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Original article

Arterial hypertension and COVID-19 in Arctic rotating shift work: the impact of chronostructure disruptions on circadian blood pressure rhythm in relation to echocardiographic parameters

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Abstract: This study investigated the effects of chronostructure disruptions on circadian blood pressure (BP) rhythms and their association with echocardiographic parameters in men with arterial hypertension (AH) who contracted COVID-19 while engaged in rotating shift work in the Arctic.

Methods – A random sample of 166 men with arterial hypertension (AH) was selected from the medical records database of patients treated at the hospital of the Medical Unit of Gazprom Dobycha Yamburg LLC in Yamburg (Nadymsky District, Russia, 68° 21' 40" N) between June 2020 and March 2021. Randomization was achieved using a random number method. These patients underwent echocardiography (ECHO) and 24-hour ambulatory blood pressure monitoring (ABPM) before the COVID-19 pandemic (November 2019 to March 2020) and again in 2021. The group was then divided into those who had contracted COVID-19 (n=94) and those who had not (n=72). ABPM was performed using a BPLab v.3.2 device (BPLab, Russia). Chronobiological analysis was performed to identify the main hypertensive BP chronotypes (CT) based on the P. Cugini classification: "MESOR AH", characterized by a 24-hour rhythm period (T); and "Aperiodic AH", characterized by a predominance of oscillations with periods (T) of 4.0, 4.8, 6.0, and 8.0 hours within the circadian rhythm. Echocardiography (ECHO) was performed using a Philips CX 50 scanner (Netherlands).

Results – Logistic regression analysis showed that the presence of the "Aperiodic AH" chronotype was associated with a threefold increase in the odds of contracting COVID-19, while a 1 g/m² increase in the left ventricular mass index (LVMI) increased these odds by a factor of 1.02. One year post-COVID-19, individuals with "Aperiodic AH", in contrast to those with "MESOR AH", exhibited increases in right atrial and inferior vena cava diameters, systolic pulmonary artery pressure, tricuspid regurgitation velocity, stroke volume, and cardiac output, as well as a more pronounced increase in left ventricular mass and LVMI. Associations were observed between structural alterations in the heart and parameters that reflect disruptions in the circadian BP rhythm.

Conclusion – Within the context of Arctic rotating shift work, men with arterial hypertension (AH) exhibiting a disrupted chronostructure of the circadian BP rhythm, characterized by a predominance of irregular, short-term oscillations, and structural alterations in the heart, are more susceptible to COVID-19. This increased susceptibility is associated with more pronounced alterations in echocardiographic parameters following the infection.

Keywords: arterial hypertension, blood pressure chronostructure, chronotypes, Arctic, COVID-19.

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Introduction

The long-term consequences of coronavirus infection are still under extensive investigation due to numerous unresolved issues [1]. Scientific inquiry is focused on examining both the risk factors for disease susceptibility [2] and long-term alterations in organs and systems [3]. Determinants of variable susceptibility to the SARS-CoV-2 virus primarily include genes associated with the initial stages of infection, such as cell surface receptor binding and viral penetration [4]. Arterial hypertension (AH) is also associated with increased susceptibility to COVID-19 infection, attributable to key pathophysiological mechanisms of AH, such as activation of the

renin-angiotensin-aldosterone system [5]. However, the direct role of arterial hypertension (AH), independent of age and comorbidities, as a risk factor for infection and COVID-19 outcomes, has not yet been definitively determined.

Researchers are particularly interested in the structural and functional alterations in the heart and blood vessels occurring during both the acute and long-term phases of COVID-19, yet findings remain inconsistent.

For example, Golukhova E.Z. et al. (2020) identified signs of progressive right ventricular dysfunction in patients who had contracted COVID-19. Depending on the observation period, the

authors developed a prognostic model for adverse outcomes in patients with COVID-19, based on the identification of echocardiographic (ECHO) factors: right ventricular (RV) dysfunction, systolic pulmonary artery pressure (SPAP), the degree of RV longitudinal contractility, and right atrial (RA) volume [6]. Simultaneously, it is suggested that pulmonary hemodynamic disorders be considered and interpreted within the context of left ventricular (LV) dysfunction and valvular abnormalities [7]. In another study, the clinical manifestations of COVID-19 did not clearly correlate with echocardiographic alterations in the patients examined [8]. According to Ovrebotten T., et al. (2022), dyspnea and tachycardia that persisted for an extended period after COVID-19 were not confirmed by progressive alterations in cardiac structure and function [9]. At present, it remains unclear whether specific long-term manifestations of COVID-19 infection exist in patients with arterial hypertension (AH), based on the current understanding of the shared pathogenesis of these conditions [10].

