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Review

Relevance of carotid bodies in COVID-19: A hypothetical viewpoint

Benedito H. Machado, Julian F.R. Paton *

Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto 14049-900, SP, Brazil

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ABSTRACT

We have considered some of the available evidence to account for the impact of SARS-CoV on the regulatory control of the autonomic nervous and respiratory systems. Apart from stimulating general interest in the subject, our hope was to provide putative explanations for some of the patients' symptoms based on described physiological and pathophysiological mechanisms seen in other diseases. Herein, we have focused on the carotid bodies. In this hypothetical viewpoint, we have discussed the plasticity of the carotid body chemoreflex and made a comparison between acute and chronic exposures to high altitude with COVID-19. From these discussions, we have postulated that the sensitivity of the hypoxic ventilatory response may well determine the outcome of disease severity and those that live at high altitude may be more resistant. We have provided insight into silent hypoxia and attempted to explain an absence of ventilatory drive and anxiety yet maintenance of consciousness. In an attempt to discover more about the mysteries of COVID-19, we conclude with questions and some hypothetical studies that may answer them.

The idea behind this hypothetical review is that after more than a year of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and the coronavirus disease 2019 (COVID-19) pandemic, we asked whether or not there is altered peripheral chemoreflex function that accounts for some of the symptoms and outcomes in COVID-19 patients.

Although our question appears simple, finding an answer from the current literature about the pathophysiology experienced by patients with COVID-19 has proved challenging. In this short review, and centred on oxygen sensing, we wish to report on our finding of the highly integrative nature of the physiological and pathophysiological responses involving the peripheral chemoreceptors that may be occurring in patients infected with SARS-CoV-2 virus. Based on recent available clinical data and previous related studies, our primary purpose was to summarise and provide putative insight into some of the complexities underpinning the physiological interactions involved in oxygen sensing with the hope that this might explain some aspects of the disease and provide new ideas for preventing some of the complications. At the time of revising this work, the vaccination in several countries is successful in reducing the numbers of infected patients, hospitalization and deaths.

1. Carotid body may be central to survival in COVID-19 patients: a hypothesis

Given the low partial pressure of oxygen in arterial blood (PaO_2) of patients infected with SARS-CoV-2 virus (Sartini et al., 2020; Chen et al., 2020), the carotid bodies and the resulting reflex responses are likely to play a central role in the symptoms and outcomes (Porzionato et al., 2020a, 2020b; Holmes, 2020). Hence, our focus will be related to the involvement of this sensory system across COVID patients expressing distinct disease characteristics and including differing age, gender, comorbidities and genetic backgrounds (Tobin et al., 2020). We recognise that a potential confounder is the reaction to hypoxia (so called, the hypoxic ventilatory response) as response sensitivity differs between individuals due to distinct thresholds of oxygen partial pressure required to activate the carotid body (Tobin, 2019; Tobin et al., 2020). Further, its sensitivity may be changed by a SARS-CoV-2 infection and this could be either sensitisation or de-sensitisation as we discuss below. In this regard, Gattinoni et al. (2020) and Porzionato et al. (2020a, 2020b) report each COVID-19 patient has an exclusive finger print and an unpredictable combination of multiple factors that determine the course of the infection and symptoms experienced. Thus, such factors will affect an individual's response profile to hypoxia this may determine the degree of involvement of carotid body activation in COVID-19 patients

* Corresponding author at: Manaaki Mānawa – The Centre for Heart Research, Department of Physiology, Faculty of Medical & Health Sciences, University of Auckland, Park Road, Grafton, Auckland 1142, New Zealand.
E-mail addresses: bhmachad@fmrp.usp.br (B.H. Machado), J.Paton@Auckland.ac.nz (J.F.R. Paton).

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affecting their response to the disease and their outcome. We recognise that the carotid bodies are not solely sensors of blood gases but are multi-modal arterial sensors responding to inflammation, low blood pressure, sympathetic activity and a variety of metabolically related hormones, so their involvement may well go beyond responding to hypoxia in COVID-19 patients (De Burgh Daly, 1997; Iturriaga et al., 2015; Zera et al., 2019; Porzionato et al., 2020a, 2020b; Gattinoni et al., 2020; Tobin et al., 2020; Holmes et al., 2019; Holmes, 2020).

We propose that the functional integrity of the carotid bodies and relative normal sensitivity provide a positive prognosis for patients infected with SARS-CoV-2 as it is a major inter-connected system recruited by the body to help defend itself. This is consistent with Comroe's viewpoint describing the carotid body chemoreflex as 'defensive' as opposed to 'regulatory' in function (Comroe and Schmidt, 1937). Its reflex responses to threatening stimuli provide ventilatory drive, sustain arteriolar and bronchiolar tone as well as cardiac protection, regulation of stress hormones, glucose and blood volume, and appropriate inflammatory and behavioural responses (Fig. 1). If defensive in function, then logically carotid body dysfunction may contribute to the rapid deterioration of COVID-19 patients as has been seen in so many around the world. Our view is different of that recently published by Simonson et al. (2021) that normal chemosensitivity by the carotid body in COVID-19 patients may develop respiratory failure via self-inflicted lung-injury. However, we are in agreement that this may occur in cases of carotid body overactivity.

2. Plasticity in the chemoreflex

There are multiple levels at which arterial chemoreception function could be modulated (either sensitised or made dysfunctional; Fig. 1) including: the carotid body glomus cells and its blood supply (Leonard et al., 2018; Mkrtchian et al., 2020; Holmes, 2020), type II sustentacular cells, the petrosal ganglion neurons (Obiefuna and Donohoe, 2020), their central synapses with neurons in the nucleus tractus solitarii (NTS) of the dorsomedial medulla oblongata (Khun, 2021; Moya et al., 2020; Rogers et al., 2020), central nervous reflex arc (Netland et al., 2008) and motoneurons in the brainstem and spinal cord (Fig. 1). Based on predominance of evidence, we will focus on the changes in sensitivity of the carotid body and to a lesser extent on alterations in down stream synaptic processing as this scenario is known to cause respiratory, cardiovascular and autonomic dysregulation during hypoxia (Porzionato et al., 2020a, 2020b; Gattinoni et al., 2020; Chen et al., 2020; Archer et al., 2020). In this regard, we compare the effects of high altitude on the carotid body and their relevance to potential mechanisms and symptoms

