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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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THE USE OF B-ADRENOBLOCKERS IN PATIENTS WITH HEART FAILURE AND CONCOMITANT THYROID DISEASE (LITERATURE REVIEW AND OWN OBSERVATIONS)

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Introduction.

It is well known that β-blockers (BABs) are an integral part of the medical treatment of patients with chronic heart failure (CHF). The use of BABs makes it possible to neutralize the adverse effect of activation of the sympathoadrenal system, which plays a leading role at all stages of this pathology. The large, randomized placebo-controlled studies have confirmed the correctness of the theoretical prerequisites for the need to prescribe beta-blockers to patients with CHF [1-3]. At the same time, there is still insufficient data on the specifics of the use of BABs in the case of a combination of CHF with dysfunction of the thyroid gland (TG), the hormones of which have a significant effect on the state of the cardiovascular system (CVS).

Aim.

The aim of this article is a systematize literature data on the use of β-adreno-blockers in patients with chronic heart failure and concomitant thyroid pathology and to present the results of own research.

Materials and methods.

The narrative review represents an assessment of the most pertinent literary sources published in English language from 1990 to 2021, which dealt with the issues of the use of β-adreno-blockers in patients with chronic heart failure and concomitant thyroid pathology. Also, the results of own research were presented.

Results and Discussion.

Thyroid dysfunction is an important general medical problem, since it causes the development of many disorders in other organs and systems associated with excessive or insufficient synthesis of thyroid hormones. The organ of CVS is especially sensitive to these changes [4,5].

It has been proven that not only clinically manifest forms of hyper- or hypothyroidism, but also subclinical manifestations of thyroid dysfunction are associated with an increased risk of developing CHF and other cardiovascular events [6]. The prevalence of thyroid dysfunction among patients with CHF significantly exceeds the corresponding figure in the general population (primarily due to individuals with subclinical thyroid dysfunction) [7].

Hormones of the thyroid gland play a significant role in ensuring the energy metabolism of the myocardium. In addition, their influence on the processes of myocardial remodeling and hypertrophy, apoptosis of cardiomyocytes, neo angiogenesis, opening of coronary artery collaterals, etc. has been proven [8,9]. The above effects are realized through the stimulation of β-adreno-receptors (BARs) synthesis on cell membranes, which contributes to an increase in the influence of the sympathoadrenal system; an increase in the activity of sodium-potassium ATPase, which is accompanied by an increase in the function of sodium-potassium pumps and an increase in the intensity of metabolism and heat generation [10-13].

Despite the rather high prevalence of thyroid dysfunction among people with CHF, data on the choice of optimal pharmacotherapy for this syndrome (including, in particular, the prescription of BABs) are quite limited. In the case of most of the relevant randomized controlled trials involving patients with CHF, individuals with concomitant thyroid pathology were either excluded from the sample in advance, or the efficacy and safety of BABs among them were not analyzed.

Since there is no specific treatment for CHF in patients with thyroid dysfunction, they should receive standard therapy. However, there is no doubt that the strategy for choosing drugs, in particular β-blockers, in such patients should have certain features.

An important issue is the possible restriction of the use of BABs in patients with CHF and concomitant hypo- or hyperthyroidism. Before delving into this problem, it is worth considering the generally accepted algorithm for using BABs in CHF.

It is necessary to start titrating the dose of BABs under the control of the patient's condition and identifying the first signs of drug tolerance. If it is not possible to achieve the target dose of the drug, it is necessary to strive to bring it to the maximum tolerated, while using various strategies [14].

In patients with heart failure with reduced left ventricular ejection fraction (LV EF), the European recommendations describe in sufficient detail the clinical situations requiring the appointment of BABs, justify the choice and dosage of a particular drug, relative contraindications, etc. [2].

It is important to remember that it takes time to develop and realize the positive effect of BABs. However, the expected reduction in mortality of 30-40%, as well as sudden death (by 50%), is worth the effort [15].