The cardiovascular system has a distinct circadian organization, including specific biorhythms that are synchronized with the sleep-wake cycle [11]. Circadian rhythms of blood pressure (BP) and heart rate (HR) are regulated by biological clocks located in the suprachiasmatic nucleus of the hypothalamus [13]. Humoral mediators and the autonomic nervous system (ANS) serve as the effectors that transmit information from the “central” clock to target organs, synchronizing the “peripheral” clock with the “central” clock [12]. The circadian organization of living organisms is well established, serving as a critical component in the activity of

the neuro-endocrine-immune system that maintains homeostasis [13].

Individuals working rotating shifts in the Arctic experience stress from harsh climate conditions, altered photoperiodism, and frequent trans-latitude travel, which strains adaptive mechanisms [14]. This can result in autonomic nervous system (ANS) dysregulation, manifesting as reduced overall tone and parasympathetic activity [15], desynchronization of physiological rhythms, and the development of desynchronization [16]. In recent years, the utility of a chronobiological approach has been convincingly demonstrated across a broad spectrum of experimental and clinical medicine.

This approach has been applied to investigate the pathogenetic mechanisms of circadian BP rhythm disruption in the development of AH, structural and functional remodeling of the left ventricular (LV) myocardium, and the rationale for chronotherapy in the treatment of AH in the Far North [17-20].

The central hypothesis of this study is that working rotating shifts in the Arctic predisposes individuals to desynchronization of the “central” circadian clock, and to a concomitant chronobiological imbalance in the regulation of circadian rhythms of blood pressure (BP), the heart, blood vessels, and immune system cells. Therefore, disruptions in the circadian BP rhythm may serve as a marker of altered immunity and may manifest as both an increased risk of susceptibility to COVID-19 infection and as specific alterations in the heart as observed by echocardiography (ECHO) in the post-COVID period, which is the focus of this study.

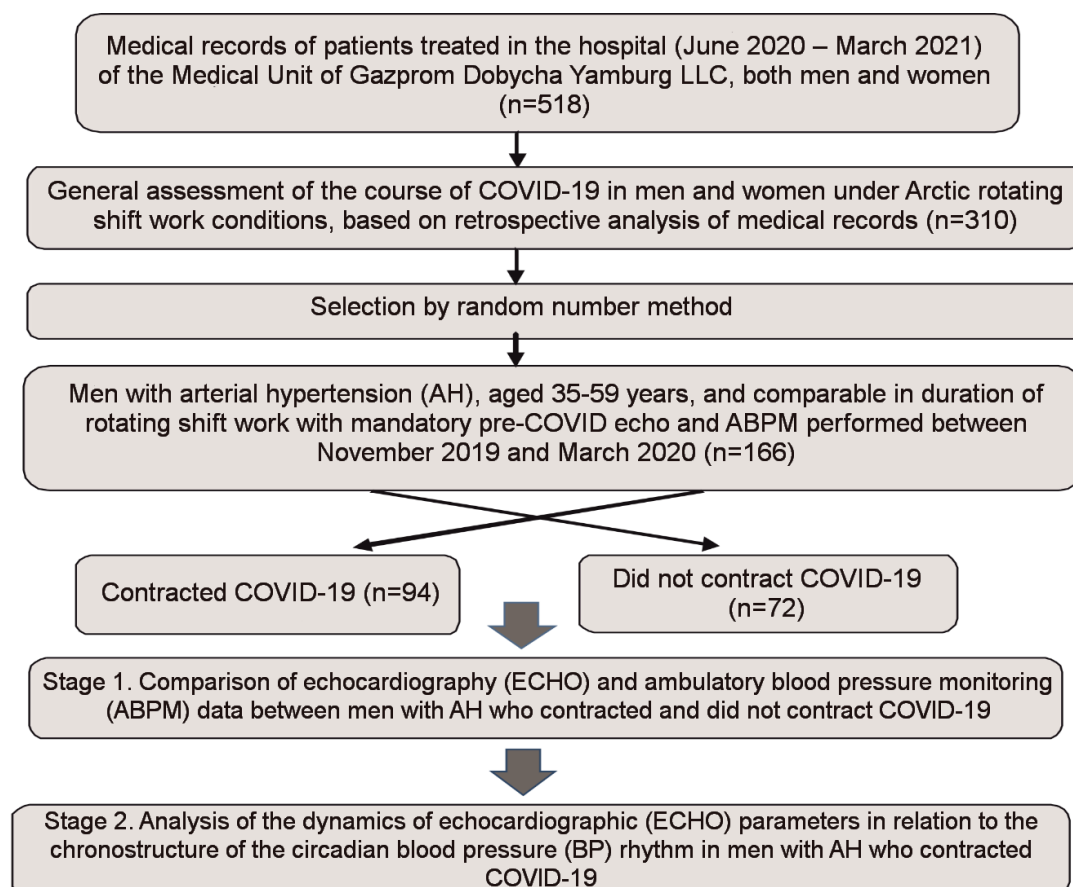


Figure 1. Study design.

