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# Hydrogen inhalation in rehabilitation program of the medical staff recovered from COVID-19

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Active hydrogen inhalation ($H(H_2O)_m$) has powerful antioxidant and antiapoptotic effects. In recent years, it has been used in a number of experimental and clinical studies.

**Aim.** To study the safety and effectiveness of inhalation of the "active form of hydrogen" (AFV;($H(H_2O)_m$)) in the rehabilitation program of coronavirus disease 2019 (COVID-19) survivors during the recovery period.

**Material and methods.** This randomized controlled parallel prospective study included 60 COVID-19 survivors with post-COVID-19 syndrome (ICD-10: U09.9) during the recovery period, with clinical manifestations of chronic fatigue syndrome (CFS), who received standard therapy in accordance with the management protocol of patients with CFS (ICD-10: G93.3): physiotherapy and medication therapy with drugs containing magnesium, B vitamins and L-carnitine. The patients were divided into 2 groups. The experimental group (n=30) included patients who received hydrogen inhalation for 90 minutes every day during 10 days (SUISONIA hydrogen inhalation device, Japan). The control group (n=30) consisted of patients who received standard therapy. In both groups, patients were comparable in sex and mean age: in the experimental group — 53 (22; 70) years, in the control group — 51 (25; 70) years. Biological markers of systemic inflammation, oxygen transport, lactate metabolism, intrapulmonary shunting, 6-minute walk test, and vascular endothelial function were determined in all patients on the 1st and 10th days of follow-up.

**Results.** In the experimental group, a decrease in following parameters was revealed: stiffness index (SI), from 8,8±1,8 to 6,8±1,5 (p<0,0001); ALT, from 24,0±12,7 to 20,22±10,61 U/L (p<0,001); venous blood lactate, from 2,5±0,8 to 1,5±1,0 mmol/L (p<0,001); capillary blood lactate, from 2,9±0,8 to 2,0±0,8 mmol/L (p<0,0001); estimated pulmonary shunt fraction (Qs/Qt, Berggren equation, 1942) from 8,98±5,7 to 5,34±3,2 (p<0,01); white blood cells, from 6,64±1,57 to 5,92±1,32 $10^9$/L. In addition, we revealed an increase in the refractive index (RI) from 46,67±13,26% to 63,32±13,44% (p<0,0001), minimum blood oxygen saturation ($SpO_2$) from 92,25±2,9 to 94,25±1,56% (p<0,05), direct bilirubin from 2,99±1,41 to 3,39±1,34 μmol/L (p<0,01), partial oxygen tension ($PvO_2$) from 26,9±5,0 to 34,8±5,6 mm Hg (p<0,0001), venous oxygen saturation ($SvO_2$) from 51,8±020,6 to 61,1±018,1% (p<0,05), partial capillary oxygen tension ($PcO_2$) from 48,7±15,4 to 63,8±21,2 mm Hg (p<0,01), capillary oxygen saturation ($ScO_2$) from 82,2±4,2 to 86,2±4,8% (p<0,01), distance in 6 minute walk test from 429±45,0 to 569±60 m.

**Conclusion.** Inhalation therapy with $H(H_2O)_m$ in the rehabilitation program of COVID-19 survivors during the recovery period is a safe and highly effective method. Manifestations of silent hypoxemia and endothelial dysfunction decreased, while exercise tolerance increased. As for laboratory tests, a decrease in the white blood cell count, estimated pulmonary shunt fraction and lactate content parameters was revealed.

**Keywords:** hydrogen, active hydrogen ($H(H_2O)_m$), COVID-19, post-COVID-19 syndrome, rehabilitation, lactate, oxygen transport, silent hypoxemia.

**Relationships and Activities:** none.

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## Introduction

The positive effect of hydrogen in pathological conditions has been known since the 1880s. Despite this, the medical community did not pay attention to its properties until the XX century. Recent research, both fundamental and clinical, has confirmed that hydrogen is an important physiological regulatory factor with antioxidant, anti-inflammatory and antiapoptotic properties.

