THE MYSTERY OF HYPOXIA IN COVID-19

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ABSTRACT

The COVID-19 pandemic has caused untimely deaths of many people. Predominantly, many of those who have been infected, have had an uneventful recovery. However, for those with co-morbidities, advanced ages, the story has been different. This review aims to highlight various pathogenesis of SARS-CoV-2 through the lens of hypoxia. The review consolidates information about virus induced hypoxia, neuroinvasive cause of hypoxia, thromboembolic cause of hypoxia, bradykinin and cytokine storms contributing to hypoxia. It brings out aspects of immune response which is aided by both coagulation cascade and the complement. In conclusion, we suggest care providers to be on the look out for asymptomatic hypoxia. We implore physicians and researchers to revisit and acutely look at the behaviour of the virus in vivo and the resulting immune response to be well equipped in this fight against the SARS-CoV-2 virus.

KEYWORDS Happy hypoxia, Cytokine storm, Bradykinin storm, Neuroinvasive SARS-CoV-2, SARS-CoV-2, COVID-19

Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) is the notorious agent implicated in the rampantly spreading COVID-19 (Coronavirus disease 2019) pandemic.[1] Like other coronaviruses, SARS-CoV-2 predominantly affects the respiratory system. The enteric, neurological system has also been reported to be affected.[2] The clinical features of this disease is a spectrum between asymptomatic to severe. Majority of the symptomatic patients complain of fever, cough, fatigue, dyspnea.[3] Nausea, vomiting, anorexia are features of enteric system involvement.[4] Loss of smell and taste have also been reported.[5] Of interest is a cohort of patients that present with ‘Happy Hypoxia’.[6] In this review, we aim to talk about this phenomenon. We also extend the discussion to understand the development of hypoxia in COVID-19 patients. Amongst the various etiologies proposed for hypoxia, we address the concepts of ‘Neuroinvasive SARS-CoV-2’, ‘Virus-induced Hypoxia’, ‘Bradykinin Storm’, ‘Cytokine Storm’, ‘Thromboembolic cause of Hypoxia’. These concepts are still evolving. This review gives a bird’s eye glimpse of COVID-19 pathophysiology in the hope of having a positive impact on prognosis and timely treatment protocols.

SARS-CoV-2: The novel virus

Coronaviruses have a single-stranded RNA (Ribonucleic acid) genome, and an envelope defines its outer surface. These viruses are present ubiquitously among humans, avians and other mammals. While most coronaviruses typically cause mild respiratory illnesses, SARS-CoV (Severe Acute Respiratory Disease Corona Virus) and MERS-CoV (Middle Eastern Respiratory Syndrome Corona Virus) cause severe disease. Genomic analysis shows that SARS-CoV-2 is part of the betacoronavirus clade. SARS-CoV and SARS-CoV-2 share nearly identical genetic makeup. It shouldn’t be of any surprise then, to know that SARS-CoV-2 shares similar infective strategies with SARS-CoV. In fact, the entry of SARS-CoV-2 into human host cells is with the same receptor as SARS-CoV, i.e. ACE2 (Angiotensin Converting Enzyme 2)[1,7,8,9,10,11].

Pathogenesis of SARS-CoV-2

The virus has a spike glycoprotein S, made of 2 subunits namely, S1 and S2. S1 binds to the host cell receptor, ACE2. ACE2 is widely present in the cell membranes of cells belonging to respiratory, cardiovascular, enteric and central nervous systems to name a few. The S2 subunit, fuses with the host cell membrane. TMPRSS2 (Transmembrane Serine Protease 2) is a transmembrane protease which allows entry of the virus into the
cells. It works by two mechanisms: as S1 is binding to ACE2, TMFRSS2 cleaves ACE2 rendering it dysfunctional. It then acts on S2 and facilitates fusion of the virus to the host membrane allowing it to enter the cell seamlessly.[12,13]

Defining dyspnea

Dyspnea is a sensation of uncomfortable, difficult, or laborious breathing and occurs when the demand for ventilation is out of proportion to an individual’s ability to tackle this discomfort. Tachypnea or fast breathing and hyperpnea or increased ventilation are used interchangeably with dyspnea but are separate phenomena. [14,15] Respiration is regulated at the higher levels through the respiratory centre (RC) which is in the medulla oblongata and pons areas of the brainstem.[6]

Mechanisms of Dyspnea

There are several known features contributing to dyspnea. Of importance are the chemoreceptors. Largely, PaO2 (Partial gas pressure of dissolved oxygen in the blood) acts at peripheral chemoreceptors while PaCO2 (Partial gas pressure of dissolved carbon dioxide in the blood) acts at the central chemoreceptors. Central chemoreceptors are present in the medulla, whereas peripheral receptors are the carotid and aortic bodies.[16,17]

