated using MathCAD 15 in optimization algorithms in general (D), and in each of its phase space coordinates (L/H, V/(L + H)).

Statistical processing of results was performed in the program «Microsoft Excel 2003». Data of average values (M) and standard deviations (sd) of parameters O, S, E for indicators D, L/H, and V/(L + H) of the first and seventh sessions in both groups were recorded in the table.

Authenticities of differences between groups on the stages of the study and between the values of the index at the current stage and before treatment were determined by using of T-Wilcoxon test [15].

RESULTS AND DISCUSSION

Values of indicators O, S, E for D, L / H, V / (L + H) at 1 and 7 sessions in both groups are shown in the table.

Table

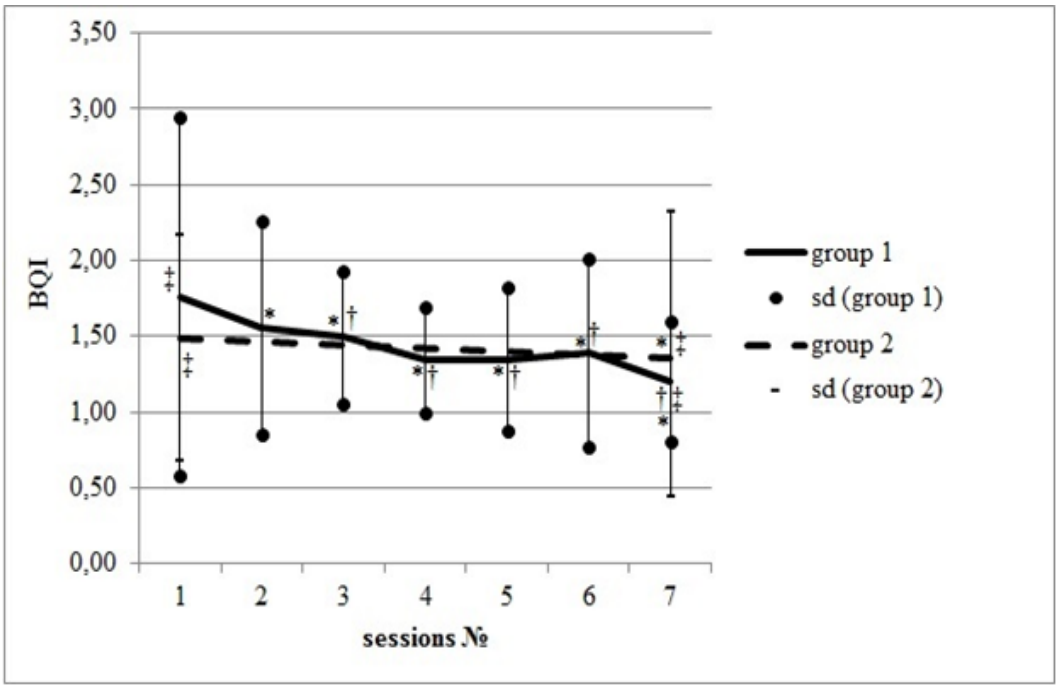
Values of indicators O, S, E for D, L / H, V / (L + H) at 1 and 7 sessions in both groups (M ± sd)

Parameters		Group 1		Group 2	
		1 session	7 session	admission	discharge
D	O	-4,09 ± 7,12	1,07 ± 2,60†	-0,90 ± 1,10*	-3,34 ± 6,53*†
	S	0,76 ± 0,41	0,77 ± 0,33†	0,41 ± 0,28*	0,49 ± 0,35*†
	E	0,05 ± 0,08	0,22 ± 0,25†	0,16 ± 0,21*	0,16 ± 0,22*†
L/H	O	-28,47 ± 61,56	-3,88 ± 8,11‡	-1,95 ± 2,96**	-12,46 ± 24,93**‡
	S	4,97 ± 1,60	5,78 ± 1,82†	4,49 ± 2,62*	5,32 ± 3,52*†
	E	0,82 ± 0,40	0,98 ± 0,02†	0,78 ± 0,44*	0,80 ± 0,45*†
V/(L+H)	O	-2,15 ± 1,04	-1,85 ± 0,98†	-1,67 ± 0,94*	-1,87 ± 1,26*†
	S	0,41 ± 0,26	0,40 ± 0,26†	0,33 ± 0,22*	0,37 ± 0,50*†
	E	0,07 ± 0,06	0,18 ± 0,13†	0,06 ± 0,13*	0,04 ± 0,08*†

Notes: * - P > 0.05 according to the indicator at the stage between the groups;
** - P < 0.05 according to the indicator at the stage between the groups;
† - P > 0.05 according to the indicator in the group against initial value;
‡ - P < 0.05 according to the indicator in the group against initial value.

Systematic BFB sessions at the same drug therapy promote better optimization of the studied parameters when they have almost identical initial values in compared series.

BQI index dynamics on all research subjects in both groups is shown in the Figure.



Notes:
* - P < 0.05 at the sessions against initial values within a group;
† - P > 0.05 in neighbouring sessions in group 1;
‡ - P > 0.05 between groups at the current session.

Systematic BFB sessions in group 1 promoted logical BQI index approximation to the optimum level, while in group 2 it remained unchanged against the values at admission.

SAD is a group of disorders that occur themselves as symptoms of internal organs or organ systems damage, however, do not have objectively recorded basis [11]. Most effective in the treatment of this condition are different neurophysiological trainings, allowing to restore the balance of the autonomic nervous system [5-7].

We have previously shown [9, 10] that an effective means of optimizing the balance of sympathovagal and neurohumoral regulation in healthy volunteers and patients with hypertension is biofeedback in the loop of paced breathing under the control of HRV parameters. As in the literature we could not find data on the effectiveness of the proposed technique in patients with SAD, this work was done.

Obtained results confirm the ability to optimize the state of the regulatory systems of the patients' body with SAD through BFB sessions in a closed loop of HRV and paced breathing with the start from free breathing. Moreover, the combination of BFB sessions and drug treatment is significantly superior in effectiveness of the isolated pharmacological therapy.

In accordance with the obtained results, BFB in a closed loop of HRV and paced breathing should be considered as an important tool for correction of the regulatory systems condition in patients with SAD as an independent means of treatment, and as a component of a complex therapy.

CONCLUSIONS

1. Biofeedback in a closed loop of heart rate variability and paced breathing allow to optimize the regulatory systems condition of the body in patients with somatoform autonomic dysfunction.

2. Combination of biofeedback sessions and drug treatment is significantly superior in effectiveness of the isolated pharmacological therapy

3. The effectiveness of biofeedback in a closed loop of heart rate variability and paced breathing allows us to recommend it as an independent means of treatment and as a component of complex therapy for patients with somatoform autonomic dysfunction.

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ANALYSIS OF BLOOD LOSS AFTER VENTRAL AND POSTERIOR CORRECTIVE SPINAL FUSION IN PATIENT WITH IDIOPATHIC SCOLIOSIS

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It was prospective analysis of 36 patients with idiopathic scoliosis in order to compare the intraoperative and early postoperative blood loss after ventral and posterior corrective spinal fusion. All patients were divided into two groups: group 1 - 18 patients (14 females and 4 males) with a mean age of 17,2 ± 3,4 years treated with ventral corrective spinal fusion and group 2 - 18 patients (17 females and 1 male) with a mean age of 15,9 ± 3,4 years with posterior corrective spinal fusion. Mean values and standard deviation of the time of surgery, intraoperative blood loss, transfusion volume, hemoglobin, blood volume loss and drainage loss and number of fused spinal levels were evaluated. The results were compared using the Mann-Whitney test ($p \leq 0,05$). It was found that group 1 had a lower intraoperative blood loss, the average volume of blood transfusion and blood loss drain in the early postoperative period compared with group 2. It was concluded that ventral corrective spinal fusion is associated with less intraoperative and early postoperative blood loss which is probably due to the less traumatic access and length of the spine instrumentation.

KEY WORDS: idiopathic scoliosis, ventral corrective spinal fusion, posterior corrective spinal fusion, blood loss

АНАЛІЗ КРОВОВТРАТИ ПІСЛЯ ВЕНТРАЛЬНОГО ТА ЗАДНЬОГО КОРИГУВАЛЬНОГО СПОНДИЛОДЕЗУ У ХВОРИХ НА ІДІОПАТИЧНИЙ СКОЛІОЗ

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Проведено проспективний аналіз 36 хворих ідіопатичним сколіозом з метою порівняння інтраопераційної і ранньої післяопераційної крововтрати після вентрального і заднього коригуючого спондилодеза. Всі пацієнти були розділені на дві групи: група 1 - 18 осіб (14 жіночої і 4 чоловічої статі) з середнім віком 17,2 ± 3,4 років, яким було проведено вентральний коригувальний спонділодез і група 2 - 18 осіб (17 жіночої та 1 чоловічої статі) з середнім віком 15,9 ± 3,4 років, яким виконаний задній коригувальний спонділодез. Визначали середні показники та стандартне відхилення тривалості хірургічного втручання, інтраопераційної крововтрати, об'єму гемотрансфузії, рівню гемоглобіну, об'єм втрати дренажної крові та кількості фіксованих імплантатом рівнів. Отримані результати порівнювали за допомогою критерію Манна-Уітні ($p \leq 0,05$). Було встановлено, що в групі 1 відзначалися менші інтроопераційна крововтрата, середній обсяг гемотрансфузії і втрати дренажної крові в ранньому післяопераційному періоді в порівнянні з групою 2. Таким чином, проведення вентрального коригувального спондилодеза супроводжується меншою інтра- і ранню післяопераційною крововтратою, що, імовірно, пов'язано із меншою травматичністю доступу і більшою протяжністю інструментації хребта.

КЛЮЧОВІ СЛОВА: ідіопатичний сколіоз, вентральний спондилодез, задній спондилодез, крововтрата

АНАЛИЗ КРОВОПОТЕРИ ПОСЛЕ ВЕНТРАЛЬНОГО И ЗАДНЕГО КОРРИГИРУЮЩЕГО СПОНДИЛОДЕЗА У БОЛЬНЫХ ИДИОПАТИЧЕСКИМ СКОЛИОЗОМ

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Проведен проспективный анализ 36 больных идиопатическим сколиозом с целью сравнения интраоперационной и ранней послеоперационной кровопотери после вентрального и заднего

корригирующего спондилодеза. Все пациенты были разделены на две группы: группа 1 – 18 человек (14 женского и 4 мужского пола) со средним возрастом 17,2 ± 3,4 лет, которым был проведен вентральный корригирующий спондилодез и группа 2 – 18 человек (17 пациентов женского и 1 мужского пола) со средним возрастом 15,9 ± 3,4 лет, которым выполнен задний корригирующий спондилодез. Определяли средние показатели и стандартное отклонение длительности хирургического вмешательства, интраоперационной кровопотери, объема гемотрансфузии, уровня гемоглобина, объема потери дренажной крови и количества фиксированных имплантатом уровней. Полученные результаты сравнивали с помощью критерия Манна-Уитни ($p \leq 0,05$). Было установлено, что в группе 1 отмечались меньшие интраоперационная кровопотеря, средний объем гемотрансфузии и потери дренажной крови в раннем послеоперационном периоде по сравнению с группой 2. Таким образом, проведение вентрального корригирующего спондилодеза сопровождается меньшей интра - и ранней послеоперационной кровопотерей, что, вероятно, связано з меньшей травматичностью доступа и протяженностью инструментации позвоночника.

