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Features of sinus rhythm restoration in patients with paroxysmal and persistent non-valvular atrial fibrillation and previous COVID-19 infection in iron-deficiency anaemia

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Abstract

Background. Currently, there are conclusive data in the literature on the effect of reduced haemoglobin concentration on sinus rhythm restoration in patients with nonvalvular atrial fibrillation. It is relevant to study the features of rhythm restoration in patients with anaemia and atrial fibrillation in COVID-19 infection.

Aim. To study the effects of iron-deficiency anaemia on sinus rhythm restoration rate and the dose of amiodarone required for this in patients with paroxysmal and persistent non-valvular atrial fibrillation and previous COVID-19 infection.

Methods. The study included 63 patients aged between 53 and 94 years (mean age 60.8±10.9 years): 26 men (41.3%) and 37 women (58.7%). The patients were divided into groups according to the presence of anaemia and computed tomography staging (CT severity score) of lung damage. Criteria for inclusion: paroxysmal or persistent non-valvular atrial fibrillation; previous COVID-infection (according to the documents, medical records). We took into account medical histories, laboratory and instrumental findings, as well as treatment. The statistical analysis was performed by using the Statistica 13.3 software. The obtained data were presented as M±σ or Me [Q_1; Q_3]. The differences between the indicators were assessed using Student's t test, the Mann–Whitney U test and the Kruskal–Wallis H test. Nominal variables were compared by using Pearson's χ^2 test with Yates correction or Fisher's criterion. The relationship between the parameters was assessed using the Pearson's or Spearman's correlation coefficient. A $p < 0.05$ was considered statistically significant.

Results. The patients with normal haemoglobin concentration restored sinus rhythm for 10 [4; 13] hours and the patients with iron-deficiency anaemia — for 5.5 [2; 10] hours ($p=0.044$). In patients with COVID-19 pneumonia, we found a direct correlation between the degree of lung damage and the dose of amiodarone ($r=0.33$, $p < 0.05$), as well as the time of sinus rhythm restoration ($r=0.48$, $p < 0.05$).

Conclusion. The presence of iron-deficiency anaemia in patients with previous COVID-19 infection and paroxysmal and persistent non-valvular atrial fibrillation is associated with a shorter time and a lower dose of amiodarone required for successful sinus rhythm restoration in comparison to patients with normal haemoglobin concentration; in patients with more severe lung damage caused by COVID-19 pneumonia, it takes more time and a large dose of amiodarone for sinus rhythm restoration.

Keywords: COVID-19 pneumonia, anemia, atrial fibrillation, cardioversion.

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Background

Atrial fibrillation (AF) is one of the most common forms of cardiac arrhythmias and is registered in the general population in 1%–2% of cases. The incidence of this pathology increases with age [1]. AF paroxysms account for more than 1/3 of all hospitalizations for arrhythmias [2]. Blood stasis in the left atrium in AF leads to hypercoagulability and an increased risk of thrombotic complications, namely systemic thromboembolism, and ischemic stroke. According to modern approaches to managing AF patients, the sinus rhythm is preferable to be restored [3].

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More than 200 million people worldwide have a history of a new coronavirus infection COVID-19 [4]. Although the primary symptoms of COVID-19 in most cases may be respiratory, several studies have pointed to extrapulmonary effects of the virus [4–6]. This phenomenon is probably due to the body's hyperinflammatory response and the ubiquitous presence in major organs of the cellular receptor of angiotensin-converting enzyme type 2, which the SARS-CoV-2 virus uses to enter cells [7].

In the range of all the systems that can be affected by the virus, the most common extrapulmonary complications can probably develop in the cardiovascular system, with complications such as myocardial injury, cardiomyopathy, acute coronary syndrome, cardiogenic shock, acute cor pulmonale, thrombotic complications, and arrhythmias [8].

Supraventricular arrhythmias are the most common in patients with COVID-19 [9]. According to a rather large study that included 517 patients with COVID-19 pneumonia, arrhythmias of various origins were found in 20.5% of patients. The most common form was AF, which was registered in 10% of cases [10].

