A FUNCTIONAL APPROACH TO TREATING COVID-19 AND OTHER ACUTE RESPIRATORY INFECTIONS USING LOW LEVEL PHYSICAL RADIANCES: A PROPOSAL

April 27, 2020

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Abstract
Outbreak of the coronavirus disease 2019 (COVID-19) calls for consideration of treatments that support physiological functions of the organism while it overcomes the infection. Since clinical data shows that the severity of COVID-19 is associated with progressive functional impairment and exhaustion of the immune system, we propose a treatment approach that is based on a combination of those low level physical radiances that have experimentally and clinically established positive effects on cellular energetic metabolism and immune function.

Introduction

The ongoing outbreak of the coronavirus disease 2019 (COVID-19) calls for the expansion of our views on developing treatments, especially for those patients who progress to severe pneumonia and eventually to acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure (*1, 2*). In the recent *Science Advances* Editorial Ayres points out that although the approach of “how do we fight infection?” is valuable, there is also a need to consider another perspective of “how do we survive infection?” (*3*). The rationale is that after infection has already occurred, the trajectory of the disease towards recovery or death depends upon whether the organism is able to sustain vital functions for long enough, while overcoming infection. The standard supportive measures for patients in severe or critical conditions, such as mechanical ventilators, oxygen therapy, medication for controlling blood pressure and anti-clotting are important but, unfortunately, are often not enough. Also, because populations of whole countries are in self-isolation at home, it is an equally important task to introduce safe and effective treatments that can be applied at the earliest stages of the disease, preferably at home, in order to prevent development of clinical symptoms and further deterioration of the disease.

A new opportunity to support physiological functions opens up when we expand our approach from the domain of mechanical/chemical manipulation to the area of modulation of physiology using biophysics. There is a class of noninvasive medical technologies that have already been used in medical practice for several decades: Low Level Laser Therapy (LLLT), Magnetic-Infrared Laser Therapy (MIL-Therapy), phototherapy with colour light, ultrasound therapy and the combined technology of these individual radiances, known as coMra therapy. These therapies are not targeted at destroying a specific pathogen such as SARS-CoV-2. Instead, they enhance the function of cells, organs and systems that experience functional/toxic/hypoxic stress by modulating the key “bottleneck” aspects of physiology.

Extensive scientific evidence and our clinical experience suggest that therapeutic methods utilising low level physical radiances could be effective, safe and highly practical tools for use both in hospitals as well as at home for the treatment of COVID-19.

Energy deficit impairs immune function in COVID-19

What aspect of physiology is the limiting factor in successful recovery from COVID-19?

Clinical data shows that the severity of COVID-19 is associated with progressive functional impairment of the immune system (*4-9*). Diao et al. reported that the number of total T cells are dramatically reduced in COVID-19 patients, particularly in elderly patients (more than 60 years old) and in Intensive Care Unit patients (*10*). Moreover, the surviving cytotoxic T cells that are necessary for control of the infection also show signs of being functionally exhausted. Zheng and colleagues provide direct evidence of elevated exhaustion levels and reduced functional diversity in T cells in peripheral blood as predicting severe progression in COVID-19 patients (*11*).

We present our hypothesis that the cause of the functional exhaustion of the immune system in COVID-19 and the subsequent worsening of patient's state is the result of a systemic energy deficit that develops when a rapid increase of energetic expenditure, due to the response of the adaptive immunity to a new pathogen (SARS-CoV-2), is not met with sufficient energy reserve of the organism.

It is a well-established fact that immune response to an infection is an energetically expensive process. Apart from self-maintenance, immune cells require energy for performing various specialised effector functions; migration, phagocytosis and so on (*12, 13*) . Also, on the first encounter with a novel pathogen, an individual's immune system needs to mount an effective response that includes energy-costly clonal expansion of T cells and B cells. Altogether, while the total energy cost of the entire immune system in an inactive state is about 20% of an average daily resting metabolic rate, inflammation (mild to sepsis) may induce an additional 25 to 60% energy expenditure (*13*).