КЛЮЧЕВЫЕ СЛОВА: идиопатический сколиоз, вентральный спондилодез, задний спондилодез, кровопотеря

INTRODUCTION

Surgery on the spine which aims spinal deformity correction involves significant blood loss. Development of new methods of prevention and the use of current generation hemostatic agents allow reducing intraoperative blood loss, but is not possible to prevent blood transfusion completely [1]. Blood transfusion increases the risk of postoperative complications such as transmission of infectious diseases, the post hemotransfusion reactions development, immune system dysfunction and acute lung injury [2].

Risk factors for significant intraoperative blood loss are concomitant blood disorders, cardiovascular and respiratory system comorbiddities, the degree of deformity, prolonged surgery, traumatic surgical approach, and greater number of the instrumented vertebras [3].

In terms of risk factors prevention that are directly related to the surgery, the use of ventral corrective spinal fusion theoretically reduces intraoperative blood loss in the virtue of less fixation length, lesser degree of muscle injury during surgical approach in comparison to posterior corrective spinal fusion. There is lack of research [4, 5] in the contemporary scientific literature, which compare the degree of blood loss after ventral corrective fusion (VCF) versus posterior corrective fusion (PCF) in patients with idiopathic scoliosis that makes this research relevant.

OBJECTIVE

Purpose of the study is to conduct comparative analysis of intraoperative and early postoperative blood loss in patients with idiopathic scoliosis after ventral and posterior corrective spinal fusion.

MATERIALS AND METHODS

The study has been performed at SE «Sytenko Institute of Spine and Joint Pathology, AMSU» within the research work «To define criteria for selecting the method of instrumental ventral spinal fusion for scoliosis correction» (№ state registration 0111U010382). Study design - prospective, comparative.

To perform the study, 36 patients operated for idiopathic scoliosis in pediatric orthopedics departments of Sytenko Institute and National specialized children hospital Okhmatdyt were selected. The inclusion criteria in the study were: the presence of thoracic or thoracolumbar idiopathic scoliosis (Lenke 1A type and 5C), age over 12 years, patients who underwent VCF and PCF. Exclusion criteria were: blood disorders, congenital and acquired chronic diseases of the cardiovascular system, respiratory insufficiency grade 3 (vital capacity less than 65 % of predicted). Depending on the type of surgery, patients were divided into two groups (18 patients each). The first group included 14 female patients and 4 male in the mean age of 17,2 ± 3,4 years. In the second group there were 17 females and 1 male. The mean age of this group was 15,9 ± 3,4 years. Index Cobb angle of the main curve before the surgery was 49º ± 7,9º in the first group and 53º ± 8,7º - in the second, and after the surgery 18,9º ± 6,7º and 11,5º ± 6,7º respectively.

During the study, we analyzed the average duration of the surgery, intraoperative blood loss, transfusion volume, hemoglobin levels before, immediately after and 3 days posto-

peratively. Also were determined the amount of drainage blood loss 3 days after the surgery and number of fused spinal levels. After VCS chest tube was placed for passive and active drainage of the pleural cavity, and after PCF - direct active wound drainage was used.

Indications for blood transfusion considered reducing hemoglobin less than 80 g / dL, hematocrit less than 25 %, and clinical signs of anemia (pale skin and mucous membranes, tachycardia, systolic murmur, etc.). As hemostatics all patients received tranexamic acid intravenously at a dose of 10 mg/kg at the beginning and 6 hours after surgery.

Mathematical testing of the obtained data was performed using Statistical Package IBM, parameters mean values and standard deviation (M ± sd) were calculated using the software. We used Mann-Whitney test ($p \leq 0,05$) to compare average time of surgery, intraoperative blood loss volume and blood transfusion, hemoglobin levels and the volume of blood drainage output between the groups.

RESULTS AND DISCUSSION

The table presents the average values in both groups of patients.

In the first group of patients preoperative hemoglobin index was 130,7 ± 7,6 g / l on the average, immediately after surgery it decreased to 119,2 ± 19,8 g / l, and on the third postoperative day it was 105.5 ± 12,7 g / l. Mean blood loss in VCF patients during surgery was 514,3 ± 42,6 ml , and duration of surgery was 345,7 ± 39,1 min. on the average. The total volume drainage blood output for the first three postoperative days was 630 ± 275,3 ml on the average. Hemotransfusion performed in one patient from the VCF group. Therefore, the average volume of transfused blood was 18,9 ± 73,1 ml. The average length of fixation was 4.8 spinal segments.

In the second group of patients mean preoperative hemoglobin was 138,1 ± 8,1 g/l, immediately after PCF - 108,5 ± 19,1 g/l and 101,7 ± 13,3 g/l three days postoperatively. Surgery duration was 276,7 ± 30,1 min on the average, estimated blood loss was 710,5 ± 58,7. In this group mean drainage blood loss was 858,2 ± 312,7 ml in the early postoperative period. Transfusion avoided in 2 patients only, and its average volume for the 2nd group was 243,9 ± 129,3 ml. Mean instrumentation length was 9.4 vertebras.

Table 1

Analyzed data of the patients from 1st and 2nd groups

Parameters	1st group		2nd group		P (Mann-Whitney test)
	M	sd	M	sd	
Hb preop, g/l	130,73	7,59	138,11	8,076	0,021
Hb postop, g/l	119,2	19,83	108,58	19,18	0,15
Hb 3 days postop, g/l	105,5	12,74	101,64	13,36	0,38
Duration , min.	345,66	39,1	276,66	30,09	0,245
Drainage output, ml	630	275,31	858,23	312,47	0,078
Hemotransfusion, ml	18,86	73,07	243,88	129,27	0,00007
Blood loss, ml	514,3	42,6	710,54	58,7	0,368

Comparing obtained data between groups showed that there were no statistically significant differences between mean hemoglobin values after surgery and on the third postoperative day. Intraoperative blood loss in PCF patients was higher by 26.6 % compared to patients after VCF, at the same time ventral spinal fusion took 20 % more time than posterior. Drainage blood loss was lower by 26.5 %, and the hemotransfused blood volume was statistically significantly lower in the first group by 92.2 % (fig.1).

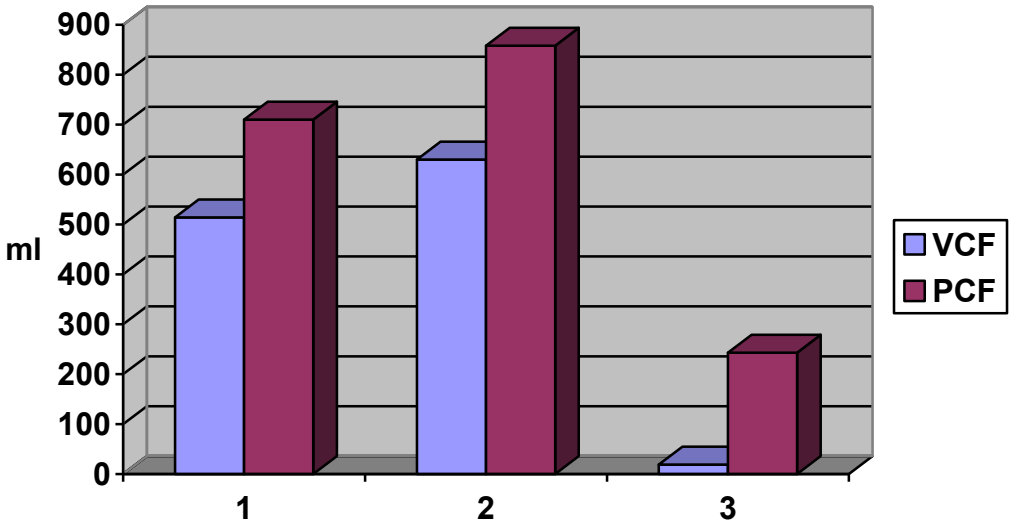

Fig. 1 Graphs of intraoperative blood loss (1), drainage blood loss (2), hemotransfusion volume (3) in VCF and PCF groups.

Significant blood loss during surgery is a serious complication that affects the quality of treatment of the spinal deformity. Modern blood salvage strategies involve measures that begins at the prehospital stage. All these measures are sufficiently effective and have certain advantages and disadvantages. Thus, the most effective is the maximum possible reduction of the surgical trauma [6].

We compared intra- and postoperative blood loss in patients with idiopathic scoliosis after short-segment VCF and selective PCF. We found that despite the greater duration of the ventral spinal fusion intraoperative blood loss was greater in patients after transpedicular fixation, due to the need of massive layer of back muscles dissection when performing posterior approach, and with the greater length of spinal fusion length. This fact can also be explained by higher volumes of drainage blood loss in the first three days after surgery in patients from the second group. Same hemoglobin values during the observation period indicate adequacy of blood salvage measures in patients from both groups, during surgery as well as in the postoperative period.

CONCLUSIONS

1. Ventral corrective spinal fusion in comparison to posterior corrective spinal fusion allows reducing intraoperative and early postoperative blood loss in idiopathic scoliosis patients.
2. In our study, application of the ventral spinal fusion for the spinal deformity correction significantly reduced the volume of blood transfusion.
3. Main factors affecting the degree of blood loss during surgery and in the early postoperative period are the type of surgical approach, fixation length, and therefore the size of the bone wound.

PROSPECTS FOR FUTURE STUDIES

Future studies should be directed to the optimization of blood salvage procedures and application of pharmaceutical agents for reducing blood loss after posterior scoliosis surgery.

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FUNCTIONAL BLOOD CIRCULATION VALUES IN PATIENTS WITH IMPLANTED PACEMAKERS IN THE FIRST SIX MONTHS OF PERMANENT PACING IN DIFFERENT STIMULATED QRS COMPLEX DURATION CLASSES

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In the department of ultrasound, clinical and instrumental diagnosis and minimally invasive technologies 100 patients (46 – women, 54 – men) who underwent permanent pacemaker therapy were examined. The average age was 69 ± 7 years. The indications for pacemaker implantation were: atrio-ventricular block of varying degrees – 66 people (60 %), sick sinus syndrome – 34 patients (30 %). Patients were divided to three classes of QRS complex duration in accordance with Haghjoo M. et al.: 1 – under 119 ms (normal), 2 − 120-149 ms (extended) and more than 150 ms (significantly extended). Permanent pacing with medical support in the first 6 months results in the elimination bradyarrhythmia rhythm disorders without significant changes of functional blood circulation values with systolic blood pressure increase only. Standard antihypertensive therapy consisting of medical support in patients with implanted pacemaker is sufficient to control systolic blood pressure in patients in classes 1 and 2 and insufficient – in class 3 of QRS complex duration. Patients with implanted pacemaker in 3 QRS complex duration class require intensification of antihypertensive therapy.

