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Control of Ventricular Rate in Permanent Atrial Fibrillation: Cardioprotection and Tissue Hemodynamics

Objective — To evaluate myocardial injury and tissue hemodynamics in elderly patients with permanent atrial fibrillation (AF) based on the achieved range of ventricular contraction rate (VCR).

Materials and Methods — This prospective, randomized, blind study included 75 patients aged ≥60 with permanent AF. All patients were prescribed bisoprolol as a VCR-reducing therapy. Patients were randomized to two groups according to the permuted-block design based on the range of resting VCR goal: group 1, 60–79 bpm (n=38) and group 2, 80–100 bpm (n=37). All patients also received perindopril and apixaban. Troponin I concentration was measured using the high-sensitivity assay (hsTn); parameters of tissue hemodynamics, including the mean blood flow velocity (Vm) and pulsatility index (PI), were measured using high-frequency ultrasound doppler flowmetry; echocardiographic indexes of left heart remodeling were recorded at baseline and after 6 month of VCR monitoring.

Results — Mean age of patients was 74±7 years. Medians [25th percentile; 75th percentile] of baseline hsTn concentrations were 10.2 [5.25; 21.2] ng/l in group 1 and 10.3 [5.4; 20.4] ng/ml in group 2 (p=0.91). 89.5% of patients in group 1 and 100% of patients in group 2 achieved the VCR range goal. At 6 month, resting VCRs were 70±4 bpm in group 1 (n=34) and 88±5 bpm in group 2 (n=37) (p_1, p_2<0.001). According to echocardiographic data significant progression of myocardial remodeling was not observed. Concentrations of hsTn significantly decreased in both groups but the decrease was more pronounced in group 1, to 8.0 [4.13; 17.23; p_1<0.001] ng/l vs. 9.2 [4.8, 17.5] ng/l in group 2 (p_1, p_2<0.001). A weak direct correlation was found between the VCR decrease and hsTn concentration (rs=0.44; p=0.009 in group 1, and rs=0.41; p=0.01 in group 2); regression coefficient was 0.78 at 95% confidence interval (CI), from 0.21 to 1.3 (p=0.009) in group 1, and 0.14 at 95% CI, from 0.04 to 0.24 (p=0.007) in group 2. Vm values were increased to 2.93±0.10 (p<0.001) and 3.21±0.09 cm/sec (p<0.001) and PIs were decreased to 1.42±0.03 conv. units (p<0.01) and to 1.34±0.02 conv. units (p<0.001) in groups 1 and 2, respectively.

Conclusion — The treatment aimed at VCR control in patients older than 60 with permanent AF was associated with a positive dynamics of myocardial injury (hsTn) and tissue hemodynamics indexes (Vm и PI). This indicates a possibility for using these indexes for further improvement of managing such patients.

Keywords — Permanent atrial fibrillation; ventricular contraction rate; high-sensitivity troponin I; parameters of tissue hemodynamics

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Management of the ventricular rate (VR) remains a possible long-term therapeutic strategy in patients with atrial fibrillation (AF). There are not enough data on the optimal parameters of VR management derived from randomized controlled trials to enable the formulation of the relevant guidelines of class I and evidence level A. The provision on VR<110 bpm (lenient rate control) as an initial rate target for the rate control therapy accepted by the European Society of Cardiology (ESC) for the treatment of patients with AF [1] is based on the findings of the RACE II (RAte Control Efficacy in Permanent Atrial Fibrillation II) [2, 3] and AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) studies [4]. The 2019 focused update of the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) 2014 Guideline for the Management of Atrial Fibrillation [5] does not cover the section on rate control because there are no study findings that clinically significantly modify the understanding of this approach for the treatment of patients with AF. Therefore the AHA/ACC/HRS experts offer, as the main provisions, a rate control strategy with resting VR<80 bpm to reduce AF symptoms (class IIa, evidence level B) and a lenient rate control strategy (resting VR<110 bpm) for patients without symptoms and with preserved left ventricular

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(LV) systolic function (class IIb, evidence level B). ESC experts mention the VR range from 60 to 100 bpm [6] as optimal for patients with AF and chronic heart failure (CHF), based on the available data [4, 7–9]. Both ESC and AHA/ACC/HRS guidelines stress the need to continue relevant studies.