In hypercapnia, central and peripheral receptors relay the message to the RC. This centre then sends efferents to the respiratory system allowing an increase in the drive to respire and an increase in the amount of air entering the lungs per minute, also known as minute volume ventilation.[6] Similarly, when there is a decrease in the PaCO2, the RC increases the ventilation in order to restore normal PaCO2. The central chemoreceptors and hypercapnia are the most important factors implicated in dyspnea.[16,17] Likewise, a similar mechanism is in play for hypoxemia. But, hypoxemia is a minor contributor to dyspnea, with dyspnea only occurring at dangerously low levels of PaO2. The Nucleus Tractus Solitarius (NTS) meanwhile also relays all afferent data received to higher sensory and motor cortices and the insula.[18] It has been found that this cortical projection produces the unpleasant sensation of dyspnea.[19]

The paradox of hypoxemia in COVID-19

Normal values of PaO2 is 75-100mmHg. Studies have shown that the quantity of hypoxemia needed to increase ventilatory capacity is the same as the amount needed to experience dyspnea. Hypoxemia and ventilation are related by a hyperbolic curve. In fact, as the partial pressure of oxygen falls to 60mmHg, there are negligible changes in ventilation. However, further decline shows a drastic increase in ventilation. Since the physiological response to hypoxemia is a rise in minute ventilation, both the number of breaths per minute and the volume of air entering the lungs is increased. Increased respiratory rate (tachypnea) and tidal volume (hyperpnea) initially, are, therefore, the most important early clinical signs of eventual hypoxemic respiratory failure.[6]

Viral pathogenic changes have shown features of ARDS (Acute Respiratory Distress Syndrome).[14] These changes indicate that there is a diffusion defect which leads to hypoxia or decreased PAO2 (Partial gas pressure of oxygen at the alveoli).[14]

So, to see a patient with tachypnea, hyperpnea, and in severe hypoxemia, presenting with dyspnea is the norm. What is astounding, however, is the lack of dyspnea in patients even with severely low PaO2 levels.[14,19]

Reports from Wuhan have shown that 62.4% of severe cases and 46.3% of cases on respiratory support and even the dead did not present dyspnea. Not surprisingly, findings with SARS-CoV infections also show that a mere 34.8% of severely affected patients reported dyspnea. These numbers are grim in contrast to other viral respiratory infections such as RSV (Respiratory Syncytial Virus) (95%) and influenza (82%) where dyspnea is frequently encountered.[18] Apart from viral pathogenic features which hinder the awareness of dyspnea, one may not see dyspnea in a SARS-CoV-2 patient because of confounding factors such as the following: Tobin et al. argue that the ODC (Oxygen dissociation curve) shows a rightward shift. Of concern in the setting of SARS-CoV-2 infection is fever which is the most common symptom in these patients.[3,19] Fever raises the core body temperature and allows the shift of the oxygen dissociation curve to the right. This means that for the same PaO2, the SaO2 (Oxygen saturation in the blood) will be low, i.e. at a body temperature of 37 degrees and 40 degrees, the PaO2 could be at 60mmHg, but SaO2 will read 91.1% and 85.8% respectively. Similarly, at a PaO2 of 40mmHg, and at below which dyspnea is expected to occur, the SaO2 is 74.1% at 37 degrees and 64.2% at 40 degrees. These shifts produce evident desaturations with no much change in the chemoreceptor input (this is so because carotid bodies respond only to PaO2 and not SaO2).[19]

Meanwhile, Dhont et al. give a contrasting explanation. They say that the ODC in fact shifts to the left, possibly in response to the respiratory alkalosis (drop in PaCO2) that develops in hypoxemia associated high minute volume ventilation. When PaCO2 is reduced, the affinity of Hb (Haemoglobin) for oxygen increases and so SaO2 increases for a given PaO2. This explains the well-preserved SpO2 (Oxygen saturation measured by pulse oximetry) even when there is dangerously low PaO2.[6]

It has also been theorised that direct viral interaction with the heme group of Hb allows harmful iron (Fe3+) to be available and lead to inflammation and cell death. In response to this, the body produces large amounts of ferritin to bind the free ions.[18] So, with the diminished amount of Hb molecules to carry oxygen, the body would lap up any oxygen molecules that it may encounter due to the now increased affinity of Hb for oxygen. Therefore, oxygen may not be released to the tissues. This gives a falsely elevated SpO2. It also gives the physician an impression that the patient does not have any dyspnea.

Another confounding factor could be pulse oximeter readings. The pulse oximeter measures SpO2. The principle of pulse oximetry lies in the illumination of the skin and measuring the differences in the amounts of light absorption of oxyhaemoglobin and reduced Hb. SpO2 can differ from true SaO2 measured with a CO-oximeter by about 4%. Pulse oximetry has also known to be less accurate at SaO2 of less than 80%.[19]

There are a wide number of patients with COVID-19 who are elderly and diabetic. The physiological response to hypoxia is down by almost 50% in patients who are 65 years or older. People with diabetes have an attenuated response to hypoxemia.[19]

Both these factors attenuate the response of the respiratory centre to hypoxia.

