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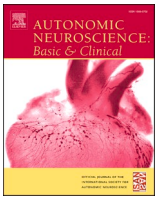

Letter to the Editor

Syncope and silent hypoxemia in COVID-19: Implications for the autonomic field

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ABSTRACT

Coronavirus-19 (COVID-19), the infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has wreaked havoc across the globe since its emergence in December 2019. Reports of patients presenting with syncope and pre-syncope, as well as hypoxemia without symptoms of dyspnea ("silent hypoxemia"), have led researchers to speculate whether SARS-CoV-2 can alter autonomic nervous system function. As viral infections are commonly reported triggers of altered autonomic control, we must consider whether SARS-CoV-2 can also interfere with autonomic activity, at least in some patients. As we are still in the early stages of understanding COVID-19, we still do not know whether syncope and silent hypoxemia are more strongly associated with COVID-19 compared to any other viral infections that severely compromise gas exchange. Therefore, in this perspective we discuss these two intriguing clinical presentations, as they relate to autonomic nervous system function. In our discussion, we will explore COVID-specific, as well as non-COVID specific mechanisms that may affect autonomic activity and potential therapeutic targets. As we move forward in our understanding of COVID-19, well-designed prospective studies with appropriate control and comparator groups will be necessary to identify potential unique effects of COVID-19 on autonomic function.

1. Introduction

Coronavirus-19 (COVID-19), the infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has overwhelmed healthcare facilities and created political and socio-economic turbulence around the world. The most common early symptoms are fever, cough, fatigue, shortness of breath, and loss of smell (Guan et al., 2020; Lechien et al., 2020; F. Zhou et al., 2020). SARS-CoV-2 infection relies on viral binding to cell membrane-bound angiotensin converting enzyme-2 (ACE2), followed by endocytotic entry mediated by host cell proteases (e.g. TMPRSS2, FURIN) (Hoffmann et al., 2020; Shang et al., 2020). Tissues vulnerable to infection must therefore express ACE2 and possess relevant host cell proteases.

The autonomic nervous system helps maintain homeostasis during infection and pathogen invasion. Both the sympathetic (SNS) and parasympathetic (PNS) branches help mediate pro- and anti-inflammatory responses to ensure the body mounts an appropriate defense, while simultaneously ensuring this response is kept in check to avoid tissue damage. Systemically, the SNS helps facilitate a pro-inflammatory response by increasing heart rate, blood pressure, lymph flow and antigen uptake, and by mobilizing energy-rich fuel sources via lipolysis, glycogenolysis, and gluconeogenesis (Pongratz and Straub, 2014). These responses are necessary to support the high-energy demands required to activate and maintain a sufficient immune response. Locally, the SNS activates anti-inflammatory β-adrenergic receptors through direct neurotransmitter release (Pongratz and Straub, 2014). Activation of the cholinergic inflammatory reflex, mediated by the PNS, also promotes anti-inflammatory mechanisms by deactivating macrophages and inhibiting cytokine release (Tracey, 2002). There is also evidence that local inflammation changes the nicotinic and muscarinic phenotype of mast cells, such that PNS cholinergic inputs switch from being anti-inflammatory to pro-inflammatory (Jendzjowsky et al., 2021).

In COVID-19, initially the throat, lungs and airways are particularly vulnerable to infection resulting in local inflammation, which, in young and otherwise healthy patients, is normally sufficient to eliminate the virus. However, in many older patients with inflammation-associated comorbidities such as obesity, diabetes and hypertension, the virus can go unchecked resulting in significant organ damage, a systemic cytokine storm (Fajgenbaum and June, 2020) presenting as sepsis, and greatly increased risk of mortality (Akbari et al., 2020; Leisman et al., 2020).

The SNS and PNS branches of the autonomic nervous system are integral for blood pressure and blood-gas homeostasis. As a result, reports of patients presenting with syncope and pre-syncope (Canetta et al., 2020; Ebrille et al., 2020; Oates et al., 2020; Singhania et al., 2020; Tapé et al., 2013), as well as hypoxemia without symptoms of dyspnea ("silent hypoxemia") (González-Duarte and Norcliffe-Kaufmann, 2020; Bickler et al., 2020; Tobin et al., 2020), have led researchers to speculate whether SARS-CoV-2 can alter autonomic nervous system function (Canetta et al., 2020; Ebrille et al., 2020; González-Duarte and Norcliffe-Kaufmann, 2020). Viral infections are commonly reported triggers of altered autonomic control, including reduced heart rate variability or orthostatic hypotension (Carod-Artal, 2018; Novak, 2020; Shaw et al., 2019; Miglis et al., 2020). While little is known about the impact of SARS-CoV-2 on the autonomic nervous system, we must consider whether SARS-CoV-2 will also interfere with autonomic activity, at least in some patients.

In this perspective, we will discuss syncope and silent hypoxemia in COVID-19 patients and explore whether these clinical presentations are the result of impaired autonomic reflexes. Notwithstanding the fact that we still do not know whether syncope and silent hypoxemia are more

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strongly associated with COVID-19 compared to any other viral infections that severely compromise gas exchange, we will explore potential mechanisms related to the SARS-CoV-2 virus as well as non-COVID specific mechanisms that may also impact autonomic activity.

