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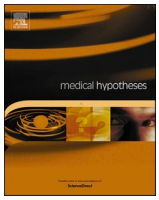

Research Article

Skeletal muscle oxygen tension as a measure of COVID-19 disease severity and predictor of disease progression

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ABSTRACT

Since the outbreak of the COVID-19 pandemic, over 7 million confirmed deaths from COVID-19 have been reported worldwide, but the true death toll is believed to be much higher. Although the risk contributions of various co-morbidities have been well documented, it remains unclear precisely why some patients become severely ill while the majority have mild symptoms or are asymptomatic, and no accurate means of predicting a patient's progression to severe illness. In this paper, it is hypothesized that reduced oxygen tension in skeletal muscle is indicative of COVID-19 disease severity and predictive of subsequent progression in severity of illness. Muscle Oxygen Tension can be measured non-invasively, offering a ready means of determining the extent to which a patient's overall oxygen inventory in the body has diminished, thereby tracking an important aspect of disease progression. It is further hypothesized that diminished muscle oxygen tension during acute illness is likely to be a predictor of long-term sequelae.

Introduction

The majority of SARS-CoV-2 infections result in mild flu-like symptoms or are entirely asymptomatic. However, some percentage of cases result in severe illness, and COVID-19 still represents a sizable health burden globally. One aspect of alleviating that burden is discovering more accurate and useful indicators predictive of progression to severe illness, permitting earlier interventions in severe cases and reducing unnecessary resource allocation in mild cases. Several mechanisms involved in progression to severe COVID-19 have been identified, along with some key blood markers, which provide valuable insights into the disease's pathology[1].

A study conducted by [2] identified key predictors of COVID-19 severity, emphasizing measurable patient characteristics and underlying physiological mechanisms of disease progression. Among hospitalized patients, comorbid conditions were independently associated with severe outcomes. Additionally, disease progression was further characterized by persistently low lymphocyte counts, heightened levels of inflammatory markers such as CRP, lactate dehydrogenase (LDH), and ferritin, as well as the presence of systemic inflammation and sustained viral load[3]. Microthrombosis and platelet consumption, linked to inflammation and lung endothelial damage, contributed to the pathophysiology of severe cases [4].

In clinical management, supplemental oxygen is a critical intervention, with mask oxygen administered to patients presenting oxygen saturation (SpO2) below 90 %. Low-dose dexamethasone (6 mg/day for up to 10 days) was used in 69 % of cases, with higher utilization among those with disease progression (87.2 %) compared to non-progressing cases (57.2 %). High-flow nasal cannula oxygen was applied in 6.7 % of patients, primarily among those with disease progression (17 %). In severe cases involving respiratory failure or acute respiratory distress syndrome (ARDS), invasive ventilation was employed as a last resort. These interventions reflect a targeted approach to managing the systemic and respiratory complications associated with severe COVID-19. [2].

While arterial SpO2 is a key parameter in assessing and managing COVID-19 severity, it is important to recognize that using pulse oximetry to measure arterial SpO2 provides an incomplete representation of the body's total oxygen inventory.[5].

The body has three major stores of accessible oxygen. In an average adult person, 820 mL of oxygen is bound to haemoglobin, 200 mL is bound to myoglobin, and 45 mL is dissolved in tissues[6]. As described in Persichini et al, approximately 70 % of available blood volume is venous blood[7]. With an arterial blood oxygen saturation of 95 % and a

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venous oxygen saturation of 75 %, it can be calculated that of the 820 ml typically in the blood, roughly 290 mL is contained in arterial blood and the remaining 530 ml are in venous blood. This means that arterial blood comprises just 27 % of the body's total oxygen inventory at any given time. Pulse oximetry, as the main means of monitoring patient oxygen status, is therefore only sampling a small portion of the total oxygen inventory in the body, as illustrated in Fig. 1.

