Review Article

Happy hypoxemia: What has been forgotten

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Abstract

Happy hypoxemia is a clinical condition that is baffling the physicians world over during this COVID 19 pandemic, which manifests with little or no dyspnoea in the presence of severe hypoxemia. Many mechanisms have been put forth to explain this paradoxical phenomenon. This article revisits some of the basic physiological concepts in respiratory physiology. Carbon dioxide is the primary controller of chemical regulation of respiration, not the oxygen as the body has mechanisms to withstand wide fluctuations in blood oxygen level. Hypercapnia is a late manifestation when compared to hypoxia in conditions where diffusion of respiratory gases is impaired, like in acute respiratory distress syndrome that often complicates severe COVID 19 cases. New findings suggest an additional role of carbon dioxide in the pathogenesis of dyspnoea, through its contribution to the development of pulmonary edema.

Key words

Happy hypoxia, Hypercapnia, Dyspnoea, COVID 19.

Introduction

A buzz word that is spreading even faster than coronavirus in the news media during this COVID 19 pandemic is "Happy Hypoxemia" though not much hyped in medical journals. It is defined as the absence of dyspnoea or minimal signs of dyspnoea in the presence of severe hypoxemia [1]. Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID 19, has resulted in a pandemic with epicenter in Wuhan, Hubei province, China [2] in December 2019. Within few weeks, the deadly pathogen has affected other parts of China and almost most of the countries of the world [3], through human to human transmission by the way of respiratory droplets or aerosol that enters the human body

(lungs) through mouth and nose [3]. Even though most of the patients of COVID 19 developed only mild to moderate illness, a consistent small portion of patients developed acute complications requiring ventilators and rigorous interventions like respiratory failure, acute respiratory distress syndrome (ARDS) and sepsis [4]. Some of the plausible concepts and mechanisms that underlie this paradoxical phenomenon of happy hypoxemia are highlighted in the first part as described by researchers. Later in the article, the role of carbon dioxide, both the basic physiology and the recent concept, is discussed.

What has been discussed so far?

Medical literature abounds with mechanisms that explain why patients exhibit little or no dyspnoea in the presence of severe hypoxemia, which depends on many interdependent factors like the sensation and perception of inadequate ventilation [5], blunting effect of carbon dioxide level in the blood on respiratory centers' response to hypoxia [6], the shift in oxygen-dissociation curve [7], effect of age and disease on the adequacy of respiratory control mechanism [8-11] and so on as comprehensively dealt by Dr. Tobin, the lead author in his study, "Why COVID-19 Silent Hypoxemia is Baffling to Physicians," appeared recently in the online American Journal of Respiratory and Critical Care Medicine [12]. Like pain, dyspnoea is a subjective symptom [13] which has an inter-individual variation (drive to breathe in response to hypercapnia and hypoxia exhibits as much as 300% to 600% variation) that explains why some hypoxic patients do not develop dyspnoea [14]. The sensation of dyspnoea develops when the end-tidal partial pressure of oxygen (pO_2) drops down below 60 mmHg [6]. The physical signs which the physicians use to estimate the level of dyspnoea, like tachycardia, tachypnoea, and facial expressions, either overestimate or underestimate the authentic level of dyspnoea [15]. The afferents from the chemoreceptors and mechanoreceptors of respiration transmit the sensory impulse to the Nucleus Tractus solitarius in the medulla (NTS). The projections from NTS to cortical structures, especially the Insular cortex, are responsible for the perception, which is the reaction of the individual to the sensation, of the adequacy or inadequacy of the ventilation and if inadequate leads to the sensation of dyspnoea [16-18]. In patients with relatively preserved elasticity of lungs, the hypoxia-induced high minute volume would wash out carbon dioxide (CO_2) resulting in hypocapnia, similar to hypoxia at high altitude [12] and hypoxia in the presence of hypocapnia induces no sensation of discomfort, rather a feeling of comfort [19].

What has been forgotten?