It should also be taken into account that BABs should be started in patients with CHF with low doses of the drug and with a stable patient's condition. Titration of the dose of BABs to the so-called target is carried out slowly (according to the recommendations). It is recommended to gradually increase the dose from the minimum, doubling it every 2-4 weeks and without stopping the drug. The patient should be warned about this and given information regarding his actions in case of possible complications. It is necessary to continue titrating the

dose to the maximum tolerated or target, carefully monitoring the patient's condition and symptoms. One should be persistent in titrating the dose, even if the patient is already feeling well. But even when the symptoms of CHF do not improve, it is necessary to carry out long-term treatment with BABs in order to prevent serious cardiovascular complications. Many patients who were considered to have recovered from CHF and stopped taking BABs had relapses of CHF decompensation over time [16].

The doctor should always remember that a higher dose of BABs is more effective. Concern about worsening CHF, bradycardia, or hypotension is a psychological barrier for a doctor who prescribes BABs (especially for a patient with a low heart rate). There is convincing evidence that the reduction in mortality and rehospitalization rates in patients with heart failure against the background of the use of BABs did not depend on the initial heart rate and correlated with the achieved reduction in heart rate during treatment [17].

Let us continue to analyze the clinical situation when a patient with CHF has concomitant thyroid dysfunction. Mostly you have to deal with two opposite situations - hyper- and hypofunction of the thyroid gland. Both hypo- and hyperfunction can cause the development of CHF, deterioration of its course and the development of complications.

Consider first the clinical scenario where a patient with CHF has concomitant hypothyroidism. It should be noted that one of the manifestations of thyroid hypofunction is a decrease in the amount of BAR in cardiomyocytes and a decrease in their sensitivity to BABs [18,19].

That is why there is a point of view that in the treatment of patients with CHF and concomitant hypothyroidism, the use of β-blockers is inappropriate, since a decrease in thyroid function is often associated with bradycardia. However, this is an erroneous point of view, since it has already been noted that β-blockers are able to reduce the mortality of patients with CHF with reduced LV EF and sinus rhythm, regardless of the initial heart rate [20].

Hypothyroidism. Thus, BABs must be prescribed to patients with CHF with reduced LV EF, regardless of the presence of thyroid hypofunction. However, the “life-saving” potential of β-blockers in patients with hypothyroidism may be somewhat less since they have a significantly lower probability of titrating the dose of β-blockers to the target due to a lower initial heart rate. However, any dose of BABs will be better than its absence, i.e., it is more expedient to prescribe even a small dose of BABs than not to prescribe it at all, since the prognosis of patients taking BABs is always more favorable than that of those with CHF who do not take them. Therefore, patients with CHF and hypofunction of the thyroid gland need to be rigorously titrated in the dose of BAB with careful monitoring of heart rate and drug tolerance.

On the other hand, in patients with hypofunction of the thyroid gland, receiving thyroid hormone replacement therapy and taking even selective BABs bisoprolol and metoprolol, the level of thyroid-stimulating hormone may increase due to inhibition of deiodinase activity, which indicates an increase in thyroid insufficiency and requires an appropriate dose adjustment of levothyroxine.

It should be remembered that a change in the level of thyroid hormones may be a consequence of the progression of CHF or these are temporary changes due to the use of BABs, but this is not a reason to change the tactics of BABs treatment. It should also be taken into account that such a typical manifestation of hypothyroidism as bradycardia can be masked while taking BABs, so such patients are recommended to conduct periodic monitoring of thyroid hormones.

Hyperthyroidism. The Hyperthyroidism, in contrast to the hypothyroid state, reflects increased symptoadrenal activity, is accompanied by a hyperdynamic cardiovascular state with high heart rate, an increase in systolic and diastolic function, and an increased risk of atrial fibrillation. Hyperthyroidism is a powerful inducer of the hyperadrenergic state, which is characterized by high β-adreno-receptors (BARs) sensitivity to catecholamines. Thyroid hormones stimulate expression, ie. increase the number of BARs on cardiomyocytes and increase their sensitivity. Therefore, the use of BABs in hyperthyroidism is fully justified [21].

According to the international recommendations of a number of thyroid associations, BABs is recommended to be prescribed to all patients with symptoms of thyrotoxicosis, especially elderly patients, if the resting heart rate exceeds 90 min^{-1} or there is a concomitant cardiovascular disease. The dose of BABs should be selected in accordance with the heart rate [22].

However, as noted in a number of recommendations for the treatment of CHF in patients with endocrine disorders, the use of BABs in patients with hyperthyroidism should be carried out with caution [23].

