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Original Research Paper

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# EFFECTS OF HYPERBARIC OXYGEN THERAPY IN PATIENT WITH ACUTE UPPER LIMB FINGER GANGRENE WITH COVID-19

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**ABSTRACT** The COVID-19 pandemic (Corona Virus Diseas) was caused by a new beta coronavirus in early 2020, also called Severe Acute Respiratory Syndrome (SARS-CoV-2).

Predilection sites of virus entry are the lungs, intestines, blood vessels, kidney, and adipose tissue cells are the virus reservoir. The virus causes a violent reaction of inflammatory cytokines - cytokine storm, activation of coagulation and formation of thrombin. The initial coagulopathy of COVID-19 is manifested by a pronounced disorder of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin time and platelet count are relatively rare at the onset of the disease. Later, the phenomenon of thrombotic microangiopathy occurs, which is a consequence of inflammation of the blood vessels endothelium. In severe cases of infection, thromboembolism or acute thrombosis of peripheral blood vessels may occur.

The paper presents a case of a patient with COVID-19 infection in whom, in addition to the usual clinical picture of the disease with changes in lung parenchyma (bilateral pneumonia), thrombosis of the a. radialis and a. ulnaris of the left hand developed, and fifteen days after the infection development, the development of gangrene of the distal articles II, III and IV of the finger occurs. In addition to therapy used according to the national guide to COVID-19, hyperbaric oxygen therapy (HBOT) was used. The effect of this therapy was used to increase vascular permeability and create factors that affect angiogenesis and improve blood flow in the ischemic region. HBOT also affected the demarcation of necrotic from healthy tissue, and stimulated wound healing. After two sessions of HBOT treatment, there was a complete restitution of blood flow with full function of the left hand and all its fingers.

**KEYWORDS :** SARS-CoV-2, endothelial cells, endotheliitis, finger gangrene, hyperbaric oxygen therapy.

## INTRODUCTION

The COVID-19 pandemic (Corona Virus Diseas) was caused by a new beta coronavirus in early 2020, also called Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), which belongs to the same group of viruses responsible for the outbreak of Severe Respiratory Syndrome (SARS-CoV) in 2002 and Middle Eastern Respiratory Syndrome (MERS-CoV) in 2012.

The virus binds to cellular receptor - Angiotensin Converting Enzyme 2 (ACE-2) which is a crucial cell receptor for SARS-CoV-2 virus penetration into human cells (1). Recognition of receptors and entry into host cell is the first step of viral infection and is a key determinant of tissue tropism. Increased binding affinity between SARS-CoV-2 and ACE-2 is known to correlate with increased virus transmission and disease severity in humans (2). Virus entry into host cells is a multi-step process involving several different domains in the S protein that mediates binding of the virus to the target cell surface, after which the viral genome is released into the cytoplasm and the virus replicates within host cells (3). It seems that the SARS-CoV-2 virus prefers respiratory epithelium as the main entry cells into organism, and it can also enter through enterocytes, as well as endothelial vascular system cells. The virus then activates a whole cascade of proinflammatory cytokines, causing infiltration through inflammatory cells, endothelial cell apoptosis, and microvascular postrombotic effect (4,5). SARS-CoV-2-induced endothelial injuries lead to organic dysfunction: vasculopathy, acute respiratory distress syndrome (ARDS), myocardial changes, thromboembolism, immune defense system changes, which makes this disease multiorgan (6,7).

The pathomorphological mechanism of severe clinical picture of COVID-19 arises due to inflammatory cytokines activation (tumor necrosis factors and interleukins, including interleukin 1 and interleukin 6). Interleukin 6 (IL-6) induces coagulation activation and thrombin production. Tumor necrosis factor and IL-1 stop and disrupt endogenous coagulation cascade, when a cytokine storm occurs (8,9,10). This hyperinflammatory condition causes changes in lungs, including damage to microvasculature and endothelial dysfunction, which are also the cause of thrombus occurance in pulmonary circulation.

Approximately 20-50% of hospitalized patients with COVID-19 have haematological changes in coagulation test (increased D-dimer, prolonged prothrombin time, thrombocytopenia) (5). Blood vessel endothelium is the location of key immunoregulatory functions and plays an important role in maintaining dynamics between procoagulant and fibrinolytic factors in the vascular system (6). Under normal conditions, endothelium forms a barrier between prothrombotic subendothelial layer and blood procoagulation factors. Endothelial cell activation activates thrombomodulin and plasminogen activator, so thrombus activation is favored. The phenomenon of thrombotic microangiopathy occurs, which is a consequence of blood vessels endothelium inflammation. Infection causes increased adhesion of platelets to the vascular endothelium, their aggregation and activation occurs, and this causes thrombocytopenia (11,12). Vascular endothelial dysfunction in the form of Sepsis Induced Coagulopathy (SIC) or Disseminated Intravascular Coagulopathy (DIC) may also occur. Thromboembolism occurs as a combination of systemic inflammation, platelet activation, endothelial dysfunction, immobility, and circulatory pathway (10).