This study is based on the therapeutic effects of hydrogen inhalation (AFV;$(H(H_2O)_m)$)[1]. Hydrogen is the simplest molecule and was previously considered an inert gas. It plays an important role in redox reactions, through which it regulates the functioning of antioxidant system.

Under normal conditions, the hydrogen molecule is inactive. A bond's strength between atoms in a hydrogen molecule is 2,3 eV. To break this bond, additional energy is needed. For this purpose, the SUISONIA system (Japan) is used, with the help of which the hydrogen supplied from metal hydride storage through the nasal cannula into the human body is in a chemically active state. In addition, AFV;$(H(H_2O)_m)$ has geometric size 2 times smaller than the initial molecule and, accordingly, has twice the penetrating power. For this reason, the use of AFV;$(H(H_2O)_m)$ obtained from metal hydride storage for inhalation is more effective.

For the first time, the favorable effects of AFV;$(H(H_2O)_m)$ inhalation were reported in 1975 after an experiment on a mouse model of squamous cell carcinoma of the skin [1]. Over the past two decades, more than 1000 papers have been published on the effectiveness of AFV;$(H(H_2O)_m)$. Hydrogen, having antioxidant and anti-apoptotic properties, functions as a "selective" scavenger of hydroxyl radicals (•OH) and peroxynitrite (ONOO-), which was confirmed in 2007 by Ohsawa I, et al. [2].

AFV;$(H(H_2O)_m)$ inhibits oxidative stress-induced inflammatory tissue injury by reducing the concentration of proinflammatory and inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor-α [3, 4], as well as other biological compounds, for example, Intercellular adhesion molecule-1, high-mobility group protein B1 (HMGB1) [5], nuclear factor κB (NF-κB) [6] and prostaglandin E2 [7]. AFV;$(H(H_2O)_m)$ improves survival and reduces organ injury by reducing the level of cytokines and other pro-inflammatory compounds in serum and tissues [8].

AFV;$(H(H_2O)_m)$ effectively penetrates into biomembranes and reaches cell nuclei and mitochondria. In addition, it can easily penetrate the blood-brain barrier by gas diffusion, while most antioxidant compounds do not have this ability [9].

[1] Japanese authors suggest using the term "active form of hydrogen" (AFH;$(H(H_2O)_m)$).

Analysis of previous studies on AFV;$(H(H_2O)_m)$ effectiveness revealed its favorable effect in diseases such as sepsis, multiple organ dysfunction syndrome, as well as during convalescence [10].

AFV;$(H(H_2O)_m)$ can inhibit collagen-induced platelet aggregation [11].

Another study showed that the gaseous hydrogen molecule and hydrogen-rich saline have a protective effect against oxidative damage to organs, including lungs and brain [12].

Based on the literature data, an assumption was made about the effectiveness of using AFV;$(H(H_2O)_m)$ during long-term period after coronavirus disease 2019 (COVID-19) to reduce hypoxemia, metabolic disorders, intoxication and chronic fatigue syndrome (CFS).

The aim of this collaborative study with Japanese colleagues was to study the safety and effectiveness of AFV;$(H(H_2O)_m)$ inhalation in the rehabilitation program of COVID-19 survivors during the recovery period.

Work on the use of AFV;$(H(H_2O)_m)$ inhalation in a rehabilitation program for COVID-19 survivors has been performed for the first time.

## Material and methods

This randomized controlled parallel-group prospective study included 60 patients (medical staff of the D. D. Pletnev City Clinical Hospital (Moscow)) from May to November 2020 with post COVID-19 condition (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10): U09.9) [13] during the recovery period, with clinical manifestations of CFS. All participants received standard therapy according to the protocol for managing patients with CFS (ICD-10: G93.3): physiotherapy and medication therapy with drugs containing magnesium, B vitamins and L-carnitine. The patients were divided into 2 groups: group 1 (experimental) — 30 people who received standard therapy and AFV;$(H(H_2O)_m)$ inhalation for 10 days, group 2 (control) — 30 medical workers who received only standard therapy. The distribution of study participants into the experimental or control group was carried out using a random number generator. Detailed patient characteristics are presented in Table 1.