Oxygen bound to myoglobin constitutes 19 % of typical oxygen stores and, assuming that approximately half of the tissue-dissolved oxygen is contained in skeletal muscle, due to its large proportion of total body mass, it can be presumed that, under typical conditions, oxygen contained in muscle constitutes in excess of 20 % of the body's total oxygen inventory.

Transcutaneous Oxygen Measurement (TCOM) using Near-Infrared Spectroscopy (NIRS) could be employed to monitor that oxygen store. NIRS is a non-invasive technique that measures tissue oxygenation directly by assessing the oxygen saturation in muscle and other tissues [8]. Unlike pulse oximetry, which only measures the oxygen saturation in arterial blood, NIRS provides insight into the oxygen status of tissues and muscles, capturing another sizable component of total oxygen inventory. This is particularly important in critically ill patients where peripheral tissue oxygenation may be compromised even when arterial SpO2 appears stable, or when oxygen administration is used to correct deficits in arterial SpO_2, but without necessarily addressing impairments in perfusion and oxygen delivery.

By utilizing NIRS in conjunction with SpO_2 measurements, clinicians can gain a clearer understanding of how oxygen is being delivered and utilized across different tissues, not just in the bloodstream. This will provide a more comprehensive assessment of a patient's oxygen status, improving clinical decision-making and guiding more effective interventions.

Hypothesis. *The hypothesis is that reduced oxygen tension in skeletal muscle is indicative of current disease severity and predictive of subsequent disease progression in COVID-19 patients.*

Muscle oxygen tension can be measured non-invasively using Near-Infrared Spectroscopy. For the majority of patients, skeletal muscle oxygen represents a sizable portion, around 21 %, typically, of the body's total oxygen inventory, and measuring it therefore offers a means of more closely tracking a patient's overall oxygenation status.

Moreover, skeletal muscle's oxygen status is also indicative of actual oxygen delivery in the body, thereby tracking a patient's status in ways not possible with pulse oximetry or blood-gas analysis and offering a more comprehensive assessment of a patient's oxygen status. It is possible for tissue hypoxia to occur in the absence of hypoxemia, for instance if oxygen delivery is impaired while blood oxygenation is not [9,10]. This can occur systemically if cardiac output is inadequate, referred to as 'stagnant hypoxia' or in a particular tissue if perfusion to that tissue is impaired [10]. Reduced cardiac output has been observed

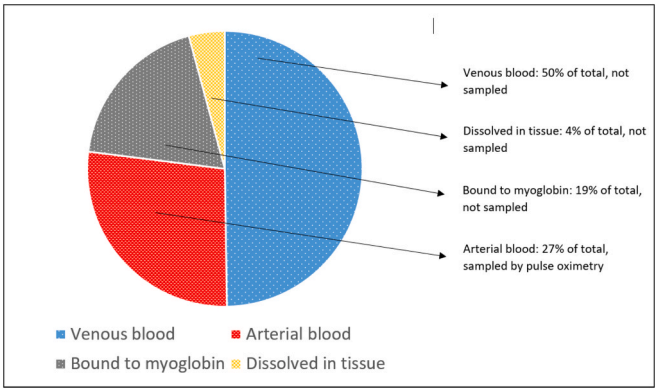

Fig. 1. Sampling status of oxygen reservoirs in the body.

in COVID-19 patients[11], as has hypercoagulability which can impair perfusion and hence there are mechanisms which could plausibly lead to hypoxia without hypoxemia in COVID patients, or alternatively lead to hypoxia with severity out of proportion to the corresponding hypoxemia. This phenomenon could plausibly be a common feature of COVID infection based on the existence of these mechanisms, but it could equally plausibly be an unusual or rare finding; the prevailing conventional understanding of hypoxia, that it occurs primarily as a by-product of hypoxemia, is also compatible with the available evidence. The objective of this paper is to make a case for the plausibility of the hypothesis and to propose lines of experimentation that could reliably discern between the two competing viewpoints.