In conclusion, SpO2 should be interpreted considering hyperventilation, arterial measurements of PaO2, measuring the alveolar to arterial oxygen, gradient, i.e. A-a gradient and keeping in mind the age of the patient, co-morbid conditions and

supplemental oxygen.[6]

The above discussion allows us to elaborate on happy hypoxia. Happy hypoxia is a state of apparent normalcy in terms of breathing, i.e. there is no perception of difficult breathing or uncomfortable breathing to the patient, and the patient seems comfortable despite the PaO2 levels being subnormal.

Neuroinvasive SARS-CoV-2 & hypoxia

Neurotropic property of CoVs has been documented for many of the βCoVs (Beta Corona Viruses), including SARS-CoV, MERS-CoV.[20,21] It is possible that SARS-CoV-2 could behave in a similar neuroinvasive fashion. The entry of SARS-CoV-2 into the nervous system could be explained by both retrograde neuronal or hematogenous routes.[22]

The ACE2 receptors in the nasal mucosa and the chemoreceptors are one of the potential areas which SARS-CoV-2 may target. The SARS-CoV-2 virus could be gaining entry into the CNS via the olfactory mucosa to reach the cribriform plate, the olfactory bulb and finally to the olfactory neurons. Here there could be a possible transsynaptic transfer of the virus, and it reaches the brain stem where the RC is encountered.[22] Here, it causes the breakdown of the RC leading to its dysfunction in a manner where hypoxia is present. However, because it has collapsed, there is no further projection of this message to the cortex and insula leading to the absence of any perception of discomfort in breathing or dyspnea. The virus could also enter the CNS via hematogenous route, in which endothelium could be the culprit.[22]

Three mechanisms can explain the hematogenous route of viral transmission into neural tissues. The virus attacks endothelial cells of the blood-brain barrier directly to allow itself access to neural tissue. It could mimic the Trojan horse model, as is seen in HIV (Human Immunodeficiency Virus) infections. In this, infected immune cells are introduced into the neural tissues. Another mechanism is via transcytosis wherein the virus crosses the endothelial cells with the help of endocytic vesicles.

There is a need for more clarity in the hematogenous spread of neurotropic SARS-CoV-2.[22] Another example to support the cause of neurotropism causing happy hypoxia is the development of hyposmia/anosmia in SARS-CoV-2 infected patients. This could be because the virus reaching the olfactory neurons damages them, which leads to the presentation of impaired smell sensation. Studies have shown that after exposure to SARS-CoV by inhalation, it was detected at the olfactory bulb and higher neural tissues a few days later. Similar observations were made with another virus of the betacoronavirus family. Another study showed that disconnecting the olfactory pathway did not allow coronavirus to reach higher neural tissues in an animal model.[23]

So, going by the high homology between SARS-CoV and SARS-CoV-2, the general nature of coronaviruses to have an affinity towards neural tissue and evidence shown in animal studies, one may not be wrong to assume that SARS-CoV-2 is indeed neuroinvasive. Moreover, it may also be one of the mechanisms driving happy hypoxia.

Happy hypoxia is being reported very frequently in literature in association with COVID-19.[14,19,24,25,26] Apart from neuroinvasive cause of happy hypoxia there has been accumulating evidence of several other contributing factors to happy hypoxia.

On the basis of many factors,Gattinoni et al. have proposed the presence of 2 phenotypes: The L phenotype has been defined for a lung which has low elastance or high compliance, low V/Q ratio, low lung weight and low recruitability. The H phenotype meanwhile encompasses a lung with high elastance, high right-to-left shunt, high lung weight and high recruitability. Gattinoni et al. say that once there is an established viral infection, there is a reasonable amount of oedema that is seen in areas of the elastic lung. The viral infection seems to affect this elastic property of a normal lung. This contributes to high compliance of the lungs. The Italian scientists also suspect a dysfunctional hypoxic vasoconstriction mechanism in SARS-CoV-2 infections. Hypoxic vasoconstriction is a physiological phenomenon where the pulmonary vessels constrict in response to hypoxemia in order to allow blood flow only to the aerated lung tissue.[27] Reasons for this could be the ensuing endothelial damage that seems to be occurring.[28]

According to figure 1, pre-existing conditions such as ageing, obesity, atherosclerosis, hypertension and diabetes mellitus play a role in endothelial dysfunction. Similarly, the endothelium is also damaged with the entry of SARS-CoV-2 virus.[28] Tang et al. have reported that 71.4% of COVID-19 non-survivors are patients with DIC (Disseminated Intravascular Coagulation).[29] Studies have shown disrupted junctions, endothelial cell swelling as well as disruption of contact between the basement membrane and the endothelium. These findings are further corroborated by the detection of SARS-CoV-2 virus in the endothelial cells itself: an ominous sign of endothelial damage ensuing dysfunction.[30]