Iron metabolism and anemia may be significant in multiple organ dysfunction syndrome in COVID-19. For example, according to Kopina and Gaevsky (2013), the latent hypercoagulable syndrome was revealed in 30.2% of patients with iron deficiency anemia [11]. Meta-analysis performed by Taneri et al. (2020) included 189 unique studies with data from 57,563 patients with COVID-19 [12]. The hemoglobin level was lower in older patients among those admitted to the intensive care unit, and more severe pneumonia has been reported among patients with lower hemoglobin levels.

Given the hypercoagulable background in both AF and COVID-19, the question of the need to restore sinus rhythm as soon as possible arises. According to the latest recommendations for the treatment of AF patients, amiodarone is the drug of choice [1]. However, at the moment, there are no convincing data in the available literature on the effect of a reduced hemoglobin level on rhythm recovery in patients with non-valvular AF. Thus, it seems relevant to study the aspects of rhythm recovery in patients with anemia and AF in case of COVID-19 infection.

This work studies the effect of iron deficiency anemia on the rate of sinus rhythm recovery and the dose of amiodarone required in patients with non-valvular paroxysmal and persistent forms of AF and history of COVID-19 infection.

Materials and methods

The observational study involved 63 patients aged 53 to 94 years (mean age 60.5 ± 11.1 years) hospitalized in the cardiology department of the medical unit of Kazan State Federal University with an event of AF. There were 26 (41.3%) men and 37 (58.7%) women among the patients included. All patients had a history of a new coronavirus infection with different periods from the disease.

The diagnosis of AF was established according to the current recommendations of the Russian Society of Cardiology based on history, physical examination, and electrocardiography [1]. 56 (88.9%) of the 63 patients had paroxysmal AF, and 7 (11.1%) patients had a persistent form. In 30 patients (group 1), the hemoglobin level and serum iron was within the normal range (136.6 ± 9.4 g/l and 19.15 [16.5; 22.3] μmol/l, respectively), while group 2 consisted of 33 a patient with signs of anemia (hemoglobin values less than 130 g/l in men, and less than 120 g/l in women). The average level of hemoglobin in group 2 was 102.9 ± 8.07 g/l, and the serum iron level was 8.4 [7.7; 9] μmol/l.

The following were study inclusion criteria:

– paroxysmal or persistent form of non-valvular AF;

– medical cardioversion with amiodarone;

– a history of new coronavirus infection;

– patient's signed informed consent.

Study non-inclusion criteria:

– myocardial infarction not earlier than one month before inclusion in the study;

– stroke within the last six months;

– cancer disease in the active stage;

– hypertrophic and dilated cardiomyopathy.

Study exclusion criteria:

– the occurrence of a severe cardiovascular event (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke);

– withdrawal of informed consent.

For all patients, anamnesis data were collected, including past illnesses, the presence of AF symptoms at the time of examination and their duration (hours), the presence of previously registered AF paroxysms, and the time from the last episode to hospitalization (in months), and the recentness of COVID before admission to the hospital (months). The history of COVID-19 infection was established according to the submitted extract.

In the presence of COVID-pneumonia, the severity of lung damage was recorded according to the medical documents provided. There was no information on lung involvement in 14 patients; in eight patients, no lung involvement was detected according to x-ray computed tomography; and the lung involvement was determined by CT 1–4 in 41 patients.

The risk of stroke and systemic embolism was calculated using the CHA2DS2-VASc[1] scale in points.

Body mass index (kg/m^2) was calculated for all patients., Laboratory tests were performed, including complete blood count, biochemical blood tests (glucose, creatinine, urea, and potassium levels), and blood test to determine the concentration of thyroid-stimulating hormone (TSH, mU/l) and brain natriuretic peptide (NT-proBNP, ng/ml).

All patients underwent echocardiography to determine the volume of the left atrium, end-diastolic dimension (EDD) of the left ventricle (LV), end-systolic dimension (ESD) of the LV, LV ejection fraction, the systolic pressure in the pulmonary artery, LV myocardial mass (LVMM), and signs of diastolic dysfunction of the LV.