2. Syncope in COVID-19

Syncope is defined as an abrupt, transient, complete loss of consciousness, associated with inability to maintain postural tone, with rapid and spontaneous recovery (Shen et al., 2017). Some common etiologies of syncope include reflex (neurally mediated) syncope and orthostatic hypotension (Shen et al., 2017) (Table 1), both of which involve the autonomic nervous system, and have been reported in COVID-19 patients (Ebrille et al., 2020; Singhania et al., 2020; Tapé et al., 2013; Birlutiu et al., 2020). Although some studies report lower prevalence of syncope (range: 3–7%) (Canetta et al., 2020; Oates et al., 2020), a recent review of 102 COVID-19 patients found that 24% of patients initially sought medical attention for syncope, near syncope or non-mechanical falls, while fever or respiratory symptoms were only found secondarily or incidentally (Chen et al., 2020a). A recent study of viral influenza patients reported syncope in only 2.2% of patients (Noh et al., 2020), suggesting syncope in COVID-19 may be more prevalent than initially thought.

In a short communication to *Autonomic Neuroscience: Basic and Clinical*, Canetta et al. (2020), detailed clinical findings of 35 COVID-19 patients who experienced one or more syncopal episodes immediately prior to a COVID-19 diagnosis. Compared to 68 COVID-19 patients without syncope, the syncopal cohort exhibited significantly lower heart rates. A noteworthy limitation to the study was that fewer patients in the syncopal cohort were febrile (17/35 vs. 48/68; chi-square $P = 0.048$), which may explain the relative bradycardia (Cunha, 2000; Karjalainen and Viitasalo, 1986). Nonetheless, lower heart rates in syncopal (n = 37) compared to non-syncopal COVID-19 patients (n = 40) were also shown by Oates et al. (2020), with both groups matched for body temperature. Among the growing number of COVID-19 studies reporting syncope, unexplained syncope is the most common, followed by reflex syncope and orthostatic hypotension. Oates et al. (2020) reported OH in 12.5% of the study cohort, and in two separate case reports, elderly females (Singhania et al., 2020; Tapé et al., 2013) also experienced OH (ΔSBP: −24 mm Hg; −31 mm Hg) and syncope prior to symptom onset. It is unknown whether these syncopal events constitute *neurogenic* OH, indicative of autonomic failure, as heart rate responses and subsequent autonomic workup were not reported. However, a separate case series reported syncope during or immediately following micturition, which can often elicit blood pressure reductions akin to performing a mild Valsalva maneuver. Impaired blood pressure responses and recoveries following a straining maneuver (with resultant syncope) may reflect impaired adrenergic function. Although supine and orthostatic vitals were not measured sequentially, two patients had significantly lower post-syncopal blood pressures (ΔSBP −45 mm Hg; ΔSBP: −30 mm Hg) relative to resting values.

For perspective, it is important to acknowledge that certain medications (i.e. antihypertensive agents, tricyclic antidepressants) can worsen OH and increase risk of syncope. Additionally, a considerable number of patients hospitalized with COVID-19 have several comorbidities that could contribute to syncope including, diabetes mellitus, heart failure, renal insufficiency, cardiac injury, atrial fibrillation, and arrhythmias (Table 1). While the case reports and case series detail several comorbidities, the studies comparing syncopal to non-syncopal patients found no significant differences in the type, number or presence of comorbidities. These findings suggest that despite the presence of comorbidities, an alternative explanation as to why some patients experience syncope while others do not remains unknown. In addition to existing comorbidities, cardiac injury, myocarditis, and arrhythmias are common cardiovascular complications in COVID-19, which can also contribute to syncope and impair heart rate and blood pressure. However, cardiac syncope related to arrhythmia, structural cardiac disease (Ebrille et al., 2020; Tapé et al., 2013), cardiomyopathy and sinus node disease (Canetta et al., 2020) were also ruled out. Similarly, syncopal patients had no significant differences in telemetry and 12-lead EKG characteristics (Canetta et al., 2020; Oates et al., 2020), mean troponin levels or differences in the percentage of patients with elevated troponin (Chen et al., 2020a) compared to non-syncope patients. Overall, reports of lower heart rate, lower blood pressure and evidence of reflex syncope/orthostatic hypotension, in the absence of cardiac factors, may elude to interference with cardiovascular autonomic reflexes.

Table 1
Neurogenic and non-neurogenic causes of syncope.

Pathophysiology	Cause
Reflex	• Vasovagal • Situational: Micturition, defecation, cough • Carotid sinus syndrome
Neurogenic	• Primary autonomic failure: Parkinson's disease, multiple system Atrophy, pure autonomic failure, Lewy body dementia • Secondary autonomic failure: Diabetic autonomic neuropathy, amyloidosis, autoimmune • Baroreflex failure: Neck radiation, carotid sinus nerve dysfunction, carotid dissection
Cardiac	• Arrhythmic conditions: Bradyarrhythmia, supraventricular tachycardia, ventricular arrhythmias • Structural conditions: Cardiomyopathy, heart failure, pulmonary emboli[a], cardiac tamponade[a] • Inheritable arrhythmic conditions: Brugada syndrome
Other	• Medications: Tricyclic antidepressants, alpha1-antagonists used for benign prostate hypertrophy, diuretics, nitrates • Endocrine: Pheochromocytoma, mastocytosis, vasoactive intestinal peptide tumour • Infection: Chagas disease[a], Lyme disease[a] • Pseudosyncope

[a] Less commonly associated with syncope.