KEY WORDS: permanent pacing, QRS complex duration, functional blood circulation

ФУНКЦІОНАЛЬНІ ПОКАЗНИКИ КРОВООБІГУ У ПАЦІЄНТІВ ІЗ ІМПЛАНТОВАНИМИ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРАМИ В ПЕРШІ 6 МІСЯЦІВ ПОСТІЙНОЇ ЕКС У РІЗНИХ КЛАСАХ ТРИВАЛОСТІ СТИМУЛЬОВАНОГО QRS КОМПЛЕКСУ

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У відділенні ультразвукової та клініко-інструментальної діагностики та мініінвазивних втручань були обстежені 100 пацієнтів (46 − жінок, 54 − чоловіків) з імплантованими електрокардіостимуляторами (ЕКС). Средній вік становив 69 ±7 років. Показаннями для імплантації ЕКС були: атріовентрикулярна блокада різних ступенів − 66 пацієнтів (60 %), синдром слабкості синусового вузла − 34 пацієнта (40 %). Пацієнти були розділені на три класи тривалості QRS комплексу відповідно до Haghjoo M. та ін: 1 − до 119 мс (нормальний), 2 − 120-149 мс (подовжений), 3 − 150 і більше мс (значно подовжений). Постійна електрокардіостимуляція з медикаментозною підтримкою в перші 6 місяців призводить до усунення брадіарітміческіх порушень ритму поза істотних змін встановлених до неї функціональних показників кровообігу з підвищенням тільки систолічного артеріального тиску. Стандартна антигіпертензивна терапія у складі медикаментозної підтримки пацієнтів з імплантованими ЕКС виявляється достатньою для контролю систолічного артеріального тиску у пацієнтів у класах 1 і 2 та недостатня − в класі 3 тривалості QRS комплексу. Пацієнти з імплантованими ЕКС з класу 3 тривалості QRS комплексу вимагають інтенсифікації артігіпер-тензівной терапії.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, тривалість QRS комплексу, функціональні показники кровообігу

ФУНКЦИОНАЛЬНЫЕ ПОКАЗАТЕЛИ КРОВООБРАЩЕНИЯ У ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРАМИ В ПЕРВЫЕ ШЕСТЬ МЕСЯЦЕВ ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИИ В РАЗНЫХ КЛАССАХ ПРОДОЛЖИТЕЛЬНОСТИ СТИМУЛИРОВАННОГО QRS КОМПЛЕКСА

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В отделении ультразвуковой и клинико-инструментальной диагностики и миниинвазивных вмешательств были обследованы 100 пациентов (46 – женщин, 54 – мужчин) с имплантированными электрокардиостимуляторами (ЭКС). Средний возраст составлял 69 ± 7 лет. Показаниями для имплантации ЭКС являлись: атрио-вентрикулярные блокады различных степеней – 66 пациентов (60 %), синдром слабости синусового узла – 34 пациента (40 %). Пациенты были разделены на три класса продолжительности QRS комплекса в соответствии с Haghjoo M. и др.: 1 – до 119 мс (нормальный), 2 − 120-149 мс (удлиненный), 3 – 150 и более мс (значительно удлиненный). Постоянная электрокардиостимуляция с медикаментозной поддержкой в первые 6 месяцев приводит к устранению брадиаритмических нарушений ритма вне существенных изменений установленных до нее функциональных показателей кровообращения с повышением только систолического артериального давления. Стандартная антигипертензивная терапия в составе медикаментозной поддержки пациентов с имплантированными ЭКС оказывается достаточной для контроля систолического артериального давления у пациентов в классах 1 и 2 и недостаточна − в классе 3 продолжительности QRS комплекса. Пациенты с имплантированными ЭКС из класса 3 продолжительности QRS комплекса требуют интенсификации артигипертензивной терапии.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, продолжительность QRS комплекса, функциональные показатели кровообращения

INTRODUCTION

Permanent pacing is the primary treatment in patients with significant bradyarrhythmias, in which rhythm slowing is associated with life-threatening hemodynamic disturbances [1, 2].

Functional blood circulation values monitoring on the follow-up periods is one of the major challenges for evaluating the effectiveness of permanent pacing with its medical support [3, 4].

Moreover, in patients with permanent pacing, QRS complex duration is associated with changes of functional blood circulation values [5−8], their relationship was not been studied until nowadays.

OBJECTIVE

The purpose of this study to assess the functional blood circulation values in patients with implanted pacemakers in the first 6 months of permanent pacing taking into account the QRS complex duration classes.

MATERIALS AND METHODS

100 patients (46 – women, 54 – men) who underwent permanent pacemaker therapy were examined in the department of ultrasound, clinical and instrumental diagnosis and minimally invasive technologies SI «Zaitsev V.T. Institute of General and Emergency Surgery NAMS of Ukraine». The average age was 69 ± 7 years. The indications for pace-maker implant-tation were: atrio-ventricular block of varying degrees (AV block) – 66 people (60 %), sick sinus syndrome (SSS) – 34 patients (30 %).

Before, in the early postoperative period (the third - fifth day after pacemaker implantation) and 6 months later was evaluated ventricular contractions (VC) spontaneous and induced rhythm, QRS complex duration; systolic (SBP) and diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), end-diastolic (EDV) and end-systolic (ESV) volumes, the thickness of the interventricular septum (IVS) and posterior wall (PW), left (LA) and right atrium (RA), right ventricular (RV) dimensions.

SBP and DBP were measured by Korotkov's method according to the recommendations of the Association of Cardiologists of Ukraine for the prevention and treatment of hypertension by tonometer Microlife BP AG1- 20 in clinostaze after 5 minutes rest. The measurement accuracy was 2 mm Hg.

Electrocardiogram (ECG) was performed on a computer electrocardiograph Cardiolab

+2000. The stimulated QRS complex duration was measured in leads II, V5, V6 (the average of three consecutive complexes) with a choice of maximum value. Measurement accuracy proved to be 1 mc.

Patients were divided to three QRS complex duration classes in accordance with Haghjoo M. et al: 1 – under 119 ms (normal), 2 − 120-149 ms (extended) and more than 150 ms (significantly extended). In selected classes defined functional blood circulation values.

Echocardiography study was conducted on the ultrasound machine Toshiba Applio 400. LF, RF, RV sizes and IVS, PW thickness was measured. To calculate the EDV and ESV used method of Simpson. LV EF was calculated using the formula EF = (EDV - ESV) / EDV * 100 %.

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

The data were brought into the Microsoft Excel base. For statistical evaluation of the results were used the parametric criteria (the mean – M, the average deviation – sd). The probability of differences between groups was determined using a non-parametric U-Mann-Whitney test. The likely result is determined by the level of reliability $p < 0.05$.

RESULTS AND DISCUSSION

Table 1 shows the comparative characteristics of functional blood circulation values in patients in different QRS complex duration classes before implantation in the early postoperative period and 6 months.

Table 1

Functional blood circulation values in patients with permanent pacemakers in different QRS complex duration classes, (M ± sd)

Functional blood circulation values		QRS complex duration, ms								
		Under 119 ms			120-149 ms			150 and more ms		
		Before	Early postoperative period	6 months later	Before	Early postoperative period	6 months later	Before	Early postoperative period	6 months later
VC, (1/min)		52 ± 11	68 ± 6*	64 ± 3	46 ± 8	71 ± 11*	69 ± 7	46 ± 9	68 ± 7*	70 ± 7
Blood pressure (mm Hg)	**SBP**	150 ± 15	154 ± 17	140 ± 27	140 ± 15	139 ± 16	124 ± 14	153 ± 18	151 ± 19	144 ± 25
	DBP	82 ± 6	89 ± 9	80 ± 7	81 ± 9	83 ± 10	84 ± 9	79 ± 7	87 ± 9	85 ± 17
Echo values	**LVEF (%)**	53 ± 10	54 ± 11	65 ± 8	47 ± 8	53 ± 8	50 ± 9	50 ± 6	47 ± 8	55 ± 12
	ESV (ml)	63 ± 28	59 ± 26	52 ± 11	70 ± 31	58 ± 22	66 ± 19	83 ± 35	81 ± 36	102 ± 64
	EDV (ml)	135 ± 44	127 ± 29	148 ± 16	133 ± 29	122 ± 24	132 ± 27	166 ± 35	153 ± 48	227±129
	IVS (sm)	1.2 ± 0.1	1.2 ± 0.1	1.0 ± 0.2	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
	PW LV (sm)	0.9 ± 0.1	0.9 ± 0.1	1.2 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
	LA (sm)	4.9 ± 0.6	4.8 ± 0.6	4.5 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.8 ± 0.6	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5
	RA (sm)	4.8 ± 1.0	4.8 ± 1.0	4.5 ± 1.0	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.5	4.6 ± 0.6
	RV (sm)	3.0 ± 0.4	3.0 ± 0.4	3.0±0.4	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.7	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.9

Notes:
* $p < 0.05$ — the level of significance of differences between values on the observation periods

In patients with permanent pacemaker in all QRS complex duration classes, VC was initially below the physiological norm, and after pacemaker implantation reached to the normal level ($p < 0.05$), which remained the whole observation period.

High baseline SBP in patients decreased more pronounced in 1 and 2 QRS complex duration classes, and less – in class 3. DBP on all follow-up periods in all QRS complex duration classes was on the physiological range.

Pacemaker implantation had no influence on the ESV and EDV, which were initially normal in classes 1 and 2, and an increase in class 3. Accordingly, LVEF after pacemaker implantation was not changed.

Pacemaker implantation did not affect on the IVS and PWLV thicknesses in selected QRS complex duration classes, and it has remained unchanged whole observation period.

LA size was increased in all QRS complex duration classes before and after pacemaker implantation. Initially normal RA and RV sizes were not changed in all classes.

In accordance with the findings the permanent pacemaker implantation has led to the elimination of bradyarrhythmias, maintaining VC in normal range during 6-month period, what corresponds to [1, 2], in all QRS complex duration classes.

SBP reductions in toward the physiological level value reaches by antihypertensive control which was not sufficient, after all, in 3 QRS complex duration class patients.

A positive result of pacemaker implantation is the preservation of geometric and hemodynamic parameters of the heart, as well as DBP.

CONCLUSIONS

1. Permanent pacing with medical support in the first 6 months results in the elimination bradyarrhythmia rhythm disorders without significant changes of functional blood circulation values with systolic blood pressure increase only.
2. Standard antihypertensive therapy consisting of medical support in patients with implanted pacemaker is sufficient to control systolic blood pressure in patients in classes 1 and 2 and insufficient – in class 3 of QRS complex duration.
3. Patients with implanted pacemaker in 3 QRS complex duration class require intensification of antihypertensive therapy.

PROSPECTS FOR FUTURE STUDIES

It seems promising to further monitoring of functional blood circulation values to evaluate circulatory long-term results of permanent pacing and medical support.

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FUNCTIONAL BLOOD CIRCULATION VALUES IN PATIENTS WITH IMPLANTED PACEMAKERS AND CARDIAC RESYNCHRONIZATION THERAPY AFTER YEAR OF PERMANENT PACING IN DIFFERENT QRS COMPLEX DURATION CLASSES

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Functional blood circulation values were prospectively investigated in 100 patients (46 – women, 54 – men) with permanent pacemakers and in 29 patients (10 – women, 19 – men) – with cardiac resynchronization therapy (CRT) with mean age 69 ± 7 years in different observation stages taking into account QRS complex duration classes (class 1 – under 120 ms (normal), 2 – 120-149 ms (long) and 3 – more than 150 ms (significantly elongated)). Medication support was included beta-blockers; amiodarone; renin-angiotensin-aldosterone system inhibitors: angiotensin converting enzyme and angiotensin II inhibitors; antithrombotic agents; oral anticoagulants; statins and diuretics. Ventricular rate of spontaneous and stimulated rhythm; systolic and diastolic blood pressure; ejection fraction, end-diastolic and end-systolic volumes of the left ventricle; interventricular septum thickness and left ventricular posterior wall, right atria and ventricle sizes were evaluated. The results showed that QRS complex widening associated with greater deviation of functional blood circulation values from physiological norms. Permanent pacing with medical support had no significant impact on the functional blood circulation values, and CRT contributed reverse remodeling higher in class 3 of QRS complex duration. Also it was concluded that there is a necessity of medical support improvement.