Searching for new approaches for studying this problem with the aim of informing and optimizing medical decisions during rate control in patients with AF means needing to assess the hemodynamic parameters in the terminal branches of the vascular network to identify the background for ischemic brain attacks [10], something that is particularly important in elderly patients. Moreover, it is relevant to explore the effects on the myocardial damage indicators of different treatment regimens for rate control in AF.

The objective of this study was to assess the extent of myocardial damage and tissue hemodynamics in elderly patients with permanent AF, depending on the achieved VR range.

Materials and Methods

The study included 75 patients aged 61–85 years with permanent AF associated with hypertension and/or permanent AF as a presentation of documented stable coronary artery disease (CAD) without angina (a category of patients with chronic coronary syndrome: patients without symptoms or patients with symptoms>1 year after initial diagnosis or revascularization according to the 2019 ESC Guidelines on Chronic Coronary Syndromes [11]), who required treatment adjustment for rate control (2b, class 3, according to the modified European Heart Rhythm Association score).

Inclusion criteria:

1) The presence of permanent AF without scheduled cardioversion, antiarrhythmic drug therapy, or ablation
2) Age>60 years old
3) Signed informed consent form to participate in the study

Exclusion criteria:

1) Intolerance/contraindications to beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, oral anticoagulants
2) Uncontrolled hypertension
3) Confirmed history of accessory conduction pathways
4) Modifiable conditions causing the development of AF (hypothyroidism, hyperthyroidism)
5) Ablation of the atrioventricular node, pacemaker rhythm, scheduled pacemaker implantation
6) Combination therapy required to achieve a target range of VR
7) Angina, signs of ischemia on electrocardiography (ECG), or new zones of decreased myocardial contractility according to echocardiography
8) CHF decompensation with intravenous administration of inotropic agents, vasodilators, or diuretics for 14 days before randomization
9) Myocardial infarction within 12 months before inclusion in the study
10) Myocarditis, pericarditis, implemented/scheduled heart transplantation
11) Hypertrophic cardiomyopathy
12) Surgical intervention within 3 months before randomization
13) Renal replacement therapy

The independent ethical committee of Kuban State Medical University approved the study.

To reduce VR, all patients took selective beta$_1$ blocker bisoprolol with dose titration to achieve resting VR within the range of 60–100 bpm as recommended by ESC [6]. Patients were randomized into two groups using the permuted blocks procedure according to the target resting VR range: Group 1, 60–79 bpm (n=38); Group 2: 80–100 bpm (n=37).

The resting VR in both groups was evaluated initially during bisoprolol dose titration and at the control visits (at 3 and 6 months) according to 12-lead ECG data (after a 3-minute resting period in the supine position). At the end of the titration period, when VR achieved the target range, rate control and 24-hour ECG monitoring (with a Myocard-Holter complex, Russia) was conducted in Group 1 to exclude bradycardia. The 24-hour monitoring of ECG was repeated, if necessary, during the follow-up (when the beta-blocker should be corrected if VR decreases). If the VR target range could not be achieved with bisoprolol, if cardioversion or ablation was required, patients were excluded from the study.

Patients in both groups received ACE inhibitor perindopril in a dose depending on the blood pressure level achieved and tolerability of treatment, and oral anticoagulant apixaban in a dose corrected according to the label.

Transthoracic echocardiography in B-mode was performed (using an ultrasound scanner UGEO H60 RUS), with a 3.5 MHz sensor according to the standard procedure [12]. Echocardiographic parameters of atrial and ventricular remodeling (left atrial [LA] dimension and volume, LV end-diastolic dimension [LVEDD]) were evaluated. Anteroposterior linear dimension of the LA was measured at end systole from the parasternal long-axis view. In addition to measurement of the linear dimension, the maximum volume of LA was estimated at end ventricular systole using the biplane method of