2.1. Potential mechanisms of syncope

The autonomic and cardiovascular systems are intricately linked such that, in healthy individuals, any disruption to cardiovascular homeostasis, especially blood pressure, will be evident through compensatory changes in autonomic activity primarily via the baroreflex. Under low blood pressure conditions, baroreceptor unloading (namely in the aortic arch and carotid sinus) will reduce afferent feedback to the nucleus tractus solitarius (NTS). This results in cardiovagal withdrawal and disinhibition of the rostral ventrolateral medulla (RVLM), which leads to increased efferent sympathetic outflow to the heart and vasculature (Dampney, 1994). As a result, heart rate and systemic vascular resistance increase to maintain blood pressure (Fig. 1A). In syncope patients, this reflex is insufficient to maintain adequate cerebral blood flow leading to syncope.

In COVID-19, a myriad of physiological phenomena may influence blood pressure. These include changes in blood volume caused by dehydration, intravascular fluid shifts and volume redistribution; changes in vascular tone caused by local and neuronal effects of hypoxia, hypocapnia, elevated body temperature and inflammatory mediators; or by direct viral effects on the cardiac or nervous system. Given this onslaught, a compromised ability to defend against a reduction in blood pressure may cause syncope. Specifically, inability to defend blood pressure may be caused by: 1) impaired blood pressure sensing, 2) impaired initiation of autonomic efferent responses to blood pressure reductions (i.e., cardiovagal withdrawal, sympathetic activation), 3) impaired target organ responsiveness to autonomic efferent activity and/or 4) overwhelming vasodilation. To our knowledge, there is currently no direct evidence to support any one of these mechanisms in COVID-19. This lack of evidence is primarily due to inadequate study.

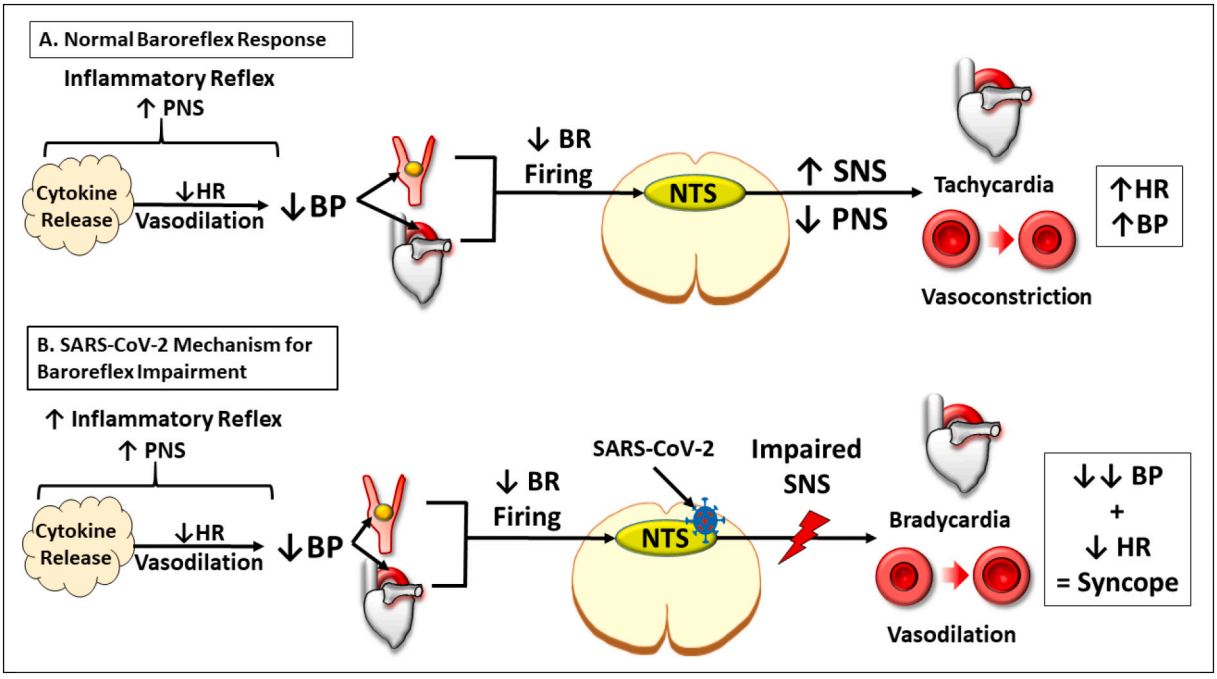

Fig. 1. A) Normal baroreflex response following activation of inflammatory reflex pathway. B) Proposed SARS-CoV-2 mechanism for baroreflex impairment.
A) A profound increase in parasympathetic nervous system (PNS) activity through the inflammatory reflex pathway would be anticipated to suppress the inflammatory response. Increased PNS activation would reduce heart rate (HR) while the inflammatory response would cause vasodilation. Baroreceptor (BR) unloading would reduce afferent firing to the nucleus tractus solitarius (NTS), eventually leading to reduce PNS and increase sympathetic nervous system (SNS) activity. Tachycardia and vasoconstriction would increase HR and blood pressure (BP).
B) If the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can infiltrate the NTS and affect the central baroreflex arc then the efferent SNS outflow to the heart and vasculature may be impaired. The bradycardic effects of PNS activation and the vasodilatory responses to inflammation would persist, leading to reductions in HR and BP, and increase potential for syncope.
Abbr. BR, baroreceptor; BP, blood pressure; HR, heart rate; NTS, nucleus tractus solitaries; PNS, parasympathetic nerve system; SNS, sympathetic nervous system; SARS-CoV-2; Severe acute respiratory syndrome coronavirus 2.