In severe COVID-19 infection, vascular complications such as thromboembolism and acute thrombosis of peripheral arteries have been described, resulting in endothelial vascular damage, platelet aggregation, and coagulation

activation causing thrombosis and ischemia (13,14). The vascular endothelium has an intricate role in immunity and inflammation regulation, and optimally balances between thrombosis and fibrinolysis factors, i.e. has an essential role in maintaining dynamics between procoagulant and fibrinolytic factors in vascular system.

## CASE STUDY

A 54-year-old man was admitted for treatment due to fever, muscle pain, unproductive dry cough, difficulty breathing and loss of taste and smell. He reported arterial hypertension as an existing disease. At admittance, he had blood pressure of 150/90mmHg, heart rate 86/min, number of respirations 20/min, body temperature 38.8°C. A serological test for COVID-19 showed IgM and IgG positivity. Multi-Slice computed tomography (MSCT) of lungs showed bilateral milk glass type consolidation, more prominent in segments of lower lobes, indicating presence of bilateral inflammatory process. Pleural areas were free and without fluid. Analysis of blood gases showed pH 7.81, pCO2 4.3 kPa, pO2 8 kPa, SaO2 91%, which indicated respiratory alkalosis and hypoxemia. Biochemical blood analysis showed: Er $4.69x10^{12}$/L, Le $8.9x10^{9}$/L, Hgb 133g/L, Hct 38.7%, Tr 214000$mm^{3}$, Se 47, D - dimer 2.95mcg/mL (<0.5mcg/mL), CRP 21mg/L.

At admittance, antibiotic, anti-inflammatory and multivitamin therapy was prescribed. Continuous oxygen therapy was given - non-invasive respiratory support was applied, with subjective and clinical improvement, radiological regression in lungs and normalization of saturation, starting from the third day of admittance, SaO2 97%.

On the fifteenth day after disease onset, the patient noticed pallor of left hand and fingers, very severe pain in hand and fingers tingling. Clinical picture of dry gangrene of end joints of II, III and IV fingers soon developed, and cyanosis from the tips of I and V finger withdrew later (Figure 1).

Color Doppler of left arm blood vessels was performed and normal flow of a.subclaviae, a.axillaris and a.brachialis was found. A.radialis and ulnaris had reduced - monophasic flow above the wrist. An intraluminal thrombus 2 cm long and narrowing of these arteries to 60% of the lumen were observed. Anticoagulant therapy - Low Molecular Height Heparin (HMWH) - 0.5 mg/kg every 12 hours was included. A vascular and orthopedic surgeon at the regional medical center suggested surgical treatment - fingers end joints amputation, which the patient refused.

**Figure 1:** End Left Hand Joints Of II, III And IV Fingers Dry Gangrene.

Therapy in the form of hyperbaric oxygenation in hyperbaric chamber was included. Hyperbaric oxygen therapy (HBOT) was applied at 2.0 ATA for 60 min, a total of 20 exposures. With regular anticoagulant and antibiotic therapy, peripheral blood vessels circulation improved, changes on IV finger of the left hand were completely repaired, and rehabilitation and demarcation of necrotic tissue on II and III fingers began (Figure 2).

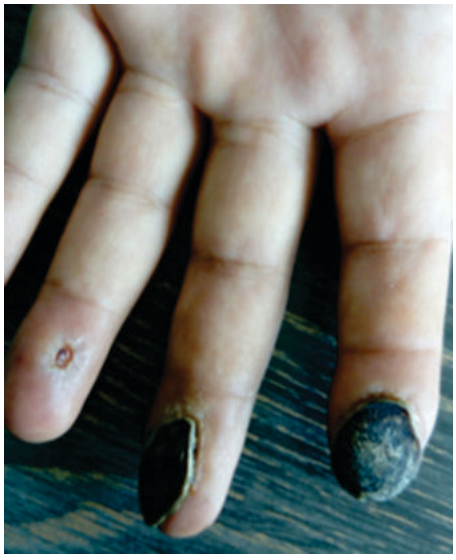

**Figure 2:** After 20 exposures in hyperbaric chamber, changes in left hand IV finger - complete sanation, beginning of rehabilitation and demarcation of necrotic tissue on II and III fingers.

A second color doppler of blood vessels was performed, and better flow through distal part of the a.radialis and a.ulnaris, and expansion of stenotic part were observed, and second hyperbaric chamber session was determined. The protocol was applied - HBOT at 1.8 ATA for 60 min, 25 exposures. After therapy, there was improvement in peripheral blood vessels circulation and complete restitution with full fingers function (Figure 3). During this session, good recovery of the patient was noticed - fatigue, exhaustion, feeling of weakness, lassitude and strength loss disappeared, and complete patient recovery occurred.

