Abstract
In severe cases of SARS-CoV-2 infection, death occurs as a result of hypo-oxygenation of peripheral tissues. The lung, severely damaged, can not ensure the transfer of oxygen to the blood. It is necessary to increase the alveolar concentration of oxygen by supplementation, with or without mechanical ventilation. The relatively poor outcomes are related to the fact that the entire chain of oxygen transport to the mitochondria is compromised. The oxygen transport capacity is drastically reduced especially by overproduction of immature red blood cells and hemoglobin damage. The oxygen excess is toxic to the lung, causing characteristic lesions that evolve to fibrosis and that add to the respiratory distress induced by COVID19. The administration of oxygen in a concentration well above the level in the atmosphere causes a real explosion of oxidizing free radicals, which are particularly aggressive.
It is recommended to use oxygen sparingly, at the borderline of coverage of the demand, for a duration as limited as possible, as well as the combination of antioxidants.

Keywords: SARS-CoV-2 infection, hypoxia, oxygen.

Rezumat
În cazurile severe de infecție cu SARSCoV2, moartea se produce ca urmare a hipooxigenării țesuturilor periferice. Plămânul, grav afectat, nu poate asigura transferul de oxigen către sânge. Se impune creșterea concentrației alveolare de oxigen prin suplimentare, cu sau fără ventilație mecanică. Rezultatele relativ slabe țin de faptul că este compromis întreg lanțul de transport al oxigenului către mitocondrii. Capacitatea de transport a oxigenului este redusă drastic, îndeosebi prin hiperproducția de hematii imature și afectarea hemoglobinei. Excesul de oxigen este toxic pentru plămân, provocând leziuni caracteristice care evoluează spre fibroză și care se adaugă suferinței pulmonare induse de COVID19. Administrarea de oxigen în concentrație mult peste nivelul din atmosferă provoacă o adevărată explozie de radicali liberi oxidanți, deosebit de agresivi.
Se recomandă utilizarea cu parcimonie a oxigenului, la limita acoperirii necesarului, pe durată cât mai limitată, precum și asocierea de antioxidanți.

Cuvinte cheie: infecție cu SARSCoV2, hipoxie, oxigen.
The atmosphere has had oxygen for five billion years, but it was only after the occurrence of photosynthesis thanks to the magnesium-centered tetrapyrrole nucleus, almost three billion years ago, that the concentration of this atmospheric component increased to its current value.

Priestley, the discoverer of oxygen, overwhelmed by his passion for this element, made an amazing statement for that time. Noticing that a candle burns very quickly under extra oxygen, he wondered if animals that would breathe oxygen in high concentration would not experience something similar. Jules Verne, in Doctor Ox, had some extraordinary premonition about influencing the human psyche. The oxygen is essential to life, ensuring cellular metabolism. The animal kingdom is adapted to the atmospheric oxygen concentration of 21%, and any deviation has negative effects, especially in case of deficiency. In case of severe forms of SARS-CoV-2 infection, death occurs as a result of intolerable tissue hypoxia. Oximeters (digital, etc.) measure accurately the degree of hypoxia and guide the treatment.

The COVID virus affects the inlet gate of the oxygen in the body, the lung, from where, after crossing the alveolar membrane, oxygen is bound by hemoglobin and transported to the tissues. In gas exchange, carbon dioxide, being much more diffusible to oxygen, becomes a secondary problem. Hemoglobin is the wonder molecule in the gas transport (O2/CO2). Severe lung damage (over 50%) drastically reduces the oxygen saturation of the arterial blood. Hence the therapeutic idea: to force, through an excess of oxygen, the arterialization of the blood that crosses the lung. We introduce into the mechanically ventilated lung a high concentration of oxygen. We force transport and save tissues which are in hypoxia. Hyperbaric oxygen therapy is a step further on this line. It was even thought that the COVID virus would be destroyed by the excess oxygen, which has not been confirmed. The procedure also has considerable risks, it cannot be maintained over time. In a healthy human, an athlete, for example, the excess oxygen over that in the atmospheric air does not improve his physical performance. The exception is high altitude hypoxia (Himalayas) where oxygen is supplemented.

Oxygen therapy is the only procedure that can save the lives of COVID patients in very severe condition. It saves time needed for the recovery of the lungs (and with the help of corticosteroids, dexamethasone being preferred). Corticosteroids, along with a number of other drugs, including nitrofurantoin and bleomycin, exacerbate excess oxygen-induced lung damage via the explosion of oxidizing free radicals\(^1\). However, the results of oxygen therapy did not live up to the expectations, the mortality remains
excessive. For what reason? Peripheral hypoxia is not just the result of lung damage. The virus attacks all the links in the chain of transport to the cells dedicated to oxygen\(^2\). The virus electively attacks the red blood cells, the lifespan of which is drastically reduced (below the normal of 120 days). The bone marrow reacts and releases immature red blood cells, whose carrying capacity of O\(_2\) is greatly reduced. But even the hemoglobin of mature red blood cells, attacked by the virus, loses about 25% of the O\(_2\) transport capacity. It is an anemia with a convenient number of red blood cells.