2.1.1. Non-COVID mechanisms for syncope

Although COVID-19 may cause specific damage to the neural pathways controlling blood pressure leading to syncope (discussed below), the added stressors influencing blood pressure in COVID-19 described above may also simply reveal patients already prone to syncope before infection. To illustrate, early COVID-19 is associated with an increase in Th-1 cytokines (TNFα, IL-β, IL-6). As disease severity progresses, the inflammatory system becomes dysfunctional generating a 'storm' of Th-1 and Th-2 (IL-4, IL-10) cytokines (Akbari et al., 2020; Angioni et al., 2020; Blanco-Melo et al., 2020; Chi et al., 2020). Elevated cytokines act directly on blood vessels to cause vasodilation (Landry and Oliver, 2001) requiring baroreflex compensation. Consequently, we might expect syncope-prone patients to be unable to mount a sufficient response.

Similarly, COVID-19-stimulated changes in cytokines, body temperature, PaO_2 and osmolarity can affect the autonomic nervous system and modulate activity of the carotid and aortic bodies, the carotid sinuses, vagal efferents, and/or cardiorespiratory centers in the brainstem. For example, cytokine and hypoxic activation of the carotid bodies initiate parasympathetic activation (Jendzjowsky et al., 2021; Jendzjowsky et al., 2018). The parasympathetic anti-inflammatory (cholinergic) reflex pathway is often necessary to prevent widespread tissue injury (Andersson, 2005; Pavlov and Tracey, 2012). However, if cardiac parasympathetic outflow were also increased, this would slow the heart rate and reduce cardiac output. If these reflexes are upregulated in syncope-prone patients we might expect a relative bradycardia during COVID-19 compared to non-syncope prone patients. Indeed, Canetta et al. (2020) and Oates et al. (2020) reported a relative bradycardia at rest in syncopal COVID-19 patients compared to COVID-19 patients presenting without syncope.

It is important to note the potential influence that systemic inflammation may also have on target organ responsiveness to autonomic efferent activity. Circulating inflammatory cytokines are known to cause adrenergic hypo-responsiveness of the peripheral vasculature (Landry and Oliver, 2001; Pleiner et al., 2002) and myocardium (Dal-Secco et al., 2017), which would impair end-organ reflex vasoconstrictor responses to blood pressure reductions. Whether there are subgroups of patients more susceptible to inflammatory-mediated adrenergic hypo-responsiveness is unknown.

Finally, low blood oxygen (hypoxemia) and reduced oxygenation to the brain would also increase susceptibility to syncope. In the study by Canetta et al. (2020), most patients had low partial pressures of oxygen and carbon dioxide (pO_2 and pCO_2), consistent with hypocapnic hypoxemia. Other studies have also reported exertional syncope related to hypoxia, which might suggest a mechanistic relationship between syncope and hypoxia. The intricate relationship between the baroreflex and chemoreflex, and their control and contributions to sympathetic nerve activity strengthens this hypothesis. However, in the case reports and case series reviewed, the SpO_2 levels on initial presentation ranged from 93% to 99%, and the studies comparing syncopal and non-syncopal cohorts showed no significant differences in SpO_2 levels.

2.1.2. Potential COVID-19 mechanisms for syncope

Another proposed mechanism of impaired autonomic efferent responses in COVID-19 includes direct neuroinvasion of autonomic peripheral ganglia and central nervous system (CNS) nuclei (Fig. 1B) expressing ACE2 receptors (Xia and Lazartigues, 2010; Villadiego et al., 2020). With regards to direct CNS effects, neurological symptoms (i.e. mental confusion, syncope, loss of smell, headache, disturbance of higher cortical functions) have been reported in COVID-19 patients (Helms et al., 2020; Mao et al., 2020). Notably, in post-mortem patients

with COVID-19, SARS-CoV-2 has been detected in cerebrospinal fluid (L. Zhou et al., 2020) and in endothelial cells within the medulla oblongata (Meinhardt et al., 2020). These findings, in addition to neuronal injury and glial activation (Meinhardt et al., 2020; Kanberg et al., 2020), provide support for the neuroinvasion hypothesis. Specific to syncope, ACE2 in the NTS modulates autonomic and baroreflex function. For example, when ACE2 activity in the NTS is pharmacologically inhibited or genetically inactivated, baroreflex sensitivity is impaired (Xia and Lazartigues, 2010; Xia et al., 2009). SARS-CoV-2 neuroinvasion of the NTS or other autonomic nuclei may also impair efferent autonomic responses to blood pressure reductions, and therefore increase susceptibility for syncope during orthostasis. Though this potential mechanism is plausible, specific injury of autonomic nuclei in COVID-19 patients has not been reported.