A bioenergetics view on COVID-19 offers a unifying framework for interpreting the variability of progression of the disease. In a relatively healthy individual the extra energy expenditure induced by immune response to SARS-CoV-2 infection could be well within the functional reserve (tolerance limit) of the body. Infection is resolved without causing apparent symptoms apart from, perhaps, unusual tiredness. However, if a person has one or more chronic condition (hypertension, cardiovascular, respiratory, oncologic, metabolic and so on) prior to infection (*14*), redistribution of energy towards the immune system could be compromised as a result of the pre-existing cellular energy deficit, a common sign of practically all diseases (*15, 16*). For example, chronic low-grade infection, such as Hepatitis C with fully compensated liver disease, increases energy expenditure by about 10% (*17*). As a result, energetically exhausted adaptive immunity fails to contain infection, thus leading to rapid progression towards more severe stages of the disease. High mortality rates in COVID-19 patients with a known history of diabetes (*18*) also suggests that glucose metabolism disorder impairs the bioenergetics of immune cells that primarily utilise glucose and glutamine on activation (*19*). And finally, since age is associated with a general decrease of energetic reserves, COVID-19 mortality rates are highest in the elderly population (*20*).

Enhancing energy metabolism with biophysical modulation

If availability of sufficient energy is the key factor determining functional reserve of the immune system and ultimately the outcome of COVID-19 then the current focus of developing treatments solely on anti-virals will not be sufficient to overcome the disease successfully. Even with an optimal medication regime, energetic exhaustion may severely impair the most basic self-sustaining physiological functions of the organism. Nearly 25% of patients in critical stage with influenza A (H1N1) still die despite receiving optimal anti-virals (*21*). There is an urgent need to explore strategies that are aimed at supporting energetic metabolism of the overworked and exhausted immune system.

We propose treatment of COVID-19 based on the application of noninvasive biophysical radiances. This treatment approach can readily complement other treatment approaches. Scientific evidence shows that we can enhance function and rescue cells and organs experiencing energy deficit due to hypoxia or elevated load using LLLT, MIL-Therapy and coMra therapy that have already been employed in medical practice over the last 10-40 years for the treatment of a very wide variety of conditions.

Since the 1980s *in vitro* experiments have demonstrated that when cells are exposed to infrared (laser) light at certain levels of intensity their energy status can be improved by up to 200-300%, as measured by intracellular ATP content (*22-26*). Even more importantly, the effect was convincingly demonstrated *in vivo* under conditions of ischemia, physical exercise or impaired mitochondrial function (*27-30*).

Although early studies showed that a weak magnetic field also has an effect on cellular energy metabolism (*31*), it proved difficult to measure that effect (*32, 33*). However, in 2005 Buchachenko demonstrated that the presence of a weak magnetic field increased efficiency of ATP synthesis by 200-300% compared with nonmagnetic conditions (*34*). Later, both theoretical studies, as well as experiments confirmed the finding that magnetic fields affect enzymatic ATP synthesis (*35-39*).

It is remarkable that both low level lasers and magnetic fields have nearly the same magnitude of effect on energy metabolism in cells: increase of ATP synthesis by 200-300%. In the 1970s a combination of the two radiances was proposed in the form of MIL-Therapy. More than 40 years of MIL-Therapy clinical experiences in Russia have confirmed the advantages of such a combination (*40-42*).

Implications for immune functional reserve

There is a significant body of literature showing improved function of immune cells after treatment with LLLT and MIL-Therapy. Benedicenti *et al.* showed enhanced ATP production in lymphocytes irradiated *in vitro* with low level infrared laser light (*26*). Sheiko *et al.* used red light to irradiate blood samples taken from oncological patients with lung cancer and reported increased spontaneous and mitogen-induced lymphocyte proliferation, enhancement of the expression of the T- and NK-cells membrane receptors and increase of cationic proteins in neutrophils (*43*). Gizinger *et al.* showed improved function of lysosomal activity of neutrophil isolated from donor peripheral blood after LLLT (*44*). Celine Lee *et al.* demonstrated enhanced cutaneous immune response to the bacterial infection by MRSA after infrared light irradiation (*45*). Gulmuradova *et al.* reported restoration of lymphocyte counts and enhancement of neutrophil activity while reducing autoimmune damage in patients with acute pancreatitis (*46*).