Patients were administered amiodarone intravenously at 5 μg/kg to restore sinus rhythm. If necessary, the daily dose could be increased to 15 μg/kg. We considered the dose of amiodarone used for pharmacological cardioversion and the time from the start of amiodarone administration to the restoration of sinus rhythm (hours).

Statistical analysis was performed using the Statistica 13.3 program (StatSoft. Inc.). Quantitative indicators were evaluated for compliance with the normal distribution using the Shapiro–Wilk test. The data obtained for quantitative indicators with a normal distribution are presented as the arithmetic mean values and their standard deviations ($M \pm \sigma$). Sets of quantitative indicators with a distribution other than normal are described using the values of the median, 25%, and 75% quartiles (Me [Q_1; Q_3]). When comparing mean values in normally distributed sets of quantitative data, Student's *t*-test was calculated, and in cases without normally distributed data, the Mann–Whitney *U*-test was used. The statistical significance of differences in quantitative indicators with an abnormal distribution was assessed using the Kruskal–Wallis test.

Pearson's correlation coefficient was used as to indicate the closeness of the relationship between quantitative indicators with a normal distribution. Spearman's rank correlation was used in the absence of a normal distribution. At a correlation coefficient value less than 0.19, the correlation was very weak; it was weak at a value of 0.20–0.29; it was moderate at 0.30–0.49; and at a value greater than 0.70, it was strong. Nominal data were compared using Pearson's χ^2 test with Yates correction or Fisher's exact test. Differences in indicators were considered statistically significant at p less than 0.05.

[1]CHA2DS2-Vasc — risk score for stroke and systemic thromboembolism in patients with AF.

The study protocol was approved by the local ethics committee of Kazan State Medical University.

Results

Most of the 63 patients included in the study had one or more complaints during the AF paroxysm, and only six (9.5%) patients had asymptomatic AF. The risk of stroke and systemic embolism was assessed using the CHA2DS2-VASc scale. A score lower than 2 was determined in 16 (61.5%) men, and that of 2 points or more was noted in 10 (38.5%) men. A total score lower than 3 was noted in two (64.9%) women, and that of 3 points or more was revealed in 13 (35.1%) women.

Nineteen (30.2%) patients had a normal body mass index, 35 (55.6%) patients were overweight, grade 1 obesity was revealed in six (9.5%) patients, grade 2 obesity was detected in two (3.2%) cases, and one (1.6%) patient had grade 3.

Analysis of comorbidities showed that in group 1, 12 (40%) patients had type 2 diabetes mellitus (DM2), 22 (73.3%) patients had arterial hypertension, five (16.7%) patients had a history of myocardial infarction, and six (20%) patients had an acute cerebrovascular accident. In group 2, DM2 was registered in 17 patients (51.5%, $p > 0.05$), arterial hypertension was noted in 29 patients (87.9%, $p > 0.05$), the history of myocardial infarction was revealed in seven patients (21.2%, $p > 0.05$), and five patients (15.2%, $p > 0.05$) had an acute cerebrovascular accident. The incidence of DM2, arterial hypertension, myocardial infarction, and the acute cerebrovascular accident did not differ in the groups.

At the time of admission to the hospital, the recentness of COVID-19 disease ranged from one to nine months (median 3 [2; 4] months). There were no differences between groups 1 and 2 ($p > 0.05$). At the same time, when comparing echocardiographic data and laboratory parameters, it was established that LVMM and the serum level of NT-proBNP both at admission and one month after the rhythm recovery in group 2 were significantly higher than in group 1 (Tables 1, 2).

It should be noted that LV diastolic dysfunction was more common in group 2 in 18 (54.5%) patients, while in group 1, it was detected in only eight patients (26.7%, $p = 0.047$).

All patients underwent pharmacological cardioversion with intravenous amiodarone at admission. Sinus rhythm was restored in 56 patients. Most of the patients who failed to restore the rhythm were in group 1 (six patients, 20%), and only one (3.03%) such patient was in group 2 ($p = 0.04$).