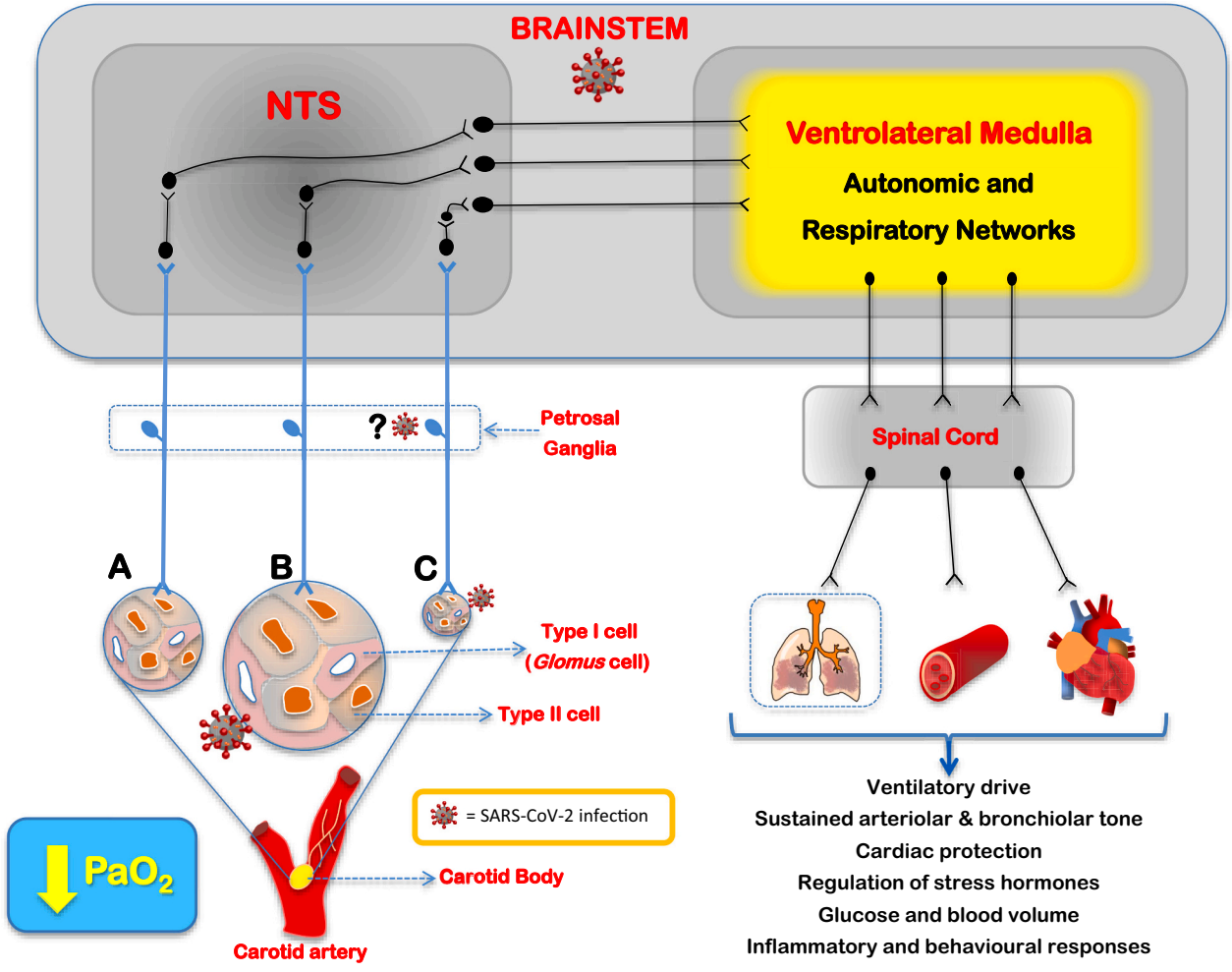

Fig. 1. Schematic drawing of the peripheral chemoreflex pathways in the brainstem and representing the different profile of carotid body in COVID-19 patients: Carotid Body A) in the majority of patients the carotid body reflex responds very well to the hypoxic challenge and the glomus cells are not infected by SARS-CoV-2; Carotid Body B) in a small percentage of patients the carotid bodies may be overactive even before the SARS-CoV-2 infection or became overactive as consequence of the acute phase of the infection; and Carotid Body C) in a smaller percentage of the population the carotid bodies are de-sensitised or non functional even before the SARS-CoV-2 infection or glomus cells were killed after the infection (Villadiego et al., 2021). We also acknowledge infection of SARS-CoV-2 in the brainstem (Bulfamante et al., 2020) and because of the loss of taste (ageusia), we cannot rule out within the petrosal ganglion (e.g. Gautier and Ravussin, 2020); both these loci could affect chemoreflex function.

expressed in COVID-19 patients.

3. COVID-19 and high altitude

The critical physiological adaptive responses produced at high altitude where the partial pressure of oxygen is low has some similarity to patients infected with SARS-CoV-2 virus (Arias-Reyes et al., 2020; Soliz et al., 2020). In both situations, the appropriate chemoreflex response to low PaO_2 is an immediate hyperventilation. This "physiological" reaction provides an adaptive response (or coping strategy) to the hypoxic challenge, ensuring increased respiratory drive to maintain arterial blood oxygen (Fig. 1). However, this system can fail in those infected with SARS-CoV-2 and it is known that sedation/neuromuscular blockade and mechanical ventilation are all positively correlated with mortality (Lim et al., 2020) indicating malfunction of the respiratory system. Those organs at greatest risk are those with the highest oxygen extraction/highest metabolic rate and include the carotid bodies themselves, the brain and heart. Chemoreflex evoked hyperventilation is associated with tachycardia, raised plasma catecholamines, hypocapnia and respiratory alkalosis (Fig. 1), and if the latter persists chronically it can cause headache, nausea, lethargy, dizziness and disturbed sleep. Hypocapnia also reduces the drive to breathe through the lack of excitatory actions because of increased pH on both peripheral and central chemoreceptors (e.g. hypocapnic braking). This respiratory alkalosis can be compensated for relatively slowly through the excretion of bicarbonate by the kidney. The latter is facilitated by administration of acetazolamide which helps to excrete excess bicarbonate to lower the pH of blood thereby removing the hypocapnic brake and boosting both peripheral and central chemoreceptor activity and hence ventilatory drive.

