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

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

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

ЕФФЕКТИВНІСТЬ ЗАСТОСУВАННЯ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ В ТЕРАПІЇ ВАЖКОКОНТРОЛЬОВАНОЇ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

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

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

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В ТЕРАПИИ ТРУДНОКОНТРОЛИРУЕМОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DIFFICULT-TO-CONTROL HT AND THE RISK OF COMPLICATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7. Invasive treatment

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

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

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

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

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

BIOFEEDBACK – PHYSIOLOGICAL ASPECTS

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

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

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

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

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

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

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

Temperature biofeedback

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

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

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

Galvanic skin response (GSR)

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

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

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

Contour with electroencephalography (EEG), or neurofeedback.

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

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

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

Respiration biofeedback

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

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

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

Electromyography (EMG)

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

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

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

Heart rate variability (HRV)

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

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

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

The combination of HRV and respiratory biofeedback

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

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

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

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

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

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

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

CLINICAL APPLICATIONS IN BIOFEEDBACK THERAPY

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

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

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

Biofeedback in cardiology

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

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

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

Experience in the use and effectiveness of biofeedback for arterial hypertension

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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