In addition, we revealed that the dose of amiodarone, which led to the successful resto-

Table 1. Clinical and laboratory parameters in patient groups

Parameters	Group 1 (n = 30)	Group 2 (n = 33)	p
Age, years	58.6 ± 11.2	62.9 ± 11.1	> 0.05
Recentness of COVID-19 infection, months	3 [2; 4]	3 [2; 5]	> 0.05
BMI, kg/m^2	26.2 [24.7; 27.4]	25.6 [24.8; 27.5]	> 0.05
Hemoglobin, g/l	136.6 ± 9.4	102.9 ± 8.07	0.001
Erythrocytes, ×10^{12}/L	4.82 ± 0.6	3.83 ± 0.5	0.001
Platelets, ×10^9/L	256.9 ± 57.4	256.5 ± 60.9	> 0.05
Glucose, mmol/l	5.74 [5.17; 7.2]	6.1 [5.34; 7.5]	> 0.05
Creatinine, μmol/l	67.8 ± 19.7	69 ± 15.4	> 0.05
Urea, mmol/l	5.96 [4.8; 7]	5.88 [4.5; 6.9]	> 0.05
Potassium, mmol/l	4.14 ± 0.26	4.1 ± 0.42	> 0.05
Thyroid-stimulating hormone, mIU/l	2.06 [1.19; 3.32]	1.65 [0.8; 3.24]	> 0.05
NT-proBNP at admission, ng/ml	171.5 [120; 300]	356 [130; 546]	0.022
NT-proBNP after 1 month, ng/ml	77.5 [60; 97]	112 [80; 211]	0.011
Serum iron, μmol/l	8.1 ± 1.2	7.9 ± 1.13	> 0.05

Note: BMI—body mass index; NT-proBNP—brain natriuretic peptide.

Table 2. Echocardiographic parameters in study group patients

Parameters	Group 1 (n = 30)	Group 2 (n = 33)	p
LVMM, g	123.1 ± 20.9	141.5 ± 39.1	0.025
LA volume, ml	71.5 [63; 75]	75 [60; 90]	> 0.05
LV EF, %	59.5 [57; 62]	58 [56; 61]	> 0.05
LV EDD, cm	5.04 ± 0.44	4.95 ± 0.52	> 0.05
LV ESD, cm	3.3 [3.2; 3.7]	3.4 [3; 3.7]	> 0.05
PASP, mm Hg	31 [28; 37]	32 [29; 38]	> 0.05

Note: LVMM—left ventricle myocardium mass; LA—left atrium; EF—ejection fraction; LV—left ventricle; EDD—end-diastolic dimension; ESD—end-systolic dimension; PASP—pulmonary artery systolic pressure.

ration of sinus rhythm, was lower in the group of patients with anemia. In group 1, the median dose of amiodarone used was 600 [450; 800] mg, and in group 2, it was 450 [300; 600] mg (p = 0.018). Similar results were obtained concerning the time from the beginning of amiodarone administration to the restoration of sinus rhythm. In group 1, the median time was 10 [4; 13] h, and in group 2, it was 5.5 [2; 10] h (p = 0.044).

Correlation analysis showed a direct moderate relationship between the level of hemoglobin and the dose of amiodarone (r = 0.38, p = 0.004), as well as the time required to restore the sinus rhythm (r = 0.35, p = 0.008), in all patients included in the study. Rhythm recovery time was also directly correlated with patient age (r = 0.39, p = 0.003), and amiodarone dose was inversely correlated with LV ESD (r = -0.36, p = 0.007). The inverse correlation between rhythm recovery time and amiodarone dose with the recentness of COVID-19 infection was of great interest (r = −0.31, p = 0.022 and r = −0.3, p = 0.025, respectively).