All patients included in the study received treatment for COVID-19 pneumonia during the acute disease phase in accordance with the temporary guidelines on Prevention, Diagnosis and Treatment of Coronavirus Disease 2019 (Version 5, 6, 7).

The study was approved by the local ethics committee of the D. D. Pletnev City Clinical Hospital (Moscow) № 10-20 dated April 20, 2020.

**Inclusion criteria.** Patients: 1) staff of the D. D. Pletnev City Clinical Hospital (Moscow); 2) age >18 years; 3) negative SARS-CoV-2 nucleic acid test using the polymerase chain reaction at the time of the study; 4) documented computed tomography (CT) of the lung with COVID-19 signs (ground-glass opacities); 5) 2 major and at least 6 minor diagnostic signs of CFS (ICD-10: G93.3) (periodic or worsening periods of fatigue, unrefreshing sleep, poor exercise tolerance, general muscle weakness, sleep disturbances, psychoemotional

**Table 1**

Patients characteristics at the time of enrollment Me ($Q_{25}$;$Q_{75}$)

| Parameter | Control group, n=30 | Experimental group, n=30 | p |
|---|---|---|---|
| Age (years) | 51 (25; 70) | 53 (22; 70) | p=0,738 |
| Sex (m/f) | 4/26 | 5/25 | p=0,718 |
| Period after COVID-19 (months) | 7 (1; 9) | 7 (2; 9) | p=0,668 |
| BMI (kg/m$^2$) | 30 (23,3; 47,5) | 29 (19,72; 56,1) | p=0,738 |
| Heart rate (bpm) | 76 (63; 98) | 78 (53; 93) | p=0,945 |
| $SpO_2$, % | 97 (94; 99) | 97 (94; 99) | p=0,437 |
| Number of smokers (n) | 6 | 8 | p=0,542 |
| Number of health workers with prior chronic respiratory diseases (n) | 3 | 5 | p=0,448 |
| Number of health workers with prior allergic diseases (n) | 8 | 10 | p=0,574 |

Note: BMI — body mass index.

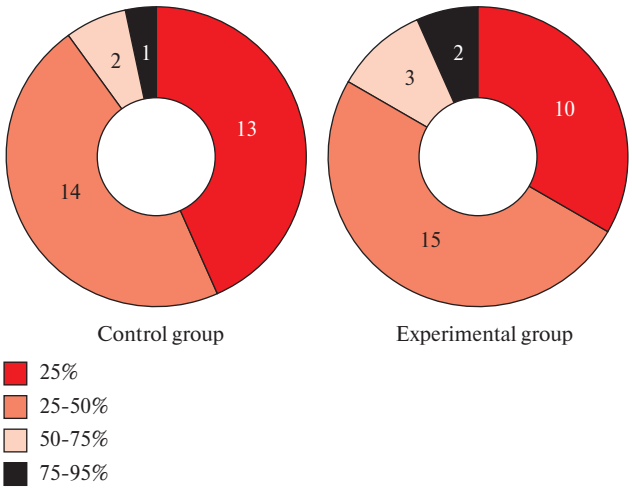



*Figure 1* Severity of lung involvement in patients according to CT data in the acute COVID-19.


*Figure 2* Study design.

disturbances, impairment of memory and attention, severe headaches that were not previously observed); 6) no signs of respiratory disorders (cough, sputum, shortness of breath).