If this hypothesis is correct, skeletal muscle oxygen tension, measured in conjunction with arterial SpO_2, will offer a more complete picture of disease progression than arterial SpO_2 by itself. Using both in conjunction would sample approximately 47 % of the body's total oxygen inventory non-invasively, as compared to the 27 % sampled by pulse oximetry alone, better tracking total oxygen inventory whilst also providing direct insights into perfusion and oxygen delivery. Tissue hypoxia directly results in the release of pro-thrombotic and pro-inflammatory molecules, making it a direct correlate for pathogenic processes which means that it would offer clinical interpretations distinct from those presented by arterial SpO_2. In particular, instances where patients exhibit normal SpO_2 but reduced muscle PO_2 would be indicative of impairments of oxygen delivery distinct from hypoxemia arising from conventional respiratory distress.

Evolution of the hypothesis

In severe cases, SARS-CoV-2 infections exacerbate oxidative stress which causes endothelial dysfunction[12]. Oxidative stress occurs when the rate of reactive oxygen species (ROS) production, specifically superoxide anions, hydroxyl radicals, hydrogen peroxide, nitric oxide, and lipid radicals, exceed the capability of the body's antioxidant defence system[13]. Many studies have demonstrated a strong correlation between COVID-19 and severe oxidative stress, leading to elevated production and inhibited elimination of ROS through several mechanisms. [14,15,16].

Upon viral entry, SARS-CoV-2 binds to human ACE2 (hACE2) receptors on the host cells. hACE2 is responsible for converting angiotensin II to angiotensin [17,18,19], as well as converting angiotensin I to angiotensin. As SARS-CoV-2 has a high affinity for hACE2, it competes with Angiotensin II for binding to the active site, thus diminishing hACE2-Angiotensin II activity and ultimately the conversion of Angiotensin II. This causes a downregulation of ACE2 expression which results in increased levels of angiotensin II. Angiotensin II produces many proinflammatory mediators such as adhesion molecules and chemokines, and also may modulate immune responses like chemotaxis, proliferation of inflammatory cells, and monocyte to macrophage differentiation[20,21]. Additionally, the increased angiotensin II levels stimulate the activity of NADPH oxidases, which are a family of enzymes that produce ROS. Hence, as hACE2 receptors are blocked by the SARS-CoV-2 molecules, levels of ROS significantly increase[22].

In severe cases, the body's immune response against COVID-19 results in the release of proinflammatory cytokines such as neutrophils, macrophages, C-reactive protein, interleukin 6, and increased levels of D-dimers. This results in a phenomenon known as a cytokine storm. In a cytokine storm, there is an amplification of activated inflammatory signals, like NADPH oxidase, which releases more ROS[23,24].

The increased number of neutrophils due to the cytokine storm causes an increase in the release of neutrophil extracellular traps, which also generates significant amounts of ROS. Leaky electron transport chains that release ROS result from mitochondrial dysfunction due to the viral infection.

Oxidative stress coupled with cytokine storm results in endothelial cell dysfunction which in turn results in the release of von Willebrand

Factor (vWF), a prothrombotic glycoprotein, as part of their cellular injury response.

Hypercoagulability results in microthrombosis, the formation of tiny blood clots, which in turn impairs perfusion to tissues throughout the body. Impaired perfusion can damage tissues through the mechanism of tissue hypoxia, and hypoxic tissues tend to release pro-thrombotic and inflammatory molecules, reinforcing the exact states that resulted in their release [25,26,27]. The same inflammatory blood markers observed in severe COVID are also present in altitude sickness [26,28].

Microthrombosis has also been found to disrupt perfusion in the alveoli of the lungs, resulting in perfusion/ventilation mismatch and inhibiting the body's ability to transport oxygen into the blood. In general, reduced arterial SpO_2 is characteristic of COVID-19 even at moderate severity, as evidenced by the phenomenon of 'Happy Hypoxia,' an observation that many COVID-19 patients exhibit arterial SpO_2 levels that would typically be associated with extreme distress in respiratory patients, but without showing signs of any particular discomfort [29].