Chronic hyperfunction of the thyroid gland can act as a trigger (trigger) for CHF with high cardiac output. The most dangerous clinical situation may be the so-called thyroid storm, a severe hypermetabolic state due to a thyroid-induced increase in the sensitivity and expression of BARs, which causes a sharp increase in the receptor response to endogenous catecholamines. This, in turn, leads to the formation of heart failure with high cardiac output (cardiac output can increase up to 300%) and low vascular resistance, atrial fibrillation. If a thyroid storm develops in a patient with heart failure with reduced LV EF, the use of beta-blockers can lead to failure of compensation, a sharp drop in cardiac output, hemodynamic instability and the development of severe hypotension [24-26].

Thus, the current recommendations indicate that the use of β-blockers in patients with hyperthyroidism and CHF with reduced LV EF requires careful monitoring of hemodynamics.

It is necessary to take into account another condition that often goes unnoticed by doctors. We are talking about low triiodothyronine syndrome (LTS) [27-29].

Low triiodothyronine syndrome. Clinical studies have shown that in a certain percentage of patients with severe acute and chronic diseases, including those with CHF, there is a decrease in the level of free triiodothyronine (T_{3f}) with normal or almost normal levels of free thyroxine (T_{4c}) and thyroid stimulating hormone (TSH) [30,31]. This condition is defined as LTS (Low T_3 Syndrome or Peripheral Dythyroidism Syndrome) [30]. It is assumed that LTS is caused by a congenital or secondary defect in the conversion of T_4 to T_3 by peripheral deiodinase types

2 and 3. Under conditions of experimental CHF, the activity of type 3 cardiac deiodinase, which converts T_4 into reverse (reverse) rT_3 and into T_2, was increased 5 times [32].

LTS is not a rare condition in patients with CHF [33]. This syndrome occurs in 20–30% of patients with dilated cardiomyopathy [34]. The presence of CHF correlates with the clinical status of CHF patients [35]. A strong association between a decrease in bioactive T_3 and mortality has been clearly documented in a large sample of hospitalized patients [31]. Currently, the concept that considers the important role of thyroid dysfunction in the progression of CHF is mainly supported by data from five clinical studies [36]. They demonstrated that LTS is not a derivative of other, more powerful parameters, such as left ventricular ejection fraction, but an independent prognostic marker. Determination of the serum level of T_3 is available in routine clinical practice and is easily interpreted, unlike most known biohumoral factors [36].

According to the results of our studies, the incidence of LTS in patients with CHF during hospitalization is 17.8% [37,38].

There is no consensus regarding the criteria for defining LTS. So, in the works [39-41] used the lower range of normal T_{3f} (from 2.5 to 4.0 pmol/l) at normal levels of T_{4f} and TSH.

Previously, using ROC analysis, we found that the risk of rehospitalization (HR) of CHF patients due to decompensation increases when the optimal split point for the serum level $T_{3f} \leq 2.07$ pmol/l is exceeded (sensitivity - 70.19%, specificity - 91.34%) [42]. It has been demonstrated that in patients with LTS (at $T_{3f} \leq 2.07$ pmol/l), compared with patients without this syndrome, FC IV is more often detected in NYHA (16.6% *vs.* 6.8%, respectively; 2=25.082, p=0.0001) and higher levels of NT-proBNP are observed (by 38.4, p=0.0001). In patients with LTS, compared with patients without the syndrome of peripheral dythyroidism, dilatation of the LV cavity was established (large end diastolic dimention (EDD) (49.31%, p = 0.046), an end diastolic volume (ESV) (by 28.2%, p = 0.046), an end systolic dimention (ESD) (8.1% , p = 0.0001) and an end systolic volume (ESV) (by 20.1%, p = 0.0001)), an increase in LV myocardial mass (by 5.9%, p = 0.030) and a lower LV EF (by 19.2% , p = 0.0001) [42]. Patients with LTS had a higher risk of rehospitalization (RH) within two years (OR = 23.35 (14.052-45.733), p = 0.0001) and the risk of reaching the combined endpoint (CEP) over the same period (OR = 20.505 (11.410-36.848), p = 0.0001). It should be noted that the presence of LTS increases the risk of RH in patients due to CHF decompensation and achievement of CEP both in the subgroup with preserved LV systolic function and in patients with EF less than 40%. Thus, in patients with reduced LV EF, the frequency of RH in the presence of LTS was 81.3%, versus 12.2% among patients without peripheral dythyroidism syndrome (p=0.0001). CET in patients with LTS reached 85.3%, against 22.6% of patients without this syndrome (p = 0.0001). In the group CHF with preserved LV EF, 70.4% of patients with CHF had RH for 2 years versus 13.0% without this syndrome (p = 0.0001). CEP occurred in 70.4% of patients with LTS versus 10.4% without this condition (p = 0.0001) [42]. Statistical analysis did not reveal a difference in the effect of LTS on the course of CHF depending on the sex of patients [42].