**Exclusion criteria.** 1) need of respiratory support; 2) acute and decompensated heart failure; 3) acute and exacerbated chronic respiratory failure; 4) stroke during the prior 6 months; 5) myocardial infarction during the prior 6 months; 6) decompensated diabetes mellitus; 7) pregnancy; 8) long-term (>14 days) immunosuppressive therapy (including topical and systemic glucocorticoids or immunomodulatory (antiviral) drugs) during the prior 6 months; 9) prior cancer.

All patients signed informed consent, which meets the requirements of Declaration of Helsinki and UNESCO Declaration "Universal Declaration on Bioethics and Human Rights".

Examination of patients revealed the problem of overweight and obesity. Characteristics of the lung involvement in patients according to CT of the lungs in the acute COVID-19 period is shown in Figure 1.

**Study design.** Prior to randomization, all patients were assessed for respiratory rate, heart rate, blood pressure (BP). According to echocardiography, cardiac output and mean pulmonary artery pressure were assessed. In addition, chest CT, pulse oximetry ($SpO_2$), and spirometry data were assessed. After randomization, on the 1$^{st}$ and 10$^{th}$ days, the following parameters were evaluated: endothelial function using plethysmography (stiffness index (SI)), reflection index (RI). In addition, capillaroscopy, pulse oximetry ($SpO_2$), 6-minute walk test were performed. The following parameters of the gas composition of arterial, venous and capillary blood were assessed: pH, arterial partial pressure of oxygen ($PaO_2$), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial oxygen saturation ($SaO_2$); bicarbonate ion ($HCO_3^-$) and lactate concentration in arterial blood, venous partial pressure of oxygen ($PvO_2$), venous partial pressure of carbon dioxide ($PvCO_2$), venous blood saturation ($SvO_2$); $HCO_3^-$ and lactate concentration in venous blood, capillary partial pressure of oxygen ($PCO_2$), capillary partial pressure of carbon dioxide ($PcCO_2$), capillary blood saturation ($ScO_2$), $HCO_3^-$ and lactate concentration in capillary blood. We calculated intrapulmonary shunting (Qs/Qt) according to Berggren's equation (1942). We also evaluated complete blood count (hemoglobin, leukocytes, neutrophils, lymphocytes, platelets), biochemical (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, ferritin, C-reactive protein, procalcitonin) and coagulation blood tests. The study design presented in Figure 2 was approved at a international meeting of the working group participants on November 19, 2020 (Protocol № 3).

**Inhalation therapy with active hydrogen.** Inhalation therapy with AFV;($H(H_2O)_m$) was carried out through a nasal cannula (Intersurgical Ltd, Great Britain) connected to SUISONIA system (Japan). All patients underwent the

*Figure 3* Patients during the atomic hydrogen rehabilitation program.

10-day 90-minute hydrogen inhalation therapy according to instructions and work experience of Japanese colleagues (Figure 3).

**Statistical analysis.** Group randomization and statistical analysis were performed using GraphPad Prism 8 and STATISTICA 12.0 software. The distribution normality was assessed using the Shapiro-Wilk test. The groups were randomized according to the initial quantitative indicators using the unpaired t-test and the Mann-Whitney test. The qualitative comparison was performed using the $\chi^2$ test with Yates' correction. In order to establish the simultaneous effect of the group and the exposure duration, as well as to assess the interaction between these factors, two-way analysis of variance (ANOVA) was carried out. For pairwise comparison of groups, paired and unpaired t-tests were used to analyze dependent and independent samples, respectively. For pairwise comparison of groups with non-normal distribution, the Wilcoxon and Mann-Whitney tests were used for dependent and independent samples, respectively. Removing outliers was performed using the ROUT criterion at Q not >1%. Qualitative data were described by absolute (n) and relative frequencies (%). Quantitative variables are presented as mean values ± standard deviation (Mean±SD) or median (Me) with interquartile range ($Q_{25}$; $Q_{75}$). Differences were considered significant at $p<0,05$.