KEY WORDS: permanent pacing, chronic heart failure, QRS complex duration

ФУНКЦІОНАЛЬНІ ПОКАЗНИКИ КРОВООБІГУ У ПАЦІЄНТІВ З ЕЛЕКТРОКАРДІОСТИМУЛЯТОРАМИ І КАРДІОРЕСІНХРОНІЗУЮЧОЮ ТЕРАПІЄЮ ЧЕРЕЗ РІК ПОСТІЙНОЇ ЕКС У РІЗНИХ КЛАСАХ ТРИВАЛОСТІ QRS

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Проспективно були вивчені функціональні показники кровообігу (ФПК) у 100 (46 – жінок, 54 – чоловіків) пацієнтів з електрокардіостимуляторами (ЕКС) і у 29 (10 – жінок, 19 – чоловіків) – з кардіоресінхронізуючою терапією (КРТ) у віці 69 ± 7 років з імплантованими електрокардіостимулятора (ЕКС) на річних етапах спостереження з урахуванням класів (1 клас – до 120 мс (нормальний), 2 – 120-149 мс (подовжений) і більше 150 мс (істотно подовжений)) тривалості QRS комплексу. Медикаментозний супровід включав бета-блокатори; аміодарон; інгібітори ренін-ангіотензин-альдостеронової системи: АПФ і рецепторів ангіотензину II; антитромботичні засоби; пероральні антикоагулянти; статини і діуретики. Оцінювали частоту шлуночкових скорочень спонтанного та стимульованого ритму, тривалість QRS комплексу; рівні систолічного і діастолічного артеріального тиску; фракцію викиду, кінцево-діастолічний і кінцево-систолічний об'єми лівого шлуночка; товщину міжшлуночкової перегородки і задньої стінки лівого шлуночка, розміри передсердь і правого шлуночка. Результати показали, що чим більше клас тривалості QRS комплексу, тим більше ухилення ФПК від фізіологічних нормативів. Ступінь їх сильніше при КРТ, ніж ЕКС. ЕКС з медикаментозною підтримкою не вплинула суттєво на ФПК, і КРТ сприяла їх зворотного ремоделюванню, більшого в класі 3 тривалості QRS комплексу. Робляться висновки про необхідність посилення медикаментозної підтримки.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, хронічна серцева недостатність, тривалість QRS комплексу

ФУНКЦИОНАЛЬНЫЕ ПОКАЗАТЕЛИ КРОВООБРАЩЕНИЯ У ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРАМИ И КАРДИОРЕСИНХРОНИЗИРУЮЩЕЙ ТЕРАПИЕЙ ЧЕРЕЗ ГОД ПОСТОЯННОЙ ЭКС В РАЗНЫХ КЛАССАХ ПРОДОЛЖИТЕЛЬНОСТИ QRS

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Проспективно были изучены функциональные показатели кровообращения (ФПК) у 100 (46 – женщин, 54 – мужчин) пациентов с имплантированными электрокардиостимуляторами (ЭКС) и у 29 (10 − женщин, 19 − мужчин) – с кардиоресинхронизирующей терапией (КРТ) в возрасте 69 ± 7 лет с имплантированными электрокардиостимуляторами (ЭКС) на годовом этапе с учетом классов (класс 1 – до 120 мс (нормальный), 2 – 120-149 мс (удлиненный) и более 150 мс (существенно удлиненный)) продолжительности QRS комплекса. Медикаментозное сопровождение включало бета-блокаторы; амиодарон; ингибиторы ренин-ангиотензин-альдостероновой системы: ангиотензинпревращающего фермента и рецепторов ангиотензина II; антитромботические средства; пероральные антикоагулянты; статины и диуретики. Оценивали частоту желудочковых сокращений спонтанного и стимулированного ритма; уровни систолического и диастолического артериального давления; фракцию выброса, конечно-диастолический и конечно-систолический объемы левого желудочка; толщину межжелудочковой перегородки и задней стенки левого желудочка, размеры предсердий и правого желудочка. Результаты показали, что чем больше класс продолжительности QRS комплекса, тем больше уклонения ФПК от физиологических нормативов. Степень их сильнее при КРТ, чем ЭКС. ЭКС с медикаментозной поддержкой не повлияла существенно на ФПК, и КРТ способствовала их обратному ремоделированию, большему в классе 3 продолжительности QRS комплекса. Делаются выводы о необходимости усиления медикаментозной поддержки.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, хроническая сердечная недостаточность, продолжительность QRS комплекса

INTRODUCTION

Permanent pacemaker implantation and cardiac resynchronization therapy (CRT) become one of the standards of skilled cardiac care nowadays, what is confirmed by an international roster of implantable devices EHRA White Book [1].

Increased frequency pacemaker implantation leads to a progressive increase in the number of persons in need, not only in monitoring effectiveness of this way of therapy, but also accompanied by adequate therapeutic management [2].

QRS complex duration relationship and functional circulation values changes in patients with permanent pacemaker and CRT in long-term observations were not wide studied [3-5].

OBJECTIVE

The purpose of the study − to assess functional blood circulation values in patients with implanted pacemaker and CRT at the annual stage taking into account QRS complex duration classes.

MATERIALS AND METHODS

100 patients (46 – women, 54 − men) with implanted pacemaker and 29 patients (10 – women, 19 − men) with CRT were examined in the department of ultrasound and clinical-instrumental diagnosis and minimally invasive interventions of SI «Zaytsev V.T. Institute of General and Emergency Surgery NAMS of Ukraine». Mean age was 69 ± 7 years. The indications for pacemaker implantation were atrio-ventricular block of various degrees (AV block) − 66 patients (60 %), sinus sick syndrome (SSS) − 34 patients (40 %). Single chamber (VVI − 40 devises) and double chamber devises (DDD − 60 devises) were implanted. The indications for CRT were chronic heart failure (CHF) NYHA functional class (FC) II-IV, QRS complex duration more than 120 ms, left ventricular ejection fraction (LVEF) ≤ 35 %. CRT-P and CRT-D devices were implanted.

Spontaneous and induced rhythm ventricular contractions, systolic (SBP) and diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), end-diastolic (EDV) and end-systolic (ESV) volumes, intervene-

tricular septum (IVS), posterior wall (PW) thicknesses, left (LA) and right atriums (RA), right ventricular (RV) sizes were evaluated before, in the early postoperative period (the third - fifth day), after 6 months and one year after pacemaker implantation.

SBP and DBP were measured by Korotkov's method according to the recommendations of the Association of Cardiologists of Ukraine for the prevention and treatment of hypertension by tonometer Microlife BP AG1 - 20 in clinostaze after 5 minutes rest. The measurement accuracy was 2 mm Hg.

Electrocardiogram (ECG) was performed on a computer electrocardiograph Cardiolab +2000. The stimulated QRS complex duration was measured in leads II, V5, V6 (the average of three consecutive complexes) with a choice of maximum value. Measurement accuracy proved to be 1 ms.

Patients were divided to three QRS complex duration classes in accordance with Haghjoo M. et al: 1 – under 120 ms (normal), 2 − 120-149 ms (extended) and more than 150 ms (significantly extended). Functional blood circulation values were defined in selected classes.

Echocardiography study was conducted on the ultrasound machine Toshiba Applio 400. LF, RF, RV sizes and IVS, PW thickness was measured. To calculate the EDV and ESV used method of Simpson. LV EF was calculated using the formula EF = (EDV - ESV) / EDV * 100 %.

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

The data were brought into the Microsoft Excel base. For statistical evaluation of the results were used the parametric criteria (the mean – M, the standard deviation – sd). Comparing of QRS duration complex classes on the observation stages was conducted on each separate functional blood circulation value using a non-parametric U-Mann-Whitney test. Probable results were determined at levels of reliability $P < 0.05$.

RESULTS AND DISCUSSION

Comparative characteristics of functional blood circulation values in patients in different QRS complex duration classes before implantation, in the early postoperative period, 6 months and a year later after permanent pacemaker implantation are presented in table 1 and in CRT patients − in table 2.

In patients with permanent pacemakers in all QRS complex duration classes VC initially was below the physiological norm, and after the pacemaker implantation went to the physiological level ($p < 0.05$), which remained the whole observation period. In patients with CRT VC did not leave the physiological range in all classes on the observation stages.

Patients with high baseline SBP pacemaker patients and decreased in step one year of observation reached physiological range in all classes QRS duration complex. In patients with MCT in classes 1 and 2 it was in the physiological range of values at all stages of observation, and grade 3 initially increased and decreased in the physiological range included in the early postoperative period. DBP at all stages of observation in all patients with a pacemaker and CRT were in the physiological range.

Pacemaker implantation did not affect the normal baseline CSR and MLC in classes 1, 2 and enlarged in class 3. In accordance with the EF also did not change. In patients with MCT by reducing the original magnification CSR and EDV increase occurred initially reduced LVEF in grades 2 and 3 of the complex QRS duration, 50 % and 87 %, respectively.

Pacemaker implantation and CMT in the selected classes QRS duration complex has not led to a significant decrease in the thickness of the IVS and PWLV.

Pacemaker implantation has not affected initially increased size of the LP on the stage of the annual observations, while the CMT contributed to its reduction in all classes QRS duration complex.

Dimensions RA and RV before and on the stages of pacemaker were normal. In patients with CMT initially increased size of the PP in the class 1 is not changed, the class 2 and 3 - Changes to decrease occurred in the period of the annual monitoring, more pronounced in the class 3 ($p< 0.05$). At baseline, the increased size of the prostate in class 1 is not changed, the class 2 and 3 - decreased.

Table 1

Functional blood circulation values in patients with permanent pacemaker on the different observation stages (M ± sd)

Functional values		QRS complex duration											
		Under 120 ms				120-149 ms				150 and more ms			
		Before	Early postoperative	6 months after	Year after	Before	Early postoperative	6 months after	Year after	Before	Early postoperative	6 months after	Year after
VC (1/min)		52 ± 11	68 ± 6*	64 ± 3	67 ± 8	46 ± 8	71 ± 11*	69 ± 7	67 ± 7	46 ± 9	68 ± 7*	70 ± 7	64 ± 8
Blood pressure (mm Hg)	**SBP**	150 ± 15	154 ± 17	140 ± 27	133 ± 13	140 ± 15	139 ± 16	124 ± 14	120 ± 8	153 ± 18	151 ± 19	144 ± 25	122 ± 22
	DBP	82 ± 6	89 ± 9	80 ± 7	78 ± 10	81 ± 9	83 ± 10	84 ± 9	82 ± 3	79 ± 7	87 ± 9	85 ± 17	80 ± 13
Echo values	**LVEF (%)**	53 ± 10	54 ± 11	65 ± 8	47 ± 8	47 ± 8	53 ± 8	50 ± 9	56 ± 7	50 ± 6	47 ± 8	55 ± 12	43 ± 16
	ESV (ml)	63 ± 28	59 ± 26	52 ± 11	65 ± 11	70 ± 31	58 ± 22	66 ± 19	67 ± 18	83 ± 35	81 ± 36	102 ± 64	124 ± 54
	EDV (ml)	135 ± 44	127 ± 29	148 ± 16	123 ± 18	133 ± 29	122 ± 24	132 ± 27	154 ± 23	166 ± 35	153 ± 48	227 ± 129	219 ± 142
	IVS (sm)	1,2± 0.1	1.2 ± 0.1	1.0 ± 0.2	1.0 ± 0.2	1.2± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
	LVPW (sm)	0.9± 0.1	0.9± 0.1	1.2± 0.1	1.0± 0.2	1.0± 0.1	1.0± 0.1	1.0± 0.2	1.0±0. 1	1.1± 0.2	1.1± 0.2	1.1±0. 2	1.2±0. 1
	LA (sm)	4.9± 0.6	4.8 ± 0.6	4.5 ± 0.5	4.7 ± 0.6	4.3± 0.5	4.3 ± 0.5	4.8 ± 0.6	3.9 ± 1.3	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5
	RA (sm)	4.8± 1.0	4.8 ± 1.0	4.5 ± 1.0	4.5 ± 1.0	4.4± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.1 ± 0.6	4.4 ± 0.5	4.3 ± 0.5	4.6 ± 0.6	4.7 ± 0.5
	RV (sm)	3.0± 0.4	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	3.2± 0.6	3.2 ± 0.6	3.2 ± 0.7	3.8 ± 0.4	3.2 ± 0.6	3.2 ±0.6	3.2 ± 0.9	3.5 ± 0.5

According to these functional blood circulation values there are significant differences ($p < 0.05$):
* − Before implantation and early postoperative observation stage;
** − Early postoperative and 6 months after implantation;
*** − 6 months and year after.