In patients with CHF and LTS, an increase in the dose of BABs leads to inhibition of deiodinase activity, followed by an even more pronounced decrease in the level of T3 and an increase in the size of the left ventricle, which may increase the risk of an unfavorable course of CHF and rehospitalization. One of the most widely used BABs in the treatment of patients with heart failure is currently bisoprolol. It is a selective β1-antagonist without intrinsic sympathomimetic activity and vasodilating properties [43].

The influence of the hemodynamic effects of bisoprolol on the prognosis of patients with CHF was studied in a double-blind, randomized, placebo-controlled study CIBIS I (Cardiac Insufficiency BIsoprolol Study) [43]. The results of the study showed a probable reduction in the frequency of PG due to decompensation of heart failure (61% *vs.* 90% in the placebo group). There was no significant difference in both overall mortality and sudden death, although the trend towards a decrease in negative events in the bisoprolol group was obvious [43]. The encouraging results of CIBIS I served as the basis for organizing the CIBIS II study. A 3-year follow-up period was planned. The main objective of the study was to evaluate the effect of bisoprolol treatment on mortality in patients with heart failure [44]. The study was terminated early after the second interim analysis. The mean duration of follow-up was 1.3 years. In the active treatment group, overall mortality was almost 2 times lower than in the placebo group (11.8% *vs.* 17.3%, p<0.0001), the frequency of sudden death while taking bisoprolol was also significantly lower - 3.6 % *vs.* 6.3%, p<0.0011. The results did not depend on the age, genesis, and initial severity of the disease [44].

Our statistical analysis did not reveal a positive effect of BABs bisoprolol on the course of HF in patients both with concomitant thyroid pathology (diffuse non-toxic goiter and autoimmune thyroiditis) and without it [45]. At the same time, in the group of patients with CHF without concomitant thyroid pathology, when using bisoprolol at a dose of > 5 mg, there was a significant reduction in the risk of RH compared with patients taking the indicated BABs at a dose of ≤ 5 mg. Excluding patients with LTS from the statistical analysis, it turned out that the administration of bioprolol at a dose of > 5 mg leads to a decrease in the risk of RH (HR = 0.112 (0.033-0.377), p = 0.0001) and CE (HR = 0.407 (0.202-0.821), p=0.016), compared with patients taking the drug at a dose of ≤ 5 mg [42]. A similar positive effect is exerted by the use of bisoprolol at a dose of > 5 mg and in the group of patients with CHF without LTS and without thyroid pathology: a decrease in the risk of RH ((HR = 0.053 (0.007-0.412), p = 0.0001) and CE (HR = 0.363 (0.143-0.917), p=0.048). In the group of patients with CHF without LTS but with concomitant thyroid pathologies, a decrease in the percentage of patients who had RH for 2 years (from 15.9% to 4.0%, respectively, p = 0.037) and who took bisoprolol at a dose of more than 5 mg was revealed [42].

We concluded that the use of bisoprolol in patients with CHF with concomitant thyroid pathologies does not have a dose-dependent effect on the course of heart pathology. A likely reason for the lack of a dose-dependent positive effect of β-blockers

on the course of CHF in patients with concomitant thyroid pathology is the high incidence of LTS among patients in this population. The use of this drug in patients with concomitant thyroid pathologies who do not have the syndrome of peripheral dythyroidism leads to a significant decrease in the frequency of RH over 2 years of treatment [42].

We conducted a study of the effect of bisoprolol in individuals with LTS on the course of CHF. In order to stratify the dose of BABs that affect the risk of RH in patients with CHF, an ROC analysis was performed. It was found that the frequency of RH in the group of patients with CHF without LTS is higher when using a dose of bisoprolol ≤ 5.0 mg compared with a higher dose of the drug (sensitivity - 91.43% and specificity - 45.49%, p = 0.0001) [42].