Table 1. Comparability of groups of men with ah who contracted and did not contract COVID-19 by age, duration of rotating shift work, and office SBP/DBP

Parameter	Contracted COVID-19	Did Not Contract COVID-19	p
n	94	72	
Age (years)	51.3±7.9	49.0±8.0	0.066
Rotating Shift Work Experience (years)	23.0±8.1	20.7±9.9	0.096
SBP, mm Hg	148.2±17.4	147.1±12.7	0.651
DBP, mm Hg	96.7±8.2	98.0±9.2	0.358

DBP, diastolic blood pressure; SBP, systolic blood pressure; p, level of significance of differences between the “contracted COVID-19” and “did not contract COVID-19” groups. Student’s t-test was used. Differences were considered significant at $p < 0.05$.

Table 2. Comparative analysis of medication use in patients with AH by drug class

Drug	Contracted COVID-19 (n=94)	Did Not contract COVID-19 (n=72)	p
ACE inhibitors	29 (31.1%)	19 (25.7%)	0.530
Angiotensin II receptor antagonists (ARAI)	12 (13.1%)	7 (11.4%)	0.542
Calcium channel blockers (CCB)	6 (6.6%)	4 (4.5%)	1.000
Beta-blockers (β-AB)	7 (8.2%)	8 (10.6%)	0.414
Combination drugs	7 (8.2%)	6 (9.1%)	0.833
HMG-CoA reductase inhibitors (statins)	28 (29.5%)	19 (26.6%)	0.630
Other drugs	6 (6.6%)	3 (6.8%)	0.733
Irregular use of medications	40 (57.4%)	26 (36.2%)	0.265

ACE, angiotensin-converting enzyme; ARAII, angiotensin II receptor antagonists; CCB, calcium channel blockers; β-AB, beta-adrenergic blockers; ACEI, angiotensin-converting-enzyme inhibitor.

Table 3. Calculation of odds ratios for COVID-19 probability in rotating shift workers with AH

Covariate	B	P	OR	- 95% CI	+95% CI
Aperiodic AH	1.070	0.004	2.917	1.410	6.035
LVMI	0.017	0.039	1.017	1.001	1.033
Constant	-1.669	0.042	0.188	-	-

B, covariate coefficient value; p, level of significance of differences between the groups (differences were significant at $p < 0.05$); OR, odds ratio, 95% CI=95% confidence interval; LVMI, left ventricular mass index.

Study Aim: To evaluate the effect of chronostructure disruption on the circadian rhythm of arterial blood pressure and its association with echocardiographic (ECHO) parameters in patients with AH who contracted COVID-19 during rotating shift work in the Arctic.

Material and Methods

Object and Study Design

A random sample of 166 men with arterial hypertension (AH) was selected from the medical records database of patients treated at the hospital of the Medical Unit of Gazprom Dobycha Yamburg LLC in Yamburg (Nadymy District, Russia, 68° 21' 40" N) between June 2020 and March 2021. Randomization was achieved using a random number method. These patients underwent echocardiography (ECHO) and 24-hour ambulatory blood pressure monitoring (ABPM) before the COVID-19 pandemic (November 2019 to March 2020). All patients in the selected group underwent repeat testing (ABPM, ECHO) between June 2021 and March 2022,

one year after contracting COVID-19, or for those with no history of COVID-19. The inclusion criteria were the absence of any history of ischemic heart disease, diabetes mellitus, heart rhythm disorders, or their complications. For comparison purposes, the patients were divided into subgroups of those who contracted COVID-19 (n=94) and those who did not (n=72). The diagnosis of COVID-19 was based on the detection of SARS-CoV-2 RNA using polymerase chain reaction (PCR) in patients with AH at the hospital of Gazprom Dobycha Yamburg LLC during hospitalization for COVID-19. This work is part of a larger study, and the study design is shown in [Figure 1](#).

A retrospective review of patient medical records indicated that all patients who contracted COVID-19 at the hospital experienced moderate disease with predominantly lung involvement, classified as CT (computed tomography) grade 1 (0-24.9% lung tissue involvement on CT) in 65.2% of patients and CT grade 2 (25.0-49.9% lung involvement) in 17.8% of patients; there were no recorded fatalities.

Patients were hospitalized in the infectious disease department of the hospital upon the first signs of an acute respiratory illness. Groups of men engaged in interregional rotating shift work from regions with a temperate climate (Russian cities of Tyumen and Ufa) underwent mandatory 2-week observation periods in base cities, followed by air transport on a special flight to the shift settlement. Between 2020 and 2021, 97% of all sequenced strains in the Russian Federation were identified as the Delta variant. (https://ru.wikipedia.org/wiki/COVID-19_в_России — (wikipedia.org), retrieved on June 3, 2024). The diagnosis of AH was confirmed using medical history, medical record data, and outpatient charts, as well as a cardiologist’s assessment. Ambulatory blood pressure monitoring (ABPM) was performed using a standardized method with a BPLab v.3.2 device (BPLab, Russia). The groups who contracted and did not contract COVID-19 were comparable in age, years of rotating shift work experience, and clinic SBP/DBP ([Table 1](#)). Before the application of the BP monitor, clinic BP was measured, and data on antihypertensive therapy were recorded.