Table 1. Comparative characteristics of the patient groups

Parameter	Group 1 (n = 38)	Group 2 (n = 37)	p
Age, years (M±SD)	73.6±7.5	73.9±7.0	0.890
Proportion of male patients, %	65.8	67.6	0.870
Duration of continuous AF, years Me (25th percentile; 75th percentile)	4 [2.25; 5.75]	4 [3; 5]	0.693
Hypertension, %	84.2	83.8	0.960
History of MI, %	18.4	16.2	0.805
Type 2 diabetes mellitus, %	15.8	13.5	0.781
CHA_2DS_2 VASc score (M±SD)	4.4±1.7	4.4±1.6	0.976
Systolic BP, mmHg (M±SD)	151.2±18.5	150.1±15.4	0.791
Diastolic BP, mmHg (M±SD)	86.6±10.4	89.6±10.2	0.216
Baseline VR, bpm (M±SD)	98±7	99±7	0.733
Modified EHRA class, %			
• 2b	39.5	40.5	0.571
• 3	60.5	59.5	
NYHA CHF FC, %			
• I	5.3	8.1	0.869
• II	57.9	54.1	
• III	36.8	37.8	
NT-proBNP, ng/L Me (25th percentile; 75th percentile)	1530 [982; 1834]	1562 [1096; 1894]	0.862
LA long-axis dimension, mm (M±SD)	46.3±4.7	46.2±3.0	0.913
Maximum volume of LA/BSA, mL/m² (M±SD)	43.4±4.1	42.8±3.7	0.508
LVEDD, mm (M±SD)	53.4±5.8	53.3±3.0	0.854
LVEDV/BSA, mL/m² (M±SD)	44.2±4.5	43.4±5.2	0.478
LVEF, % (M±SD)	51.6±3.5	51.3±4.2	0.737
Maximal tricuspid regurgitation velocity (continuous-wave Doppler), m/s (M±SD)	2.93±0.31	2.89±0.28	0.559
Septal e' velocity, cm/s (M±SD)	7.2±2.0	7.0±1.8	0.651
Lateral e' velocity, cm/s (M±SD)	8.1±1.7	7.9±2.3	0.669
Mean E/e' ratio (M±SD)	15.1±1.9	15.4±2.1	0.518
Drugs			
• Bisoprolol, mg/day (M±SD)	5.3±0.8	2.5±1.0	<0.001
• Perindopril, mg/day (M±SD)	2.8±0.8	3.6±1.3	0.002
• Apixaban, mg/day (M±SD)	9.2±1.8	9.1±2.0	0.821
• Diuretics, %	71.1	70.3	0.941
• Statins, %	39.5	40.5	0.925
• Mineralocorticoid receptor antagonists, %	63.2	64.9	0.883

M = mean; SD = standard deviation; AF, atrial fibrillation; MI, myocardial infarction; BP, blood pressure; VR, ventricular rate; EHRA, European Heart Rhythm Association; FC, functional class; CHF, chronic heart failure; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; LA, left atrium; BSA, body surface area; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume, LVEF, left ventricular ejection fraction; e', early diastolic velocity from the septum and lateral side of the mitral annulus; E, peak velocity of early left ventricular rapid filling.

disks (modified Simpson method) in four- and two-chamber apical views [12]. LA volume was indexed according to body surface area (BSA), calculated using the Mosteller formula. LVEDD was measured from the parasternal long-axis view. The LV end-systolic and end-diastolic volumes (LVESV, LVEDV) were estimated from the apical view in four- and two-chamber sections using the biplane method of discs. The LV ejection fraction (LVEF) was calculated: (LVEDV–LVESV)/LVEDV [12]. The LVEF was not used as a remodeling indicator as it might be inaccurate in AF, particularly at a high VR; therefore, its dynamics were not included in the analysis. Only data collected at the baseline examination are given. The baseline characteristics also include Doppler indicators of diastolic dysfunction determined in AF according to the guidelines of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) [13] (see Table 1). The early diastolic velocity of the mitral annulus (e') at the level of the interventricular septum and lateral walls were measured using pulse-wave tissue Doppler imaging in the apical four-chamber view, and mean e' was calculated [13]. Clinical symptoms of CHF were identified by the Clinical Assessment Scale (SHOKS, Mareev modification) [14].

Myocardial damage was estimated by the levels of troponin I using a high-sensitivity method hsTn (an ARCHITECT i2000SR analyzer; 99th percentile 12 ng/L). The parameters of tissue hemodynamics were evaluated by the mean blood flow velocity (Vm) and the tissue pulsatility index (PI) (nailfold capillaries) with high-frequency ultrasound Doppler flowmetry (Minimax – Doppler K 20 MHz), which has several differences from laser Doppler flowmetry due to the different properties of waves used [15]. According to the adopted method [15, 16], the sensor was put on the distal phalanx of the second right finger at the angle of 60° without skin compression. The visual and acoustic control of the correctness of its position was implemented. PI was calculated using the formula:

$$PI=((Vps - Vd))/Vm,$$

Where *Vps* is the peak systolic blood flow velocity, and *Vd* is the end-diastolic blood flow velocity [17].