Furthermore, when red blood cells (RBCs) are exposed to excessive oxidative stress, the oxygen-carrying ferrous iron (Fe^{2+}) in haemoglobin is oxidized to ferric iron (Fe^{3+}), converting haemoglobin into methemoglobin. Methemoglobin cannot bind oxygen, reducing the blood's oxygen-carrying capacity and potentially leading to hypoxia[30].

Endothelial inflammation could contribute to system tissue hypoxia by directly impeding the diffusion of oxygen out of the blood and into the tissue. This means that the mechanisms underlying progression to severe COVID-19 impair Oxygen transport in several ways – they obstruct the body's ability to get oxygen into the blood, and they obstruct the discharge of oxygen from the blood into tissues, creating a positive feedback loop.

The transport of oxygen into muscle tissue is also mediated by a number of transcriptional cascades activated by physical activity and so, the sedentary state of severely ill COVID-19 patients is also likely to play a role in affecting the dynamics of oxygen uptake and usage in myoglobin. On one hand, this could create a correlation between muscle oxygen and disease severity regardless of the presence of a causative relationship, but on the other could create an additional positive feedback loop where inactivity resulting from illness exacerbates deficiencies in muscle oxygenation.

In short, severe COVID-19 is characterized by hyperinflammatory and hypercoagulable states which exhibit positive feedback loops, which may explain the rapid disease progression often seen in severe COVID-19.

Testing of hypothesis

Testing the hypothesis would therefore require a clinical trial recruiting COVID-19 patients and measuring their muscle oxygen saturation, via NIRS, along with their SpO_2 at intake, and monitoring both variables during disease progression.

Correlative evidence could be collected by measuring muscle oxygen tension for patients at time of intake and ascertaining the degree of correlation between muscle oxygen tension and other markers of disease severity. This comparison, when combined with the SpO_2 measurements, would also reveal whether diminished muscle oxygen tension occurs solely as a by-product of reduced arterial SpO_2, in line with the conventional view that hypoxia is primarily a by-product of hypoxemia, or whether there are instances where hypoxia occurs independently. This line of inquiry would be useful for determining whether muscle hypoxia in the absence of hypoxemia is a prevalent feature of COVID-19 disease, but would nevertheless only show a correlative, rather than causative, relationship.

The second part of the hypothesis is that diminished muscle oxygen tension is predictive of future disease progression. Testing this aspect of the hypothesis could be achieved fairly straightforwardly by measuring muscle oxygen tension in COVID-19 patients at intake at participating treatment facilities and subsequently evaluating the correlation between muscle oxygen at intake and subsequent disease progression to severe illness and/or mortality. The statistical strength of the correlation between muscle oxygen tension at intake and subsequent disease progression would indicate the predictive usefulness of TCOM as a diagnostic or triage tool for COVID-19 patients. If this aspect of the hypothesis is correct then there will be a correlation between severe disease outcomes and initial muscle oxygen tension.

The hypothesis further posits that muscle oxygen tension plays a direct causative relationship in subsequent disease progression. Testing this in a clinical setting would require ongoing monitoring of skeletal muscle oxygen tension and disease progression over time and evaluating the correlation between the two, observing in particular whether changes in skeletal muscle oxygen precede other signs of deterioration or lag behind them. If this aspect of the hypothesis is correct, it would be expected that in patients who experience the inflammatory cascade, it would be preceded or accompanied by a decline in muscle oxygen tension.

Ideally, subjects in such trials should be matched not just in terms of age, but other known co-morbidities and confounding factors. COVID-19′s most prominent co-morbidities include Type 1 and Type 2 diabetes and metabolic syndrome, each of which can independently affect muscle oxygen status. Disease severity has also been linked to environmental factors such as air pollution and temperature, each of which would independently affect oxygen uptake dynamics[31]. Consequently, without adequate matching it would be expected that a correlation would be present even in the absence of a causative relationship. Hence, clinical findings showing a relationship between muscle oxygen tension and disease progression could only be considered as strong evidence of causation if the trial design meticulously excludes confounders.