In group 1, a direct correlation of the sinus rhythm recovery time with patient age was determined (r = 0.6, p = 0.02). In addition, a correlation was found between age and body mass index (r = −0.43, p = 0.02) and LVMM (r = 0.4, p = 0.03). In group 2, an inverse correlation was noted between the amiodarone dose and LV ESD (r = −0.45, p = 0.009). In addition, a direct correlation was established between the erythrocyte count in the blood and echocardiographic parameters such as LV ESD and LV EDD (r = 0.42, p = 0.02 and r = 0.44, p = 0.01, respectively), and inverse correlation between hemoglobin and TSH levels (r = −0.38, p = 0.03).

Patients who had pneumonia associated with COVID-19 were distributed into three subgroups according to their lung damage severity. Group 1 included 16 patients with CT 1 and Group 2 included 18 patients with CT 2. Since the lesion volume of CT 4 was registered in only one patient, group 3 consisted of seven patients with CT 3 and CT 4. Data from laboratory and echocardiographic parameters, the amiodarone dose, and the

Table 3. Clinical and laboratory-instrumental parameters of patients with different degrees of lung lesions

Parameters	Subgroup 1 (CT 1, $n = 16$)	Subgroup 2 (CT 2, $n = 18$)	Subgroup 3 (CT 3 and CT 4, $n = 7$)	Significance level
NT-proBNP at admission, ng/ml	187.5 [145.5; 370]	343 [130; 440]	120 [100; 580]	$p > 0.05$
NT-proBNP after 1 month, ng/ml	101.5 [62; 211.5]	94.5 [69; 178]	65 [64; 165]	$p > 0.05$
Hemoglobin, g/l	103.5 [97.5; 125]	110.5 [98; 137]	112 [101; 131]	$p > 0.05$
Erythrocytes, $\times 10^{12}$/L	3.91 [3.66; 4.41]	4.1 [3.56; 4.76]	4.21 [3.26; 5.22]	$p > 0.05$
TSH, mIU/l	3.1 [1.69; 4.01]	2.13 [0.6; 5.7]	0.9 [0.5; 1.1]	$p = 0.06$
LVMM, g	113 [106; 153.5]	132.5 [110; 152]	155 [125; 176]	$p > 0.05$
LV EDD, cm	4.8 [4.6; 5.15]	5.2 [4.6; 5.4]	4.9 [4.7; 5.1]	$p > 0.05$
LV ESD, cm	3.3 [3.2; 3.55]	3.65 [2.9; 3.7]	3.3 [3.1; 3.7]	$p > 0.05$
LA volume, ml	71 [59.5; 79.5]	71.5 [63; 90]	74 [65; 93]	$p > 0.05$
PASP, mm Hg	30 [27.5; 37]	30.5 [28; 42]	37 [30; 44]	$p > 0.05$
Amiodarone dose, mg	450 [150; 450]	600 [300; 600]	600 [550; 600]	$p_{1-3} = 0.04$
Rhythm restoration time, h	3 [2; 5]	7 [3; 12]	10 [8; 10]	$p_{1-3} = 0.04$

Note: CT 1–4—the degree of lung damage according to computed tomography; NT-proBNP—brain natriuretic peptide; TSH—thyroid-stimulating hormone; LVMM—left ventricle myocardial mass; EDD—end-diastolic dimension; LV—left ventricle; ESD—end-systolic dimension; LA—left atrium; PASP—pulmonary artery systolic pressure.

time to restore the sinus rhythm are presented in Table 3.

We revealed that between patient subgroups 1 and 3, there was a significant difference in parameters, such as the time to restore sinus rhythm and the effective dose of amiodarone required to restore the sinus rhythm. Correlation analysis showed that in patients who had pneumonia associated with COVID-19, there is a direct moderate relationship between the degree of lung damage according to computed tomography and the amiodarone dose ($r = 0.33$, $p < 0.05$) and the time to restore the sinus rhythm ($r = 0.48$, $p < 0.05$). In addition, a tendency toward the lowest level of TSH among patients with the greatest lung involvement should be noted.

Subgroup 1 patients declared the absence of repeated arrhythmia during the follow-up period (12 months). At the same time, almost all subgroup 2 and 3 patients noted episodes repeated AF paroxysms during this period. The shortest period of sinus rhythm retention was recorded in subgroup 3 ($p = 0.02$).