Table 2

Functional blood circulatory values in patients with CRT on the observation stages (M ± sd)

Functional blood circulatory values		QRS complex duration											
		Under 120 ms			120-149 ms				150 and more ms				
		Early postoperative	6 months after	Year after	Before	Early postoperative	6 months after	Year after	Before	Early postoperative	6 months after	Year after	
VC (1/min)		69 ± 9	70 ± 7	68 ± 7	72 ± 7	74 ± 19	68 ± 6	68 ± 2	69 ± 7	70 ± 7	76 ± 6	68 ± 5	
Blood pressure (mm Hg)	**SBP**	126 ± 15	122 ± 12	120 ± 12	137 ± 11	133 ± 18	120 ± 12	133 ± 5	148 ± 18	129 ± 8	126 ± 19	123 ± 8	
	DBP	79 ± 13	80 ± 7	80 ± 8	83 ± 4	80 ± 7	81 ± 5	83 ± 3	81 ± 4	81 ± 2	84 ± 11	80 ± 9	
Echo values	**LVEF (%)**	30 ± 18	35 ± 9	35±7	26 ± 7	29 ± 9	32 ± 8	39 ± 5***	23 ± 4	29 ± 5*	34 ± 8	43 ± 9***	
	ESV (ml)	228 ± 160	226 ± 78	219± 66	300 ± 96	242 ± 63*	221 ± 68	173 ± 64	381 ± 89	262 ± 129*	229 ± 100	206 ± 89	
	EDV (ml)	324 ± 195	346 ± 18	336± 76	405 ± 94	340 ± 14*	326 ± 18	284 ± 81	497 ± 78	370 ± 80*	346 ± 128	359 ± 73	
	IVS (sm)	1.1 ± 0.2	1.1 ± 0.2	1.1±0 .2	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.3 ± 0.2	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	
	LVPW (sm)	1.1 ± 0.2	1.1 ± 0.2	1.1±0 .2	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	
	LA (sm)	5.5 ± 0.5	5.4 ± 0.7	5.4±0 .7	5.4 ± 1.0	5.2 ± 1.0*	4.8 ± 1.0	4.8 ± 1.0	5.4 ± 1.0	5.2 ± 1.0*	5.2 ± 1.0	5.2 ± 1.0	
	RA (sm)	5.5 ± 0.5	5.5 ± 0.5	5.5±0 .5	6.0 ± 0.1	6.0 ± 0.1	5.9 ± 0.2	5.5 ± 0.4	6.0 ± 0.1	6.0 ± 0.1	5.1 ± 0.6	5.2 ± 0.8	
	RV (sm)	4.7 ± 0.3	4.5 ± 0.3	4.5±0 .3	3.5 ± 0.7	3.4 ± 0.7	3.2 ± 0.7	3.0 ± 1	3.6 ± 0.7	3.4 ± 0.7	3.2 ± 0.7	3.3 ± 0.7	

Our findings are broadly consistent with Molina L. et al. [6] showed less favorable in patients with longer QRS complex changes in functional parameters in a permanent pacemaker.

That we found in patients with a longer QRS complex after initiation of CMT trend towards greater improvement in functional parameters in general agreement with the data [7], as well as a multicenter randomized trial RAFT [8, 9], which included 1.483 patient with CMT.

It should be noted that the data on the changes in DBP and SBP in patients with permanent pacemaker and MCT have been studied previously.

CONCLUSIONS

1. The more complex QRS duration, the greater the deviation from the functional parameters of the circulatory physiological standards, the extent of which is stronger in patients undergoing CRT versus patients with permanent pacemaker.

2. On the one-year period of observation ECS with medical support no significant effect on the functional performance of circulation, with the exception of SBP, whereas MCT contributes to their reverse remodeling, the extent of which is greater, the higher the initial duration of the QRS complex.

3. Partial normalization of functional parameters of blood circulation in the class 3 patients with pacemaker and trend improvement in patients with CMT, the degree of which the lower, less complex QRS duration indicates not just necessary, but strengthening medical support.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate further study this group of patients to assess the long-term changes of functional blood circulation values in different QRS complex duration classes.

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Clinical case

UDC 616.12-008: 615.015

ESSENTIAL ARTERIAL HYPERTENSION WITH INSUFFICIENT DEGREE OF NOCTURNAL BLOOD PRESSURE REDUCTION: THE NEED OF CHRONOBIOLOGY APPROACH

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A clinical case of chronotherapy in hypertension with insufficient degree of nocturnal blood pressure (BP) reduction was described. Patient M., average 24-h BP according to ambulatory blood pressure monitoring was160/98 mm Hg, systolic and diastolic blood pressure profile had non-dipper pattern. Taking into account individual circadian BP profile, the patient was recommended to take antihypertensive drug – lisinopril – at bedtime. As a result of this treatment, after 3 months the target levels and normalization of circadian rhythm of BP were achieved.

KEY WORDS: hypertension, chronotherapy, ambulatory blood pressure monitoring, non-dipper

ГІПЕРТОНІЧНА ХВОРОБА З НЕДОСТАТНІМ СТУПЕНЕМ НІЧНОГО ЗНИЖЕННЯ АРТЕРІАЛЬНОГО ТИСКУ: НЕОБХІДНІСТЬ ХРОНОТЕРАПЕВТИЧНОГО ПІДХОДУ

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Описано клінічний випадок хронотерапии при гіпертонічній хворобі з недостатнім ступенем нічного зниження артеріального тиску (АТ). Пацієнт М., середньодобовий АТ за даними добового моніторування артеріального тиску 160/98 мм рт. ст., порушення добового ритму систолічного і діастолічного артеріального тиску за типом «недостатня ступінь нічного зниження АТ». Пацієнту рекомендовано час прийому антигіпертензивних препаратів з урахуванням добового індивідуального профілю АТ: лізиноприл ввечері перед сном. В результаті проведеного лікування через 3 місяці досягнуті цільові рівні і нормалізація добового ритму АТ.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, хронотерапія, добове моніторування артеріального тиску, недостатня ступінь нічного зниження АТ

ГИПЕРТОНИЧЕСКАЯ БОЛЕЗНЬ С НЕДОСТАТОЧНОЙ СТЕПЕНЬЮ НОЧНОГО СНИЖЕНИЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ: НЕОБХОДИМОСТЬ ХРОНОТЕРАПЕВТИЧЕСКОГО ПОДХОДА

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Описан клинический случай хронотерапии при гипертонической болезни с недостаточной степенью ночного снижения артериального давления (АД). Пациент М., среднесуточное АД по данным суточного мониторирования артериального давления 160/98 мм рт.ст., нарушение суточного ритма систолического и диастолического артериального давления по типу «недостаточная степень ночного снижения АД». Пациенту рекомендовано время приёма антигипертензивных препаратов с учётом суточного индивидуального профиля АД: лизиноприл вечером перед сном. В результате проводимого лечения через 3 месяца достигнуты целевые уровни и нормализация суточного ритма АД.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, хронотерапия, суточное мониторирование артериального давления, недостаточная степень ночного снижения АД

INTRODUCTION

A disorder of circadian rhythm of blood pressure (BP) with insufficient degree of its night-time reduction is one of the unfavorable variants of the essential hypertension (EH) course. [1, 2].The incidence of this disorder, according to different authors, ranges within 40-70 % [3, 4]. Many studies have been proven relationship between insufficient degree of blood pressure reduction at night-time, and an increased incidence of fatal and nonfatal cardiovascular events [5]. Antihypertensive therapy according to circadian blood pressure profile is particularly important in these patients, as illustrated by our clinical case.

CLINICAL CASE

Patient M., male, born in 1956 (57 years) complained of increase in blood pressure to 200-220/110-116 mmHg, accompanied by headache in the occipital region, pressing retro-sternal pain, nausea, a significant worsening of overall health.

Retired engineer, does not smoke, alcohol abuse. The living conditions are satisfactory. Physical activity is average - every day working in the garden. Anamnesis vita is unremarkable.

Increased blood pressure numbers - about 150/90 mm Hg - were first recorded in 2004 while passing a routine examination. Nowhere was examined, was not treated. In December 2013 the first time increased blood pressure to 200/106 mm Hg was noted, and therefore patient sought medical advice to the outpatient clinic. The treatment was prescribed: Vasar (valsartan) 160 mg 1 time, Nebikard (nebivolol) 1 tablet (dosage can not specify) 1 time daily. Prescribed medications took about 3 months. According to home monitoring (HBPM) BP stabilized at 130-140/80 mm Hg. Due to the improvement of general health and a reduction in blood pressure patient stopped taking the prescribed treatment. In May 2014 periodic BP ups to 150-160/90 mm Hg reappeared. 20/05/14 there was an increase in blood pressure to 206/119 mm Hg, accompanied by headache in the occipital region. Patient didn't seek medical care. Took captopril 25 mg sublingually twice with an interval of 1 hour by himself. 2 hours after the last dose of captopril blood pressure was fixed at 145/88 mm Hg. Over the next 4 days no antihypertensive agents have been taken, blood pressure according to HBPM was 150-160/90-98 mm Hg, well-being was satisfactory.

24.05.14 patient came to the Department of Internal Medicine of the Karazin Kharkiv National University Medical School to consult a doctor.

At the time of the examination were no complaints. Overall state of the patient was relatively satisfactory. Patient was of normal constitution, proper nutrition, BMI 23.8 kg/m^2. Peripheral edema wasn't found. Over the entire surface of lung vesicular breathing has been auscultated, no wheezing. Cardiac activity was rhythmic with a heart rate of 62 beats/min. Cardiac sounds were clear, sonorous, accentuate 2 tone over the aorta. Borders of the relative cardiac dullness are not expanded. BP_{dex} was 164/90 mm Hg and BP_{sin} was166/91 mm Hg. Abdominal while palpation was soft and painless. Liver was at the edge of the costal arch, painless while palpation. Pasternatsky's sign was negative bilateral.

Taking into account the absence of antihypertensive therapy in the preceding days, the BP monitor was set. Further examination according to current standards [6-8] was prescribed. In the study of quality of life (QOL) using the SF-36 questionnaire revealed significant difficulties in performing the ordinary work or other daily activities due to emotional status and physical health – 0 points on a scale of Role-Physical (RP) and Role-Emotional (RE). Also decline in general and mental health was noteworthy (tab. 1).

The other obtained results:

- Full blood count, urinalysis, fasting blood glucose, serum creatinine, urea, serum electrolytes, ALT, AST, total cholesterol − within normal ranges, ECG, renal ultrasound − unremarkable.

- Ultrasound of the heart − left ventricular hypertrophy (left ventricle wall thickness in diastole 1.3 cm), ejection fraction is 58 %.