When exposed to a high altitude challenge some people may face clinical problems such as hypoxic pulmonary vasoconstriction, pulmonary hypertension and pulmonary oedema – which is associated with dyspnoea, mild fever, cough, headache, cerebral oedema, ataxia and sputum often containing blood (Soliz et al., 2020; Archer et al., 2020). Many of these symptoms have been reported at presentation in COVID-19 patients (Bohn et al., 2020; Gattinoni et al., 2020; Frohman et al., 2020; Iadecola et al., 2020) and, as at high altitude, they can be fatal. The main clinical symptoms of COVID-19 patients are: fever, dry cough, fatigue, ageusia, anosmia and headache (Guzik et al., 2020) but may also present dizziness and cerebral oedema due to inflammation in the cerebral vasculature (Soliz et al., 2020); the latter are often seen in patients with mountain sickness.

We fully acknowledge that there are differences between COVID-19 and living at high altitude and that the disease is distinct and far more complex than mountain sickness. We will briefly review these distinctions and then focus on other aspects of carotid body evoked reflex responses seen at high altitude with COVID-19 patients. Importantly, and as Archer et al. (2020) suggests that there is a failure of the body's homeostatic oxygen-sensing systems, including carotid bodies in COVID-19 patients. This failure of the carotid bodies is supported in a case study by the presence of SARS-CoV-2 in the glomus cells of the carotid body of a COVID-19 patient (Lambermont et al., 2021) and by the high expression of ACE2, the functional receptor of SARS-CoV-2, in the glomus cells of the human carotid body (Villadiego et al., 2021).

In COVID-19 patients, Archer et al. (2020) reminds us that hypoxia induced vasoconstriction in the lung is an important physiological mechanism to shunt blood to better ventilated regions of the lungs. They report that the low pulmonary artery pressure is caused by a severe impairment of the hypoxic pulmonary vasoconstriction in COVID-19 patients and suggest that this is severely detrimental to ventilation because of the loss of the physiological shunting mechanism. Archer et al. (2020) points out that the pulmonary oedema in COVID patients is a result of alveolar infiltrates triggered by viral induced inflammation and not pulmonary hypertension (as seen at high altitude) as pulmonary arterial pressure is typically low.. Thus, it appears that patients are unable to generate pulmonary artery pressure and that SARS-CoV-2 uncouples mechanisms by which hypoxia triggers vasoconstriction, which is in stark contrast to the physiology occurring at high altitude. A possibility is that the virus hijacks a redox oxygen sensor located in the mitochondrion, such that this reduces or oxidizes potassium channels, resulting in hyperpolarisation (rather than depolarisation) of pulmonary artery/arteriole vascular smooth muscle (Archer et al., 2000).

4. Can one predict COVID-19 disease severity based on the sensitivity of the hypoxic ventilatory response?

The similarity of some symptoms of high altitude sickness and COVID-19 begs the question of whether one might predict disease severity based on the magnitude of the hypoxic ventilatory response and hence the sensitivity of the carotid bodies. Although investigated, there appears to be no conclusive evidence of an association between genetic polymorphisms and susceptibility to high-altitude illness (Basnyat and Murdoch, 2003; Rupert and Koehle, 2006), which suggests genomic screening may be futile. However, there is an association between a *low* ventilatory response to hypoxia and the risk of developing severe high altitude–related illnesses (Richalet et al., 2012), which has been proposed as a way to detect high-risk subjects before a sojourn to high altitude to guide prophylactic treatment. Could such a test predict severity of life-threatening diseases such as COVID-19? We acknowledge the technical difficulty of performing such a 'hypothetical' test in a pandemic. Alternatively, is there any link between those susceptible to high altitude sickness, which appears to be approximately ~26% of people (Richalet et al., 2012), and those facing severe complications with a SARS-CoV-2 infection? This remains unknown.

The majority of people exposed to high altitude or to COVID-19 overcome the challenges induced by hypoxia through adaptive mechanisms. Despite the lack of epidemiological evidence, one interesting new finding is that the incidence of COVID-19 in populations living at high altitude (e.g. the Andes) is relatively low when compared to lowlanders (Arias-Reyes et al., 2020; Soliz et al., 2020). This reasons for this remain uncertain and it may reflect differences in ethnicity related/genetic, environmental factors related to viral transmission, social structure, success and extent of lockdown measures, amount of ultra-violet light, temperature, humidity, population density, social distancing, a population without a high prevalence of pre-existing medical conditions (Pun et al., 2020). However, Pun et al. (2020) acknowledge physiological adaptations to hypoxia. Whether or not the adaptative response of the carotid body of highlanders to sustained hypoxia contributes to the relative resistance of these people to SARS-CoV-2 infection remains unproven (Arias-Reyes et al., 2020; Soliz et al., 2020) but is an intriguing association. It would not be the first time that different forms of hypoxia have provided therapeutic benefit (Serebrovskaya and Xi, 2016; Christiansen et al., 2020) but in this case it may also play a protective role. Taken together, we surmise that the sensitivity of the carotid body may determine how a patient adapts to, and survives, COVID-19 (Fig. 1). We next turn our attention to sensitivity changes in the carotid body in health and disease.

5. COVID, cardiorespiratory disease and excessive carotid body excitability

In relation to the role of carotid body function in patients with SARS-CoV-2 infection, we suggest as illustrated in Fig. 1 that: 1) in some patients the carotid body reflex overcomes the hypoxic challenge of the initial mild infection and this group recover well and without hospitalization. 2) In a smaller percentage of patients the carotid bodies may be *overactive* either before SARS-CoV-2 infection or become sensitised as a result of the infection; this leads to intense autonomic and respiratory responses, and subsequent pathophysiology affecting the heart, lungs and kidneys. In this scenario hospitalization may be needed and could include intensive care. This possibility of the self-inflicted lung-injury

due to carotid body overactivity in COVID-19 patients was also suggested by Simonson et al. (2021). We discuss this scenario further below. 3) In a small percentage of the population, in which the carotid bodies are de-sensitised or non functional even before but certainly during SARS-CoV-2 infection, we see *silent hypoxia*. These patients are at high risk because they present very late when the infection is well established. The latter group may include those patients in which the carotid bodies become inactivated by SARS-CoV-2 even though they were functioning normally in health. We acknowledge that all these possibilities in relation to the role of carotid body function in patients with SARS-CoV-2 may vary in accordance with the level of virus loading, which is unpredictable.