Approximately half of the patients with AH in both groups, those who contracted and those who did not contract COVID-19, reported inconsistent use of antihypertensive medication, citing the mild or asymptomatic nature of their condition, or infrequent episodes of elevated blood pressure, as reasons for nonadherence. In terms of antihypertensive therapy, the men with AH who contracted and did not contract COVID-19 did not significantly differ during the study period, as they received virtually identical medications under the medical unit’s cardiovascular disease prevention program. Most commonly, patients with AH received angiotensin-converting enzyme inhibitors or sartans without substantial therapy adjustments throughout the study period ([Table 2](#)).

Chronobiological and spectral analysis of ABPM data was performed using computer software to determine blood pressure (BP) chronotypes (CT) according to the Cugini P. classification [21], which identified four main hypertensive BP CTs: “MESOR AH”, characterized by mesor values (midline-estimating statistic of rhythm) $>140/90$ mm Hg, with amplitude and phase within the normal range, and a 24-hour rhythm period (T); “Amplitude AH”, characterized by partially increased mesor values and a pronounced increase in rhythm amplitude (>20 mm Hg), with (T)=24 hours; and “Aperiodic AH”, characterized by increased

mesor values, low or undefined amplitude, an undefined rhythm period (T), and oscillations in the blood pressure (BP) rhythm spectrum with periods (T) equal to 3.43, 4.8, 6.0, 8.0 hours (short-term oscillations in the circadian BP rhythm); “Phase AH”, characterized by partially increased mesor values and an inverted rhythm phase (insufficient decrease or increase in blood pressure (BP) at night), with (T)=24 and 12 hours. The spectral analysis method of successive harmonics involves multiples of the primary (24-hour) rhythm, with the successive harmonics derived by dividing 24 by 2, 3, 4, 5, 6, 7, and 8 (24/2=12 hours; 24/3=8 hours; 24/4=6 hours; 24/5=4.8 hours; 24/6=4 hours; 24/7=3.43 hours; 24/8=3 hours). These values represent the duration of the periods in hours. The diagnostic and clinical significance of chronostructure disruption of the circadian blood pressure (BP) rhythm, as well as the identification of BP chronotypes according to the Cugini P. classification, in individuals with high and normal BP has been repeatedly demonstrated in independent studies [18-20].

Echocardiography (ECHO) was performed using a Philips CX 50 expert-class ultrasound scanner (Netherlands), using generally accepted methods according to the guidelines of the European Association of Echocardiography [22].

Statistical Analysis

Data were analyzed using Statistica 8.0 (StatSoft, USA) and IBM SPSS Statistics (versions 16.0.0.0 and 26, USA). Parametric and non-parametric statistical methods were employed for quantitative variables, depending on the type of data distribution. In cases of normal distribution, Student's t-test was used to compare two independent groups; if data were not normally distributed, the non-parametric Mann-Whitney U test was applied. The chi-square test was applied for the analysis of categorical variables. Correlation analysis was performed using parametric Pearson and non-parametric Spearman methods. Stepwise logistic regression, including the analysis and construction of the ROC curve, was used to evaluate the sensitivity and specificity of the developed COVID-19 risk model, based on structural changes in the heart and chronobiological parameters of the BP rhythm. The Wilcoxon signed-rank test was used to assess the changes in absolute values within two dependent groups, while the McNemar test was applied to assess the changes in categorical variables within dependent groups. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

In our previous work aimed at identifying factors associated with COVID-19, logistic regression was conducted. Parameters that were significantly different between the groups of men who contracted (n=94) and did not contract (n=72) COVID-19, as measured during the pre-COVID period, were included in the model: left ventricular mass (LVM) and left ventricular mass index (LVMI) (p=0.010 and p=0.028, respectively); relative wall thickness of the LV (RWT) (p=0.003), interventricular septum (IVS) (p=0.009), posterior wall of the LV (PWL) (p=0.010); ambulatory blood pressure monitoring (ABPM) data: SBPn (p=0.051), DBP24 (p=0.041), HR24 (p=0.054), HRn (p=0.049); and blood pressure (BP) chronotype (CT), including “Aperiodic AH” (p=0.002) and “MESOR AH” (p<0.0001). Based on the results of the stepwise logistic regression analysis and the calculation of odds ratios, two factors associated with COVID-19 in patients with AH working rotating shifts in the Arctic were identified ([Table 3](#)).

Chronobiological analysis indicated that the presence of the “Aperiodic AH” chronotype in patients increased the odds of contracting COVID-19 threefold (95% CI: 1.410-6.035, p=0.004). Structural changes, specifically a 1 g/m² increase in LVMI, increased these odds by a factor of 1.02 (95% CI: 1.001–1.033, p=0.039). The model demonstrated a specificity of 81% and a sensitivity of 77.2%. The overall predictive power was 77.1%, with an area under the ROC curve of 0.888.