Particularly relevant to COVID-19 is a study by Burduli *et al.* that showed significantly enhanced functional activity of neutrophils after LLLT in patients presenting with community-acquired pneumonia (*47*). Kovaleva *et al.* reported improved clinical

outcomes, increased number of T cells and improvement of their functional activity after treating patients with severe pneumonia with MIL-Therapy (*48*). Shadrina *et al.* used MIL-Therapy as a means for immunotherapy of paediatric patients with cystic fibrosis and noted highly significant increases in T cells, Iga and IgG and improved function of neutrophils (*49*).

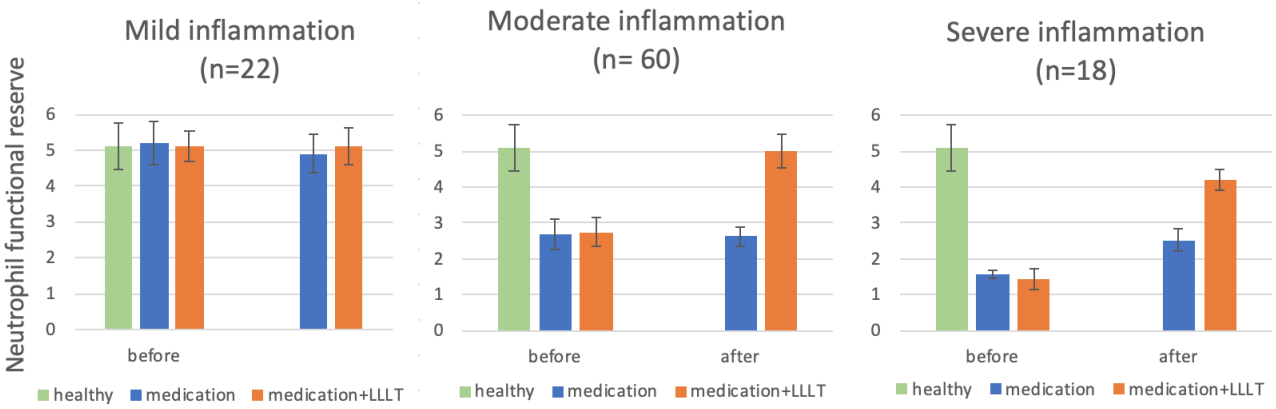

Figure 1. Neutrophil functional reserve before and after 7-day treatment course with medication (blue) and medication combined with low level laser blood irradiation (orange) in patients with community-acquired pneumonia (data from 47). Functional reserve of healthy individuals (n=30) is shown in green for comparison. The functional reserve of neutrophils was estimated from their ability to reduce nitroblue tetrazolium in both spontaneous and stimulated NBT-tests.

While LLLT has been shown to improve immune function, there are also reports that LLLT reduces autoimmune injury. Mafra de Lima *et al.* described effects of LLLT on pulmonary inflammation, adhesion molecule, mRNA expression and protein levels of inflammatory chemokines in a model of acute lung injury in rat aerosolized with LPS and showed inhibition of LPS-induced neutrophilic lung inflammation by LLLT (*50*). Cury *et al.* also concluded that LLLT is able to reduce inflammatory reaction in lungs exposed to LPS without affecting the pulmonary function and recovery in a model of acute lung injury (*51*). Batirova *et al.* complemented standard medication with LLLT treatment of patients with pleural effusions of various aetiologies and reported correction of imbalances between pro-inflammatory and anti-inflammatory cytokines (*52*). Sutyagina *et al.* reported that addition of LLLT to the standard medication treatment of patients with infiltrative pulmonary tuberculosis leads to a more pronounced reduction of cytokinemia, faster elimination of clinical symptoms such as cessation of bacterial excretion, closure of decay cavities and decrease of hospital stay (*53*).

