"Silent hypoxaemia in COVID-19 patients"

***J Phys* Topical Review**

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Abstract

The clinical presentation of COVID-19 due to infection with SARS-CoV-2 is highly variable with the majority of patients having mild symptoms while others develop severe respiratory failure. The reason for this variability is unclear but is in critical need of investigation. Some COVID-19 patients have been labeled with 'happy hypoxia,' in which patient complaints of dyspnoea and observable signs of respiratory distress are reported to be absent. Based on ongoing debate, we highlight key respiratory and neurological components that could underlie variation in the presentation of silent hypoxaemia and define priorities for subsequent investigation.

Tatum S. Simonson

Introduction

COVID-19 presentation is highly variable, with most patients having minimal symptoms and others developing severe respiratory failure and acute respiratory distress syndrome

(COVID-19 ARDS). COVID-19 can cause profound hypoxaemia with near normal arterial carbon dioxide ($PaCO_2$) levels due to ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) maldistribution and shunt as well as increased $\dot{V}_E$ to augment CO_2 elimination in better and more normal functioning lung units. Although some individuals with COVID-19-induced hypoxaemia experience dyspnoea, defined as breathing discomfort (Parshall *et al.*, 2012), others do not; these latter patients have been labeled with 'happy hypoxia' (Couzin-Frankel J 2020), a misleading term since these individuals are certainly not 'happy,' and the terminology tends to trivialize the pathology. Another previously used term, 'silent hypoxaemia' (Tobin et al. 2020; Ottestad and Søvik 2020), is perhaps more appropriate. Below, we propose that the silent hypoxaemia of COVID-19 can be explained by known physiological principles of gas exchange combined with published observations of dyspnoea neurobiology. However, observations in individual patients combined with data from the physiology laboratory are needed to test this proposal and to determine whether further studies are needed.

Hypoxaemia is a well appreciated phenomenon from classic physiological literature. Dyspnoea typically does not occur with hypoxaemia alone, particularly if PCO_2 is normal or near normal, although this response is variable. Generally, a secondary stimulus, such as activation of pulmonary afferent neurons and/or CO_2 chemoreceptors, is necessary for dyspnoea to be evoked by all but the most severe hypoxaemia (Moosavi *et al.*, 2003; Parshall *et al.*, 2012; Nakano *et al.*, 2015). The sensation of dyspnoea may represent a conscious awareness of the outgoing respiratory motor command, in which areas of the brain that control ventilation send efferent commands to the ventilatory muscles, and a neurological copy of these commands is sent to the sensory cortex (Nishino, 2011). This hypothetical exchange between motor and sensory cortex is called corollary discharge. Therefore, the corollary discharge hypothesis describes a disconnect that can occur between the control of breathing and respiratory sensation, when anticipated responses to stimuli do not occur because of impaired lung or chest wall mechanics (Banzett *et al.*, 1989; Chen *et al.*, 1992). Secondary factors, such as cytokines, may independently either trigger or suppress dyspnea, depending on how the specific cytokine interacts with immune cells (Tung *et al.*, 2018; Galeas-Pena *et al.*, 2019), such as the 'cytokine storm' typically associated with ARDS (Malhotra, 2007).

The presentation of patients with silent hypoxaemia varies and is noted before more advanced stages in severe disease (Tobin et al. 2020). Some patients have fever, fatigue, and cough but only slight dyspnoea. Their oxygen saturation (SpO_2), determined via pulse oximetry, may be in the 80s or lower on presentation, but they present without discomfort (Tobin et al. 2020). The other silent hypoxaemia presentation includes those with hypoxaemia who communicate that they perceive no symptoms but, who on further questioning, appear to suffer from cognitive impairment (McMorris *et al.*, 2017; Needham *et al.*, 2020; Ritchie *et al.*, 2020). Infection or severe hypoxaemia may cause confusion and mask symptoms. This finding may be due to variation in disease stage, respiratory chemoreflexes, stoicism, and/or undescribed genetic factors. In this topical review, we gathered experts and interested parties to reach consensus on the physiological basis of silent hypoxaemia and to define research priorities.