## Results

During AFV;($H(H_2O)_m$) inhalation therapy, there were no objective, procedure-related side effects in patients. On the 3rd, 3 participants dropped out from the control group, and 2 patients — in the experimental group on the 2nd and 3rd days due to non-compliance with protocol requirements and signed informed consent.

As a result, there were 27 and 28 patients in the experimental and control groups, respectively. All the results obtained were divided into blocks of clinical studies: vascular endothelial function; systemic inflammation markers; 6-minute walk test; oxygen transport and intrapulmonary shunting.

**Vascular endothelial function**

Initially, the SI value in control group, on average, was 8,1±2,0 m/s, and in experimental one, — 8,8±1,8 m/s, $p>0,05$. Against the background of AFV;($H(H_2O)_m$) inhalation therapy in the control group there was a slight increase in SI from 8,19±2,0 to 8,5±2,0 m/s, while in the experimental one, on the contrary, there was a significant decrease in SI from 8,8±1,8 to 6,8±1,5 m/s (by 23±3%) ($p<0,0001$), which also significantly differed from control group at follow-up endpoint ($p<0,01$).

The mean RI of pulse wave in the control and experimental groups initially differed as follows: 59,5±11,86 and 46,67±13,27%, respectively ($p<0,01$). After 10-day AFV;($H(H_2O)_m$) inhalation therapy, there were no changes in the control group in this indicator. In the experimental group, there was a significant increase in RI from 46,67±13,26 to 63,32±13,44% ($p<0,0001$). In all patients, the initial vascular pattern was depleted: capillary network density was reduced. After inhalation, the number of capillaries increased by 1 mm in the length of distal phalanx of each finger, while the size, width, length and diameter of capillaries changed. Figure 4 shows a photograph of capillaroscopy of one of the subjects before and after AFV;($H(H_2O)_m$).

**Markers of systemic inflammation**

The results of systemic inflammation dynamics are presented in Table 2, which shows that only white blood cell level changed, which in the experimental group significantly decreased on the 10th day.

**Biochemical blood tests**

When comparing the results of inhalation therapy on the 10th day, no significant changes in levels of ALT, AST, total bilirubin were observed in the control group. In the experimental group, there was a significant decrease in ALT from 24,0±12,7 to 20,22±10,61 U/L ($p<0,001$), an increase in direct bilirubin level from 2,99±1,41 to 3,39±1,34 μmol/L ($p<0,01$). The result of ferritin level changes is shown in Figure 5, which demonstrates its significant decrease on the 10th day in the experimental group.

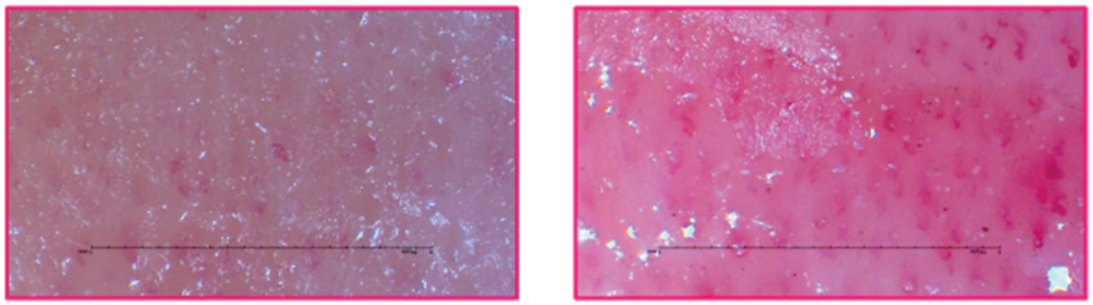
**Six-minute walk test**

The average 6-minute walk distance was initially higher in the experimental group than in the control one and amounted to 430±45 and 397±30 m, respectively ($p<0,001$). On the 10th day, a significant increase in 6-minute walk distance up to 569±60 m was noted only in the experimental group ($p<0,0001$). Comparison of the results of two groups, obtained on the 10th day, showed that this parameter was, on average, 30% higher in the AFV;($H(H_2O)_m$) inhalation group than in the control one ($p<0,0001$).

