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

serdечного ритма EHRA являются позитивные, менее благоприятными — отсутствующие, и неблаго-
приятными — негативные ОР ЧЖС. Показано, что контроль ФП бета-адреноблокаторами (БАБ)
возможен при любом типе ОР ЧЖС, за исключением позитивного квалифицированного, а комбинаци-
ей БАБ и амидорана при неэффективности БАБ, контроль ФП амидораном предпочтительно 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 chronic ventricular rate irregularity which is
found among 1–2 % of people in total populati-
on. 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 hemo-
dynamic better preventing the development of
tachycardiomiopathy [1, 2].

Antiarrhythmic therapy of the patients with
AF is directed to the achievement of VR con-
trol and decrease of symptoms severity class
connected with AF according to EHRA scale,
but it also influences the autonomous regula-
tion of cardiovascular 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 be-
came 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» includ-
ed into the coordination plan of priority direc-
tions 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 Ukrzaliz-
nysya (Ukrainian Railway)» and Kharkov city
colicinics № 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 func-
tional class (FC) (according to the classifica-
tion of Canadian Cardiologists Association) was
found in 35 %, II FC — in 65 % of patients,
III FC — was absent. In 5 % of patients myo-
cardial 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 diag-
nosed 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.—Vasilen-
ko V. Ch. HF I was diagnosed in 30 %, II A —
in 70 %, IIIB and III stages were absent. Ac-
cording to NYHA classification in 11 % of pa-
tients 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 circu-
lation. The patients with stable voltage angina
of the IV FC, acute coronary syndrome, HF of
the IV FC were not included into the investi-
gation.

The comparison group consisted of 73 pa-
tients (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 detec-
ted. According to the classification of Strazhes-
ko N. D.—Vasilenko V. Ch. I stage HF was
diagnosed in 35 %, II A — in 65 %, IIIB 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 ce-
rebral circulation. The patients with stable vol-
tage angina of the IV FC, acute coronary synd-
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 clinostasis 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 х² 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 (%)

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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 | - | - | - | - | - | - | - | - | - |
| > 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 connected 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.
Определение частоты появления OR различных типов (n (%) ± Sp) и клинических признаков AF на один год после начала терапии

<table>
<thead>
<tr>
<th>Тип OR VR</th>
<th>Всего</th>
<th>Градация AF (EHRA)</th>
<th>Тип OR VR контроля (при отсутствии)</th>
<th>Степень OR контроля</th>
<th>БАА</th>
<th>Амиодарон</th>
<th>БАА + Амиодарон</th>
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<tr>
<td>Positive</td>
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<td>Negative</td>
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<td>III</td>
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<td></td>
<td>Shut (VR ≤ 80)</td>
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<td></td>
<td>18 ± 6</td>
<td>4 ± 2</td>
<td>2 ± 2</td>
<td>27 ± 7</td>
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<td></td>
<td>Lenient (VR ≤ 110)</td>
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<td></td>
<td>54 ± 7</td>
<td>15 ± 5</td>
<td>9 ± 4</td>
<td>14 ± 5</td>
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<td></td>
<td>Out of control &lt; 60</td>
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<td>&gt; 110</td>
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<td>4 ± 3</td>
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В ходе БАА-терапии увеличение положительных OR различных типов VR было отмечено (от 41 % до 76 %) при одновременном уменьшении частоты положительных OR VR частоты уменьшения отрицательных OR VR частоты (от 18 % до 35 %) на фоне увеличения отрицательных OR VR частоты (от 35 % до 9 %) и отсутствия (от 24 % до 15 %). В ходе БАА-терапии только в 8 % случаев пациентов VR контроль был отменен, однако у всех из них были положительные OR VR. Число пациентов в группе умеренного контроля составило 78 % (54 % с положительным, 15 % — с отсутствующим и 9 % — с отрицательными OR VR), а в группе острого контроля — 32 % (20 ± 2 %). В ходе терапии (в 6 месяцев после начала терапии) 13 % пациентов перешли из группы умеренного контроля в группу умеренного контроля по частоте смертности (от 44 % до 0), при этом у всех пациентов с отсутствием частоты отрицательных OR VR, которые встречались в других градациях OR VR, не произошли значимые изменения. Частота частоты увеличения положительных OR VR контроля составила 56 % (44 % с положительным, 9 % — с отсутствующим и 7 % — с отрицательными OR VR). При этом число пациентов из группы умеренного контроля составило 2 % (20 ± 2 %). В ходе терапии (в 6 месяцев после начала терапии) 13 % пациентов перешли из группы умеренного контроля в группу умеренного контроля по частоте смертности (от 44 % до 0), при этом у всех пациентов с отсутствием частоты отрицательных OR VR, которые встречались в других градациях OR VR, не произошли значимые изменения. Частота частоты увеличения положительных OR VR контроля составила 56 % (44 % с положительным, 9 % — с отсутствующим и 7 % — с отрицательными OR VR). При этом число пациентов из группы умеренного контроля составило 2 % (20 ± 2 %).
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 (χ² = 43.09 > χ²0.95 (2) = 5.99) and classes of symptoms severity connected with AF according to EHRA scale (χ² = 40.072 > χ²0.95 (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 (χ² = 56.934 > χ²0.95 (2) = 5.99) and the class of symptoms severity connected with AF according to EHRA scale (χ² = 33.782 > χ²0.95 (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 cardiovascular 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).
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.

REFERENCES