Pulmonary pathology and control of breathing in COVID-19 patients

Lung pathology

Lungs of COVID-19 patients can show heterogeneous consolidation (Bos *et al.*, 2020) leading to hypoxaemia with normal to low $PaCO_2$. There is minimal dyspnoea early in the response to virus, with pathophysiological consequences of $\dot{V}_A/\dot{Q}$ non-uniformity, dead-space ventilation ($\dot{V}_D$) and small shunt, with near-normal compliance and high tidal ($\dot{V}_T$) and minute ventilation ($\dot{V}_E$). Expectations of dyspnoea in COVID-19 ARDS patients relate to more common experiences with influenza patients who experience ARDS. However, based on autopsy reports, COVID-19 is associated with greater pulmonary endotheliosis, micro-thrombosis, and angiogenesis (Ackermann *et al.*, 2020) without large decrements in lung compliance (Li & Ma, 2020), although information about distinct time points in disease progression are needed (Hariri & Hardin, 2020). This profile disrupts $\dot{V}_A/\dot{Q}$ relationships, with lesser increases in the work of breathing or respiratory drive needed to achieve appropriate oxygenation.

Additional abnormalities include measures of shunt fraction that are disproportionate to the area of unventilated lung (Gattinoni *et al.*, 2020a), striking perfusion abnormalities on dual-energy CT (Lang *et al.*, 2020), and evidence of endothelial pathology in post-mortem tissue studies (Ackermann *et al.*, 2020). Later in disease progression, patients often resemble more typical ARDS with associated impairments in gas exchange and mechanics.

Chemoreflexes

Once $\dot{V}_A/\dot{Q}$ relationships are impaired, blood gases are abnormal and chemoreflexes activated, including central CO_2 and the peripheral carotid body chemoreceptors that also sense low O_2. As peripheral chemoreceptors respond to both CO_2 and O_2, there is considerable interplay between the hypercapnic and hypoxic ventilatory responses and assessment of arterial chemoreflex function is complex; ideally the response to hypoxia and hyperoxia is tested with controlled CO_2 (Duffin, 2007). Hence, despite the fact that $PaCO_2$ is near normal in early COVID-19 patients (authors' personal observations; (Tobin *et al.*, 2020)), it is difficult to be sure that these chemoreflexes are fully intact. Bilateral carotid body resection, performed to treat hereditary carotid paragangliomas or, historically, the dyspnea of asthma (Nakayama, 1961; Overholt, 1961), typically results in an increase in $ETCO_2$ relative to pre-operative levels. However, this varies with time following resection and between individuals, with some subjects exhibiting near normal $PaCO_2$ and pH but markedly reduced ventilatory responses to hypoxia (Wood *et al.*, 1965; Honda *et al.*, 1979; Honda & Hashizume, 1991; Dahan *et al.*, 2007). The latter might be difficult to detect clinically when monitoring respiratory rate, as the arterial chemoreflex typically has a greater

effect on tidal volume. Carotid body stimulation also triggers a number of cardiovascular responses through increased sympathetic activity, hence other observations of COVID-19 patients, such as limited changes in heart rate on arterial desaturation, may also indicate impaired chemoreflexes.