All patients at rest had normal pulse oximetry ($SpO_2$) parameters, but desaturation was recorded during exercise. When comparing this indicator on the 1st and 10th days, there was no significant difference between the groups. Within the AFV;($H(H_2O)_m$) inhalation group, there was a significant increase in the minimum $SpO_2$ from 92,25±2,9 to 94,25±1,56% ($p<0,05$), which was not observed in control group.

**Oxygen transport**

The results of assessing acid-base balance, oxygen transport and intrapulmonary shunting are presented in Table 3. On the 10th day, against the background AFV;($H(H_2O)_m$) inhalation therapy, there was a significant increase in $PaO_2$ ($p<0,0001$) and blood



Before After

*Figure 4* Capillaroscopy of the patient before and after AFV;($H(H_2O)_m$) inhalation (autofocus microscope VIEWTY).

**Table 2**

Systemic inflammation parameters

| Parameter | Control group 1st day | Control group 10th day | Experimental group 1st day | Experimental group 10th day |
|---|---|---|---|---|
| Leukocytes ($10x^9$ U/l) | 6,54±1,23 (n=25) | 6,55±1,08 (n=25) | 6,64±1,57 (n=22) | 5,92±1,32* (n=22) |
| Lymphocytes (%) | 35,41±6,23 (n=25) | 35,82±7,9 (n=25) | 31,61±5,49 (n=22) | 32,40±6,84 (n=22) |
| C-reactive protein (mg/l) | 1,44±1,3 (n=23) | 2,86±3,09 (n=23) | 1,96±1,75 (n=17) | 1,86±1,54 (n=17) |
| Eosinophils (%) | 2,62±1,47 (n=23) | 2,87±2,30 (n=23) | 1,89±1,08 (n=22) | 1,92±1,16 (n=22) |
| Myelocytes (%) | 0,28±0,13 (n=25) | 0,28±0,13 (n=25) | 0,25±0,08 (n=22) | 0,28±0,13 (n=22) |
| Segmented neutrophils (%) | 52,52±8,04 (n=24) | 51,24±6,1 (n=24) | 55,94±6,3 (n=22) | 54,07±12,9 (n=22) |
| ESR (%) | 8,30±6,52 (n=24) | 8,12±5,82 (n=24) | 8,95±8,51 (n=22) | 8,81±8,80 (n=22) |

Note: * — Experimental group 1st day vs 10th day, p<0,05, ESR — erythrocyte sedimentation rate.

lactate level (p<0,0001). The arterial lactate level in the experimental group was lower in comparison with the control one (p<0,0001). In addition, in the experimental group, there was a significant decrease in intrapulmonary shunt fraction by more than 60% (p<0,01). On the 10th day, there was an increase in $PaO_2$ (p<0,01) and lactate content (p<0,05) only in venous and capillary blood in the control group.

## Discussion

According to the University of California Global Health Institute, doctors, nurses and technical staff working in healthcare facilities are in the first place at risk of COVID-19 [14].

Countries facing the pandemic at the end of 2019 and the first months of 2020 experienced a significant rise in morbidity and mortality among medical staff due to COVID-19 [15].

In the D. D. Pletnev City Clinical Hospital (Moscow), the incidence of COVID-19 among employees ranged from 30 to 100%, depending on the department and the type of care provided. The highest morbidity was observed in intensive care unit, neurology and cardiology departments. The severe COVID-19 consequences are detected in these patients both in the subacute and in the recovery period and require rehabilitation due to a significant quality of life decrease.

The results of studies in 2020-2021, the time criteria for subacute syndrome and recovery period of patients after COVID-19 were identified [16].