Based on the results of the logistic regression analysis, we hypothesized the possible presence of more pronounced alterations in echocardiographic (ECHO) parameters in patients with “Aperiodic AH” following COVID-19. To investigate this, we analyzed the changes in structure and function of the left ventricular (LV) myocardium in patients with “Aperiodic AH” (n=44) and “MESOR AH” (n=52), characterized by a normal (24-hour) circadian blood pressure (BP) rhythm, after they contracted COVID-19. The “Aperiodic AH” chronotype (CT), unlike “MESOR AH”, is characterized by the absence of a 24-hour circadian blood pressure (BP) rhythm, and is defined by short-term BP oscillations with periods ranging from 3.43 to 4.8, 6.0, 8.0 hours, which distort the circadian BP curve. The groups were comparable by age (p=0.929), length of work experience in the Far North (p=0.119), and shift work experience (p=0.223).

Initially, during the pre-COVID period, patients with “Aperiodic AH”, compared to those with “MESOR AH”, demonstrated significant differences in left atrial (LA) volume and index (p=0.049 and p=0.045, respectively), peak tricuspid regurgitation (TR) velocity (p=0.053), and relative wall thickness (RWT) of the left ventricle (LV) (p=0.046). No significant differences were found for left ventricular mass (LVM) and left ventricular mass index (LVMI), although these values were higher in patients with “Aperiodic AH”.

Table 4. Dynamic structural changes in the heart in men with “Aperiodic AH” and “MESOR AH” who contracted COVID-19

Parameter	Pre-COVID-19	Post-COVID-19	p
Aperiodic AH (n=44)			
LA (volume, mL)	47.3±16.7	49.9±14.1	0.098
RA (volume, mL)	40.5±14.2	45.4±15.8	0.005
SPAP (mm Hg)	21.4±4.4	24.1±6.2	0.018
IVC (mm)	21.1±1.9	22.4±2.1	0.004
IVS (diastole, mm)	1.17±0.18	1.24±0.18	0.001
PWL (diastole, mm)	1.15±0.17	1.22±0.16	0.003
LVEDD (mm)	5.1±0.4	5.2±0.4	0.006
LV SV (mm)	85.7±18.7	95.5±23.5	0.017
LVO (L/min)	6.3±1.7	7.1±2.1	0.020
E' wave (cm/s)	9.1±1.2	8.6±1.2	0.064
Peak TR velocity (m/s)	190.9±67.9	193.7±67	0.003
LVM (g)	230.6±55.3	265.3±62.5	<0.0001
LVMI (g/m ²)	105.8±22.9	121.1±24.1	<0.0001
MESOR AH (n=52)			
LA (volume, mL)	43.3±16.7	46.9±11.2	0.060
IVC (mm)	21.1±1.6	22.1±1.9	0.093
IVS (diastole, mm)	1.12±0.2	1.25±0.21	<0.0001
PWL (diastole, mm)	1.11±0.18	1.24±0.16	0.001
LVM (g)	206.4±32.6	242.1±33.8	<0.0001
LVMI (g/m ²)	99.1±14.3	116.4±24.2	0.001

The Wilcoxon signed-rank test was used to assess the significance of differences between time points. PWLV, posterior wall of the left ventricle; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVM, left ventricular mass; LVMI, left ventricular mass index; IVS, interventricular septum; LVO, left ventricular output; IVC, inferior vena cava; RV, right ventricle; RA, right atrium; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; LV SV, left ventricular stroke volume.

Table 5. Dynamics of blood pressure (BP) chronotypes in men with AH who contracted and did not contract COVID-19.

Parameter	Pre-COVID-19	Post-COVID-19	p
Contracted COVID-19 (n=94)			
Normotension	0 (0%)	0 (0%)	1.000
Iso-normotension	7 (7.6%)	8 (8.7%)	1.000
Allo-normotension	2 (2.2%)	8 (8.7%)	0.070
MESOR AH	40 (43.5%)	23 (25%)	0.018
Aperiodic AH	40 (43.5%)	63 (68.5%)	0.041
Amplitude AH	1 (1.1%)	1 (1.1%)	1.000
MESOR Phase AH	4 (4.3%)	10 (10.9%)	0.180
Did Not Contract COVID-19 (n=72)			
Normotension	1 (1.6%)	18 (29.5%)	0.014
Iso-normotension	1 (1.6%)	1 (1.6%)	1.000
Allo-normotension	1 (1.6%)	4 (6.6%)	0.375
MESOR AH	45 (73.8%)	27 (44.3%)	<0.0001
Aperiodic AH	14 (23%)	8 (13.1%)	0.424
Amplitude AH	0 (0%)	1 (1.6%)	1.000
MESOR Phase AH	0 (0%)	2 (3.3%)	0.500

The McNemar p-criterion was used to assess the significance of differences between the first and second measurements.