Genesis of dyspnoea

Air hunger is the most prominent sensation in severe dyspnoea (Stevens *et al.*, 2019); it is the extremely uncomfortable sensation that arises when ventilation (sensed via stretch receptors) fails to meet demand (conveyed by corollary discharge from brainstem to cerebral cortex) (Abstract Figure). Under conditions of fixed mechanical ventilation, air hunger can be induced by either hypoxia and/or hypercapnia in proportion to level of chemoreflex stimulation of ventilation (Moosavi *et al.*, 2003). The fundamental neurobiological issue that remains is: how is dyspnoea and its negative affect generated? Using functional neuroimaging, several forebrain areas have been consistently implicated (insula, cingulate and sensory cortices, amygdala and periaqueductal gray matter) (Marlow *et al.*, 2019) Banzett et al., 2020 (in press). The lateral parabrachial complex is an important region that receives inputs from central chemoreceptors (retrotrapezoid nucleus, serotonergic neurons), peripheral chemoreceptors, and cardiopulmonary afferents via relays in the nucleus of solitary tract and respiratory pattern generator (ventral respiratory column, Kölliker-Fuse nucleus) (Kaur & Saper, 2019). A parabrachial subnucleus called PBel-CGRP, possibly an "alarm bell" (Palmiter, 2018), mediates CO_2-induced arousal via massive projections to hypothalamus, amygdala and basal forebrain. Indeed, humans with congenital central hypoventilation syndrome generally experience no ventilatory stimulation, dyspnoea, or arousal from sleep when exposed to hypercapnia or asphyxia. They breathe normally while awake, have a preserved volitional control of breathing, and exhibit exercise-induced hyperpnea. Congenital central hypoventilation syndrome largely spares brain regions above the pons but alters carotid body development, cardiopulmonary receptors, and several lower brainstem structures, including the retrotrapezoid nucleus that are required for an effective hypercapnic ventilatory reflex (Guyenet *et al.*, 2019).

Innate differences

The impact of individual variation in ventilatory chemoreflexes and dyspnoea responses remain to be examined in the context of respiratory failure. Ventilatory responses vary markedly with up to 10-fold differences in isocapnic hypoxic and hypercapnic responses (McGurk *et al.*, 1995; Swenson *et al.*, 1995; Beall *et al.*, 1997). Variation is observed in high-altitude populations (Beall 2009), and blunted ventilatory responses are noted among the elderly (Peterson *et al.*, 1981) as well as individuals with diabetes (Nishimura *et al.*, 1989; Weisbrod *et al.*, 2005). While sub-phenotypes and heterogeneity are recognized in ARDS (Wilson & Calfee, 2020), silent hypoxaemia, noted primarily in clinical contexts with viral-induced ARDS, has become increasingly apparent with the COVID-19 pandemic (Couzin-Frankel, 2020; Ottestad & Sovik, 2020; Tobin *et al.*, 2020).

Is "happy hypoxia" a paradoxical finding?

Reports of hypoxaemia without dyspnoea in COVID-19 raise the question of whether lack of dyspnoea is truly paradoxical or simply conforms to expectations given blood gases, ventilatory parameters, and individual variation (Moosavi *et al.*, 2003; Nakano *et al.*, 2015). Over time, some 'silent hypoxemics' are expected to develop dyspnoea. First, beyond the first few hours of hypoxaemia, we would anticipate that drive increases ("ventilatory acclimatization" (Powell *et al.*, 1998; Pamenter & Powell, 2016)) through augmented carotid chemosensitivity, increased central nervous system (CNS) translation of this sensory information into ventilatory drive, and the accompanying hyper-additive influence of increased carotid chemoreceptor input on medullary CO_2 sensitivity. Second, with further lung inflammation and increased pulmonary vascular and interstitial fluid pressures, pulmonary C fiber stimulation likely adds additional drive – tachypnea – and falling dynamic compliance and hyperinflation adds elastic loads – dyspnoea ensues, relieved by reoxygenation. How this course of events unfolds likely varies among COVID-19 patients and contributes to notable individual differences, including presentation of silent hypoxaemia.

Let us consider the patient with SpO_2=76%. Hypoxaemia likely arises from shunt as a consequence of unventilated alveoli – in this case P_{CO_2} is expected to be normal or low. If we assume $PaCO_2$=40 mmHg, this would imply PaO_2=41 mmHg during air breathing. Using published air hunger versus PO_2 stimulus-response data (Figure 3 from (Moosavi *et al.*, 2003)) we estimate that 3/10 normal individuals would experience no significant dyspnea when P_{ETO_2}=41 Torr and P_{CO_2}=40, as illustrated by the data from individual C in Figure 1; thus silent hypoxaemia is expected to be a common occurrence when P_{O_2} is low but P_{CO_2} is not elevated. Silent hypoxaemia is noted in aviation medicine (Ottestad and Søvik (2020) as well as competitive diving, whereby divers develop startlingly low PO_2 after a long breath hold, yet PCO_2 at the end of breath hold is near normal due to pre-apnea hyperventilation (Lindholm & Lundgren, 2006; Overgaard *et al.*, 2006). Competitive divers often report diminished cerebral function – versus dyspnoea – as the proximal reason to terminate the breath hold (Lindholm & Lundgren, 2006; Binks *et al.*, 2007). The lack of significant air hunger after a long breath-hold does not reflect intensive training but is likely a result of established physiology (Binks *et al.*, 2007). These studies help illustrate why some COVID-19 patients could also experience little discomfort despite profound hypoxaemia.