Now, the normal response to hypoxemia is increased respiratory drive, i.e. there is an increase in tidal volume, which again is a consequence of an increase in the negative intrathoracic pressure, further increasing compliance. This gives a picture of a proportional increase in both negative intrathoracic pressure and ventilation, maintaining near-normal compliance. This explains why a happy hypoxic could present without any dyspnea as the patient is inhaling the volume of air that is expected.[27]

Effect of various strains of SARS-CoV-2 on Happy Hypoxia

There is evolving literature on the genomic diversity of SARS-CoV-2. There is a paucity of data in this aspect. However, a British physician has proposed that the severity of COVID-19 hangs more on the host’s response than a variation in genome diversity.[31]

Co-morbidities and Happy hypoxia

Although this is an evolving topic, there has been a fairly comprehensive study from France that has delineated data on the relationship between comorbidities, age, gender with happy hypoxia.

Patients as they age and diabetics tend to have a respiratory centre which may be desensitised to changes in gaseous elements. Silent hypoxia or happy hypoxia is more likely to have a poor outcome in those who are aged, male and those with chronic diseases.[32]

Virus-induced C-dysfunction & hypoxia

The peripheral afferent fibres present in respiratory tract respond to relevant stimuli and drive responses such as cough, tachypnea and dyspnea. These fibres are pulmonary C-fibres. Local changes in viral pneumonia could stimulate C-pulmonary fibres. The cytokine storm syndrome, a phenomenon touted to be characteristic of SARS-CoV-2 infection has the potential to damage these fibres and can be incriminated in a total or partial loss of their function. However, this hypothesis does collide in that some viral respiratory pathogens can induce upregulation of these fibres.[18,33] Virus-induced C fibres dysfunction could contribute to the absence of dyspnea in SARS-CoV-2 pneumonia.[18,33]

Role of RAS and Bradykinin in SARS-CoV-2

What is Renin Angiotensin System?

The RAS (Renin-Angiotensin System) maintains an equilibrium between blood volume and pressure with several products of the peptide angiotensin and its receptors. Figure 2 depicts the actions of ACE (Angiotensin Converting Enzyme) and ACE2.AT1 (Angiotensin receptor 1) allows vasoconstriction and sodium retention. The AT2 (Angiotensin receptor 2) receptor allows vasodilation and natriuresis. AngII (Angiotensin II) is an agonist at the AT1 receptor. The MAS1 receptor allows for vasodilation, anti-inflammatory and anti-fibrotic processes. Ang1-7 (Angiotensin 1-7) is an agonist at the MAS1 receptor and the AT2 receptor. Ang1-9 (Angiotensin 1-9)also is an agonist at the AT2 receptor. All these must be viewed as an interlinked web.[34]

Vitamin D is a RAS regulatory molecule. Renin expression can be suppressed by Vitamin D. This invariably increases AngII levels and with it, enhances its deleterious effects. ARDS has been implicated in those with vitamin D deficiency.[35]

What is Bradykinin?

BK (Bradykinin) is a product formed via thekinin-kallikrein pathway. In conjunction with the B2R (Bradykinin receptor 2) receptor, bradykinin’s actions include vasodilation, natriuresis, and plasma exudative behaviour, increased vascular permeability. It perpetuates chronic inflammation with the B1R (Bradykinin receptor 1) receptor. It is responsible for a cough reflex, bronchoconstriction, and increases airways resistance.[35]

Bradykinin regulation

The kinin-kallikrein system on activation produces kinins. BK binds to its receptors on endothelial cells to increase vascular permeability and cause capillary leakage.

As pictured, BK is generated by proteolysis of kallikrein on kininogens. Kallikreins are serine proteases and can be divided into plasma kallikreins and tissue kallikreins.[35,36,37] In order to regulate these Bks, there are measures in place to degrade these molecules in a timely fashion.