Table 1

Health-related quality of life (in points by SF-36 scale)

Scale	Baseline	3 months later
Physical Functioning (PF)	80	85
Role- Physical (RP)	0	50
Bodily Pain (BP)	74	100
General Health (GH)	45	57
Physical Component Summary (PCS)	43,04	51,92
Vitality (VT)	50	60
Social Functioning (SF)	75	87,5
Role- Emotional (RE)	0	33,3
Mental Health (MH)	48	64
Mental Component Summary (MCS)	32,59	42,39

- Ambulatory BP monitoring (ABPM) − the daily means of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were increased. Indicators of pressure load – 24-h SBP percent time of elevation (24h SBP PTE) and 24-h DBP percent time of elevation (24h DBP PTE) were increased − recorded stable systolic and diastolic hypertension during the entire 24 hours. Values of BP variability for SBP and DBP were increased both in daytime and at night. Circadian rhythm violation of SBP and DBP was by type of «insufficient degree of nocturnal blood pressure reduction» – non-dipper. Pulse pressure (PP) daily mean was increased (tab. 2, fig. 1).

Table 2

ABPM indices

Indices	Baseline	3 months later
SBP, daily mean, mmHg	160	127
SBP, awake mean, mmHg	160	131
SBP, asleep mean, mmHg	160	116
24h SBP PTE, %	95,5	27,5
Awake SBP variability, mmHg	19.0	12,2
Asleep SBP variability, mmHg	22.5	13
DBP, daily mean, mmHg	98	84
DBP, awake mean, mmHg	100	88
DBP, asleep mean, mmHg	96	74
24h DBP PTE, %	82	66,4
Awake DBP variability, mmHg	27.0	10,4
Asleep DBP variability, mmHg	23.4	13
The sleep-time SBP decline, %	0,3	11,6
The sleep-time DBP decline, %	4,0	16,0
SBP circadian index	1	1,13
DBP circadian index	1,04	1,19
Pulse pressure daily mean, mmHg	62	43

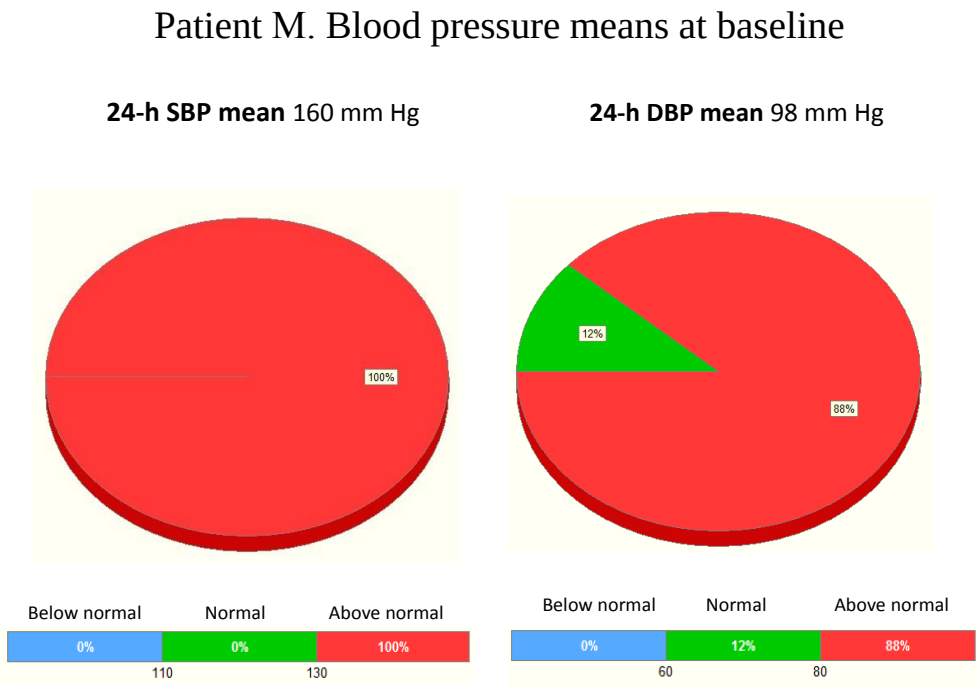
Based on the obtained data the following diagnosis was made:

Arterial hypertension II degree, stage 2, violation of BP circadian rhythm by type of

«insufficient degree of nocturnal blood pressure reduction» – non-dipper. Moderate additional cardiovascular risk. Heart failure, stage 0.

Moderate physical activities and diet low in salt, animal fat, easily digestible carbohydrates and rich in fibers were recommended.

Taking into account the circadian blood pressure profile lisinopril in dose of 10 mg at bedtime under the control of HBPM was prescribed. Three weeks later, the patient was examined repeatedly to control the therapy efficacy. According HBPM blood pressure was within 150/90 mm Hg. On physical examination any changes were detected. BP_{dex} = BP_{sin} = 154/88 mmHg. Lisinopril dose increased to 20 mg/day at bedtime.



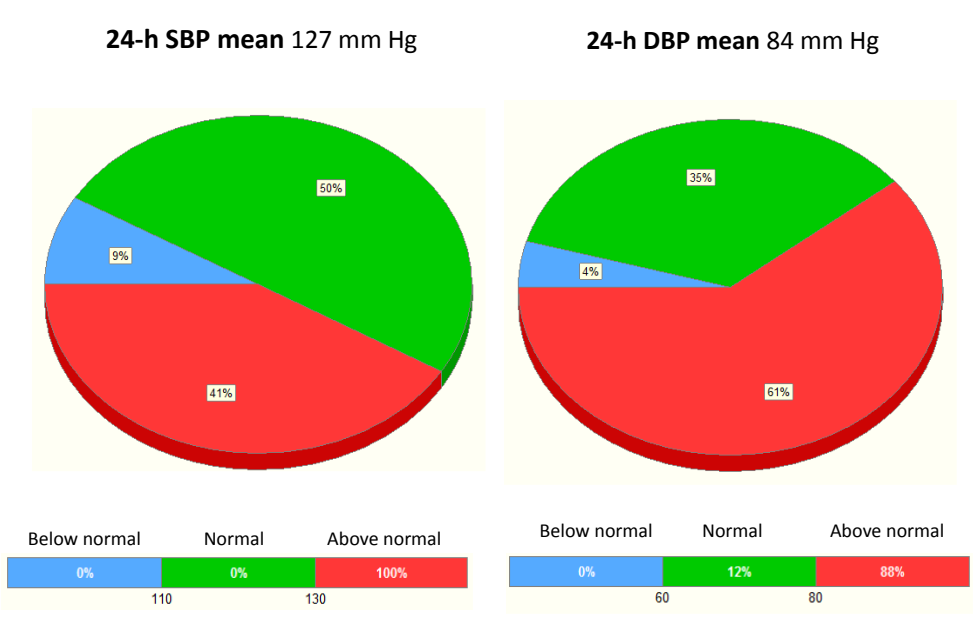


Fig.1. Blood pressure means at baseline and 3 months after

Due to the treatments regimen the patient's condition was significantly improved: headaches regressed, BP according to HBPM was stabilized at the level of 130/80 mm Hg, and overall health status was also improved. Repeated evaluation of QOL found an increase in quality of life on all scales of the questionnaire of various degrees (tab. 1). A clinically significant improvement in role and emotional functioning was marked – increase readings by more than 20 points; pronounced increase in the scale « Bodily Pain» to the maximum possible score, indicating the absence of any restriction of daily activity due to pain. In general, there is a moderate clinically significant improvement of physical and mental health components. After three months of treatment with lisinopril, a repeated blood pressure monitoring was performed. Daily blood pressure means were 127/84 mm Hg - 131/88 mm Hg awake and 116/74 mmHg asleep (tab. 2, fig. 1). Circadian indices of systolic and diastolic blood pressure increased to 1.13 and 1.19, respectively. 24h SBP and DBP PTE stayed increased, however, in comparison with the entering data showed a significant - up to border values - reducing 24h SBP PTE and less pronounced decrease in 24h DBP PTE. SBP variability was within the normal ranges during entire 24 hours. Awake DBP variability was in the normal ranges, but asleep DBP variability showed a slight increase. A decline in PP daily mean to normal levels was registered. Physiological degree of nocturnal blood pressure reduction was recorded - the blood pressure profile by type of «dipper». Patient was recommended to take lisinopril 20 mg / day in the same mode.

Thus, this clinical case shows the practical value of chronobiology approach in arterial hypertension management without nocturnal BP reduction. Prescription to the patient an antihypertensive drug at bedtime allowed reaching during 3 months target blood pressure levels using the drug in small doses.

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POLYMORBIDITY IN CLINICAL PRACTICE

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The interaction of diseases for their clinical features, severity type, quality of life of patients and preferable drug therapy are reviewed on the example of clinical case. Clinical examination, diagnosis and choice of optimal drug management are outlined in patient with polymorbid pathology.

KEY WORDS: polymorbidity, geriartriya, drug therapy, quality of life

ПОЛІМОРБІДНІСТЬ В КЛІНІЧНІЙ ПРАКТИЦІ

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На прикладі клінічного випадку розглядається взаємовплив захворювань на їх клінічну картину, характер течії, якість життя пацієнтів та вибір лікарської терапії. Викладені діагностика, постановка клінічного діагнозу та вибір оптимальної медикаментозної терапії у пацієнтки з поліморбідною патологією.

КЛЮЧОВІ СЛОВА: поліморбідність, геріатрія, медикаментозна терапія, якість життя

ПОЛИМОРБИДНОСТЬ В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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На примере клинического случая рассматривается взаимовлияние заболеваний на их клиническую картину, характер течения, качество жизни пациентов и выбор лекарственной терапии. Изложены диагностика, постановка клинического диагноза и выбор оптимальной медикаментозной тактики у пациентки с полиморбидной патологией.

КЛЮЧЕВЫЕ СЛОВА: полиморбидность, гериартрия, медикаментозная терапия, качество жизни

Polymorbidity is an actual problem in geriatric practice [1, 2, 3]. Clinical examination of elderly and old patients is often diagnosed at least 4-5 diseases [3, 4].

Atherosclerotic vascular lesions of heart and brain, hypertension, emphysema, chronic gastritis with secretory insufficiency, diabetes, osteochondrosis, arthritis, diseases of the eye (cataracts, glaucoma), and others are observed most often in different combinations and varying degrees of clinical symptoms [4, 5, 6].

Currently, there are many regimens for treatment of comorbid conditions, however, patients compliance to treatment remains low [7, 8, 9, 10].

The aim of the article is to highlight the importance of polymorbidity in elderly patients with their compliance to drug therapy.

CLINICAL CASE

Woman, 75 years old, retired, resident of the city.

COMPLAINTS

Complained of rare pressing pain behind the breastbone during moderate physical and

emotional stress, without irradiation, stopped taking 1 tab. nitroglycerin; transient increase in blood pressure to 150/80 mm Hg, accompanied by headache in the neck, stopped by medication (captopres or anaprilin), periodic heartbeat with heart rate over 100 beats/min., appearing without a clear connection with the provoking factors and accompanied by shortness of breath; moderate shortness of breath when walking up to 15-20 m, stopped by rest; swelling of the lower third of legs in the evening, held in the morning after sleep; numbness fingertips on both feet, pain in the calf muscles when walking up to 50 m.