Although reports of syncope in COVID-19 may be growing, two noteworthy limitations of many of these accounts include: 1) the lack of autonomic work up, including evaluation of orthostatic vitals, which may help explain the high rates of *unexplained* syncope, and 2) when orthostatic blood pressures are measured, heart rates are not reported making a diagnosis of *neurogenic* OH (i.e. autonomic failure) difficult to ascertain. Overall, recognizing syncope as a potential early clinical presentation of COVID-19 may help mitigate missed or delayed diagnoses of COVID-19, which in turn could prevent transmission and exposure. As such, orthostatic vital signs should be standard for any patient seeking medical treatment for syncope, pre-syncope or non-mechanical fall.

3. Silent hypoxemia

3.1. Dyspnea

Shortness of breath is a primary symptom of COVID-19. However, there have been intriguing reports of "silent hypoxemia" in some patients, whereby the presence of profoundly low blood oxygenation fails to induce conscious awareness (i.e. symptoms of dyspnea) (González-Duarte and Norcliffe-Kaufmann, 2020; Bickler et al., 2020; Tobin et al., 2020). Dyspnea is a sensation or perception of breathing discomfort, sometimes characterized as "air hunger". The underlying mechanisms of dyspnea are poorly understood, and likely involve central and peripheral neural inputs, and emotional factors (Fukushi et al., 2021; Mechanisms, 1999; Burki and Lee, 2010). Several peripheral receptors are involved in the perception of dyspnea including the two peripheral chemoreceptors (aortic and carotid bodies), vagal receptors in the lungs and airways, and chest wall mechanoreceptors. In brief, vagal C-fibers innervating the airways and lungs detect irritants such as prostaglandins, histamines, and bradykinins, which project to the medulla (Bonham et al., 2006). C-fiber afferents are relayed to the limbic system and insular cortices via the NTS and thalamus. Similarly, changes in lung volume and muscle tension detected by chest wall mechanoreceptors send afferent projections to the brain via the vagus nerve (Fukushi et al., 2021; Burki and Lee, 2010). Higher cortical centers (i.e. cingulate gyri, insula, amygdala, cerebellum and somatosensory cortices) receive these afferent inputs, which can give rise to dyspneic sensations (Fukushi et al., 2021). As silent hypoxemia is the focus of this review, we will focus on the role of the oxygen sensitive peripheral chemoreceptors in the production of dyspneic sensations.

Low blood oxygen levels (<60 mm Hg PaO_2 (Chen et al., 2020b)) during severe SARS-CoV-2 infection arises from alveolar damage impairing O_2 uptake. The normal physiological response to arterial hypoxemia includes detection by peripheral aortic and carotid body chemoreceptors and initiation of afferent neural feedback to medullary nuclei and higher cortical centers. During spontaneous breathing, central integration of afferents inputs results in increased phrenic, sympathetic and parasympathetic nerve activity to maximize oxygen transport to vital organs and to re-establish blood-gas homeostasis (Jendzjowsky et al., 2018; Machhada et al., 2017). Hypoxic stimuli can also directly excite neurons in the hypothalamus, NTS, pre-Botzinger complex, and C1 region of the RVLM to enhance ventilatory drive and autonomic efferent outflow (RJA and Teppema, 2016). Peripheral chemoreceptor activation, primarily the carotid body, can also contribute to symptoms of dyspnea (Winter, 1973) (Fig. 2A). However, the specific influence of hypoxemia on dyspnea remains unclear. On one hand, alleviating hypoxia can relieve perceptions of dyspnea, suggesting hypoxia, as a stimulus, may be important. On the other hand, the severity of hypoxemia is not always proportionate to dyspneic symptoms. For example, in patients with chronic obstructive pulmonary disease, some patients without hypoxia can report severe dyspnea, while other patients report no symptoms of breathlessness (Swinburn et al., 1984; Marciniuk et al., 2011). These conflicting results call into question whether hypoxia itself is a direct stimulus for triggering perceptions of dyspnea. To reconcile these differences, Fukushi et al. (2021) proposed that dyspnea depends on whether the hypoxic conditions are acute or chronic, as well as the neuronal sensitivity. Both factors are important considerations in COVID-19 patients as the duration of hypoxia and individual carotid body sensitivity may be quite variable. For example, the most prevalent comorbidities in hospitalized COVID-19 patients (i.e. hypertension, diabetes mellitus II, obesity, etc.) are commonly associated with excessive sympathetic nerve activity, in part due to increased carotid body sensitivity. Therefore, duration and severity of existing comorbidities may influence carotid body sensitivity to hypoxemia, which may explain why some patients experience dyspnea while others do not.

3.2. Potential mechanisms of silent hypoxemia

The clinical presentation of low pO_2 without symptoms of dyspnea in COVID-19 may be 1) a normal physiological response to poikilocapnic hypoxia, 2) impairment of peripheral oxygen-sensing and/or 3) impairment of central processing of hypoxia-stimulated afferent inputs within higher-order somatosensory brain regions that manifest perceptions of dyspnea.