Kinins are broken down to inactive molecules by kininases I and II. Plasma carboxypeptidase M/N is another name for kininase I. It acts on BK or Lys-Bradykinin to yield des-arg9-bradykinin or Lys-des-arg9-bradykinin, respectively, which are ligands for B1R. B1R is a bradykinin receptor on endothelial cells that are up-regulated under pro-inflammatory conditions. Cytokine storm is one of the hypotheses suggested for SARS-CoV-2 and inflammatory mediators like IL-1 and TNF-α as part of this syndrome can up-regulate B1R. Kininase II is identical to ACE. Bradykinin and Lys-bradykinin are the ligands that stimulate the constitutively produced B2R receptors on endothelial cells.[36,37]

RAS and Kinin-Kallikrein pathways

About 90% of bradykinin is degraded by ACE. This keeps bradykinin localised and keeps its varied effects in check. About 11% of bradykinin, however, is converted into des-Arg9-bradykinin by kininase IACE2 which strongly prefers to cleave des-Arg9-bradykinin is dysfunctional in SARS-CoV-2. This allows an unchecked increase in AngII, which can potentiate...
its vasoconstrictor role just as increased des-Arg9- bradykinin can potentiate its damaging role in vasculature via B1R activation.[36,37]

From this discussion, we can infer that ACE and ACE2 are important for keeping excessive kinins in check and its supposed dysfunction by the SARS-CoV-2 virus could lead to lung injury and more importantly severe outcomes like ARDS. Upregulation of ADAM-17 and subsequent activation of inflammatory mediators further suppress ACE2 expression. This, in turn, upregulates RAS and AngII, pronouncing its effects. In part, due to the inflammation of respiratory tissue, programmed death of ACE2 producing cells occurs, i.e. Clara cells and type II pneumocytes die, further reducing ACE2.[38]

These pathogenic developments could be damaging to mechanisms of dyspnea, leading to the lack of it or increasing the severity of it in later stages of the disease course.[36,37] So, it wouldn’t be odd to deduce that SARS-CoV-2 interaction with ACE2 down-regulates the function and expression of ACE2. To summarise, the kinin-kallikrein system is affected by SARS-CoV-2 patients. Studies have detected BK precursor kininogen, and kallikreinzymogens in SARS-CoV-2 patient samples and bradykinin degradative enzymes have been noted to be down-regulated.B1R is normally expressed at basal levels. However, in the case of SARS-CoV-2, both BK receptors are expressed in great amounts.SERPING1 gene that codes for the C1-Inhibitor that inhibits FXIII, the starting point for the extrinsic pathway of coagulation is highly down-regulated, which further increases BK.[38] This leads to the discussion of Bradykinin Storm.

**Hyaluronic acid synthesis and degradation**

Before we begin to explain bradykinin storm, we must understand another component of it which is hyaluronic acid (HA). HA is a complex carbohydrate polymer found in connective tissues. HA is known to be able to trap about 1000 times its weight in water, and when in conjunction with water, it results in a hydrogel. One could compare it to 'jello'. Hyaluronan synthase is an enzyme that is coded by the HAS1, 2, and 3 genes. It is the enzyme responsible for HA production. HA is degraded by hyaluronidases, and they are encoded by the HYAL1 and HYAL2 genes. Both of these genes interact with CD44 (an HA receptor) for their activity.[38]

In SARS-CoV-2, studies have suggested that HA synthases are up-regulated and hyaluronidases down-regulated. CD44 gene codes for the HA receptor required for its degradation. As a result, there is increased amounts of HA in the lung tissues, which along with increased kinins could form hydrogel material of thick consistency, negatively impacting gas exchange or diffusion.[38] Additionally, it has been suggested that Ang II up-regulates CD44 expression.

Elevated kinins can induce IL-2, which has been found in high concentrations, via CD44, causing vascular hyperpermeability. Interestingly, CD44 knockout models do not show hyperpermeability features.[38] This involvement of HA in association with RAS and BK pathways strengthen the hypotheses that there is in fact, the involvement of all these pathways in the pathogenesis of SARS-CoV-2.

Build up of such ‘jello’ material, and further development of ARDS would definitely lead to diffusion defects in the pulmonary alveoli, thereby hypoxemia and an increase in the A-a gradient all of which will finally materialise as respiratory symptoms of breathlessness, air hunger. It also implies that apart from the cytokine storm, which has been cited as one of the damaging factors of SARS-CoV-2, there are other pathways too in play.

**Bradykinin storm**

Increased production of HA, dysfunctional RAS and bradykinin pathways all culminate to affect the gas exchange. The viscous ‘jello’ accumulating in the bronchoalveolar spaces is incriminated for this phenomenon. HA has long been associated with the development of ground-glass opacities, and rightly so, hyaline membranes correlating to ground glass radiographic appearance have been seen in SARS-CoV-2 patients. The hydrogel is also responsible for somewhat heavy lungs that are seen in severe SARS-CoV-2 patients as discovered by a study which states SARS-CoV-2 lungs are 4.6 heavier than healthy ones. Although this hydrogel formation seen in ARDS patients represents a late-stage event in severe cases of SARS-CoV-2 infections, if the cause is indeed an overproduction of HA, it could be a point of valuable intervention as the condition can be easily identified, and treated.[29]