Table 6. Correlation analysis of the association between main structural heart parameters as measured by echocardiography and dominant harmonics of the blood pressure rhythm in patients with ah before and after COVID-19

Parameter	Pre-COVID-19	Post-COVID-19
LA Diameter and T6.0	-	r=0.302; p=0.049
RV Diameter and T12.0	-	r=0.337; p=0.027
RV Diameter and T8.0	r=0.292; p=0.053	-
SPAP and T3.43	-	r=0.277; p=0.047
SPAP and T8.0	r=0.308; p=0.045	-
RWT and T8.0	-	r=0.327; p=0.032
LVM and T3.43	-	r=0.261; p=0.044
IVC Diameter and T8.0	r=0.434; p=0.004	-
IVC Diameter and T6.0	r=0.310; p=0.043	-

Spearman correlation analysis was used. LA, left atrium; LV, left ventricle; LVM, left ventricular mass; RV, right ventricle; SPAP, systolic pulmonary artery pressure; RWT, relative wall thickness of the LV; IVC, inferior vena cava. T (rhythm period), 3.43, 4.8, 6.0, 8.0 hours (high-frequency periodicities in the BP rhythm spectrum).

As presented in [Table 4](#), the changes observed in patients with “Aperiodic AH” who contracted COVID-19, compared to patients with the “MESOR AH” chronotype (CT) at the initial ambulatory blood pressure monitoring (ABPM), included more pronounced structural alterations, such as a significant increase in right atrial (RA) volume ($p=0.005$), an increase in systolic pulmonary artery pressure (SPAP) ($p=0.018$), an increase in the diameter of the inferior vena cava ($p=0.004$), and peak tricuspid regurgitation velocity ($p=0.003$), as well as a significant increase in hemodynamic parameters: stroke volume ($p=0.017$) and cardiac output ($p=0.020$). Conversely, changes in these parameters in patients with “MESOR AH” were not significant. Notably, in patients with “Aperiodic AH”, both before and after COVID-19, left ventricular mass (LVM) and left ventricular mass index (LVMI) values were significantly higher compared to those with “MESOR AH”.

Analysis of changes in AH chronotypes revealed a significant decrease in the number of individuals with “MESOR AH” in both those who contracted and those who did not contract COVID-19 (from 43.5% to 25%, $p=0.018$, and from 73.8% to 44.3%, $p<0.0001$, respectively) ([Table 5](#)). In the group that did not contract the infection, the decrease in “MESOR AH” frequency was associated

with a significant increase in the frequency of the normotensive blood pressure (BP) chronotype (CT) ($p=0.014$) and a non-significant decrease (from 23% to 13%) in the frequency of “Aperiodic AH”. In the group that contracted COVID-19, this was due to a significant increase in the number of individuals with “Aperiodic AH” (from 43.5% to 68.5%, $p=0.041$), with no significant change in the frequencies of normotensive chronotypes (CTs).

The correlation analysis confirmed the findings, revealing a clear, direct association between the disturbed chronoperiodicity of the diurnal blood pressure rhythm and echocardiographic (ECHO) parameters in patients with AH who subsequently contracted COVID-19, as well as those who had recovered from the infection ([Table 6](#)).

For example, men with AH who subsequently contracted COVID-19 showed direct correlations between systolic pulmonary artery pressure (SPAP) and the 8.0-hour period (T) ($r=0.308$; $p=0.045$); inferior vena cava (IVC) diameter and the 8.0-hour period (T) ($r=0.434$; $p=0.004$); IVC diameter and the 6.0-hour period (T) ($r=0.310$; $p=0.043$); right ventricular (RV) diameter and the 8.0-hour period (T) ($r=0.292$; $p=0.053$). These correlations indirectly support the association between disruption of the chronostructure of the circadian blood pressure (BP) rhythm and changes in parameters that reflect the load on the right heart chambers. This was further substantiated by the correlations observed between alterations in echocardiographic (ECHO) parameters and the dominant short-term rhythms in the circadian blood pressure (BP) spectrum: left atrial (LA) diameter and the 6.0-hour period (T) ($r=0.302$; $p=0.049$); right ventricular (RV) diameter and the 12.0-hour period (T) ($r=0.337$; $p=0.027$); systolic pulmonary artery pressure (SPAP) and T3.43 ($r=0.277$; $p=0.047$); left ventricular mass (LVM) and the 3.43-hour period (T) ($r=0.261$; $p=0.043$); and relative wall thickness of the left ventricle (LV) and the 8.0-hour period (T) ($r=0.327$; $p=0.032$). However, these correlations were not significant in patients who did not contract COVID-19.

Discussion

The COVID-19 pandemic has posed a significant challenge to global healthcare, impacting various organs and systems of human physiology, including circadian rhythms [23–25]. Scientific interest in the COVID-19 pandemic is further driven by its function as an epidemiological model, allowing for the accumulation of scientific data to combat particularly dangerous infections in the future.