Discussion

Our results suggest that anemia in AF patients after COVID-19 infection contributes to the efficiency of pharmacological cardioversion. Previous studies have shown that a new coronavirus infection can affect the functioning of almost all human organs and systems even after clinical recovery [7].

Our study demonstrated that in AF patients with anemia, who have had COVID-19, the level of NT-proBNP was increased upon admission. It is essential that even one month after cardioversion in this patient group, the level of the N-terminal precursor NT-proBNP remained higher than in the group without anemia. The changes revealed in NT-proBNP are used as an indicator of more pronounced myocardial dysfunction, which can significantly worsen the prognosis in this patient category.

Echocardiography showed a larger median LVMM in group 2. Our data correlate well with the results obtained by international authors that anemia, even in the absence of other cardiovascular factors, contributes to an increase in myocardial mass due to a compensatory increase in its contractility [13]. This process can subsequently lead to the development of diastolic dysfunction [14]. Indeed, in group 2, the proportion of patients with diastolic dysfunction was significantly higher than in group 1.

For us, the issue of the influence of comorbid conditions in AF patients for the sinus rhythm restoration period and the required dose of an antiarrhythmic drug was relevant. Thus, in group 2, the rhythm was restored significantly more often, faster, and required a lower dose of amiodarone.

Correlation analysis of the entire study cohort showed that the dose of amiodarone sufficient for effective cardioversion and the time of the sinus rhythm recovery are associated with the hemoglobin level. The shorter it is, the lower the required amiodarone dose, and the faster the rhythm is

restored. We have not found any publications on this issue in the scientific literature. Obviously, according to our results, the presence of anemia in AF patients who have had COVID-19 infection may have the well-known risk of worsening further prognosis and a beneficial effect on emergency care efficiency in an arrhythmia episode, which, at first glance, looks like a paradox.

We also established that the time required to restore the sinus rhythm during pharmacological cardioversion also increases with increasing patient age. Some echocardiographic parameters were also associated with age. The older the patient was in group 1, the higher was the LVMM and the calculated systolic pressure values in the pulmonary artery. However, in group 2, the value of age is leveled, and blood counts come to the fore. For example, a decrease in the number of erythrocytes is accompanied by a decrease in LV EDD and LV ESD, which, in the absence of heart failure symptoms, can be considered a compensatory mechanism, as mentioned above [13]. A decrease in the hemoglobin concentration in our patient cohort correlates with an increase in the TSH level. Indeed, TSH metabolism can indirectly influence iron deficiency and lead to anemia. At the same time, studies indicate the opposite effect when the existing anemia contributes to hypothyroidism development over time [15].

In addition to AF, all the studied patients were united by a history of COVID-19 infection. The results of our study showed the role of the recentness of a new coronavirus infection in the restoration of the sinus rhythm. The less time passed since disease onset, the greater the dose of amiodarone the patient needs to stop an episode of AF. This may be because myocarditis often occurs in COVID-19 with myocardial involvement. In this case, inflammatory tissue increases in the effective refractory period resulting in an increase in drug dose. Our data indicate that the volume of lung damage affects medical cardioversion. However, these issues require further study in a larger number of patients.

Conclusions

1. The presence of iron deficiency anemia in patients with a history of COVID-19 infection and non-valvular (AF) is associated with a shorter time and lower dose of amiodarone required to restore the sinus rhythm successfully compared with patients with normal hemoglobin levels.

2. In patients with more severe lung disease induced by COVID infection, more time and a higher dose of amiodarone are required to restore the sinus rhythm.

Author contributions: M.H.V. collected the data, analyzed and interpreted the results, proposed the discussion and conclusions on the work; N.R.H. performed the scientific guidance, and corrected the main sections of the article.

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Conflict of interest: The authors declare no conflict of interest.

Study limitations: The study included a small number of patients. Clarification of the significance of anemia during cardioversion in patients with paroxysmal and persistent forms of AF, with a history of COVID-19, requires further study.

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