Greatly increased kinins can cause electrolyte derangements like hypokalemia which is a known arrhythmogenic and can cause sudden cardiac death. A recent report on this matter corroborates that hypokalemia occurs in severe SARS-CoV-2 infections. Symptomatic SARS-CoV-2 patients may also present with features like myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, all of which are seen in conditions of increased kinins. Keeping these pieces of evidence and theories in mind, it could be postulated that the pathology of SARS-CoV-2 could likely be the result of a predominant bradykinin storm than a cytokine storm, although, given the induction of IL-2 by BK, the two may be intricately linked.[38]

**Coagulation cascade and SARS-CoV-2**

Venous thromboembolism, acute limb ischemia, pulmonary embolism are some of the features of hypercoagulability. These have been reported in many SARS-CoV-2 patients. However, these seem to be a feature of severe COVID-19 disease. In light of inflammation, these thrombotic complications are being known as thromboinflammation or COVID-19-associated coagulopathy.[39] After entering the body, SARS-CoV-2 is recognised by the PAMP (Pathogen Associated Molecular Pattern) in the body to activate the immune system to clear the virus. However, excessive activation can cause a cytokine storm, damage the microvascular system, activate the coagulation system, inhibit fibrinolysis and the anticoagulant system. The resulting extensive thrombosis in microvessels could lead to DIC, microcirculation disorders and even MODS (Multiple Organ Dysfunction Syndrome).[40]

**Thromboinflammation**

Once a viral pathogen enters the realm of the immune system, it triggers the cascading coagulation reactions. These reactions are capable of now influence the inflammatory response. The action of both inflammation and coagulation together is called thromboinflammation.[39] TNF-α, IL-6, and IL-1β are inflammatory mediators and are produced in excess in thromboinflammation. These mediators in excess cause a cytokine storm. In particular, IL-6 encourages the expression of tissue factor to activate thrombin. IL-6 has been seen in increased amounts in COVID-19 patients.[39]

Tissue factor is also the trigger that switches on the extrinsic coagulation cascade.[41] The intrinsic pathway is also activated.
in the presence of inflammatory mediators because of their action on vascular endothelium. The enormous cytokine explosion, in conjunction with viral inflammation, leads to increased vascular permeability, multi-organ failure, and even death if high cytokine concentrations persist.\[39\]

These thrombotic features can be seen even in pulmonary vasculature foci of bleeding and microthrombi and can cause impaired gas exchange leading to hypoxemic conditions.\[39\] In this environment of inflammation and widespread thrombosis, there is increasing hypoxemia. This further starves the endothelial cells of oxygen, allowing more damage to it and circling back to increase coagulation. This set up is a vicious cycle of thromboinflammation.\[39\]

Alternative explanations for procoagulant blood with SARS-CoV-2 infections have also been suggested. Anticardiolipin, anti-B2 glycoprotein antibodies have been detected in SARS-CoV-2 patients. These are components seen in antiphospholipid syndrome and are known for their hypercoagulable activities.\[42\]

**IL-6 Hypoxia and Protein S**

Another aspect of hypoxia and the IL-6 induced cytokine storm is that both factors down-regulate a key anticoagulant, Protein S. It has been shown that in a population of stroke patients, IL-6 was up-regulated, and it caused downregulation of Protein S that resulted in venous thrombosis. It has also been demonstrated that hypoxia down-regulates Protein S expression. Protein S supplementation in experimental setups alleviated some symptoms of the infection. A substantial number of cases of severe infection with SARS-CoV-2 manifest both hypoxia and prothrombotic complications. As both hypoxia and IL6-induced inflammation depress Protein S abundance, it may be reasonable to consider administration of Protein S in severe SARS-CoV-2 patients.\[39\]

**Cytokines and SARS-CoV-2**

**Immune dysregulation in SARS-CoV-2**

ACE2 is dysfunctional upon interaction with SARS-CoV-2. This signals changes in the RAS with AngII activating NF-xB and ADAM17. sIL-6Ra, the soluble form of IL-6Ra, is formed under the influence of ADAM17, sIL-6Ra allows the activation of STAT3. With both STAT3 and NF-xB turned on, IL-6, the main mediator of inflammatory cytokines, is formed under the influence of C5b-9 induce the release of NF-κB under the influence of C5b-9 induce the release of IL-6 from vascular smooth muscle cells.\[43,44\]

Studies have shown that mice models deficient in C3 loads had milder SARS-CoV induced pathologic features like better respiratory function, reduced pathologic findings in the respiratory system, and lower circulatory and tissue cytokines and chemokines. This shows that activation of the complement system in the lungs of SARS-CoV infected mice leads to immune-mediated damages in the lungs.\[44\] Recent studies reported the involvement of excessive complement activation in SARS-CoV-2 via viral nucleocapsid N protein-mediated MBL (mannose-binding lectin) pathway Accelerated inflammatory behaviour, and lung damage is seen with MASP-2, a protease in the lectin pathway that induces downstream complement cascade.\[44\]

There is enough evidence that goes to show the involvement of complement and its role in immune-mediated damage in SARS-CoV-2 patients.