We would like to point out that there is no contradiction between the reports of enhanced immune response and studies showing reduction of inflammation-related injury. In our opinion, it is misleading to try to link biophysical effects directly to specific adaptive/defensive responses of an organism. The primary biophysical effects, such as enhanced ATP production and consequent elevation of immune functional reserve are disease-independent and are observed even in healthy individuals. But the dynamic response of the immune system to an infection undergoes different stages during which enhanced energetic metabolism can manifest as enhanced pro-inflammatory or anti-inflammatory processes.

Neuromodulation with colour light

Availability of sufficient energy reserve underpins an adequate immune response to infection. However, the central nervous system can take control of energy distribution in some situations, such as perception of imminent (imaginary or real) danger.

Psychomotor activity induced by anxiety, acute psychological stress and sleeping problems may reach up to 30% of the energy budget of a healthy individual (*13*) thus actively suppressing immune functional reserve. Therefore, the regulatory aspect is also an important part of the overall functional reserve of the organism.

Phototherapy with colour light is another noninvasive biophysical modality that can play a role in improving immune functional reserve in COVID-19 by modulating the nervous system. The colour red stimulates the sympathetic nervous system (‘fight or flight’ response). Indigo and blue colours activate the parasympathetic nervous system (‘rest and digest’ response). In the mid-section between these two opposites, the yellow-green colour promotes physiological balance (*54-56*).

Enhancing enzyme efficiency with low level ultrasound

Besides the energy and regulatory aspects, functional reserve also depends on the extent of activation of molecular transport and synthesis of proteins. These processes become highly important at the stages of when a disease extends beyond energetic deficit and manifests as microstructural cellular injury.

By using low frequency and low intensity ultrasound we can enhance transport and enzyme efficiency and we can do so without interfering with the actual regulation of cellular metabolism (*57-59*). Longer term (hours to days) regulation of cellular metabolism involves a response of a cell to signals from the extracellular environment, such as hormonal stimulation (*60*). But on a short-term scale of seconds to minutes the activity of enzymes is mostly determined by flows of substrates and changes in their local concentrations around an enzyme (*61*). Lack of substrate could be especially inhibiting where clumping or aggregation occurs, thus masking the enzyme from the substrate or limiting diffusion of substrate to enzymes or vice versa (*62, 63*).

In patients with chronic obstructive pulmonary disease, sequential application of LLLT and ultrasound therapy was found to be effective in stimulating excretion of sputum, reduction of inflammatory markers, improvement of external respiration function and the general state of the patients (*64*).

Practical considerations

Physiotherapeutic methods based on application of low level biophysical radiances are widely used in medical practice in Russia and have been established during the last 40 to 50 years for conditions including the treatment and rehabilitation of various respiratory infections and their complications. The low level therapeutic technologies are also very safe; there are no known reports of any adverse side effects (*65*). In our personal clinical experience (Dr Anna Klassen MD) the best results are achieved using a combination of these methods. And this is necessarily so, because the functional reserve of an organism depends on three closely interrelated aspects: energetic, regulatory and structural (*66*).

Therefore, in the light of the COVID-19 global health challenge we propose a novel treatment approach based on application of coMra therapy, a technology that implements the inherent therapeutic synergy between near infrared laser, magnetic field, colour LEDs and ultrasound (*56*). The fine-tuned coherent action of these radiances in one therapeutic energetic stream overcomes the challenge of combining separate devices - a skill requiring specialised medical training. At the same time, the use of biophysical radiances at much lower intensities in coMra therapy has created an unparalleled, to our knowledge, benefit to risk ratio.