The indicators of myocardial damage and tissue hemodynamics, as well as the echocardiographic data of atrial and ventricular remodeling, were compared before randomization and after 6 months of rate control within the target ranges.

Statistical analysis was carried out using SPSS Statistics version 25.0. Data are presented as the mean±standard

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deviation (M±SD) or the median and interquartile range (Me [25th percentile; 75th percentile]), according to the distribution of data for continuous variables and the rate of identification (%) for categorical variables. The differences between continuous data with normal distribution within the groups were analyzed using the Student's t-test for dependent and independent samples, respectively. Continuous data with the distribution other than normal were compared using the Mann-Whitney U-test for independent samples and the Wilcoxon test for dependent samples. The categorical data were compared using the chi-squared test and Fisher's exact test. The correlations between indicators was assessed using the Spearman's rank correlation coefficient (rs). A scatterplot was built, and a least-squares linear regression line was plotted. The differences were statistically significant with $p<0.05$.

Results

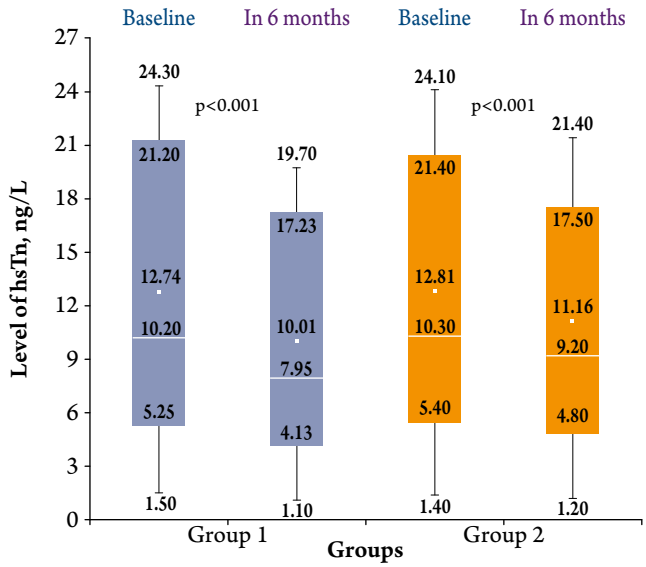
The initial values of the parameters studied were similar in both groups. The median [25th percentile; 75th percentile] of hsTn before randomization was 10.2 [5.25; 21.2] ng/L in Group 1 and 10.3 [5.4; 20.4] ng/L in Group 2 (p=0.91). A total of 48% of patients included in the study had elevated levels of hsTn (above the 99th percentile). In Group 1, Vm in was 2.89±0.10 cm/s, and in Group 2 it was 2.90±0.07 cm/s (p=0.49); PI was 1.43±0.03 and 1.43±0.02 units (p=0.22) in Groups 1 and 2, respectively. Other key characteristics of patients in the groups being compared did not show statistically significant differences (see Table 1). The study included patients with CHF and preserved or midrange LVEF diagnosed according to the algorithm given in the Russian Clinical Guidelines [18].

The target VR range was achieved in 89.5% of patients in Group 1 and 100% in Group 2. The analysis included patients who completed the study protocol.

Resting VR at the end of the bisoprolol titration period was 72±5 bpm in Group 1 (n=34) and 89±6 bpm in Group 2 (n=37) ($p_1<0.001$ vs. the baseline values, $p_2<0.001$ for Group 1 vs. Group 2); at 6-month follow-up these were 70±4 bpm and 88±5 bpm in Groups 1 and 2, respectively (p_1, $p_2<0.001$).

The echocardiographic examinations showed no clinically significant progression of remodeling of the left heart in either group. Within 6 months of VR control, LA dimension was 46.5±4.9 mm in Group 1 (p=0.15 vs. the initial value) and 46.2±3.0 mm in Group 2 (p=0.14)/LA volume indexed to BSA in Groups 1 and 2 was 43.8±4.1 (p=0.09) and 43.2±3.7 mL/m² (p=0.11) and LVEDD was 53.3±6.0 (p=0.15) and 53.2±3.0 mm (p=0.10), respectively.