**Treatment protocols**

Hypoxia and its subtype, happy hypoxia can be identified fairly easily with the help of pulse oximetry and ABG (Arterial Blood Gas) analysis. When identified early, it can influence management strategies and avoid inadvertent iatrogenic errors.

In the initial days of the pandemic, the worst-hit nations faced before them cases of severe hypoxia. In the absence of clear cut protocols and the fear of aerosolisation of viral particles upon NIV (Non-Invasive Ventilation) and HFNC (High Flow Nasal Cannula), intubation became the primary management tool.\[45\]

Usually, hypoxia irrespective of symptoms is treated, but in a stepwise manner which includes high flow nasal cannula and non-invasive ventilation. This step-wise manner for various reasons was not employed in the treatment of COVID-19.\[45,46\] There was excessive dependence on invasive ventilation for the treatment of COVID-19 patients. This resulted in a high mortality rate.\[45\]

The L phenotype, as discussed allows an increase in negative intrathoracic pressure and this over time may lead to a state of P-SILI (Patient Self Inflicted Lung Injury) in the backdrop of increasing inflammation to combat the virus. This ongoing situation increases oedema, thereby adding extra pressure. When this process reaches the threshold, the quantities of gas and the tidal volumes reduce. This can cause atelectasis. At this point, there could be a transit from L type to H type. The H type is prototypical for severe ARDS criteria which includes severe hypoxemia, bilateral infiltrates, high lung weight, decreased compliance and high recruitability.\[27,47\]
The L-type deals with a dysfunctional hypoxic vasoconstriction mechanism and a V/Q mismatch leading to hypoxia. It would be useful, therefore, to first provide FiO2 to which these patients respond well. [27,47]

Prone positioning is another way to allow better oxygen delivery. It is a simple, effective, cost and personnel saving measure. Half an hour to two hours each in prone left lateral decubitus and right lateral decubitus have been helpful.

It could even be escalated to the use of non-invasive methods of oxygen delivery, i.e. HFNC, continuous positive airway pressure (CPAP) and NIV. [45]

If the respiratory drive is still uncontrolled, this would mean there is still a strong inspiratory effort which could further worsen P-SII.[27,47]

Such patients may do well with early intubation. Type L patients with their increased compliance can tolerate high tidal volumes better than a Type H patient. Such patients require ventilator settings with reasonably high tidal volumes (7-9 mL/kg) and a low positive end-expiratory pressure (PEEP) of about 8-10cm of H2O.

In type H, use of higher PEEP (>10 cm of H2O) and lower tidal volumes (5-7 mL/kg) could be beneficial.[27,47] In conclusion, identifying and differentiating these 2 types of presentations may not only help with management but also drastically bring down mortality rates. Apart from treating hypoxia, there are several other target points in this disease which if identified, can help in recovery.

As depicted in figure 4, there may be a vague demarcation in the phases of this infection. [49] Accordingly, one must be able to identify and stratify the patients so that they are treated in a timely fashion and accurately. [49] In the first week of the infection, the viral load is high. It is high enough to cause pathology.[49] Drugs have been instituted to uniquely affect the lifecycle of SARS-CoV-2 in vivo. Frantic measures such as repurposing of drugs have also come to the forefront in the form of ivermectin, Hydroxychloroquine, doxycline, to name a few.[49] After being tested in a variety of clinical trials, there have been polarising results on remdesivir’s beneficial effects. [41,47] Hydroxychloroquine, lopinavir-ritonavir have been shown to have no beneficial effects on COVID-19 mortality rate, hospitalisation duration or even initiation of ventilation according to the landmark Solidarity trial. [47]

Soon enough, the host immune system is triggered to fight the invading pathogen as seen around day 7.[48] Unfortunately, it has been observed that the immune system is activated too little and too late.[48]

Since cytokines are being incriminated in the pathogenesis of SARS-CoV-2, blocking these cytokines may be beneficial. Antagonising NF-κB translocation, TNF-α, IL-1 will down-regulate their actions at the B1R. Anakinra is a well-known drug with a remarkable safety profile and blocks both alpha and beta components of IL-1.[35]

Tocilizumab, an IL-6 receptor blocker, is being tried to combat inflammatory actions of IL-6.[50] TNF blockers is a therapeutic intervention.[35] One must, however be aware of their well documented adverse effects. Since severe SARS-CoV-2 patients have a long drawn out disease, and there are many inflammatory characteristics in this disease, anti inflammatory drugs in the form of corticosteroids may be used.[34] Another approach would be the modulation of Renin levels via Vitamin D supplementation.[34]