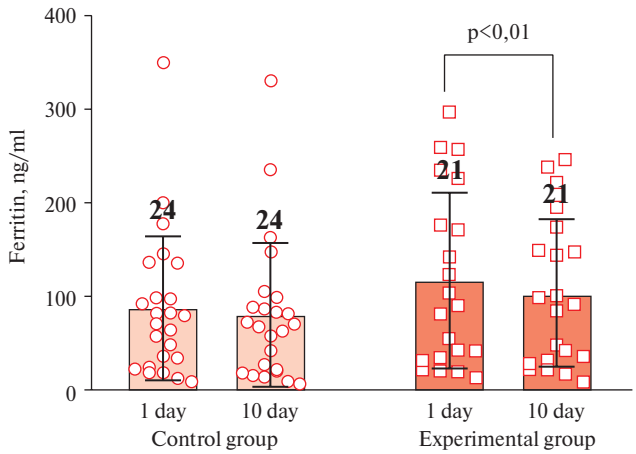



*Figure 5* Blood ferritin content on the 1st and 10th days.

This article discusses CFS as one of the leading symptom complexes during the recovery period of patients after COVID-19, as well as the effect of AFV;($H(H_2O)_m$) inhalation therapy on the disease dynamics.

There are various reasons for CFS development in patients after COVID-19:

— direct viral damage to organs and tissues during a protracted disease course, as well as during resuscitation measures and exacerbation of chronic diseases in the acute period [17];

— dysfunction of limbic system and hypothalamus structures [18];

**Table 3**

Dynamics of acid-base balance, oxygen transport and intrapulmonary shunting

| Parameter | Units | Control group (n=27) | | Experimental group (n=28) | |
|---|---|---|---|---|---|
| | | 1st day | 10th day | 1st day | 10th day |
| Arterial blood | | | | | |
| pH | - | 7,38±0,08 | 7,40±0,04 | 7,35±0,15 | 7,40±0,0 |
| $PaO_2$ | mm Hg | 86,0±10,1 | 88,9±4,8 | 82,28±6,0§ | 89,5±5,7 |
| $PaCO_2$ | mm Hg | 41,4±3,2 | 42,5±2,5 | 41,53±4,1 | 42,1±3,3 |
| $SaO_2$ | % | 93,9±3,8* | 95,8±2,2 | 93,6±2,3‖ | 96,5±2,1 |
| $HCO_3^-$ | mmol/l | 26,1±2,1 | 26,64±1,6 | 25,66±3,0 | 25,5±2,8 |
| Lactate | mmol/l | 1,74±0,5 | 2,04±0,4‖ | 2,06±0,9‖ | 1,10±0,5 |
| Cenous blood | | | | | |
| pH | - | 7,35±0,03 | 7,35±0,13 | 7,35±0,03 | 7,33±0,04 |
| $PaO_2$ | mm Hg | 31,0±6,1*,§ | 36,0±4,8 | 26,9±5‖ | 34,8±5,6 |
| $PaCO_2$ | mm Hg | 50,34±6,7 | 46,3±7,2 | 50,9±8,1 | 50,2±6,3 |
| $SaO_2$ | % | 64,6±14,4¶ | 66,5±18,3 | 51,8±20,6* | 61,1±18,1 |
| $HCO_3^-$ | mmol/l | 26,13±2,1 | 26,6±1,6 | 25,6±3,0 | 25,5±2,7 |
| Lactate | mmol/l | 2,05±0,6§ | 1,1±0,8 | 2,51±0,8§ | 1,55±1,0 |
| Capillary blood | | | | | |
| pH | - | 7,33±0,03 | 7,35±0,04 | 7,36±0,07 | 7,36±0,04 |
| $PaO_2$ | mm Hg | 41,8±5,1† | 56,7±5,4 | 48,7±15,4† | 63,8±21,2 |
| $PaCO_2$ | mm Hg | 46,5±4,2 | 44,1±5,5# | 43,3±6,7 | 39,7±5,5 |
| $SaO_2$ | % | 80,8±1,6§ | 84,8±2,2 | 82,2±4,2§ | 86,2±4,8 |
| $HCO_3^-$ | mmol/l | 29,5±3,0 | 27,9±3,0 | 29,0±3,6 | 27,5±3,3 |
| Lactate | mmol/l | 1,77±0,4* | 1,24±0,3** | 2,9±0,8‖ | 2,0±0,8 |
| Intrapulmonary shunting | | | | | |
| Qs/Qt | % | 7,14±5,5 | 4,32±1,35 | 8,98±5,07† | 5,34±3,2 |