The severity and prevalence of SARS-CoV-2 infection appears highest in older males and those with co-morbidities such as hypertension, heart failure, obesity and diabetes (Guzik et al., 2020). In all these clinical conditions, increased carotid body excitability has been found (Porzionato et al., 2020a, 2020b). [Note: we use the term excitability to describe both reflex sensitivity (e.g. hyperreflexia) as well as aberrant basal tonic discharge as reported from the carotid body in respiratory, cardiovascular, renal and metabolic comorbidities, which is associated with increased morbidity/mortality in patients with COVID-19 (Porzionato et al., 2020a, 2020b).] Pre-existing hyperexcitability of carotid bodies may increase both susceptibility to infection and disease severity based on the known pro-inflammatory function they exert (McBryde et al., 2013; Pijacka et al., 2016). Equally, inflammation of the carotid body induced by nonrelated SARS-CoV-2 pathogen-associated molecular changes or damage-associated molecular patterns (Ackland et al., 2013; Mkrtchian et al., 2020; Holmes, 2020) will cause hyperreflexia and raise their tonicity (Del Rio et al., 2012). As found in patients with cardiovascular disease and sleep disturbed breathing, this hyperexcitability may be deleterious in patients with COVID-19 and could trigger the sequelae of excessive hyperventilation inducing extreme hypocapnia and associated problems as described earlier in relation to acute mountain sickness, as well as intense vasomotor sympathetic activity elevating vascular resistance, which may impede tissue oxygenation. Due to the autonomic imbalance imposed, cardiac arrhythmias may be evoked and sleep apnoeas (Cheynes Stokes breathing) may be provoked (Schultz et al., 2015) by excessive carotid body activity. Thus, the increased susceptibility of patients with cardio-respiratory-metabolic disorders may in part be due to the problem of carotid body hyperactivity. A common denominator here is the renin angiotensin system in which angiotensin II is elevated in these patients and is a potent activator of the carotid body; these patients also express higher levels of angiotensin converting enzyme 2, which is essential for infectivity from SARS-COV-2. In stark contrast to mechanisms accounting for hyperexcitability of carotid body function, we now consider those COVID-19 patients with "*silent hypoxia*".

6. Explaining silent hypoxia in COVID-19 patients

In a small percentage of the population the carotid body and peripheral chemoreflex may not be fully functional (Tobin et al., 2020; Gonzalez-Duarte and Norcliffe-Kaufmann, 2020; Dhont et al., 2020; Wilkerson et al., 2020) and either have depressed sensitivity or a relatively high hypoxic threshold and fail to yield an appropriate hypoxic ventilatory response even if the hypoxia is severe (Fig. 2). In accordance with Tobin et al. (2020) the number of COVID-19 cases in elderly patients with diabetes is high and we know that diabetes increases the mortality risk of COVID-19 (Zhu et al., 2020). Notably, the ventilatory response to hypoxia is decreased by 50% in people >65 years and there is an inverse relationship between PaO_2 and age (Tobin, 2019). It is also important to note that the chemical drive to breathe in response to hypercapnia and hypoxia presents a large variation among individuals, which may explain why some patients with hypoxia do not develop dyspnoea (Tobin et al., 2020).

Individuals may not be aware of their inability to stage an appropriate hyperventilatory response to hypoxia before infection by SARS-COV-2 but appear remarkably calm not complaining of shortages of breath yet are clearly cyanotic/severely hypoxic. In the absence of chemoreflex function, the consequences to COVID patients would be a weak or absence hypoxic ventilatory response, which has been reported in some patients and termed "*silent hypoxia*". We refrain from the other term coined ("happy hypoxia") on the basis that there is nothing happy about COVID-19 and propose the term be dropped and we are in agreement with Simonson et al. (2021) that it should be named "silent hypoxia". Because the patient perceives mild symptoms they present late at hospital and as a result their disease state is well progressed and their outcome is poor. Silent hypoxic COVID-19 patients may have a slightly raised respiratory frequency (~30 breaths/min) but minute ventilation is rarely quantified with some reports suggesting shallow breathing (Soliz et al., 2020). This may be a consequence of activation of juxtacapillary receptors (J-receptors) triggered by pulmonary oedema or release of histamine within the bronchioles of the lung responding to already established pulmonary oedema (De Burgh Daly, 1997; Tobin et al., 2020; Fig. 2).

SARS-CoV-2 infection may suppress directly carotid body function either at the carotid body, as shown by Lambermont et al. (2021), or the petrosal ganglia triggering insufficiency (Fig. 2). The common symptom of a loss of taste is consistent with mal-functional petrosal neurons which, in part, mediate taste signals to the brain. We also do not rule out neural damage to the brainstem areas regulating cardiorespiratory control as found previously with SARS-CoV (Netland et al., 2008; Fig. 1). Netland and colleagues found that in mice SARS virus enters the brain via the olfactory bulb and transneuronal infection spreads to connected areas including those located in the medulla oblongata controlling