Blocking kallikreins will result in less kinines and decreases both B1R and B1R ligands at the site of infection and subsequently less leakage via B1R and B2R. The drugs namely are aprotinin/ecallantide. [35,36] Mechanism of action of aprotinin is that it is a nonspecific serine protease inhibitor and preferentially works against plasmin and kallikrein. Aprotinin inhibits factor XII and prevents the activation of the extrinsic coagulation pathway. It also has a role to play in inhibition of the intrinsic pathway of coagulation, fibrinolysis, and attenuation of the pro-inflammatory response.[51] There has also been supportive date to support the anti-inflammatory actions of Aprotinin.[51,52]

Lanadelumab is a monoclonal antibody against the plasma kallikrein. Lanadelumab has been used for the treatment of angio oedema. The rationale to suggest lanadelumab is that this mAb can block the upstream axis that leads to kinin formation, avoiding the inflammatory and coagulation storm besides the complement system in SARS-CoV-2 infected patients, likely preventing the exacerbation of COVID-19.[53]

Blocking B1R and B2R signaling is another target for therapy. A B2R antagonist drug by the name of Icatibant has been approved for the treatment of hereditary angio oedema. A B1R antagonist drug is not yet available. Antagonism at the receptor level would be a good way to contain the virus severity.[35,36] Zinc could be of valuable mention here. Zinc is known to inactivate the serine proteases that the kallikreins are. This could explain the rationale behind zinc supplementations that have been suggested by authorities in the prevention and treatment of SARS-CoV-2 infections.[36]

Since coagulopathy has become a common observation in severe COVID-19 patients, it has become a norm to check on patients’ coagulation parameters. Moreover, these parameters are also helping predict the progression of this disease. D-Dimer is one such parameter. Deranged parameters of coagulation warrants LMW heparin as a prophylactic. This therapy has become commonplace in the treatment of SARS-CoV-2.[54,55]

**Conclusion**

Asymptomatic hypoxia must be identified and addressed early in order to institute prompt care. In general, clinicians must have a low threshold for suspecting breathing troubles. Tachypnea and decreasing SpO2 must raise the alarm for an impending respiratory failure. Frequency of respiration, chest retractions and use of accessory muscles must be accounted for when examining a patient. A high minute volume is must be looked into, and the clinician must identify the possible compensation...
happening because of deranged gas exchange. Such patients likely require admission and radiographic studies can be used to aid in the diagnosis and management of this patient. Meanwhile, more studies to establish neurotropic causes for this silent hypoxia should be determined in order to allow better treatment protocols and early recovery for patients. The RAS, bradykinin system, coagulation cascade, complement system and the cytokines are all in place to aid the body in destroying pathogens, and they work hand in hand. These interactions are complex and need more elucidation. Therapeutic agents, be it repurposed drugs or tailor-made drugs need more backing in terms of safety profile and efficacy. A clear picture of the pathogenesis of SARS-CoV-2 virus still seems to be evolving. As this evolves, so does our understanding of symptoms and signs such as breathlessness and dyspnea and so also, the management protocols.

Abbreviation
- COVID-19: Corona Virus Disease 2019
- SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2
- RNA: Ribonucleic acid
- SARS-CoV: Severe Acute Respiratory Syndrome Corona Virus
- MERS-CoV: Middle Eastern Respiratory Syndrome Corona Virus
- ACE2: Angiotensin Converting Enzyme 2
- TMPRSS2: TransMembrane Serine Protease 2
- Respiratory centre: RC
- PaO2: Partial gas pressure of dissolved oxygen in the blood
- PaCO2: Partial gas pressure of dissolved carbon dioxide in the blood
- NTS: Nucleus Tractus Solitarius
- ARDS: Acute Respiratory Distress Syndrome
- RSV: Respiratory Syncytial Virus
- ODC: oxygen dissociation curve
- SaO2: Oxygen saturation in the blood
- Hb: Haemoglobin
- SpO2: Oxygen saturation measured by pulse oximetry
- βCoVs: Beta Corona Viruses
- DIC: Disseminated Intravascular Coagulation
- RAS: Renin-Angiotensin System
- ACE: Angiotensin-Converting Enzyme
- AT1: Angiotensin receptor 1
- AT2: Angiotensin receptor 2
- Ang II: Angiotensin II
- Ang 1-7: Angiostatin 1-7
- Ang 1-9: Angiostatin 1-9
- BK: Bradykinin
- B2R: Bradykinin receptor 2
- B1R: Bradykinin receptor 1
- HA: Hyaluronic acid
- PAMP: Pathogen Associated Molecular Pattern
- MODS: Multiple Organ Dysfunction Syndrome
- MBL: Mannose-Binding Lectin
- ABG: Arterial Blood Gas
- NIV: Non-Invasive Ventilation
- HFNC: High Flow Nasal Cannula
- P-SILI: Patient Self Inflicted Lung Injury

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Conflict of interest
There are no conflicts of interest to declare by any of the authors of this study.

References