Figure 1. Changes in resting high-sensitivity troponin I levels



hsTn—high-sensitivity troponin

Under rate control, hsTn significantly decreased in 6 months in both groups. However, a more prominent decrease was observed in the group with the VR range of 60–79 bpm, to 8.0 [4.13; 17, 23] ng/L ($p_1<0.001$ vs. the baseline value) versus 9.2 [4.8; 17.5] ng/L in Group 2 ($p_1<0.001$, $p_2<0.001$ between Group 1 and Group 2). The reduction in Group 1 was 2.0 [1.1, 3.9] ng/L; in Group 2, 1.2 [0.7, 2.7] ng/L (p=0.02) (Figure 1).

Analysis of the correlation between the decrease in VR and level of hsTn identified a weak direct correlation (rs=0.44; p=0.009 in Group 1 and rs=0.41; p=0.01 in Group 2) (Figure 2).

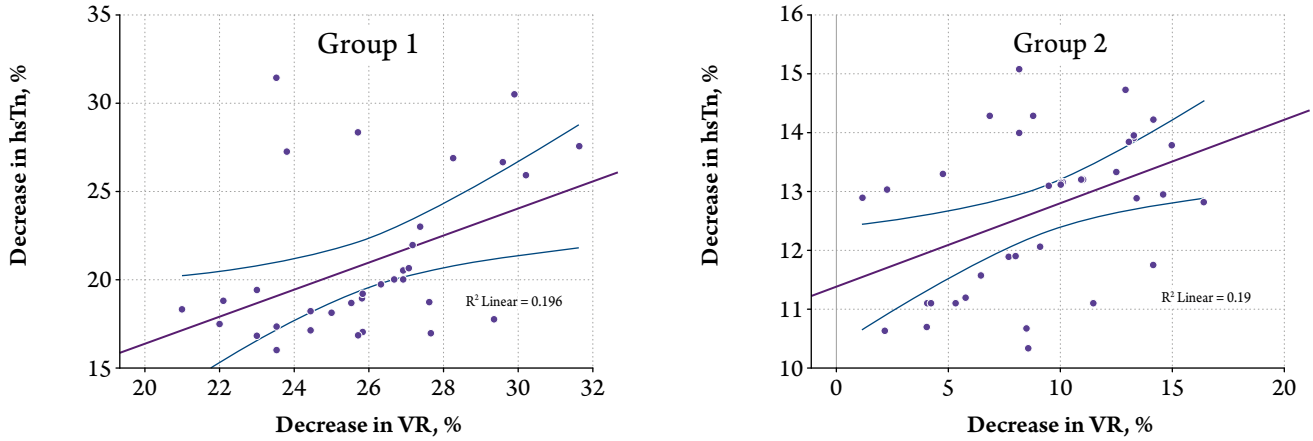
At the same time, there was a trend toward an increase in Vm and a decrease in PI in both groups. This was more pronounced in the group with VR 80–100 bpm. Vm increased to 2.93±0.10 cm/s ($p_1<0.001$ vs. the baseline value) and 3.21±0.09 cm/s ($p_1<0.001$, $p_2<0.001$ in Groups 1 and 2, respectively); PI decreased to 1.42±0.03 ($p_1<0.001$) and 1.34±0.02 units. (p_1, $p_2<0.001$) in Groups 1 and 2, respectively.

Discussion

Our findings show a reduction in myocardial damage in patients with AF with VR control within the ESC-recommended range (60–100 bpm). More significant positive dynamics for hsTn was observed in the group with the target VR range of 60–79 bpm.

Continuous release of cardiac-specific troponin is known in patients with AF [19–21], and a persistent elevation of its level is associated with a worse prognosis than in a transient increase [22]. Analysis of hsTn levels in patients with A in the ARISTOTLE study (Apixaban

Figure 2. Scatterplot demonstrating the correlation of the decrease in VR (%) and the decrease in high-sensitivity troponin I levels (%)



Approximated lines of linear regression and 95% confidence interval (CI) curves were plotted.
Regression coefficient in Group 1, 0.78 (95% CI 0.21–1.3 [p = 0,009]); in Group 2, 0.14 (95% CI 0.04–0.24 [p = 0,007]). VR, ventricular rate.