Additional consideration should also be given to direct effects of hypoxaemia on important neural structures involved in respiratory sensation. Low tissue PO_2 can damage and/or reduce neuronal activity in these critical areas, resulting in a disconnect between respiratory drive and respiratory sensation, and hypoxaemia is known to diminish cognitive function (Berry *et al.*, 1989; McMorris *et al.*, 2017). The fact that known physiology can explain observations reported thus far does not, however, discount the possibility that neural damage due to COVID-19 further impairs respiratory chemoreflexes and perception of dyspnea. Because COVID-19 is known to invade the nervous system, causing derangement

of other sensations (see section below), it is crucial to discover whether it directly impairs respiratory neural responses.

SARS-CoV-2 and the neural control of breathing

Potential neuroinvasion by SARS-CoV-2

Although silent hypoxaemia in COVID-19 could be explained by the above theories, there might also be deficits in the neural control of breathing and/or mechanisms of respiratory sensation. In addition to innate differences described above, direct viral entry into respiratory control centres has been proposed as a potential mechanism underlying respiratory failure in some COVID-19 patients (Hoffmann *et al.*, 2020; Li *et al.*, 2020; Manganelli *et al.*, 2020). For example, infection of the peripheral chemoreceptor carotid body may impair hypoxic chemoreflexes, allowing startling hypoxaemia to develop. It is unclear, however, whether the carotid body expresses the proteins required for infection by SARS-CoV-2, namely: ACE2, the SARS-CoV cell entry receptor, and TMPRSS2, the serine protease that cleaves the viral S protein to allow host cell entry (Hoffmann *et al.*, 2020). Although ACE2 expression was reported based on immunoblotting the carotid body (Schultz, 2011), our own unpublished observations suggest minimal ACE2 protein expression by immunohistochemistry in the mouse carotid body, in contrast to its abundant expression in the epithelium of the lungs, gut, and kidney (authors' unpublished observations).

Early reports suggest CNS infection by SARS-CoV-2, although the precise structures infected remain uncertain (Li *et al.*, 2020; Mao *et al.*, 2020; Moriguchi *et al.*, 2020; Paniz-Mondolfi *et al.*, 2020). However, the related coronaviruses SARS-CoV and MERS-CoV infect brainstem respiratory neurons and result in mortality from respiratory insufficiency (McCray *et al.*, 2007; Netland *et al.*, 2008; Li *et al.*, 2016). Thus, detailed anatomical information of SARS-CoV-2 infection targets in critical regions controlling breathing and respiratory sensation, such as vagal sensory receptors, peripheral chemoreceptors, and brainstem neurons critical for respiratory rhythm and pattern formation, are of considerable interest (Li *et al.*, 2020; Mao *et al.*, 2020; Paniz-Mondolfi *et al.*, 2020). Ultimately, loss of these critical neural elements may lead to ventilatory failure and death. Although current reports do not demonstrate an immediate impact of SARS-CoV-2 on crucial neural structures for the genesis of respiratory rhythm, consideration must be given to more long-lasting effects that may destabilize breathing and impact recovery including weaning from mechanical ventilation (Manganelli *et al.*, 2020).

Anosmia

Similarly, COVID-19-induced anosmia, the loss of sense of smell, may be indicative of peripheral and/or central nervous system effects of the virus. Breathing-related signals of olfactory origin that project to hippocampus, prefrontal cortex, etc., are likely affected, which may impact dyspneic sensation (Peiffer *et al.*, 2001; Netland *et al.*, 2008; Harper *et al.*, 2015; Esser *et al.*, 2017). Recent RNAseq and single-cell RNAseq analyses suggest non-neuronal

cells in the olfactory system, which express transcripts and proteins associated with SARS-CoV-2 entry, contribute to COVID-19 anosmia (Brann *et al.*, 2020).