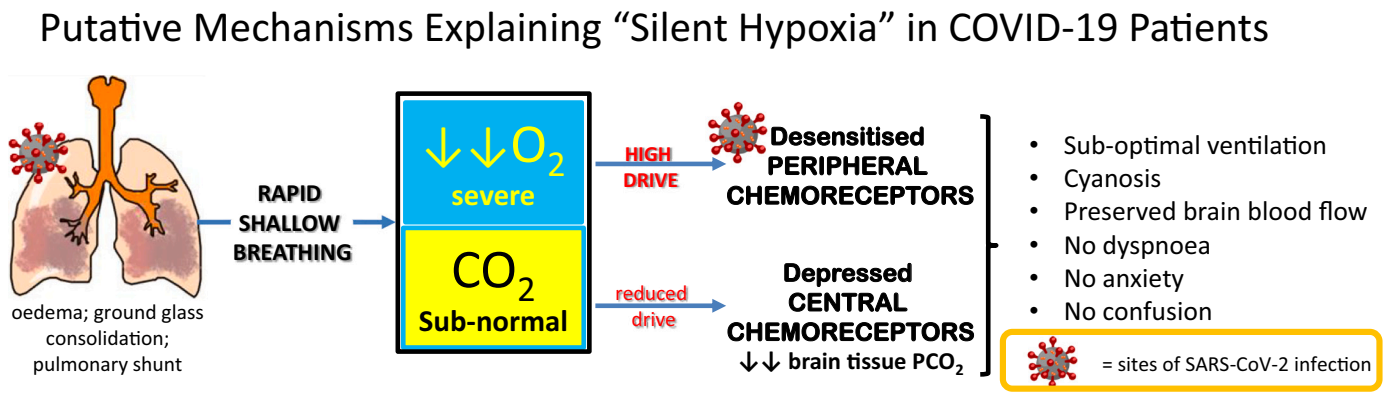

Fig. 2. Schematic to summarise the interactions of respiratory blood gases and chemoreceptor (peripheral and central) ventilatory drive in the condition of COVID-19 induced silent hypoxia. For details see text. Note, the recent finding of Lambermont et al. (2021) is consistent with infection of the carotid body itself via ACE2, which expression is high in the carotid body of humans (Villadiego et al., 2021).

autonomic and respiratory function. This study showed that medullary neurons are a highly susceptible target for SARS-CoV. In this context, there are also reports of the virus within the brainstem from patients with COVID-19 supporting its tropism for neurons (Li et al., 2020). Equally, SARS-CoV-2 may down regulate hypoxia inducible factor, which is essential for oxygen sensing in the carotid body, as has been shown by some respiratory viruses (Marchetti, 2020). Dysfunctional peripheral chemoreceptor input remains to be validated, but it would be consistent with the mediocre hyperventilatory response and mild hypocapnia observed in COVID-19 patients with silent hypoxia (Dhont et al., 2020; Gonzalez-Duarte and Norcliffe-Kaufmann, 2020; Tobin et al., 2020). Villadiego et al. (2021) suggest that carotid body infection by SARS-CoV-2, via ACE2, could lead to inflammation and glomus cell death, which may contribute to reduce the chemosensitive by these bodies. The mild hypocapnia would shift the oxyhaemoglobin curve to the left increasing haemoglobin's affinity for oxygen (Tobin et al., 2020). However, this classic physiological mechanism may be futile in face of ground glass patterning of the lungs and some pulmonary consolidation seen at time of presentation of silent hypoxic COVID-19 patient (Wilkerson et al., 2020). Evidence of microfibrinous clotting within alveolar capillaries, endothelialitis and possibility of reduced affinity of haemoglobin for oxygen could all contribute to the severe systemic hypoxaemia and indeed mortality (Zhang et al., 2020).

The presence of "silent hypoxia" observed in some COVID-19 patients defies all prior presentations of patients with acute respiratory distress syndrome and viral pneumonias (Tobin et al., 2020). With peripheral chemoreceptor sensitivity already suppressed before infection or by the virus does explain the absence of hyperventilation. However, silent hypoxic COVID-19 patients can have blood oxygen saturations as low as 60% (PaO_2 ~70 mm Hg) yet they maintain a sub-normal $PaCO_2$ of ~35 mm Hg and are poorly responsive to supplemental oxygen. Classically the early signs of hypoxia are anxiety, confusion, and restlessness, yet silent hypoxic COVID-19 patients remain calm, composed and follow directions even though they are obviously cyanotic (Brouqui et al., 2020). This might be explained by the case observation of SARs-CoV infection of the carotid body (Lambermont et al., 2021) rendering it dysfunctional.. So how can these mysteries be disentangled and why is it that patients do not sense dyspnoea or lose consciousness. For this, we consider the arterial tension of carbon dioxide and its importance for maintaining cerebral blood flow (Fig. 2).

Normally, continual exposure to severe hypoxia causes pronounced hyperventilation resulting in hypocapnia, which can cause loss of consciousness. Loss of consciousness during severe hypoxia is caused by the reduced cerebral blood flow that occurs because cerebral arteries vasoconstrict in the presence of low CO_2 thereby diminishing the delivery of oxygen to the brain. With respectable $PaCO_2$'s in silent hypoxic COVID-19 patients brain blood flow may well be maintained with minimal cerebral vasoconstriction (Fig. 2). The tachycardia seen in these patients acts to support cardiac output and as a result arterial pressure is near normal, thus maintaining good cerebral perfusion pressure (Dhont et al., 2020).

At normocapnia, central chemoreceptors, which are exquisitely sensitive to CO_2 and protons, are active and critical for driving normal breathing. Central chemoreceptor activation plays a major role in triggering the sensation of dyspnoea and anxiety via their neuronal connections to the reticular activating and limbic systems (Guyenet et al., 2019; Simonson et al., 2021). Thus, it is quite possible that silent hypoxic COVID-19 patients have depressed central chemoreceptor activity. This may either be a consequence of the depressant effect of hypoxia or reduced brain tissue CO_2. Within the brain, which is highly metabolically active, the presence of severe hypoxia increases metabolic rate and lactate production but reduces locally generated CO_2 (Vestergaard et al., 2016). If cerebral blood flow is maintained as argued above, then the CO_2 generated will be rapidly washed out. This may temper central chemoreceptor activity levels and reduce the patients' sensation of dyspnoea (Fig. 2). However, it may also reduce the drive to breathe which in the presence of depressed carotid body function could explain the silent hypoxia phenotype. This raises the question of whether CO_2 could be added to the inspirate to re-engage central chemoreceptors and increase central respiratory drive to enhance ventilation in the silent hypoxic COVID patient. Equally, doxapram (Dopram, Stimulex or Respiram), which is well known to stimulate peripheral and central chemoreceptors could be infused intra-venously, and oral benzolamide or acetalzolamide could be used to dam-up CO_2 in tissue, thereby enhancing arterial CO_2. This will have the advantage of maintaining good brain blood flow. This is consistent with the use of partial rebreathing masks in patients with COVID-19 in some intensive care units.