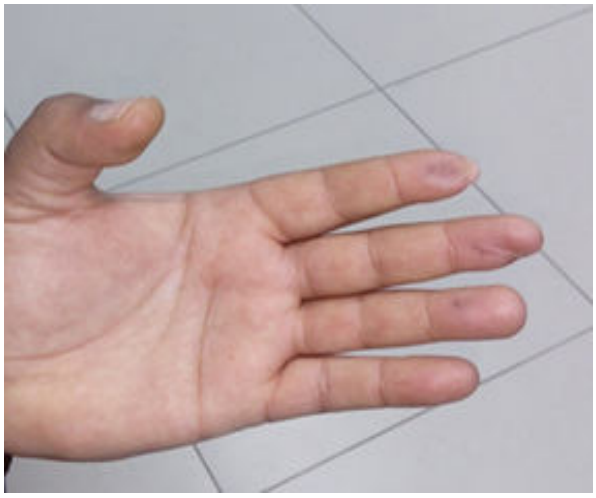

**Figure 3:** After completion of HBOT, both sessions - improvement of circulation in peripheral blood vessels and complete restitution of pathological changes.

## DISCUSSION

The mode of COVID-19 virus action on coagulation is not completely clear: hematological changes may exist due to

severe inflammation in the form of sepsis-induced coagulopathy (SIC) or are specific effect caused by the virus (4,10). The role and importance of vascular endothelium is great.

Approximately 20-55% of hospitalized patients with COVID-19 infection have hematological changes in coagulation test: increased D-dimer, prolonged prothrombin time and thrombocytopenia (5,15), which was also registered in our patient. The incidence of thromboembolism of 25 - 31% is reported in literature (16).

The presence of patient comorbidity increases risk of severe forms of COVID – 19 (17). Our comorbid patient had arterial hypertension. Acute limb ischemia occurs between 5 and 15 days since onset of infection symptoms, and is accompanied by severe pain in affected limb (13,16,18). In our patient, extreme pain in left arm appeared 15 days after hospitalization. After cyanosis, dry gangrene of fingertips soon developed. The American Society of Haematology (ASH) and our national COVID-19 treatment guide recommend thromboprophylaxis - administration of low molecular heparin at dose of 0.5 mg/kg every 12 h, or anticoagulant per os (5,16). We have applied this recommendation with our patient.

Many authors state that thrombectomy or amputation is indicated in such condition (15 -17). We suggested end limbs amputation to our patient, which the patient refused. Treatment was continued with HBOT.

The strategy of HBOT is to increase total amount of oxygen transported through blood at the expense of dissolved oxygen in plasma. The amount of oxygen bound to hemoglobin is limited regardless of pressure, and the amount of dissolved oxygen in plasma increases with increase of alveolar oxygen pressure. The total plasma capacity increases in proportion to increase in oxygen pressure, whether it is received at lungs level or from hemoglobin, at capillaries level. The transport of oxygen from plasma to cell is done by diffusion, and depends on pressure gradient. Inhalation of oxygen in hyperbaric chamber produces up to 20 times more oxygen dissolved in blood than through air inhalation under normal conditions (19). HBOT produces Vascular Endothelial Growth Factor (VEGF), which stimulates capillary awakening and wound granulation, and Fibroblast Growth Factor (FGF) is also produced, which affects angiogenesis, and wound edges granulate and epithelialize (20). The main goal of HBOT is revascularization and recanalization of clogged arteries, thus demarcating edges between devitalized and healthy tissue.

HBO therapy is traditional therapy in patients with peripheral arterial occlusive disease (21-2). It increases vascular permeability and produces factors that affect angiogenesis and improve blood flow in ischemic zone. Endothelial Progenitor Cells (EPCs) production occurs. These cells stimulate angiogenesis and new blood vessels formation. Angiogenesis - neovascularization, is the only mechanism that can only be stimulated by hyperoxia. High oxygen gradient presence (difference in oxygen pressure between ischemic zone and healthy tissue) is important in this process. Low oxygen gradient prevents angiogenesis (23). In addition to restoring blood flow, these cells play central and key role in wound healing (24-6). Due to this effect, at the 10th European Congress of Hyperbaric Medicine, HBO therapy was recommended for delayed wound healing and ischemic lesions, and for revascularization (27-8). Adequate levels of tissue concentration and oxygen pressure (TcPO2) are achieved by applying hyperbaric oxygenation, which is a basic prerequisite for normal fibroblast proliferation, angiogenesis, collagen deposition, epithelialization and enhanced bactericidal effect of antibiotics. HBOT leads to improved ischemic tissue perfusion, and perfusion itself represents adequate tissue supplying with energy and building materials and oxygen.

## CONCLUSIONS

Occurrence of hypercoagulation in SARS-CoV-2 infection is common, while acute limb ischemia is rare. Early thromboprophylaxis is the key to preventing coagulopathy.

Embolectomy and amputation are suggested in presented literature for ischemic extremities blood vessels changes. In case of our patient, limb amputation was abandoned and HBOT was applied, which led to complete revascularization, hand preservation and restoration of full limb function.

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