Despite the unprecedented quarantine measures implemented in the region, the COVID-19 pandemic also affected Arctic rotating shift workers. Preventative measures included a preliminary 2-week observation period, the provision of medical care in situ (at the Yamburg Medical Unit), and the option of emergency evacuation for critically ill patients to nearby northern cities (Novy Urengoy, Nadym, and Salekhard). Given the significant importance of the northern (Arctic) regions to the Russian economy, and the necessity of preserving the health of workers in these regions, it became imperative to investigate factors that may increase both the risk of infection and exacerbate the long-term effects of COVID-19 on the cardiovascular system.

Individuals working rotating shifts in the Arctic experience stress from harsh climate conditions and altered photoperiodism, which strains adaptive mechanisms, manifesting as a “syndrome of incomplete adaptation” and the desynchronization of physiological rhythms. Occupational stress associated with rotating shift work

results in increases in heart rate and blood pressure (BP) due to heightened sympathetic activity, which also disrupts circadian rhythms [26] and dysregulates the autonomic nervous system (ANS), manifesting as a reduction in overall ANS tone and parasympathetic activity. These factors contribute to the development of chronobiological imbalance (desynchronization).

To confirm the working hypothesis that desynchronization of the circadian blood pressure (BP) rhythm may increase susceptibility to COVID-19 infection and contribute to more pronounced alterations in echocardiographic (ECHO) parameters in the post-COVID period in patients with AH, we performed a search and analysis of these associations.

Numerous studies investigating the novel coronavirus infection in relation to AH (without comorbidities) are largely inconsistent and are currently under active investigation.

Emerging data indicate that individual variations in circadian rhythms may affect susceptibility to COVID-19 infection and its sequelae. For example, studies [27, 28] have demonstrated that circadian rhythms play a critical role in adaptive and innate immune responses, and their misalignment can alter the response to vaccination [29].

Our study showed that patients with AH who have a disrupted chronostructure of the circadian blood pressure (BP) rhythm are more susceptible to COVID-19 infection. For instance, according to logistic regression analysis, the probability of contracting COVID-19 in individuals with AH decreased with a normal 24-hour circadian BP rhythm and increased threefold when there was a disruption of the chronostructure of the circadian BP rhythm (characterized by a replacement of the 24-hour rhythm with dominant short-term oscillations in the circadian spectrum).

The results of our study are consistent with data from Biswas M., et al. (2021), who showed that work-related circadian rhythm disturbances in rotating shift work are associated with an increased risk of contracting COVID-19, irrespective of occupation. When examining the conditions for the development of COVID-19, the authors found that constant rotating shift work increased the probability of contracting COVID-19 by a factor of 2.5, even after controlling for other factors, including age, gender, and smoking [30]. Another study also showed that disruption of the light–dark cycle and rotating shift work significantly increased the risk of contracting COVID-19 [31].

The changes in blood pressure (BP) chronotypes in patients with AH who contracted and did not contract COVID-19 showed a significant decrease in the number of individuals with a 24-hour rhythm (“MESOR AH”) in both groups, and a significant increase in the “Aperiodic AH” chronotype only in patients with AH after contracting COVID-19, indicating a further deterioration in the chronostructure of the circadian BP rhythm in the post-COVID period.

Recent studies have emphasized the importance of circadian rhythm stability for both susceptibility to SARS-CoV-2 infection and recovery from COVID-19, including cases of long COVID, as well as the severity of alterations in organs and systems following the infection [32, 33].

Disruption of regulation by the “central” clock of the circadian rhythm across all systems, including components of the peripheral nervous system, contributes to the disruption of the body’s homeostasis. The autonomic nervous system (ANS) plays a crucial homeostatic role through its effects on organs, systems, and immune cells, which may manifest as immune system dysfunction,

endothelial dysfunction, and systemic manifestations, such as phenotypes of premature aging, including organ fibrosis and tissue degeneration. Furthermore, it has been hypothesized that COVID-19 infection affects the ANS [34].

Thus, chronobiological imbalance resulting from autonomic nervous system (ANS) dysfunction and manifesting as a disruption in the chronostructure of the circadian blood pressure (BP) rhythm in patients with AH may increase susceptibility to COVID-19 infection, leading to a further deterioration of the circadian BP rhythm following the infection.

While the necessity for widespread use of echocardiography (ECHO) was considered controversial at the beginning of the pandemic, the method is now recognized as a critical tool for evaluating the prognosis and severity of the sequelae of the disease [35]. Additionally, according to the results of clinical studies, MRI, and echocardiography (ECHO) data obtained during the pre-COVID period, cardiac damage during and after COVID-19 was frequently observed in patients without a prior history of cardiovascular diseases [36]. Other data confirm that myocardial damage caused by SARS-CoV-2 may exhibit specific patterns of left ventricular (LV) deformation, even in patients with mild and moderately severe disease [37].