Immature red blood cells (normally 1%) reach over 50%, the transport capacity of O\(_2\) being thus greatly reduced. Immature red blood cells are more susceptible to viral attack because they massively express the ACE2 receptor and the MPRSS2 co-receptor, which favors their infection and consecutive destruction\(^3\). Especially immature red blood cells are destroyed. Microthromboses also contribute to the tissue hypoxia, as well as endothelial capillary distress. Similarly, in the lungs, the ventilation of the alveoli is affected by the viscous mucus that clogs the small bronchi, (plugging), with diffuse atelectasis, and the decrease in mucociliary clearance favors superimposed bacterial infection. The problem of the alveolar surfactant is still under study. Although it is a lifesaver in severe hypoxia, in the lungs (alveolar), oxygen has a certain toxicity. Hyperoxia increases the formation of free oxygen radicals (H\(_2\)O\(_2\), hydroxyl radical and superoxide anion) particularly aggressive on the tissues, especially if the antioxidant capacity of tissues is exceeded, provided mainly by superoxide dismutase and catalase, plus ascorbic acid. (The Cantacuzino Institute used to produce a medicinal product containing these enzymatic substances.)

Damage to mitochondria becomes a central piece in determining cell death, and the most vulnerable are nervous and myocardial cells. In case of myocardial infarction, the initial ischemic lesion extends to the penumbra (between life and death of myocytes), after repermeabilization and brutal oxygenation. It is the so-called oxygen paradox. The research carried out regarding the protection of ischemic myocardium led to the development of magnesium ascorbate. Magnesium is a mitochondrial protector, the ascorbic anion provides the transfer of this element inside the myocardial and nervous cell. In the German literature it is referred to as “Schlepper”, i.e. carrier. The cells with the highest concentration in ascorbic acid are the encephalic cells, followed by cardiac myocytes. At least vitamin C should be administered massively in the ICU. Bryan C.L. and Jenkinson S.G., in Oxygen Toxicity, (Clinics in Chest Medicine 1988,9,(1) 141-152) insist on the development of agents with counteracting potential of oxidizing free radicals (OFR)\(^4\).

The longer the concentration of O\(_2\) in the air supplied by the ventilator, and the longer the duration of administration, the faster the lung lesions appear, becoming obvious even after 24 hours. Transgenic mice lacking superoxide dismutase (SOD) die rapidly after birth under an excess of oxygen, presenting severe mitochondrial lesions with degeneration of neurons and cardiomyocytes\(^5\) (White C.,W. et al), research resumed in 2020 by Malhotra Atul et al. that emphasizes the importance of introducing OFR scavengers.

Under conditions of hypoxia, the production of hypoxia-inducible factor 1-alpha (HIF1\(\alpha\)) increases, by ACE2 and furin. Furin is an enzyme that promotes the entering of the COVID virus into the cells through the proteolytic cleavage of the viral envelope glycoprotein. In case of severe lung damage, the decrease in ACE2 leads to insufficient
conversion of AT2, the increase of which induces pulmonary fibrosis and inflammation via interleukin 6. Post-COVID fibrosis is debilitating, has evolutional potential, and deserves more attention in recovery procedures.

Returning to the toxicity of oxygen, as a matter of fact, it has been known for a long time. Neonatologists are aware of the risk of eye injuries (retrolental) and pulmonary fibrosis, and there is even a rigorous GUIDELINE developed by the Ministry of Health, the College of Physicians and Neonatologists.

In adults, it is worth emphasising the value of the study done by Barber R,E., Lee J, L et al (oxygen toxicity in man). Patients with irreversible brain damage were randomized in the air-ventilated group and pure oxygen group. Ten cases, followed up to death. In the oxygen group, the lung damage was much higher. Towards the end, the arterial O2 pressure was lower in the oxygen group: after 50 hours, 400 Torr in those ventilated with air compared to 120 Torr in those under oxygen, in whom the intrapulmonary shunt increased significantly. The total weight of the lungs, as well as the radiological appearance, were the same. The impeccable study conducted in Modena (Italy) on 134 patients with severe lung damage randomized in the conventional therapy group (oxygen on the ventilator for PaO2 of 70-100 mmHg and Hgb saturation 92-98%) and the group supplemented with oxygen to achieve PaO2 of 150 mmHg and Hgb saturation practically 100% was cut off as a result of excessive mortality recorded in the superoxygenated group (Early termination of trial). The administration of oxygen in severe cases of COVID must also take into account the severity of the sequelae made by this disease.

**Conclusions**

1. In severe cases of COVID, the administration of oxygen is indispensable, but it must be done at the lowest possible concentration.
2. The duration of administration of oxygen in a higher than normal concentration should be shortened as much as possible.
3. Pulmonary sequelae made by COVID combine with those related to oxygen toxicity.
4. We recommend the combination of protective medication against oxidizing free radicals.

**References:**

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