Anosmia is a common feature of COVID-19 (Giacomelli *et al.*, 2020) and associates with a milder clinical course (Yan *et al.*, 2020), and stratification of such patients could improve individual plans of action. Whether anosmia is associated with other phenotypes is important for understanding this hallmark feature of COVID-19 as well as underlying mechanisms. Therefore, testing COVID-19 patients for anosmia and assessing smell in the context of silent hypoxaemia may be instructive.

Inflammatory responses

Neuroinflammatory responses to acute lung injury may contribute to dyspnoea in COVID-19 patients. Acute lung injury elicits systemic inflammation and increases pro-inflammatory cytokine expression in brainstem regions important in respiratory control, and cytokines may elicit tachypnea with acute lung injury. Indeed, focal microinjection of IL-1β into the nucleus of the solitary tract is sufficient to induce tachypnea, even in the absence of hypoxaemia/hypercapnia (Hsieh et al., 2020). It is unknown if CNS cytokine expression leads to dyspnoea, and investigation into the role of circulating cytokines with varying degrees of hypoxaemia, and whether these patterns differentiate COVID-19 patients, are of considerable interest.

Clinical implications

Many "asymptomatic carriers" may be patients with silent hypoxaemia. Addition of central cyanosis (bluish coloration) or SpO_2<93% as an indication for testing may help identify such cases, which could reduce disease spread and provide much needed insight regarding out-of-hospital mortality rates (Friedman *et al.*, 2020). If it is clinically validated that the majority of patients with silent hypoxaemia recover spontaneously, delaying intubation until respiratory distress may be warranted. Conversely, if most progress to distress and ultimately require intubation, early intubation might be preferable.

It remains unclear if silent hypoxaemia patients exhibit more or less severe outcomes. It is plausible that individuals with an adequate hypoxic ventilatory response mask their risk of clinical deterioration through normal saturations. However, at late stages of disease, an important question is whether the lack of ventilatory response mitigates deterioration as a very excessive ventilatory response may promote damage through self-induced lung injury (Mascheroni *et al.*, 1988; Esnault *et al.*, 2020; Gattinoni *et al.*, 2020b). Another possible factor may be that PO_2, PCO_2, and pH influence viral growth and invasiveness. Since these variables can be readily adjusted during mechanical ventilation, laboratory studies concerning their impact on viral behavior may guide ventilator management.

Research directions

Important research is needed regarding neural control of breathing and respiratory sensation in COVID-19 patients. Silent hypoxaemia forces us to consider fundamental principles of respiratory physiology, including principles of gas exchange, sensory feedback, central neural regulation of breathing, and respiratory sensation as well as the importance of individual variation in the context of personalized medicine. COVID-19 has highlighted some of our deficiencies of knowledge concerning these key elements.

We suggest collection of critical data during COVID-19 progression including blood gases, breathing pattern, the patient's quantitative report of dyspnoea (dyspnoea rating), and the patient's description of the quality of dyspnoea using a standard instrument. Assessment of hypercapnic and hypoxic ventilatory responses would help determine whether there is a specific defect of ventilatory control. There are clear practical challenges in conducting these studies on patients with active infection but the study of recently recovered patients may also be informative. In addition to such functional analyses, it will be informative to perform morphological analyses of the respiratory control centres and peripheral chemoreceptors such as the carotid body to look for signs of viral infection, as well as for morphological abnormalities that may result in respiratory defects that persist beyond the period of active infection (hence the interest in testing respiratory function in patients that have recovered from viral infection). Assessment of ACE2 and TMPRSS2 expression across these respiratory control centres may prove informative in predicting sites of infection; of note in this regard, ACE2 expression has been reported to vary with hypoxia (Zhang *et al.*, 2009; Joshi *et al.*, 2019) and the hypoxaemia experienced during COVID-19 may alter the dynamics of viral cell entry.