ANAMNESIS MORBI

Since 1990 fluctuations in blood pressure with the rise to 150-170/80 mm Hg (usual BP - 140/80 mm Hg) were marked, in the autumn of 2007 - ischemic heart disease (IHD), angina pectoris functional class (FC) III, obliterating atherosclerosis of the lower extremities due to insulin-depended type 2 diabetes, since 2013 paroxysmal atrial fibrillation (AF). Repeatedly treated inpatient, outpatient, constantly taking nitrates, beta-blockers, aspirin, insulin. In November 2008 right femoropopliteal bypass was conducted for obliterating atherosclerosis of the arteries of the lower extremities. The patient was treated repeatedly for angina FC III-IV, paroxysmal AF, out takes antianginal drugs without full effect. In 2009 renal artery bypass surgery was performed, in 2010 - covered stenting (4 covered stents in the left anterior descending (LAD), the diagonal branch (I DB), the circumflex branch (CB)) of the coronary arteries, in 2011 - stent plastic in LAD, in 2012 - stenting of one of the branches of coronary arteries, unspecified. The patient was hospitalized in the clinic in connection with an increase in heart attacks.

ANAMNESIS VITAE

The patient has two children. 40 years of experience teaching, 20 years - the director of the school. In 1963 suffered encephalitis. Since 1972 diagnosed with insulin- depended type 2 diabetes mellitus (1972-1974 - took maninil 5-10 mg/day, since 1974 insulin (24 units/day Actrapid HM, 24 units/day Lantus). In 1980 - hysterectomy, appendectomy, removal of atheroma on the right hand, 2009 - phacoemulsification in both eyes, surgery for retinal detachment, osteochondrosis of L3-L4, L4-L5, L5-S1, osteoarthritis of the right shoulder and knee joints unidentified ago. The patient denies viral hepatitis, tuberculosis, sexually transmitted diseases. Allergic anamnesis is not burdened. Patient does not have bad habits. Family history was not burdened by coronary artery disease and hypertension

OBJECTIVE EXAMINATION

The patient's condition is satisfactory, active, height - 156 cm, weight - 65 kg, body mass index (BMI) = 26.7 kg/m^2. Skin has pale pink color. Peripheral lymph nodes: submandibular, axillary and inguinal lymph nodes soft consistency, painless, moderately agile and not soldered to each other and the skin. Lobes of the thyroid gland are not palpable, the isthmus is palpated in the form of a uniform cross-strand smooth, 1 cm wide. Musculoskeletal system is without singularities, pain in the lumbosacral palpation. Above lungs the mild lung sound, weakened vesicular breathing in the lower parts in auscultation. Border of the heart expanded to the left, activity of the heart is rhythmic, tachycardia (heart rate (HR) 95 beats/min). Heart sounds are muffled, II tone accent on the aorta. Diffuse systolic murmur, with its epicenter in the aorta. BP is 140/80 mm/Hg on hypotensive therapy. Abdomen is normal sized, sensitive to palpation. Liver is at the costal margin, painless. Physiological functions: a tendency to constipation. Effleurage symptom on the lumbar region is negative on both sides. Auscultation of vessels is normal. Swelling is at lower third of the leg in the evening.

LABORATORY AND INSTRUMENTAL TESTS

Clinical analysis of blood and urine are normal.

According to the biochemical analysis of blood - creatin 101.5 mmol/l (normal 53 - 97 mmol/l), blood glucose - 10.39 mmol/l (4.2 - 6.1 mmol/l), creatin clearance using the formula Cockcroft - Gault = 52 ml/min ($\geq$ 90 ml/min); lipid profile within the normal range.

ECG from 29/09/14: atrial flutter, tachysystolic form with carrying out 2:1, heart rate = 111 beats/min. Signs of left ventricular hypertrophy. Violation of repolarization is in the anterior-posterior-lateral parts of the left ventricle.

According to the ultrasound of the heart from 10/01/14: sclerotic changes of the aortic wall, fibrosis and calcification of the aortic and mitral valves, aortic valve stenosis. Mild mitral valve stenosis. Left ventricular hypertrophy, concentric type. Dilatation of both atria. Tricuspid regurgitation II stage. Left ventricular injection fraction – 55 %.

Chest X-ray: signs of venous hypertension. Diffuse fibrosis. Roots structurally enhanced by the vascular component. Right sinus is obliterated. Heart is aortic configuration, extended to the left. Aorta in arc is sclerotic.

Ultrasound of abdominal and retro-abdominal organs: diffuse changes of liver and pancreas parenchyma without magnification. Cholesterosis of gallbladder. Microcalculosis of kidneys. Right gydrokalikosis.

X-ray of lumbosacral spine and pelvis: diffuse osteoporosis, left-sided scoliosis, osteochondrosis of L5-S1 with spondillo-artrosis, deforming spondylosis, fragmented calcification of blood vessels. Degenerative-dystrophic changes in the hip joints due to osteoporosis.

DIAGNOSIS

The underlying disease: Systemic atherosclerosis (atherosclerosis of aorta, aortic stenosis, coronary atherosclerosis, atherosclerotic mild mitral stenosis, atherosclerosis of kidneys arteries (renal artery bypass surgery (2009)), pelvic arteries and the arteries of the lower extremities (femoral-popliteal bypass-tibial segment vessels right lower extremity (2008)). IHD: stable exertional angina FC III. Eluting stenting of the LAD, the I DB, the CB of the coronary arteries (5 stents, 2010-2012). Isolated systolic hypertension III stage, soft degree. High additional risk. Persistent AF, atrial flutter, tachysystolic form. HAS-BLED score is 2, CHA2DS2-VASC score is 6. CHF IIA stage with preserved left ventricular pump function (injection fraction = 55 %), III FC.

Comorbid conditions: Phacoemulsification in both eyes, surgery for retinal detachment (2009). Overweight (BMI = 26.7 kg/m^2). Insulin-depended type 2 diabetes mellitus, subcompensation stage, average severity. Irritable bowel syndrome with constipation predominance. Chronic kidney disease stage 3. Chronic pyelonephritis, remission. Osteoarthritis, polyosteoarthrosis of right shoulder, double-sided gonartrosis, activity 0, Ro III. Osteochondrosis of the lumbar spine. FJD I stage.

RECOMMENDATIONS

Lifestyle modification with dietary interventions based on comorbid pathology, physiotherapy.

Rosuvastatin 20 mg 1 time per day, Isosorbide mononitrate 50 mg 1 time per day, nitroglycerin (tablet or spray) on demand, ramipril 5 mg 1 time per day before sleeping under the control of blood pressure, amiodarone 200 mg per day under the control of HR, dabigatran 110 mg 2 times per day, torasemide 5 mg by the scheme in the morning before a meal, insulin short and prolonged action by the scheme.

On the background of optimally chosen therapy the patient's condition has stabilized, marked improvement of hemodynamic parameters.

CONCLUSIONS

Clinical case demonstrated that the optimal choice of the minimal medical therapy and adequate lifestyle modification will allow to the patient stabilize the condition and achieve better quality of life.

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Lecture

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ANTACIDS CLINICAL PHARMACOLOGY

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Antacids clinical pharmacology is represented according to the international classification of drugs ATC (anatomical-therapeutic-chemical). The article elucidates antacids indications and contraindications, administration details and side effects.

KEY WORDS: antacids, clinical pharmacology

КЛІНІЧНА ФАРМАКОЛОГІЯ АНТАЦИДІВ

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Представлена клінічна фармакологія антацидів відповідно до міжнародної класифікації лікарських препаратів АТХ (анатомо-терапевтично-хімічної). Висвітлено показання та протипоказання до застосування антацидів, особливості їх застосування та побічні ефекти.

КЛЮЧОВІ СЛОВА: антациди, клінічна фармакологія

КЛИНИЧЕСКАЯ ФАРМАКОЛОГИЯ АНТАЦИДОВ

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Представлена клиническая фармакология антацидов в соответствии с международной классификацией лекарственных препаратов АТХ (анатомо-терапевтическо-химической). Освещены показания и противопоказания к применению антацидов, особенности их применения и побочные эффекты.

КЛЮЧЕВЫЕ СЛОВА: антациды, клиническая фармакология

INTRODUCTION

Antacids (gr. anti - against, lat. acidus - acid) - alkaline compounds used to neutralize hydrochloric acid in the stomach. Antacids have been used for more than 100 years in medical practice in the treatment of acid-related diseases of gastrointestinal tract. For a long time sodium carbonate (baking soda) was used as an alkalinizing agent [1].

ANTACIDS CLASSIFICATION

ATC classification

A: Alimentary tract and metabolism
A02 Drugs for acid related disorders
A02A Antacids
A02AA Magnesium compounds
A02AB Aluminum compounds
A02AC Calcium compounds
A02AD Combinations of aluminum, calcium and magnesium compounds
A02AF Antacids with antiflatulents
A02AG Antacids with antispasmodics
A02AH Antacids with sodium bicarbonate
A02AX Antacids, other combinations

The classification according to the digestive absorption

According to the digestive absorption

classification antacids are divided into 2 main categories which are very important in practice [1, 2]:

1. Absorbable:
- sodium carbonate (baking soda);
- magnesium oxide (magnesia);
- magnesium carbonates;
- calcium carbonates;
- Bourget mixture (sodium bicarbonates, sulphate, phosphate);
- Rennie mixture (calcium carbonates, magnesium carbonates);
- Tums mixture (calcium carbonates, magnesium oxide).

2. Non-absorbable:
- aluminum phosphate;
- aluminum hydroxide;
- magnesium silicate;
- magnesium hydroxide;
- aluminum-magnesium combination;
- aluminum-magnesium combination with other active ingredients (anesthetics, antiflatulents, alginates, etc.).

PHARMACOKINETICS

Absorbable antacids are rapidly dissolving substances that immediately react with hydrochloric acid in the stomach forming carbon dioxide and water. Carbon dioxide causes gastric distention which provokes gastroesophageal reflux and stimulates gastric secretion enhancement. Sodium carbonate is different from other antacids its systemic effects, as it is absorbed into the blood and affects the organism pH in whole. In patients with normal renal function, the excess of bicarbonate is rapidly excreted, and in case of parafunction it can be accumulated and may cause systemic alkalosis [2, 3].

Most antacids used in medical practice are non-absorbable, without systemic pharmacokinetics.

PHARMACODYNAMICS

Absorbable antacids are rarely used in clinical practice due to the large number of systemic side effects. Such antacids come into direct neutralization reaction with hydrochloric acid in the stomach. They are characterized by quick onset of therapeutic action and short-term effects, because after the administration of absorbable antacids, the level of intragastric pH increases up to 7 or more in a short period of time (15-20 min) that stimulates secondary acid hypersecretion (the «rebound» syndrome) [1, 4].

Non-absorbable antacids have fewer systemic adverse effects than absorbable ones. Their main mechanism of action is associated with the absorption of hydrochloric acid. Non-absorbable antacids begin acting later (within 10-30 minutes), however, they have longer period of therapeutic action – nearly 2.5-3 hours [5]. Buffer (neutralizing) capacity of non-absorbable antacids is higher than of the absorbable. Their neutralizing activity lasts until the pH does not exceed 3.0-4.0 (the physiological pH when there is a normal digestion and hydrochloric acid has an antimicrobic action). Non-absorbable antacids have many others favorable properties:
- absorb pepsin, resulting in reduced proteolytic activity of gastric acid;
- connect lysolecithin and bile acid, which have a damaging effect on the gastric mucosa;
- possess cytoprotective function through the activation of prostaglandin synthesis, which stimulate a secretion of mucin and bicarbonates, improve microcirculation;
- possess ambient function, forming a protective film on the gastric mucosal surface;
- able to bind epithelial growth factor and fix it in the ulcerous defect region effectively stimulating cell proliferation, angenesis and angiogenesis.