7. Future hypothetical studies in COVID-19 patients

Whilst acknowledging the logistical nightmare of performing any clinical studies on COVID-19 patients, there are many unresolved questions concerning respiratory and autonomic control. One of the complications is that symptoms change as the disease becomes more severe. Nevertheless, we propose some hypothetical questions for consideration:

a) What is the carotid body sensitivity in COVID-19 patients with hyperventilatory versus silent responses to hypoxia?
b) What proportion of the systemic hypoxaemia is due to damage to the alveoli/lung versus incompetence of the carotid body?
c) Is the severity of the illness seen in COVID-19 patients related to carotid body excitability as we know this change in patients with cardiovascular, metabolic and respiratory diseases, and it is these patients that exhibit highest mortality?
d) In the silent hypoxic COVID-19 patients, is the non-respiratory reflex arcs of the chemoreflex also derailed or can sympathoexcitation occur, which might explain their reasonable level of arterial pressure?
e) In patients recovering from severe COVID-19 after hospitalization, are the carotid bodies functional? If they are depressed is this correlated with dysgeusia? What are the neurological sequelae in the brainstem respiratory network of these patients?
f) Could a test of association between a *low* ventilatory response to hypoxia and the risk of developing severe high altitude–related illnesses also predict severity of life-threatening diseases such as COVID-19?

8. Concluding thoughts

We have proposed that the level of sensitivity of the peripheral chemoreceptors may contribute to the symptoms and outcomes of COVID-19. Through their dysregulation of either heightened excitability (as may well be present in the most susceptible patients with existing cardio-metabolic and respiratory diseases) or loss of function (silent hypoxic COVID-19 patients) chemoreflex may exacerbate the symptoms described in patients infected by SARS-CoV-2. COVID-19 has challenged clinicians and academics globally because of the unique patterns of symptoms presented. Only through continued integrated thinking across research and clinical specialties and disciplines and applying what we already know about systems physiology will we discover the secrets of how best to clinically treat SARS-CoV-2 patients and help the peripheral chemoreceptors play their best physiological role.

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References

Ackland, G.L., Kazymov, V., Marina, N., Singer, M., Gourine, A.V., 2013. Peripheral neural detection of danger-associated and pathogen-associated molecular patterns. Crit. Care Med. 41 (6), e85–e92. https://doi.org/10.1097/CCM.0b013e31827c0b05. Jun.

Archer, S.L., Weir, E.K., Reeve, H.L., Michelakis, E., 2000. Molecular identification of O2 sensors and O2-sensitive potassium channels in the pulmonary circulation. Adv. Exp. Med. Biol. 475, 219–240.

Archer, S.L., Sharp, W.W., Weir, E.K., 2020. Differentiating COVID-19 pneumonia from acute respiratory distress syndrome and high altitude pulmonary edema. Circulation 142, 101–104. https://doi.org/10.1161/CIRCULATIONAHA.120.047915.

Arias-Reyes, C., Zubieta-DeUrioste, N., Poma-Machicao, L., Aliaga-Raduan, F., Carvajal-Rodriguez, F., Dutschmann, M., Schneider-Gasser, E.M., Zubieta-Calleja, G., Soliz, J., 2020. Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? Resp. Neurobiol. 103443e. https://doi.org/10.1016/j.resp.2020.103443.

Basnyat, B., Murdoch, D.R., 2003. High-altitude illness. Lancet 361 (9373), 1967–1974 (7 June).

Bohn, M.K., Hall, A., Sepiashvili, L., Jung, B., Shannon Steele, S., Adeli, K., 2020. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. Physiology 288–301 (2020), 35. https://doi.org/10.1152/physiol.00019.2020.

Brouqui, P., Amrane, S., Million, M., Cortaredona, S., Parola, P., Lagier, J.C., Raoult, D., 2020. Asymptomatic hypoxia in COVID-19 is associated with poor outcome. Int. J. Infect. Dis. S1201-9712 (20), 32271–32272.

Bulfamante, G., Chiumello, D., Canevini, M.P., Priori, A., Mazzanti, M., Centanni, S., Felisati, G., 2020. First ultrastructural autoptic findings of SARS-Cov-2 in olfactory pathways and brainstem. Minerva Anestesiol. 86, 678–679.

Chen, T., Wu, D., Chen, H., Yan, W., Yang, D., Chen, G., Ma, K., Xu, D., Yu, H., Wang, H., Wang, T., Guo, W., Chen, J., Ding, C., Zhang, X., Huang, J., Han, M., Shusheng Li, S., Luo, X., Zhao, J., Ning, Q., 2020. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368, m1091. https://doi.org/10.1136/bmj.m1091.

Christiansen, L., Chen, B., Lei, Y., Urbin, M.A., MSA, Richardson, Oudega, M., Sandhu, M., Rymer, W.Z., Trumbower, R.D., Mitchell, G.S., Perez, M.A., 2020. Acute intermittent hypoxia boosts spinal plasticity in humans with tetraplegia. Exp. Neurol. 113483, 25.

Comroe, J.H., Schmidt, C.F., 1937. The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog. Am. J. Physiol. 121 (1), 75–97.

De Burgh Daly, M., 1997. Peripheral arterial chemoreceptors and respiratory-cardiovascular integration. In: Monographs of the Physiological Society-46. Clarendon Press, Oxford, UK.

Del Rio, R., Moya, E.A., Parga, M.J., Madrid, C., Iturriaga, R., 2012. Carotid body inflammation and cardiorespiratory alterations in intermittent hypoxia. Eur. Respir. J. 39 (6), 1492–1500. https://doi.org/10.1183/09031936.00141511 (Jun, Epub 2011 Dec 19).

Dhont, S., Derom, E., Braeckel, E.V., Depuydt, P., Lambrecht, B.N., 2020. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir. Res. 21, 198 https://doi.org/10.1186/s12931-020-01462-5.

Frohman, E.M., Villemarette-Pittmand, N.R., Melameda, E., Cruza, R.A., Longmuire, R., Varkeya, T.C., Steinmanh, L., Zamvili, S.S., Frohman, T.C., 2020. Part I. SARS-CoV-2 triggered 'PANIC'1 attack in severe COVID-19. J. Neurol. Sci. 415, 116936 https://doi.org/10.1016/j.jns.2020.116936.