Dyspnoea is complex, involving multiple peripheral sensory receptors and central neural relays. Understanding the impact of COVID-19 on feedback from pulmonary receptors, peripheral chemoreceptors, brainstem respiratory neurons, limbic system, and cortex is critical. Key studies must also consider other factors that could influence dyspnoea, such as the 'cytokine storm' associated with ARDS and markers of inflammatory and/or viral presence in key respiratory nuclei of brainstem and cortex. Ancillary studies of SARS-CoV-2-induced anosmia may also predict dyspnoea in COVID-19.

Reports of inter-individual variation in COVID-19 severity suggest genetic factors may underlie distinct responses to the virus and ensuing phenotypes (Initiative, 2020). Possible studies should include cohorts well characterized for chemosensitivity and genomic information to assess which patients were at greatest risk of developing respiratory failure during COVID. This strategy could determine the extent of response that may afford protective effects or whether patients with robust chemosensitivity develop respiratory failure via self-inflicted lung injury. Considering elderly individuals (Peterson *et al.*, 1981) and those

with diabetes (Nishimura *et al.*, 1989; Weisbrod *et al.*, 2005) exhibit a decreased ventilatory response to hypoxia and comprise a large proportion of the population impacted by COVID-19, it is plausible these individuals may experience more silent hypoxaemia and rapid decompensation. Future studies could also reevaluate COVID-19 survivors who exhibited a range of ventilatory and/or dyspnoea profiles during active infection in a post-COVID-19, controlled experiment with targeted genetic assessments (Simonson & Malhotra, 2020). If high ventilatory drive is injurious, we would advocate for randomized studies to suppress respiratory drive (using narcotic or benzodiazepine) in patients at high risk of respiratory failure and only in an intensive care unit setting. Recognizing that pharmacological agents clearly have risks and benefits, cautious suppression of respiratory drive may be beneficial for subsets of patients who induce mechanical lung injury via breathing pattern.

The recent development of animal models may provide valuable insights concerning COVID-19 changes in respiratory behaviors. However, the extent to which these animal models faithfully recapitulate lung pathology, breathing patterns, and blood gases in COVID-19 remains to be determined. Furthermore, dyspnoea is a perception; at this time, we are able to assess this perception only in humans, who can report what they feel. Pending development of a reliable animal model that recapitulates important aspects of human COVID-19 disease, studies should be directed toward understanding neural elements that may be crucial in respiratory sensation. Respective contributions to dyspnoea by olfactory cortex, parabrachial complex (alarm/CO_2 arousal pathways), among other ascending brainstem relays are unclear. Mechanistic experiments should tease apart COVID-19 pathophysiology in the neural control of breathing and respiratory sensation that may elucidate roles of innate variation and potential infection by SARS-CoV-2 in human disease.

Conclusion

We offer some take-home messages. First, we believe the term ‘happy hypoxia’ should be avoided as these patients are clearly not enjoying their severe hypoxaemia but are profoundly hypoxemic without apparent distress. The term silent hypoxaemia is more appropriate and does not trivialize the abnormality. Second, basic and clinical research regarding control of breathing and individual variation in response to hypoxaemia and COVID-19 specifically is clearly needed. Finally, recommendations to stay home until symptoms become severe may be problematic, since necessary interventions may be unnecessarily delayed (Friedman *et al.*, 2020; Luks & Swenson, 2020).

Additional Information

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Abstract Figure. Genesis of air hunger. In a working model of mechanisms giving rise to air hunger, brainstem respiratory centers send projections (corollary discharge) to the forebrain, giving rise to breathing discomfort in proportion to the magnitude of corollary discharge (Banzett *et al.*, 2020). These brainstem respiratory centers also send descending projections, driving respiratory motor neurons and respiratory muscle activity to generate ventilation. Inputs to the brainstem centers include chemoreceptor inputs, exercise, and voluntary inputs from the motor cortex. Afferent feedback from lung stretch receptors modulate different qualities of dyspneic sensation. Slowly adapting lung stretch receptors (SAR) are inhibitory to air hunger. Pulmonary C-fiber receptors contribute to air hunger, but precise neural projections are not well understood. Whenever corollary discharge reaches a certain threshold, or when ventilation fails to meet demand, dyspnoea ensues. Inputs contributing to dyspnoea are indicated by blue arrows; inputs that inhibit dyspnoea are indicated with blue circles. Black arrows indicate homeostatic regulation of breathing.

