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

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

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

ОРТОСТАТИЧНІ РЕАКЦІЇ ЧАСТОТИ ШЛУНОЧКОВИХ СКОРОЧЕНЬ ПРИ МЕДИКАМЕНТОЗНОМУ КОНТРОЛІ ПОСТІЙНОЇ ФІБРИЛЯЦІЇ ПЕРЕДСЕРДЬ

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

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

ОРТОСТАТИЧЕСКИЕ РЕАКЦИИ ЧАСТОТЫ ЖЕЛУДОЧКОВЫХ СОКРАЩЕНИЙ ПРИ МЕДИКАМЕНТОЗНОМ КОНТРОЛЕ ПОСТОЯННОЙ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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

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

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

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

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

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

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

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

MATERIALS AND METHODS

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

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

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

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

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

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

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

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

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

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

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

RESULTS AND DISCUSSION

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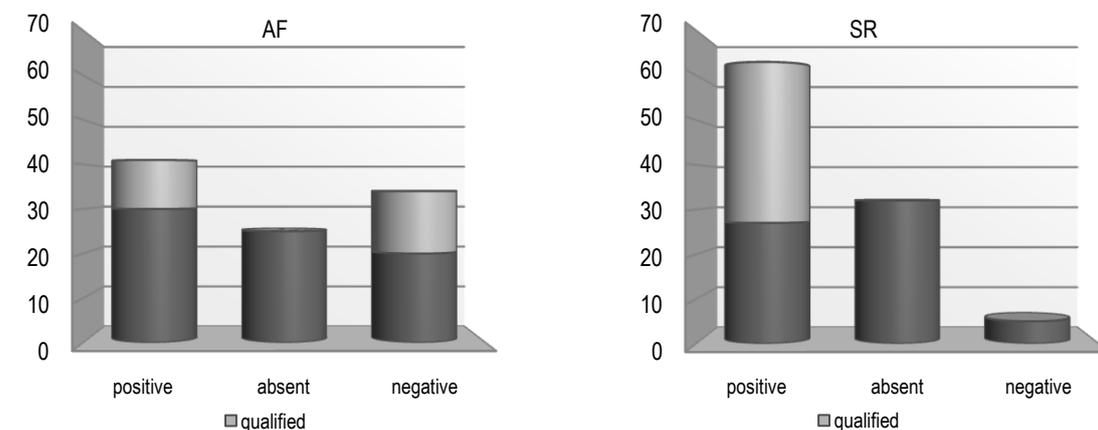

Fig. 1. Occurrence frequency of OR of VR (HR) various types in patients with AF and SR (%)

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

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

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

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

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

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

ted with AF according to EHRA scale, in 14 % — with positive and 9 % — with negative OR of VR type, in 5 % — the I class of symptoms severity connected with AF according to EHRA scale only with positive OR of VR type.

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

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

Table 2

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

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

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

crease according to EHRA scale gradual increase of physiological OR of VR was marked.

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

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

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

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

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

The estimation of the significance of differences between the studied groups with OR of VR various types demonstrated that the change of VR control classes ($\chi^2_{\kappa p}$ = 56,934 > $\chi^2_{0,95}$(2) = 5,99) and the class of symptoms severity connected with AF according to EHRA scale ($\chi^2_{\kappa p}$ = 33,782 > $\chi^2_{0,95}$ (2) = 5,99)

before the amiodarone therapy beginning and in a year are statistically significant.

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

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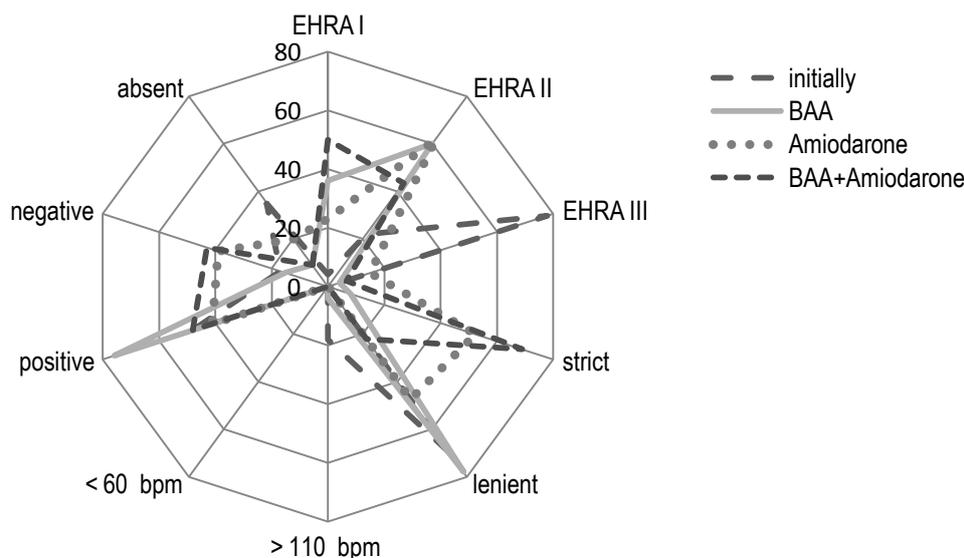
Fig. 2. OR of VR occurrence frequency, distribution of symptoms severity classes connected with AF according to EHRA scale initially and under a year's BAA, amiodarone therapy and their combination

CONCLUSIONS

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

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

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

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

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