Among patients with CHF without LTS, the two-year incidence of RH with bisoprolol at a dose of less than 5 mg was 19.4%, compared with 2.6% when taking the drug at a dose of > 5 mg (p = 0.0001). The relative risk of RH in these patients during the use of bisoprolol at a dose of > 5 mg was 0.136 (0.042 - 0.433) (p = 0.0007) [42].

At the same time, the reverse effect of bisoprolol was found in patients with LTS. In these patients, the two-year incidence of RH when using bisoprolol at a dose of less than 5 mg was 68.1% compared with 89.1% when taking > 5 mg of the drug (p=0.019). The relative risk of RH in the presence of LTS against the background of using a dose of > 5 mg of the indicated BABs is 1.309 (1.054 - 1.625) (p = 0.015) [42].

Of the 102 patients with CHF and LTS (at T_{3f} < 2.07 pmol/l), 75 (73.5%) had a eject fraction of a left ventricular < 40%. Of these, 70 (93.3%) patients took bisoprolol for two years. In 31 (41.3%) patients, the maximum tolerated dose of the indicated BABs did not exceed 5 mg. 39 (52.0%) patients took bisoprolol at a dose > 5 mg. 5 (6.7%) patients could not take this drug due to adverse reactions [42].

In the group of patients with CHF with reduced eject fraction of a left ventricular and concomitant LTS, when using bisoprolol at a dose of 1.25-5 mg for 2 years, an increase in the level of T_{3f} (by 0.18 pmol/l, p = 0.021) was observed. However, if in this group of patients, the dose of bisoprolol exceeded 5 mg, then within 24 months there was a further decrease in the serum level of T_{3f} (by 0.12 pmol/l, p = 0.040), an increase in the value of T_{4f} (by 1.09 pmol /l, p = 0.043) and a decrease in the ratio of T_{3f} / T_{4f} (p = 0.025). In the group of patients with LTS who took bisoprolol at a dose of 1.25-5 mg, during 2 years of observation, a decrease in end diastolic dimension of left ventricular by an average of 1.04 cm (p = 0.012), end systolic dimension by 30.1 ml (p = 0.010) and an increase in the ejection fraction of a left ventricular from 32.36 [27.15-37.68]% to 36.24 [33.33-42.80]% (p = 0.034), as well as a decrease in the size of the right ventricle by an average of 0, 20 cm (p=0.039) [42].

In the group of patients with CHF with reduced left ventricular ejection fraction and LTS, who took bisoprolol at a dose of > 5 mg, there was a significant increase in left ventricular end diastolic dimension by 0.30 cm (p = 0.020) and left ventricular end diastolic volume by 16.71 ml (p = 0.034), as well as an increase in the size of the right ventricle by 0.45 cm (p = 0.009) [42].

In both groups, a decrease in heart rate was observed during 2 years of taking bisoprolol. Thus, in patients taking BABs at a dose of 1.25-5 mg, heart rate decreased from 78.00 [68.00-84.00] min-1 to 56.85 [51.31-63.24] min-1 (at 21.15 min-1, p=0.0010). In the group of patients taking BABs at a dose of more than 5 mg, the decrease in heart rate was 16.62 min-1 (from 72.56 [66.00-83.24] min-1 to 55.41 [50.38-63.08] min-1, p = 0.0010) [42].

The frequency of RH in the group of patients with CHF with reduced ejection fraction of left ventricular and concomitant LTS was higher when using bisoprolol at a dose of > 5 mg, compared with a subgroup of patients taking the drug at a dose of 1.25-5 mg (92.3%, *vs*. 5%, respectively; p = 0.004). On the contrary, in patients with CHF with reduced the ejection fraction of left ventricular without LTS, the frequency of RH was higher when using bisoprolol at a dose of 1.25-5 mg compared with a subgroup of patients in whom the dose of the drug was titrated to 5 mg or more (p = 0.021) [42].