3.2.1. Non-COVID mechanisms for silent hypoxemia

Ventilatory rate can significantly influence symptoms of dyspnea. Specifically, acute mild hyperventilation has been associated with increased sensations of breathlessness (Burns and Howell, 1969). Data from large COVID-19 cohort studies indeed report ventilatory rates consistent with tachypnea (ventilatory rate > 20 bpm) in some patients (Chen et al., 2020b; Wang et al., 2020). Similarly, Chen et al. (Chen et al., 2020b) reported that 73% of patients had a PaO_2:FiO_2 < 300, suggestive of hypocapnia hypoxemia, while only 44% reported dyspnea. In many ways, the apparent mismatch between dyspnea and hypoxemia mirrors breathing at high altitude where observations of dyspnea are rare despite low pO_2 (Del Volgo and Noel-Jorand, 1992; Nakano et al., 2015). During altitude exposure, and possibly in COVID-19 patients, even mild hyperventilation can cause hypocapnia (Chen et al., 2020b; Willie et al., 2014). As carbon dioxide is more strongly associated with symptoms of dyspnea than hypoxia (Kobayashi et al., 1996), even slight reductions in arterial CO_2 could be sufficient to mitigate dyspneic sensations. Indeed, one important effect of hypocapnia, and a potential mechanism inhibiting the occurrence of dyspnea, is to blunt the excitatory effect of hypoxia on both peripheral and central chemoreceptors (RJA and Teppema, 2016) (Fig. 2A). Therefore, if respiratory rates are even slightly elevated in patients with COVID-19 (enough to cause hypocapnia), the resultant inhibitory effects of hypocapnia on chemosensing may be sufficient to reduce afferent feedback to higher cortical centers. As a result, dyspnea would not be perceived despite profound hypoxemia.

3.2.2. Potential COVID-19 mechanisms for silent hypoxemia

The carotid bodies are the main peripheral chemoreceptors responsible for detecting hypoxemia and are important receptors for perceptions of dyspnea. SARS-CoV-2 may interfere with carotid body oxygen