Gattinoni, L., Chiumello, D., Caironi, P., Busana, M., Romitti, F., Brazzi, L., Camporota, L., 2020. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 46, 1099–1102, 2020 Intensive Care Med (2020) 46:1099–1102. https://doi.org/10.1007/s00134-020-06033-2.

Gautier, J.F., Ravussin, Y., 2020. A new symptom of COVID-19: loss of taste and smell. Obesity (Silver Spring) 28, 848.

Gonzalez-Duarte, A., Norcliffe-Kaufmann, L., 2020. Is 'happy hypoxia' in COVID-19 a disorder of autonomic interoception? A hypothesis. Clin. Auton. Res. https://doi.org/10.1007/s10286-020-00715-z.

Guyenet, P.G., Stornetta, R.L., Souza, G.M.P.R., Abbott, S.B.G., Shi, Y., Bayliss, D.A., 2019. The retrotrapezoid nucleus: central chemoreceptor and regulator of breathing automaticity. Trends Neurosci. 42, 807–824.

Guzik, T.J., Mohiddin, S.A., Dimarco, A., Patel, V., Savvatis, K., Marelli-Berg, F.M., Madhur, M.S., Tomaszewski, M., Maffia, P., D'Acquisto, F., Nicklin, S.A., Marian, A. J., Nosalski, R., Murray, E.C., Guzik, B., Colin Berry, C., Touyz, R.M., Kreutz, R., Wang, D.W., Bhella, D., Sagliocco, O., Crea, F., Thomson, E.C., McInnes, I.B., 2020. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc. Res. 2020 https://doi.org/10.1093/cvr/cvaa106.

Holmes, A.P., 2020. Damage control: carotid body activation and remodelling in response to aseptic tissue injury. Exp. Physiol. 1–3 https://doi.org/10.1113/EP088923, 22-07-20.

Holmes, A.P., Ray, C.J., Thompson, E.L., Alshehri, Z., Coney, A.M., Kumar, P., 2019. Adrenaline activation of the carotid body: key to CO2 and pH homeostasis in hypoglycaemia and potential pathological implications in cardiovascular disease. Respir. Physiol. Neurobiol. 265, 92–99. https://doi.org/10.1016/j.resp.2018.05.008 (Jul, Epub 2018 May 25).

Iadecola, C., Anrather, J., Kamel, H., 2020. Effects of COVID-19 on the nervous system. Cell 2020. https://doi.org/10.1016/j.cell.2020.08.028.

Iturriaga, R., Moya, E.A., Del Rio, R., 2015. Inflammation and oxidative stress during intermittent hypoxia: the impact on chemoreception. Exp. Physiol. 100, 149–155.

Khun, M.A., 2021. Lessons from neuronal HIF1α: understanding it's role in ventilatory acclimatization to hypoxia. J. Physiol. 598.21, 4751–4752. https://doi.org/10.1113/JP280205.

Lambermont, B., Davenne, E., Maclot, F., Delvenne, P., 2021. SARS-CoV-2 in carotid body. Intensive Care Med. 2021 (47), 342–343.

Leonard, E.M., Salman, S., Nurse, C.A., 2018. Sensory processing and integration at the carotid body tripartite synapse: neurotransmitter functions and effects of chronic hypoxia. Front. Physiol. 6 (225), 2018. https://doi.org/10.3389/fphys.2018.00225.

Li, Y.C., Bai, W.Z., Hashikawa, T., 2020. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J. Med. Virol. 92 (6), 552–555. https://doi.org/10.1002/jmv.25728 (Jun, Epub 2020 Mar 11).

Lim, Z.J., Subramaniam, A., Reddy, M.P., Blecher, G., Kadam, U., Afroz, A., Billah, B., Ashwin, S., Kubicki, M., Bilotta, F., Curtis, J.R., Rubulotta, F., 2020. Case fatality rates for COVID-19 patients requiring invasive mechanical ventilation: a meta-analysis. Am. J. Respir. Crit. Care Med. https://doi.org/10.1164/rccm.202006-2405OC.

Marchetti, M., 2020. COVID-19-driven endothelial damage: complement, HIF-1, and ABL2 are potential pathways of damage and targets for cure. Ann. Hematol. 99 (8), 1701–1707 (Aug).

McBryde, F.D., Abdala, A.P., Hendy, E.B., Pijacka, W., Marvar, P., Moraes, D.J., Sobotka, P.A., Paton, J.F., 2013. The carotid body as a putative therapeutic target for the treatment of neurogenic hypertension. Nat. Commun. 4, 2395. https://doi.org/10.1038/ncomms3395.

Mkrtchian, S., Kåhlin, J., Gómez-Galán, M., Ebberyd, A., Yoshitake, T., Schmidt, S., Kehr, J., Hildenborg, M., Fagerlund, M.J., Harris, H.E., Eriksson, L.I., 2020. The impact of damage-associated molecular patterns on the neurotransmitter release and gene expression in the ex vivo rat carotid body. Exp. Physiol. https://doi.org/10.1113/EP088705. April 23.

Moya, E.A., Go, A., Kim, C.B., Fu, Z., Simonson, T.S., Powell, F.L., 2020. Neuronal HIF-1α in the nucleus tractus solitarius contributes to ventilatory acclimatization to hypoxia. J. Physiol. 598, 2021–2034.

Netland, J., Meyerholz, D.K., Moore, S., Cassell, M., Perlman, S., 2008. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J. Virol. 82 (15), 7264–7275. https://doi.org/10.1128/JVI.00737-08. Aug. (Epub 2008 May 21).

Obiefuna, S., Donohoe, C., 2020. Neuroanatomy, nucleus gustatory. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL). Bookshelf ID: NBK554522.

Pijacka, W., Moraes, D.J., Ratcliffe, L.E., Nightingale, A.K., Hart, E.C., da Silva, M.P., Machado, B.H., McBryde, F.D., Abdala, A.P., Ford, A.P., Paton, J.F., 2016. Purinergic receptors in the carotid body as a new drug target for controlling hypertension. Nat. Med. 22 (10), 1151–1159.

Porzionato, A., Emmi, A., Stocco, E., Barbon, S., Boscolo-Berto, R., Macchi, V., De Caro, R., 2020a. The potential role of the carotid body in COVID-19. Am. J. Physiol. Lung Cell. Mol. Physiol. 319, L620–L626.