The ease of use and safety of coMra devices encourages home use that is especially relevant in times of home self-isolation, very limited access to health services and the need to prevent worsening of COVID-19 that would require hospitalisation. During our 10-year clinical experience with coMra therapy we have observed that timely treatments with coMra devices reduces the duration of normal colds and flu by at least 40-50%. The severity of symptoms such as headaches, fever, fatigue is also significantly reduced. We found that home users of coMra devices also have a markedly reduced need for medication (if any) to control those symptoms. And when coMra therapy is also applied preventatively, in advance, before seasonal outbreaks, whole families go through these times with minimum down time.

Treatment protocols

Below are custom coMra programs compiled for colds, flu, COVID-19. These programs use combinations of existing treatments as published in the current coMra-Therapy User Guide Revision 4.1, available online at https://ug.comra-therapy.com/ as well as in PDF format, or alternatively as an APP for Apple iOS and Android. Note that when the combined treatments have overlapping points, do these points only once.

All safety rules and precautions apply as outlined in the “BEFORE YOU START” section of the coMra-Therapy User Guide.

Protocol 1

Preventative program for an individual without chronic diseases and below 50 years old.

Recommended device: coMra Palm, coMra Delta with 980 or 905 nm Medical terminal

- Universal 2
- Universal 3

Do this treatments once daily for 12 days. Repeat the course of treatments every 3 months if necessary.

Protocol 2

Preventative program for an individual with chronic diseases, over 50 years old, with high risk of infection.

Recommended device: coMra Palm, coMra Delta with 980 nm Medical terminal.

- Universal 2
- Universal 6

Do this treatments once daily for 12-21 days.

Protocol 3

Treatment program for common colds, flu, COVID-19 at appearance of symptoms of a respiratory infection, such as fever, cough, sore throat that do not require hospitalisation.

Recommended device: coMra Palm, coMra Delta with 980 or 905 nm Medical terminal.

- Universal 3, done every 4 hours except during sleep time
- Universal 2, done once a day
- In case of headache add Universal 1, done 1-2 a day
- In case of respiratory symptoms add Pulmonology 1, done 1-2 times a day
- In case of sore throat add Otorhinolaryngology 8, done 1-2 times a day

Do this treatments until condition significantly improves. Then continue with *Protocol 1* for another 1 week.

Protocol 4

Treatment program for hospitalised COVID-19 patients with moderate symptoms, percentage of lymphocytes in peripheral blood more than 20%, without comorbid conditions.

Recommended device: coMra Delta with 905 nm Medical terminal.

- Universal 3, done 2 times per day
- Universal 2, done once a day
- Pulmonology 1, done 1-2 times a day
- Add other coMra treatments as needed

Do this treatments until release from hospital. Then continue with *Protocol 1* for another 14-30 days at home until all symptoms disappear. Add Pulmonology 1 to *Protocol 1* in case of residual signs in the lungs.

Protocol 5

Treatment program for hospitalised COVID-19 patients with severe symptoms, critically ill patients, percentage of lymphocytes in peripheral blood less than 20%, with or without comorbid conditions.

Recommended device: coMra Palm or coMra Delta with 980 nm Medical terminal.

- Universal 3, done 2 times per day
- Universal 5, done 2 times per day
- Pulmonology 3, done 2 times a day
- 3 points on spleen, 1 min per point @50Hz, done once per day

Do this treatments until release from hospital. Then continue with *Protocol 5* for another 14-30 days at home until all symptoms disappear using coMra Delta with 905 nm Medical terminal.

Protocol 6

Rehabilitation program after COVID-19.

Recommended device: coMra Palm, coMra Delta with 980 or 905 nm Medical terminal

- Autoimmune 1
- Pulmonology 1, done once a day

Start the first course of daily treatments 1 month after recovery from the disease. Then repeat the course every 3 months for one year. Recommended duration of each course is 14-21 days depending on the severity of the initial disease.

Declaration of interest

The first author Arzhan Surazakov is the director of Research and Development at Radiant Life Technologies Ltd, the manufacturer of coMra therapy devices. The second author Anna Klassen does not declare conflicting interest.

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