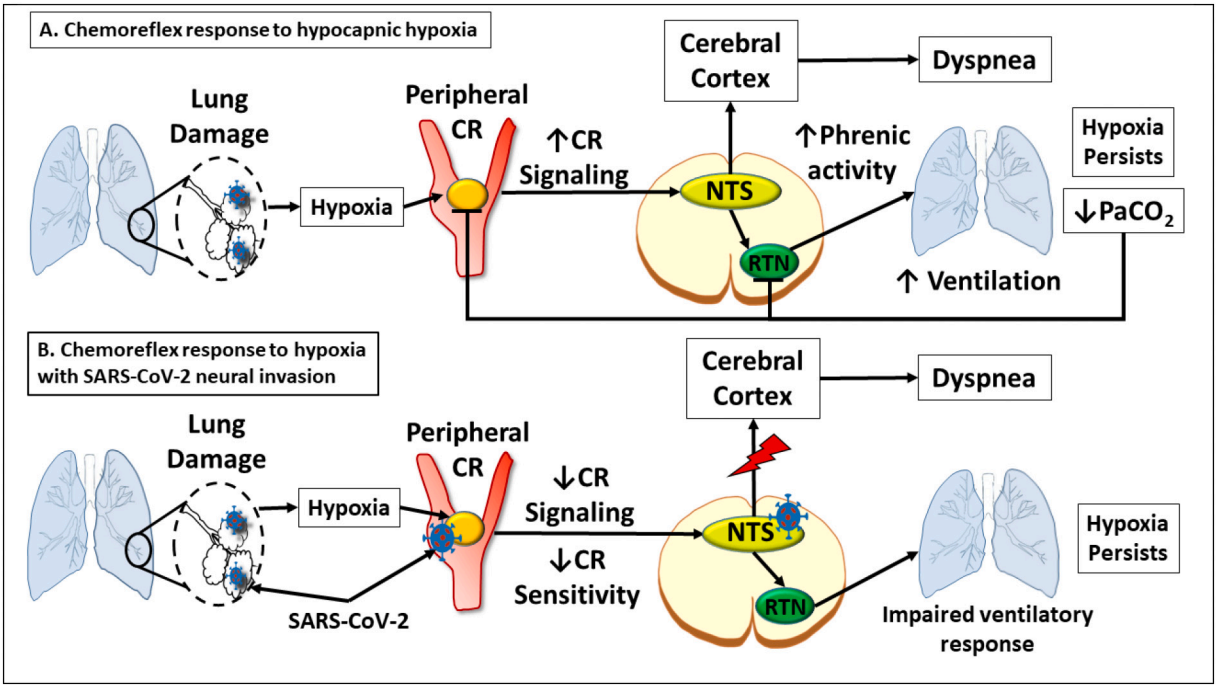

Fig. 2. A) Normal chemoreflex response to hypoxia. B) Proposed mechanisms for impaired chemoreflex response to hypoxia induced by SARS-CoV-2.
A) Arterial hypoxemia is primarily detected by peripheral chemoreceptors (CR) located within the carotid body. When the carotid body is stimulated, neural CR afferents are sent to the nucleus tractus solitarius (NTS). The NTS will facilitate an increase in sympathetic nervous system activity, phrenic nerve activity and ventilation in an attempt to re-establish partial pressure of oxygen (PaO_2). Once arterial CO_2 drops, this can feedback to partially inhibit the ventilatory drive initially stimulated by hypoxia. If PaO_2 drops below a certain threshold, individuals may experience symptoms of dyspnea.
B) A possible mechanism for impaired chemoreflex responses involves SARS-CoV-2 viral interference with oxygen-sensing properties of the peripheral CR located within the carotid body. Carotid body dysfunction could impair CR signaling and/or sensitivity. Alternatively, neural invasion by the SARS-CoV-2 virus within the NTS may also interfere with central processing of the carotid body afferents or subsequent SNS efferent outflow. Both mechanism could impair compensatory increases in ventilatory drive and sensations of dyspnea.
Abbr. CR, chemoreceptor; NTS, nucleus tractus solitaries; PaO_2, partial pressure of oxygen; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2; SNS, sympathetic nervous system; flat arrow heads indicate inhibition.

sensing and/or function (Fig. 2B); a plausible hypothesis based on evidence of ACE2 receptors within the carotid body vasculature (Schultz, 2011) and the oxygen sensing glomus cells (Villadiego et al., 2020). The SARS-CoV-2 virus could bind to the ACE2 receptors on the glomus cells, damaging the mitochondrial electron transport chain involved in O_2 sensing and cause cell death (Archer et al., 2020). This hypothesis is supported by evidence from the previous SARS-CoV virus that was found to alter mitochondrial protein expression (Archer et al., 2020; Lai et al., 2007). Damage to the oxygen sensing cells within the carotid body would reduce afferent feedback to the brain despite systemic hypoxemia and thus reduce the sensation of dyspnea.

Alternatively, evidence of tachypnea suggests that some afferent information, even if reduced, is processed centrally enough to elicit an efferent ventilatory response. These data suggest that the SARS-CoV-2 virus may interfere with central processing of sensory afferent neural inputs (Meinhardt et al., 2020). Carotid body afferents terminate at the NTS, which projects to several autonomic and respiratory nuclei (RJA and Teppema, 2016). The NTS also relays respiratory and autonomic inputs to the hypothalamus and higher cortical structures involved in dyspnea sensation including somatosensory cortices, cingulate, amygdala, cerebellum and insula (Burki and Lee, 2010). Viral neural invasion of the NTS and other structures (Nampoothiri et al., 2020) could therefore interfere with several upstream and downstream signal processes and in turn interfere with perceptions of dyspnea (Fig. 2B).

In this perspective, we describe several mechanisms that may explain the lack of dyspnea in the setting of hypoxemia in some COVID-19 patients. However, these mechanisms are likely countered to some degree by cytokine activation of the carotid bodies (Jendzjowsky et al., 2021; Jendzjowsky et al., 2018) and hypoxia-mediated carotid body plasticity, which increases chemoreflex sensitivity (Kumar and Prabhakar, 2012). To date, altered carotid body function and histology have not been specifically studied in COVID-19 patients, nor has chemoreflex function. Reports of dyspnea have not been a primary symptom of investigation, and as such, specific comparison of respiratory rates, age, ethnicity, comorbidities and other contributing factors between dyspneic and non-dyspneic cohorts have not been explored.

4. Therapeutic targets

ACE2 is an important regulatory enzyme within the renin-angiotensin system. In this system, renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II (Ang II) by angiotensin converting enzyme (ACE). When bound to AT1 receptors, Ang II promotes vasoconstriction, inflammation, fibrosis, thrombosis, and cell proliferation (Xia and Lazartigues, 2010). Activation of the renin-ACE-Ang II axis can also blunt baroreflex function and increase sympathetic activity (Patel and Schultz, 2013). Conversely, Ang II can be converted to Ang (1–7) via ACE2, which will bind to Mas receptors. The ACE2-Ang (1–7)-Mas receptor axis mediates vasodilation, anti-inflammation, anti-fibrosis, and apoptosis (Patel and Schultz, 2013). This axis also enhances baroreflex function, and reduces overall sympathetic activity (Patel and Schultz, 2013) (Fig. 3). Therefore, conversion of Ang II to Ang (1–7) via ACE2 facilitates an important pathway for modulating sympathetic tone.

The functional role of ACE2 (SARS-CoV-2 receptor) indicates this receptor may be an important target to limit SARS-CoV-2 infections. In the context of COVID-19, altering the expression and/or availability of ACE2 through the use of ACE inhibitors (ACEi; to block the production