for the Prevention of Stroke in Subjects with Atrial Fibrillation) identified a relationship of this indicator with an increased risk of stroke, death resulting from cardiovascular causes, and severe bleeding [23]. The ability of drug-induced rate control to influence hsTn levels was observed in a cross-sectional study [24] in 60 patients aged 71±9 years with AF and without CAD and CHF with the alternative administration of diltiazem, verapamil, metoprolol, and carvedilol. (However, no echocardiographic assessment of diastolic function was carried out. Thus, it is not excluded that patients with CHF and preserved EF were included in the study.) Both beta-blockers used in this study reduced resting levels of hsTn by 18% after being administered for 3 weeks: VR was 81±15 bpm for metoprolol and 78±11 bpm for carvedilol. The authors also showed a pronounced positive effect of bisoprolol. As there is only a weak correlation between VR and hsTn levels, in order to make a conclusion on the superiority of one range over the other, not only a decrease in VR under the administered therapy should be taken into account. In the study [25], a reduction of troponin levels was achieved when blood pressure became normal. However, this effect was obtained with the administration of amlodipine and was absent when angiotensin receptor blockers, in combination with hydrochlorothiazide, were used. An increase in cardiac levels of angiotensin II, which causes additional oxidative stress damaging to the LV microvessels, resulting in myocardial ischemia and dysfunction, is assumed to be a mechanism for troponin release in patients with AF [26–28]. The distinction of our study may be the use of a similar therapy in both groups, including an ACE inhibitor combined with bisoprolol, which decreased VR to varying degrees. The fact that there was an equal number of patients in this category in the study groups had a significant effect on the difference in the outcomes of anti-ischemic treatment with beta-blockers in patients with AF as a manifestation of stable CAD.

The presence of CHF must also be taken into account when analyzing the results obtained during the VR, reducing treatment in patients with AF. It has been shown that the elevated levels of hsTn in patients with CHF and preserved EF were associated with an increased number of emergency visits, repeated hospitalizations, and risk of death [29]. In another study [30], 30.2% of patients with CHF and preserved EF had AF, with which the hsTn levels correlated. In general, data on the significant prognostic indicators for patients in this category are still limited, unlike those for patients with CHF with reduced EF. It has been proven that, in such patients, elevated hsTn levels are associated with adverse clinical outcomes even in the absence of coronary complications [31–34]. The early estimation of hsTn has already been recommended for risk stratification in the management of patients with acute heart failure [6]. In our study, patients of both groups had similar severity of CHF.

There is evidence that the violation of tissue hemodynamics plays an essential role in the development of ischemic strokes in patients with AF, as well as cardiogenic thromboembolism. Bokeria et al. [10] showed that patients aged more than 50 years with AF lasting for more than 5 years and ventricular flutter had a significant decrease in Vm, which increases the risk of local clotting in tissues. In our study, adequate rate control had a positive effect on tissue hemodynamics, as shown by high-frequency ultrasound Doppler flowmetry. In the management of elderly patients with permanent AF using bisoprolol, maintenance within the range of 60–79 bpm can be accompanied by a more marked limitation of myocardial damage. However, tissue hemodynamics tend

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to improve in VR within the range of 80–100 bpm. Taking into account the method aspects and significant variability of the observed results, in particular, we noted the trends in Vm and PI in the same patients receiving rate control therapy. The organ-specific nature of microcirculation is also a factor mediating an indirect role of parameters obtained in the assessment of tissue hemodynamics in the nailfold capillaries. However, Bokeria et al. [10] showed that revealing the common pathological tendencies – distal deceleration, in particular – makes it possible to obtain objective data on the increased risk of local clotting. Capillary deceleration increases blood viscosity and low fluid shear stress, and is therefore a reason for the development of endothelial dysfunction in AF. Prolonged exposure to these factors can result in the decompensation of nitric oxide production and progression of the local prothrombotic condition, which increases the risk of ischemic stroke in the cerebral blood flow [35].

Conclusion

Our study showed that during ventricular rate control in patients aged more than 60 years with permanent atrial fibrillation, there was a positive trend in the indicators of myocardial damage (high-sensitivity troponin I) and tissue hemodynamics (mean blood flow velocity and pulsatility index). This finding demonstrates the opportunities for using these parameters to further improve the management of such patients. At the same time, the trends in the opposite direction are likely for the indicators of myocardial damage and tissue hemodynamics within the ventricular rate range of 60–100 bpm. Stricter control of the ventricular rate in permanent atrial fibrillation provides a more significant decrease in myocardial damage. However, the optimal peripheral blood flow can be achieved with a lesser decrease in the ventricular rate within the recommended range. This suggests the possibility of individual selection of the target ventricular rate in permanent atrial fibrillation for selective cardioprotection or improvement of the tissue blood flow, particularly cerebral blood flow..

No conflict of interest is reported.

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