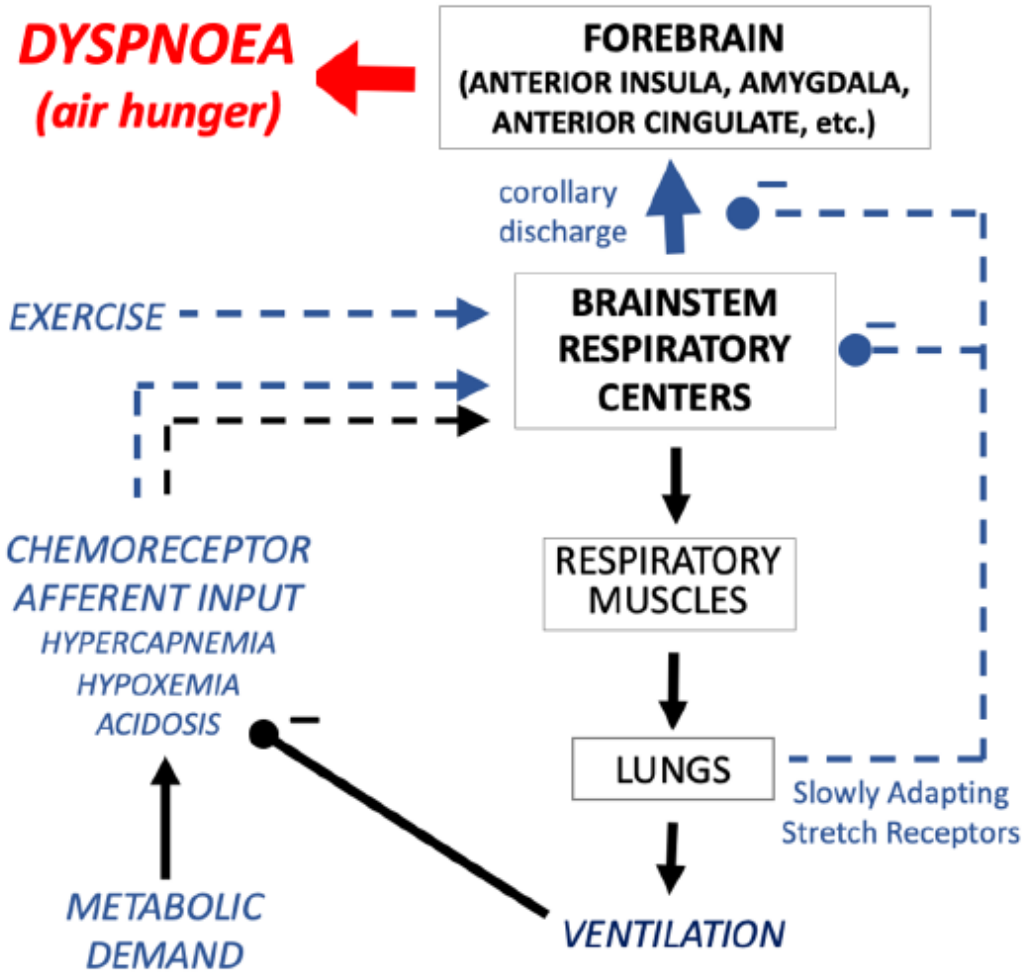

Figure 1. Variable air hunger responses to different levels of steady-state hypoxia, with $\dot{V}_E$ set at resting levels by mechanical ventilation, in three individuals (A, B, and C represent subjects 3, 1, and 5, respectively, from (Moosavi *et al.*, 2003)). Studies were conducted at eucapnia. The three selected individuals show the range of normal sensitivities in the sample of 10. A response similar to Individual C could represent a patient with SpO_2 = 76% and no dyspnoea.