In order to identify the dependence of the risk of RH in patients with CHF with reduced the ejection fraction of a left ventricular on the time of titration of the dose of bisoprolol up to 5 mg / day, an ROC analysis was performed. It was found that the frequency of RH in the group of patients with CHF without LTS is higher when the indicated dose is reached longer than 85 days, compared with a shorter titration period (sensitivity - 85.71% and specificity - 56.76%, p = 0,0265). At the same time, in the group of patients with LTS, an inverse relationship was established between the risk of RH and the time to reach a daily dose of bisoprolol 5 mg. The frequency of RH in this category of patients increases if the period of titration of the dose of bisoprolol was less than 63 days (sensitivity - 95.38% and specificity - 85.22%, p = 0.0001) [42].

Along with the treatment of patients with heart failure, β-blockers are also used in the treatment of symptomatic patients with thyrotoxicosis. The drugs block the extrathyroidal metabolism of thyroid hormones by inhibiting the activity of type 1 deiodinase [46]. This effect is more characteristic of non-selective BABs, but it is also characteristic of selective drugs with an increase in their dose [47]. The intake of BABs in such patients is accompanied by a decrease in the serum concentration of T_3 [48,49] and an increase in the level of T_{3r} due to the inhibition of its breakdown. Typically, patients remain euthyroid and have stable serum TSH values [50]. But in individuals with initially low levels of T_4 or T_3 (including those with LTS), the effect of prescribing β-blockers may have clinical significance in the long-term period [32]. With sharp fluctuations in the levels of thyroid hormones, clinical manifestations are also associated with the abolition of BABs [51]. It is possible that our study results are due to dose-dependent blocking of the activity of peripheral deiodinases by bisoprolol.

It was concluded that the use of bisoprolol in patients with CHF with reduced the ejection fraction of a left ventricular and concomitant LTS does not lead to a decrease in the incidence of RH due to decompensated CHF. The frequency of RH in the group of patients with CHF without LTS is expectedly higher at a dose of bisoprolol 1.25-5.0 mg compared with a higher dose.

On the contrary, the effect of the use of bisoprolol in LTS is the opposite: the risk of RH increases when the daily dose of the drug exceeds 5 mg. At the same time, there is a further decrease in the serum level of T_{3f}, an increase in the value of T_{4f}, a decrease in the ratio of T_{3f} / T_{4f}, a progressive increase in the heart cavities and a decrease in the ejection fraction of a left ventricular. It is likely that in patients with CHF on the background of LTS it is inappropriate to titrate the dose of bisoprolol above 5 mg and the time of titration of the drug to the indicated dose should be at least 63 days [42].

Conclusions.

In conclusion, it should be said that the final chapter in the history of the use of β-blockers in patients with CHF with reduced the ejection fraction of left ventricular and thyroid pathology has not yet been written.

Further studies are needed, including pharmacogenetic ones.

However, today it can be argued that, in general, recommendations for the use of BABs in patients with CHF with reduced the ejection fraction left ventricular apply to patients with concomitant thyroid dysfunction, taking into account the above limitations.

Prospects for further research. Our work included a relatively small number of patients and had a limited follow-up period, which reduces the statistical power of the data obtained and requires further research.

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Conflict of interest. None.

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SUMMARY

USE OF B-ADRENOBLOCKERS IN PATIENTS WITH HEART FAILURE AND CONCOMITANT THYROID PATHOLOGY (LITERATURE REVIEW AND OWN OBSERVATIONS)

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The systematization of literature data on the use of β-adrenoblockers in patients with heart failure and concomitant thyroid pathology was carried out, and the results of our own study were presented.

It has been suggested that the final chapter in the history of the use of β-adrenoblockers in patients with heart failure with reduced left ventricular ejection fraction and thyroid pathology has not yet been written. Further studies are needed, including pharmacogenetic ones.

The use of a selective β-adrenoblockers - bisoprolol in patients with chronic heart failure with reduced left ventricular ejection fraction and concomitant low triiodothyronine syndrome does not lead to a decrease in the frequency of rehospitalization due to decompensation. At the same time, the frequency of rehospitalization in the group of patients with heart failure without low triiodothyronine syndrome is higher at a dose of 1.25-5.0 mg of bisoprolol compared with a higher dose. The effect of bisoprolol is reversed in patients with low triiodothyronine syndrome: the risk of re-hospitalization increases when the dose of bisoprolol is exceeded, there is a decrease in the serum level of triiodothyronine, an increase in thyroxine levels, a decrease in the ratio of triiodothyronine / thyroxine; further increase in the cavities of the heart and decrease in size. Probably, in patients with heart failure, against the background of low triiodothyronine syndrome, it is not advisable to titrate the dose of bisoprolol above 5 mg, and the time to titrate the drug to the indicated dose should be more than 63 days.