Analysis of the changes in heart structure in patients with AH who contracted COVID-19 while working rotating shifts in the Arctic revealed a significant increase in the load on the right heart chambers, including increases in right atrial (RA) volume, systolic pulmonary artery pressure (SPAP), inferior vena cava diameter, tricuspid regurgitation velocity, a more pronounced increase in left ventricular mass (LVM) and left ventricular mass index (LVMI), and a significant increase in hemodynamic parameters (stroke volume and cardiac output) as a manifestation of heightened sympathetic activity. These alterations were observed in patients exhibiting a disruption of the chronostructure of the circadian rhythm with “Aperiodic AH” compared to “MESOR AH.”

The results obtained are consistent with data from other authors, who showed that the most frequently encountered cardiac alterations in individuals who had contracted COVID-19 are disturbances in right ventricular (RV) systolic function, manifestations of pulmonary hypertension, and systolic and diastolic dysfunction of the left ventricle (LV) [38].

Our study has shown that disruption of the chronostructure of the circadian blood pressure (BP) rhythm in patients with AH may be associated with both an increased risk of contracting COVID-19 and more pronounced alterations in echocardiographic (ECHO) parameters following infection, alongside a worsening circadian BP rhythm.

Regrettably, there are currently no studies in the available literature addressing the structural and functional state of the left ventricle (LV) in relation to alterations in the chronobiology of the circadian blood pressure (BP) rhythm in patients with AH after COVID-19, which underscores the importance and relevance of conducting such studies.

The issue of the association between chronobiological imbalance and structural alterations in the heart in patients with AH in the Far North remains unresolved, although it is of substantial interest from both a scientific and practical perspective. Furthermore, the development of desynchronization is associated with alterations in the synthesis of melatonin and its immunotropic effects, which are linked to its action through

melatonin receptors on immunocompetent cells and its activating effect on cytokine production by these cells [39].

Thus, this study has revealed that COVID-19 more frequently affected patients with pre-existing structural alterations in the heart combined with chronobiological disruptions in the circadian blood pressure (BP) rhythm. In addition, COVID-19 infection in men with AH who had contracted the disease contributed to a more pronounced subsequent increase in left ventricular mass, alterations in the right heart chambers (including an increase in systolic pulmonary artery pressure [SPAP]), and an increased disruption of the circadian blood pressure (BP) rhythm. These findings allow for an indirect assessment of the body's immune resistance and the identification of patients with a disrupted architecture of the circadian blood pressure (BP) rhythm and structural alterations in the heart as the most susceptible and at risk for infections. Such patients should be considered a special group for dispensary monitoring within a rotating shift work medical facility.

Further research is necessary, as the study of existing interactions between infections and circadian rhythms, including blood pressure (BP), substantiates their influence on the body's susceptibility, immunity, severity, and sequelae of diseases, and suggests that the use of "clock mechanisms" may lead to new opportunities for countering epidemics in the future.

Conclusion

Within the context of Arctic rotating shift work, patients with arterial hypertension exhibiting a disrupted chronostructure of the circadian blood pressure (BP) rhythm and structural alterations in the heart are the most sensitive and susceptible to COVID-19 infection. This increased susceptibility is associated with more pronounced alterations in echocardiographic (ECHO) parameters and further deterioration of the circadian BP rhythm following COVID-19 infection.

Limitations

The overall sample size in this study is a limitation. Therefore, the interaction between infection and circadian blood pressure (BP) rhythms, particularly under the desynchronizing conditions of the Far North and rotating shift work, requires further investigation.

Authors' Contributions

Shurkevich N.P., Vetoshkin A.S., and Kareva M.A. conceived and designed the study; Shurkevich N.P., Vetoshkin A.S., Kareva M.A., and Gubin D.G. processed the data; Shurkevich N.P. and Vetoshkin A.S. wrote the manuscript; and Shurkevich N.P., Vetoshkin A.S., and Gubin D.G. edited the manuscript.

Ethical Approval

This retrospective analysis was performed as part of routine clinical practice. Patients provided written informed consent for data processing in accordance with Order # 36/1 dated January 29, 2020, and using an approved informed consent form. The comprehensive examination of patients was conducted in accordance with the ethical standards of the Declaration of Helsinki and the rules of clinical practice in the Russian Federation (2005) ["Good Clinical Practice", Russian state standard GOST R 52379-2005], based on a protocol approved by the Academic Council of the Tyumen Cardiology Research Center and the institutional ethics committee # 149 dated June 3, 2019. The study participants were offered the

opportunity to participate in the research project, and after providing a positive response, they all signed a voluntary informed consent form. This cross-sectional study, "Light Arctic", adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Tyumen State Medical University (protocol # 101 dated September 13, 2021). All participants provided written informed consent.

Conflict of Interest

The authors declare that they have no competing interests.

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