Patient follow-ups to track long-term sequelae would also reveal whether there is a correlation between diminished muscle oxygen during acute illness and subsequent Long COVID.

Another limitation on any single clinical trial is the genetic diversity of COVID-19; mutations in the virus affect its precise pathogenicity in the body[32] and so a one-off trial would be limited to the dominant variant at that time.

Implications of hypothesis

If the hypothesis is correct, and the severity of COVID-19 illness correlates closely with diminished skeletal muscle oxygen tension, it would have widespread implications for our fundamental understanding of COVID-19 disease progression and for clinical management of COVID-19 patients.

In terms of fundamental understanding of disease progression, the proposed positive feedback loop, whereby the presence of systemic tissue hypoxia promotes conditions which further inhibit oxygen delivery, would provide a compelling explanation for the rapid progression of the inflammatory cascade in COVID-19 patients with severe illness. It would also provide an explanation for an unusual feature of severe COVID-19, which is that a patient's condition is often stable for a period without observed progression of symptoms, and then after a delay of around 8–10 days, severity then progresses rapidly. This behaviour would be consistent with "invisible" progression of symptoms in the form of declining oxygen inventory in oxygen reservoirs that are not tracked under current COVID-19 management protocols.

The hypothesis, if true, would also suggest that skeletal muscle oxygen tension would be predictive of subsequent disease progression, as it would be a direct indicator of the progression of pro-thrombotic and hyper-inflammatory conditions.

If the hypothesis is true, then TCOM could be added to existing protocols for patient monitoring in COVID-19, augmenting blood-gas analysis and pulse oximetry, the latter of which would remain the primary indicator of disease severity. In that scenario, periodic measurement of muscle oxygen could be utilized as a means of identifying

patients with elevated risk of progressing disease severity and could plausibly be an additional criterion for hospital admission.

A study tracking past COVID-19 patients found that myopathy and neuropathy can occur even following asymptomatic infection, which implies underlying mechanisms of pathology independent of primary symptoms such as respiratory distress [33]. This would suggest that muscle oxygen tension, even if not a primary indicator of disease severity, may have clinical usefulness as an indicator of these mechanisms and therefore may be clinically useful as a predictor of the various long-term sequelae referred to as Long Covid.

Conclusions

There are strong arguments that measuring muscle oxygen tension using NIRS would be a valuable clinical tool in managing COVID-19 patients. Treatment protocols that currently depend primarily on pulse oximetry or invasive blood sampling could be modified to utilize muscle oxygen tension not just as a measure of overall severity but also as an indicator of specific mechanisms of disease progression with clinical significance. In particular, declining oxygen tension in muscle could be considered an early warning sign of an impending inflammatory cascade and therefore a signal for initiating appropriate treatment.

Even if the main component of the hypothesis presented is not subsequently borne out, and the proposed mechanisms do not play a significant role in COVID-19 disease progression, a correlative relationship would still make TCOM a useful clinical tool in monitoring COVID-19 and in other disorders as a tracker of total oxygen inventory, offering a more comprehensive measure of disease severity.

If TCOM becomes a widespread practice in clinical settings, particularly in respiratory distress, correlations between muscle oxygen status and other conditions and indications would likely emerge over time. In light of muscle oxygen representing a sizable fraction of total body oxygen inventory, its routine measurement in clinical settings would represent a significant improvement in clinical monitoring of overall oxygen status in patients.

Ethics statement

The research activities conducted in the accompanying manuscript did not involve human or animal subjects. All activities were conducted in accordance with the rules and regulations of the University of the Witwatersrand and in compliance with local laws. The manuscript has not been published elsewhere, in full or in part, and the authors hold the publishing rights. No generative AI was utilized in the writing of this manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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