Today it can be argued that, in general, recommendations for the use β-adrenoblockers in patients with chronic heart failure with reduced left ventricular ejection fraction apply to patients with concomitant thyroid dysfunction, subject to the above restrictions.

Keywords. Heart failure, β-adrenoblockers, bisoprolol, thyroid gland, low triiodothyronine syndrome.

β-ადრენობლოკერების გამოყენება პაციენტებში გულის უკმარისობით და თანმხლები ფარისებრი ჯირკვლის პათოლოგიით (ლიტერატურის მიმოხილვა და საკუთარი დაკვირვებები)

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სახელმწიფო დაწესებულება „თერაპიის ეროვნული ინსტიტუტის სახ ლ.ტ. Malaya NAMS of Ukraine", ხარკოვი, უკრაინა

ჩატარდა ლიტერატურული მონაცემების სისტემატიზაცია ბეტა-ბლოკატორების გამოყენების შესახებ პაციენტებში გულის უკმარისობით და ფარისებრი ჯირკვლის თანმხლები პათოლოგიით და წარმოდგენილი იყო ჩვენივე კვლევის შედეგები.

ვარაუდობენ, რომ ბეტა-ბლოკატორების გამოყენების ისტორიის ბოლო თავი პაციენტებში გულის უკმარისობით შემცირებული მარცხენა პარკუჭის განდევნის ფრაქციის და ფარისებრი ჯირკვლის პათოლოგიით ჯერ კიდევ არ არის დაწერილი. საჭიროა შემდგომი კვლევები, მათ შორის ფარმაკოგენეტიკური.

სელექციური β-ბლოკატორის - ბისოპროლოლის გამოყენება პაციენტებში გულის ქრონიკული უკმარისობით მარცხენა პარკუჭის განდევნის ფრაქციის შემცირებით და თანმხლები დაბალი ტრიიოდთირონინის სინდრომით არ იწვევს რეჰოსპიტალიზაციის სიხშირის შემცირებას დეკომპენსაციის გამო. ამავდროულად, დაბალი ტრიიოდთირონინის სინდრომის გარეშე გულის უკმარისობის მქონე პაციენტების ჯგუფში ხელახალი ჰოსპიტალიზაციის სიხშირე უფრო მაღალია ბისოპროლოლის 1,25-5,0 მგ დოზით უფრო მაღალ დოზასთან შედარებით. ბისოპროლოლის მოქმედება შებრუნებულია პაციენტებში დაბალი ტრიიოდთირონინის სინდრომის მქონე პაციენტებში: ხელახალი ჰოსპიტალიზაციის რისკი იზრდება ბისოპროლოლის დოზის გადაჭარბებისას, აღინიშნება შრატში ტრიიოდთირონინის დონის დაქვეითება, თიროქსინის დონის მატება, თანაფარდობის დაქვეითება. ტრიიოდთირონინი / თიროქსინი; გულის ღრუების შემდგომი ზრდა და ზომის შემცირება. სავარაუდოდ, გულის უკმარისობის მქონე პაციენტებში დაბალი ტრიიოდთირონინის სინდრომის ფონზე არ არის მიზანშეწონილი ბისოპროლოლის დოზის 5 მგ-ზე მეტი ტიტრირება, ხოლო პრეპარატის მითითებულ დოზამდე ტიტრირების დრო უნდა იყოს 63 დღეზე მეტი.

დღეს შეიძლება ითქვას, რომ, ზოგადად, გამოყენების რეკომენდაციები

ბეტა-ბლოკატორები გულის ქრონიკული უკმარისობის მქონე პაციენტებში მარცხენა პარკუჭის განდევნის შემცირებული ფრაქციის მქონე პაციენტებში გამოიყენება ფარისებრი ჯირკვლის თანმხლები დისფუნქციით, ზემოთ აღნიშნული შეზღუდვების გათვალისწინებით.

საკვანძო სიტყვები: გულის უკმარისობა, β-ბლოკერი, ბისოპროლოლი, ფარისებრი ჯირკვალი, დაბალი ტრიიოდთირონინის სინდრომი