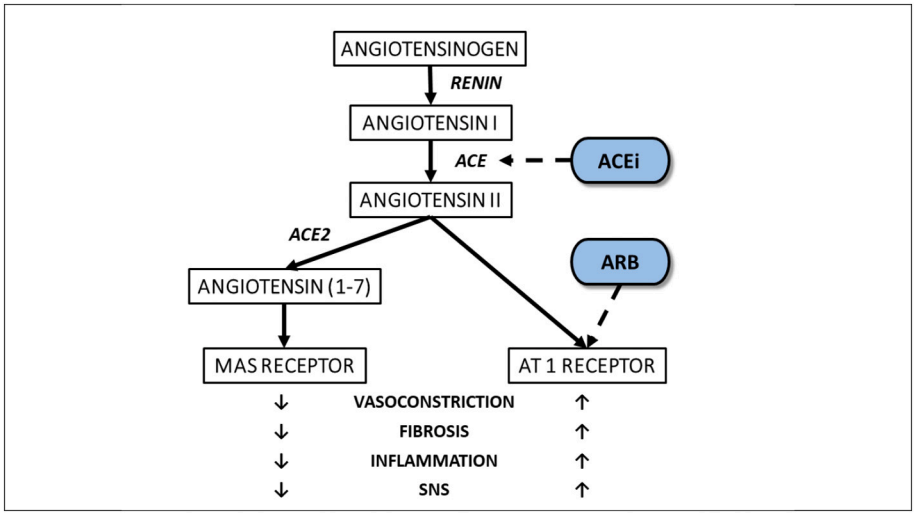

Fig. 3. Role of ACE2 in the renin angiotensin system opposing the effects of angiotensin II.
In this system, renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II (Ang II) by angiotensin converting enzyme (ACE). When bound to AT1 receptors, Ang II promotes vasoconstriction, inflammation, fibrosis, and increased sympathetic nervous system (SNS) activity. Conversely, Ang II can be converted to Ang (1–7) via ACE2, which will bind to Mas receptors. The ACE2-Ang (1–7)-Mas receptor axis mediates vasodilation, anti-inflammation, anti-fibrosis, and decreased SNS. The use of ACE inhibitors and angiotensin II receptor blockers are commonly prescribed to prevent the outcomes associated with Ang II-AT1 binding.
Abbr. ACE, angiotensin converting enzyme; ACEi; ACE inhibitor; ARB, angiotensin II receptor blockers; SNS, sympathetic nervous system.

of Ang II) or Ang II receptor blockers (ARBs), remains controversial (Murray et al., 2020). Some reports have cautioned against the use of ACE inhibitors and ARBs over concerns that ACE2 is up-regulated and thus would provide additional opportunity for viral binding and cell entry (Murray et al., 2020). This concern arises from pre-clinical studies whereby lisinopril, enalapril and losartan reduced plasma Ang II, increased plasma Ang (1–7), and increased ACE2 mRNA (Ferrario et al., 2005). Other studies, however, found ramipril had no effect on ACE2 (Burrell et al., 2005). In a clinical study of viral pneumonia patients, the use of ACE inhibitors was also associated with increased need for intubation and risk of death (Swinburn et al., 1984). In contrast, other studies have argued for continued use. This argument is based on evidence showing that, when bound, Ang II induces ACE2 internalization, which is mediated by an AT1 receptor-dependent mechanism. In the presence of an ARB (losartan); however, ACE2 internalization is inhibited (Henry et al., 2018). These findings argue that ARBs decrease SARS-CoV-2 cell entry by reducing ACE2 internalization. A recent prospective, randomized, open-label trial recently investigated continuation vs. discontinuation of ACEi or ARB therapy in COVID-19 patients, and showed no differences on clinical outcomes (Cohen et al., 2021). Of note, patients with heart failure with reduced ejection fraction were excluded from the trial. This may be important, as a separate study found that withdrawal of ACEi and ARBs was significantly associated with higher mortality in COVID-19 patients with a prior diagnosis of heart failure (Rey et al., 2020). Overall, these results agree with the current recommendations to continue to prescribe these medications to patients with COVID-19, barring any clear medical contraindications. Studies exploring ACEi and ARB therapy (NCT04335786, NCT04311177, NCT04328012), as well as ACE2 as a therapeutic target are already underway. Monteil et al. (2020) have demonstrated that exogenous administration of clinical grade human recombinant soluble ACE2 prevents SARS-CoV-2 infection in both engineered human blood vessel and kidney organoids by acting as a decoy.

Should evidence reveal acute or permanent autonomic impairment as a result of COVID-19, then ACE2 may be an important therapeutic candidate to help re-establish cardiovascular autonomic homeostasis. To date, none of these treatments have been tested clinically, so carefully designed trials are essential before clinical recommendations can be made.

5. Conclusions

We are in the early stages of understanding COVID-19, including the mechanisms that may specifically target the autonomic nervous system. Highlighted in this review, two of the more intriguing phenotypes attributed to COVID-19, namely syncope and silent hypoxemia. On one hand, it may be possible that these clinical presentations represent non-COVID related physiological processes. However, there is still a necessity for an appropriate control and comparator groups (i.e. other viral strains that cause pneumonias) to identify potential unique aspects, if any, of COVID-19 on autonomic function. We are in even earlier stages of understanding whether deficits will lead to long-term chronic complications. Although chronic autonomic complications are not the focus of the current perspective, readers are encouraged to read a recent review on this topic (Goldstein, 2020). As we move forward in our understanding of COVID-19, well-defined patient registries, along with collaborative and comprehensive studies, will be critical for future research and care. As autonomic specialists and researchers, we are uniquely positioned to understand multisystem disorders. As a community, we need to be prepared to test and care for autonomic outcomes that may emerge from the COVID-19 pandemic.

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Declaration of competing interest

None.

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