Note: 1st day vs 10th day: * — p<0,05, † — p<0,01, § — p<0,001, ‖ — p<0,0001; Control group vs Experimental group: ¶ — p<0,05, # — p<0,01, ** — p<0,0001.

— dysregulation of parasympathetic and sympathetic nervous systems [19];

— direct viral damage to vascular endothelium [20];

— viral persistence in the human body [21];

— changes in circulating serotonin level due to impaired hemostasis [22];

— blood clots and their lysis products in capillaries and venules, provoking an inflammatory reaction [23].

SARS-CoV-2 replication process is accompanied by a disturbance in redox reactions, an increase in urine concentration of oxyketosteroids and an impaired hepatic cortisol clearance. Ultimately, all these metabolic processes affect nitrogen metabolism. A gradual restoration of nitrogen balance occurs later, in the subacute and recovery periods, when the clinical signs of acute illness disappear. All these changes possibly cause metabolic disorders and dysfunction of vascular connective tissue, latent hypoxia, which are clinically manifested in the form of CFS.

Of 100% of our clinic employees after COVID-19, at the time of the study, 99% had started their professional duties, but most of them needed rehabilitation.

Recently, among the rehabilitation measures, a special place is occupied by AFV;$(H(H_2O)_m)$ inhalation. Inhalation of 1-4 AFV;$(H(H_2O)_m)$ has been shown to be effective and safe. None of the patients in the study had any complications during the recovery period after COVID-19 against the background of AFV;$(H(H_2O)_m)$ inhalation and at the end of procedure.

AFV;$(H(H_2O)_m)$ inhalation therapy was accompanied by a significant decrease in white blood cells and an increase in lymphocytes — markers of inflammation, which is a consequence of antioxidant and antiinflammatory effect of active hydrogen.

We demonstrated the unique advantages of AFV;$(H(H_2O)_m)$. All studied patients initially had signs of endothelial dysfunction as a manifestation of direct damage to endothelium, impaired coagulation, partially caused by free radicals. Improvement of SI and RI endothelial function indices is also a consequence of antioxidant and anti-inflammatory effect of therapy with active hydrogen.

A decrease in endothelial dysfunction signs made it possible to restore blood rheology balance, impairment of which inevitably leads to organ damage and multiform pathology [24].

All patients of both groups had signs of latent hypoxia, impaired oxygen transport, lactate metabolism, and a high intrapulmonary shunting. With AFV;$(H(H_2O)_m)$ inhalation therapy, a significant increase in $PaO_2$ and $SaO_2$, a decrease in blood shunt fraction, which is associated with an improvement in microcirculation. This was clearly demonstrated by capillaroscopy before and after AFV;$(H(H_2O)_m)$ inhalation (Figure 4). Res-

toration of blood circulation and oxygen transport specifies the restoration of lactate levels, a decrease in anaerobic load on the body and an increase in exercise tolerance.

## Conclusion

Inhalation therapy with AFV;($H(H_2O)_m$) in the rehabilitation program of COVID-19 survivors during the recovery period is a safe and highly effective method. Manifestations of silent hypoxemia and endothelial dysfunction decreased, while exercise tolerance increased. As for laboratory tests, a decrease in the white blood cell count, estimated pulmonary shunt fraction and lactate content parameters was revealed.

**Relationships and Activities:** none.

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