Antacids efficiency is evaluated by their acid neutralizing capacity (ANC) which is expressed in mEq of hydrochloric acid that is neutralized by a standard dose of antacids raising the pH to approximately 3.5 during a predetermined time (usually – about 15 minutes). ANC varies widely and is dissimilar among the various antacids. The average daily dosage of antacids should provide 200 to 400 mEq neutralizing capacity, ANC is considered to be low if it is less than 200 mEq / day and high if it is more than 400 mEq / day.

Pharmacodynamics properties of antacids depend on their cationic composition (tab. 1).

Table 1

Characteristic of the antacids cationic composition

Effect	Cations			
	Aluminum	Magnesium	Calcium	Bismuth
Neutralizing	++/+++	+++	+	–
Absorbing	+	–	–	–
Ambient	+	–	–	+++
Astringent	+++	+	+	+
Cytoprotective	+++	–	–	+

Remarks: «-» No effect, «+» low activity, «++» average activity, «+++» high activity.

Antacids containing aluminum cations, have the greatest medicinal effect (along with hydrochloric acid neutralization, such antacids possess high cytoprotective function and bind effectively bile acid) [2, 5]. However they promote a slowdown of intestinal motility and may cause constipation, magnesium salts, vice versa, – possess slight laxative action. The administration of combined antacid containing aluminum and magnesium hydroxide provides more rapid onset of therapeutic effect (due to magnesium hydroxide), increases period of action(due to aluminum hydroxide) and minimizes side effects. The exposure to the drug on motility depends on the quantitative ratio of aluminum / magnesium at the combined antacid: the closer this ratio to 1, the less likely this effect.

INDICATIONS AND PRINCIPLES OF CLINICAL USE

Antacids therapeutic indications

In the treatment of acid disorders the proven effectiveness belongs to proton pump inhibitors (PPIs), H2 antagonists (H2 blockers) and eradication therapy of infection Helicobacter pylori (Hp). In this regard, antacids are mainly examined as an adjunctive therapy. Due to quick symptomatic effect, convenient presentation (suspensions, chewable tablets), pleasant organoleptic properties, high security antacids are the drugs of choice for self-treatment.

1. Gastroesophageal reflux disease (GERD)

Antacids neutralize hydrochloric acid, inactivate pepsin, absorb bile acids, stimulate the synthesis of bicarbonates, raise the tone of the lower esophageal sphincter, thus affecting on the majority of units in the GERD pathogenesis. Along with that antacids possess cytoprotective effect on the esophageal and gastric mucosa that allows achieving positive clinical and endoscopic dynamics faster.

When GERD is non-erosive (NERD), antacids may be used as monotherapy. In case of monotherapy failure (heartburn saving), and in erosive form of GERD antacids are prescribed as a co-drug to the PPIs main course [5, 6].

It is better to use liquid form of non-absorbable combined antacids: antacid containing aluminum phosphate, as well as pectin gel and agar; aluminum-magnesium antacids; aluminum magnesium antacids with alginic acid (is derived from seaweeds). Alginic acid produces a gel foamy layer in the cardiac orifice, which in case of backflow, instantaneously gets into the esophagus and prevents aggressive action of gastric acid. Besides, alginic acid increases the residence time of antacid in the esophagus and stomach, thereby prolonging their cytoprotective effect to the mucous membrane.

2. Gastric and duodenal ulcers

In gastric and duodenal ulcers, antacids are used for severe pain management during the screening phase and within first day of PPIs administration before the acid production blockade (after 1-3 days).

In case when ulcer is unassociated with Hp, antacids are administered in combination with PPIs (in order to enhance cytoprotective effect when ulcers are nonhealing).

When ulcer is Hp-associated, antacids (in combination with PPIs) are recommended in case of difficultly cicatrizing ulcer (the phenomenon of growth factors fixation) after eradication therapy or on retention of

dyspeptic symptoms. Antacids administration during the eradication therapy is undesirable because of its potential self-tapering action [7].

Antacids are the drugs of choice for contraindications to antisecretory agents' administration, side effects of PPIs and H_2-blockers. They are also recommended for H_2-blockers administration and their withdrawal in order to relief the «rebound» phenomenon. Long-term maintenance administration of antacids is effective as an anti-relapse treatment.

3. Acute gastritis / gastroduodenitis

Antacids are used in addition to PPI therapy, H_2-blockers in the treatment of acute gastritis, gastroduodenitis, especially with severe pain and dyspeptic syndromes [7].

4. Chronic gastritis / gastroduodenitis

To prevent recurrences, antacids are used either alone or in conjunction with antisecretory agents. They are the drugs of choice for treatment and prevention of reflux gastritis, where bile acids and lysolecithin are the main disturbing factors.

5. Gastropathy caused by nonsteroidal anti-inflammatory drugs (NSAIDs - gastropathy)

Antacids can be taken alone or in addition to antisecretory drugs in order to prevent gastro- and duodenopathies affected by the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

6. Pain and dyspeptic syndromes

Antacids are recommended for healthy people with discomfort or epigastric pain, dyspeptic symptoms (heartburn, belching, meteorism). Non-absorbable antacids are used as the essential drug to relieve heartburn in pregnancy, which occurs in approximately (50-80) % [2, 4].

6. Cholecystitis, biliary dyskinesia

Antacids are included in the treatment regimen for patients with acalculous and calculus cholecystitis, biliary dyskinesia's to eliminate the symptoms of bail and mixed refluxes. Antacids efficacy is associated with their ability to absorb bile acids and lysolecithin, which get into the esophagus and stomach in case of duodenogastric and gastroesophageal refluxes. Thus, antacids prevent damaging effect of bile acids on the gastric and esophageal mucosas and their stimulating effect on the secretion of hydrochloric acid.

7. Chronic pancreatitis in the exacerbation phase

Taking into account the role of gastric acid in the stimulation of pancreatic secretion during the exacerbation of chronic pancreatitis, PPIs, H_2-blockers and antacids are necessary components of treatment. By raising the stomach pH, antacids promote the evacuation process normalization, reduce intragastric and intraduodenal pressure, thereby negating the flatulent distention. Enzyme drugs are used in chronic pancreatitis to correct a digestion and in order to reduce pain syndrome. But the action of hydrochloric acid leads to rapid inactivation of the main components of enzyme drugs - lipase and trypsin. Besides, during chronic pancreatitis a normal process of duodenal contents «alkalinity» is disrupted and consequently the release and activation of enzyme drugs particles with enteric coating (activated only in the alkaline environment) is disrupted as well. Therefore, to increase the effectiveness of enzyme therapy it is advisable to use a co-administration of antacids and / or anti-secretory drugs. Even if a starvation for 2-3 days is prescribed to the patient, antacids and antisecretory drugs are recommended from the first day of treatment [8].

8. Prevention of «stress» ulcers

Antacids are used in the intensive care units to prevent so-called «stress» ulcers (in patients after a major operation, with craniocerebral traumas - Cushing's ulcers or with severe burns – Curling's ulcers, etc.).

Administration principles

Antacids are used in the form of tablets and suspensions. These presentations are differ significantly in the ANC. Solubility affects the ANC, as antacids react with hydrogen ions only in a solute form. In comparison with tablets, suspensions consist of smaller particles, they have a larger surface area and are dissolved faster in the acid environment of the stomach. Thus, antacids are more active in the form of suspension [1, 2].

The average therapeutic dose of antacid is 10-15 ml (1 tablespoon or 1 package content) of liquid or 1-2 tablets 3-4 times a day. Tablets should be chewed or dissolved well

before swallowing. In some patient information leaflet of antacids it is recommended to take them before a meal. However, when antacids are taken on an empty stomach they are rapidly emptied into the duodenum, in addition their effect is negated because food acts as a buffer for antacids. It is advisable to take antacids 1-1.5 hours after meals or at bedtime (to reduce the aggressive action of hydrochloric acid on the gastric mucosa during the night). Additional intake of antacids 3-4 hours after a meal can be recommended in special cases, for example, when there are long intervals between meals. Antacids can be used singly as a symptomatic treatment in case of complaints («on-demand therapy») or on a regular basis as a course. Course duration may range from 1 to 3-4 weeks.

Antacids side effects

1. When administered absorbable antacids (sodium hydrogencarbonate, rarely - calcium carbonate) after a short-term effect of acid neutralization a secondary acid hypersecretion (the «rebound» syndrome) occur in the result of pH increases up to 7 and / or as a result of a direct effect of calcium ions. In long-term treat and in high doses antacids can cause systemic metabolic alkalosis (with a headache, sicchasia, vomiting).

2. Sodium bicarbonate may adversely affect the water-salt metabolism: 2 g of sodium retains fluid as well as 1.5 g of sodium chloride. In elderly patients with pathology of the cardiovascular system may rise blood pressure, appear or enlarge swelling, increase signs of cardiovascular failure.

3. Antacids containing carbonates (sodium hydrogencarbonate, calcium and magnesium carbonate) in reaction with hydrochloric acid produce carbon dioxide gas. This causes gastric distension (pain syndrome), belching and meteorism which are especially undesirable in case of GERD.

4. Urinary alkalization occurs under the influence of sodium hydrogencarbonate and magnesium drugs (oxide, hydroxide and carbonate), which may lead to settling phosphates forming phosphate stones.

5. Antacids containing calcium may cause hypercalcemia, which promotes kidney stones formation and reduces parathormone production. Consequently, the excretion of phosphorus is delayed and calcium phosphate is accumulated. That causes tissue calcification and nephrocalcinosis progression.

6. The combination of calcium antacids and milk is undesirable, because such intake promotes «milk-alkali» syndrome (sicchasia, vomiting, polyuria, mental disorders).

7. Non-absorbable antacids have fewer adverse effects than absorbable ones and more frequently these effects are caused by long-term and uncontrolled drug administration. With long-term administration of aluminum hydroxide, the intestinal absorption of phosphate can be decreased that sometimes may cause hypophosphatemia. That complication is more common in patients who abuse alcohol. In patients with severe renal failure, antacids may cause clinically significant increased aluminum and magnesium levels in the blood. In such cases the cumulation of aluminum can lead to encephalopathy and osteohalisteresis. During the antacids treatment in patients with normal or moderately reduced kidney function a visible increase of aluminum level in the blood does not occur.

8. The most common adverse reaction in the aluminum hydroxide administration is constipation, magnesium hydroxide have a laxative effect that may cause diarrhea. In the combined aluminum / magnesium antacids the exposure to the drug on motility of the gastrointestinal tract depends on the quantitative ratio of aluminum / magnesium. If this ratio is 1 or a shade more, the drug has no effect on motility or, in rare cases may cause a laxative effect (as a rule, at a dose increase).

CONTRAINDICATIONS

Currently, the administration of absorbable antacids is undesirable. Contraindications for non-absorbable antacids are severe kidney failure, Alzheimer's disease. Aluminum phosphate is contraindicated in pregnancy [5].

Antacids interaction with other drugs

Antacids that contain calcium, magnesium and aluminum ions are chelators. They bind a great number of drugs such as digitoxin, tetracycline, bishydroxycoumarin, indomethacin, aspirin, cimetidine, ranitidine, famotidine, theophylline etc. Antacids administration reduces the bioavailability of weak acids: barbiturates, sulfonamides,

penicillins and others. The absorption of weak bases increases (atropine, chlor-promazine, propranolol etc.) [1, 2].

It is advisable to combine antacids with M-anticholinergics (to prolong the effect of antacids) and with PPIs (to reduce their destruction in the stomach).

Because of pharmacodynamic drug incompatibility, antacids cannot be combined with bismuth subcitrat and sucralfate.

To avoid undesirable interactions, antacids are usually used 2 hours before or after taking any medication.

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