Porzionato, A., Emmi, A., Barbon, S., Boscolo-Berto, R., Stecco, C., Stocco, E., Macchi, V., De Caro, R., 2020b. Sympathetic activation: a potential link between commorbidities and COVID-19. FEBS J. https://doi.org/10.1111/febs.15481.

Pun, M., Turner, R., Strapazzon, G., Brugger, H., Swenson, E.R., 2020. Lower incidence of COVID-19 at high altitude: facts and confounders. High Alt. Med. Biol. 21, 217–222.

Richalet, J.P., Larmignat, P., Poitrine, E., Letournel, M., Canou-Poitrine, F., 2012. Physiological risk factors for severe high-altitude illness. A prospective cohort study. Am. J. Respir. Crit. Care Med. 185 (2), 192–198.

Rogers, R.C., Hasser, E.M., Hermann, G.E., 2020. Thrombin action on astrocytes of the rats dysrupts glycemic and respiratory control. Am. J. Physiol. Regul. Integr. Comp. Physiol. 318 (2020), R1068–R1077. https://doi.org/10.1152/ajpregu.00033.2020.

Rupert, J.L., Koehle, M.S., 2006. Evidence for a genetic basis for altitude-related illness. High Alt. Med. Biol. 7 (2), 150–167. https://doi.org/10.1089/ham.2006.7.150.

Sartini, C., Tresoldi, Moreno, Scarpellini, Paolo, Tettamanti, Andrea, Carcò, Francesco, Landoni, Giovanni, Zangrillo, Alberto, 2020. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA 323 (22), 2338–2340. https://doi.org/10.1001/jama.2020.7861 (Jun 9).

Schultz, H.D., Marcus, N.J., Del Rio, R., 2015. Role of the carotid body chemoreflex in the pathophysiology of heart failure: a perspective from animal studies. Adv. Exp. Med. Biol. 860, 167–185.

Serebrovskaya, T.V., Xi, L., 2016. Intermittent hypoxia training as non-pharmacologic therapy for cardiovascular diseases: practical analysis on methods and equipment. Exp. Biol. Med. 241, 1708–1723.

Simonson, T.S., Baker, T.L., Banzett, R.B., Bishop, T. Dempsey, J.A., Feldman, J.L., Guyenet, P.G., Hodson, E.J., Mitchell, G.S., Moya, E. A., Nokes, B.T., Orr, J.E., Owens, R.L., Poulin, M., Rawling, J.M., Schmick, C.N., Watters, J.J., Younes, M. and Malhotra, A. Silent hypoxaemia in COVID-19 patients. J. Physiol. 599.4 (2021) pp. 1057–1065.

Soliz, J., Schneider-Gasser, E.M., Arias-Reyes, C., Aliaga-Raduan, F., Poma-Machicao, L., Zubieta-Calleja, G., Furuya, W.I., Trevizan-Baú, P., Dhingra, R.R., Dutschmann, M., 2020. Coping with hypoxemia: could erythropoietin (EPO) be an adjuvantetreatment of COVID-19? Respir. Neurobiol. https://doi.org/10.1016/j.resp.2020.103476.

Tobin, M.J., 2019. Why physiology is critical to the pratice of medicine: a 40-year personal perspective. Clin. Chest Med. 40, 243–257.

Tobin, M.J., Laghi, F., Jubran, A., 2020. Why COVID-19 silent hypoxemia is baffling to physicians. Am. J. Respir. Crit. Care Med. 302 (3), 356–360. https://doi.org/10.1164/rccm.202006-2157CP.

Vestergaard, M.B., Lindberg, U., Aachmann-Andersen, N.J., Lisbjerg, K., Christensen, S. J., Law, I., Rasmussen, P., Olsen, N.V., Larsson, H.B.W., 2016. Acute hypoxia increases the cerebral metabolic rate – a magnetic resonance imaging study. J. Cereb. Blood Flow Metab. 36, 1046–1058.

Villadiego, J., Ramírez-Lorca, R., Cala, F., Labandeira-García, J.L., Esteban, M., Toledo-Aral, J.J., Lopez-Barneo, J., 2021. Is carotid body infection responsible for silent hypoxemia in COVID-19 patients? FUNCTION 2 (1), zqaa032. https://doi.org/10.1093/function/zqaa032.

Wilkerson, R.G., Adler, J.D., Shah, N.G., Brown, R., 2020. Silent hypoxia: a harbinger of clinical deterioration in patients with COVID-19. Am. J. Emerg. Med. 2020 https://doi.org/10.1016/j.ajem.2020.05.044.

Zera, T., Moraes, D.J.A., da Silva, M.P., Fisher, J.P., Paton, J.F.R., 2019. The logic of carotid body connectivity to the brain. Physiology 34 (4), 264–282. https://doi.org/10.1152/physiol.00057.2018. Jul 1.

Zhang, J., Tecson, K.M., McCullough, P.A., 2020. Endothelial dysfunction contributes to COVID-19-associated vascular inflammation and coagulopathy. Rev. Cardiovasc. Med. 21, 315–319.

Zhu, L., She, Zhi-Gang, Cheng, Xu, Qin, Juan-Juan, Zhang, Xiao-Jing, Cai, Jingjing, Lei, Fang, Wang, Haitao, Xie, Jing, Wang, Wenxin, Li, Haomiao, Zhang, Peng, Song, Xiaohui, Xi, Chen, Xiang, Mei, Zhang, Chaozheng, Bai, Liangjie, Da, Xiang, Chen, Ming-Ming, Liu, Yanqiong, Yan, Youqin, Liu, Mingyu, Mao, Weiming, Zou, Jinjing, Liu, Liming, Chen, Guohua, Luo, Pengcheng, Xiao, Bing, Zhang, Changjiang, Zhang, Zixiong, Zhigang, Lu, Wang, Junhai, Haofeng, Lu, Xia, Xigang, Wang, Daihong, Liao, Xiaofeng, Peng, Gang, Ye, Ping, Yang, Jun, Yuan, Yufeng, Huang, Xiaodong, Guo, Jiao, Zhang, Bing-Hong, Li, Hongliang, 2020. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 31, 1068–1077 (June 2).