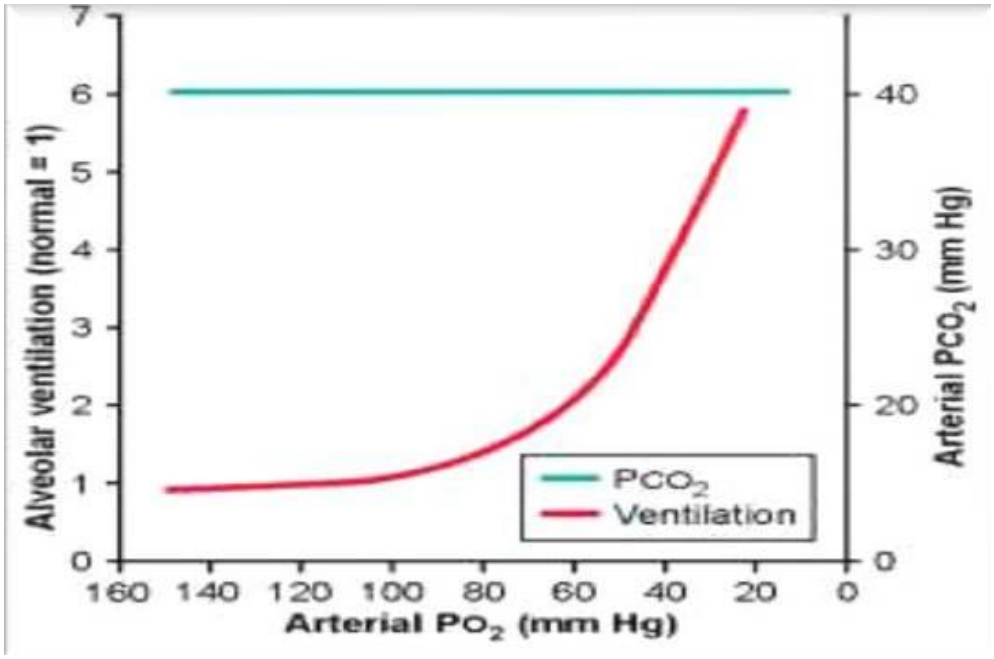
The basic physiological concepts were not given adequate thought in explaining the condition. The major controller of respiration is carbon dioxide and not oxygen. The respiratory center in the medulla oblongata reacts to even minimal changes in the blood carbon dioxide level whereas it is not so for blood oxygen level. The chemical regulation of respiration operates to maintain the alveolar partial pressure of carbon dioxide (pCO_2) and blood hydrogen ion (H^+) at a normal level and raise the pO_2 when it falls to potentially dangerous level [20]. The human body has a mechanism to pitch in when the blood oxygen level falls without disturbing respiration. The hemoglobin oxygen buffer system delivers almost exactly normal amounts of oxygen to the tissues even when the pulmonary pO_2 changes to a value as low as 60 mm Hg from normal 100 mmHg [21]. Though the impulse traffic increases in the nerves that carry the information about the oxygen level in the blood from peripheral chemoreceptors, the respiration is not stimulated due to; a) less H^+ ions in the blood thus less stimulation of respiratory center when the pO_2 falls, as the reduced hemoglobin (Hb) is less acidic than the oxygenated Hb and b) any small increase in ventilation would wash way the CO_2 from the blood thus removing the potential stimulus for respiration. Therefore the stimulatory effects of hypoxia on ventilation need to become strong enough to override the

counterbalancing inhibitory effects of a low H^+ concentration and pCO_2 level in the blood [20].

The above-discussed concept is depicted in the graph of **Figure - 1**. There is no much stimulation of respiration until the pO_2 falls to as low as 60 mmHg. Beyond this level, there is the stimulation of respiration that increases the ventilation, sometimes up to 6 times normal when, the pO_2 falls to around 20 mmHg. This stimulation is less (as carbon dioxide level is kept constant) when compared to conditions where pH is decreased and carbon dioxide level is increased.

Figure - 2 shows the effect of hypoxia on ventilation when the pH is reduced (more H+ ion concentration) and carbon dioxide level is increased. There is strong stimulation of ventilation under these conditions when compared to stimulation of ventilation by hypoxia alone.

Figure - 1: Effect of falling pO_2 level on ventilation when pCO_2 level kept constant. (Courtesy: Guyton & Hall. Textbook of Medical Physiology)



Hypercapnia is a late manifestation than hypoxia

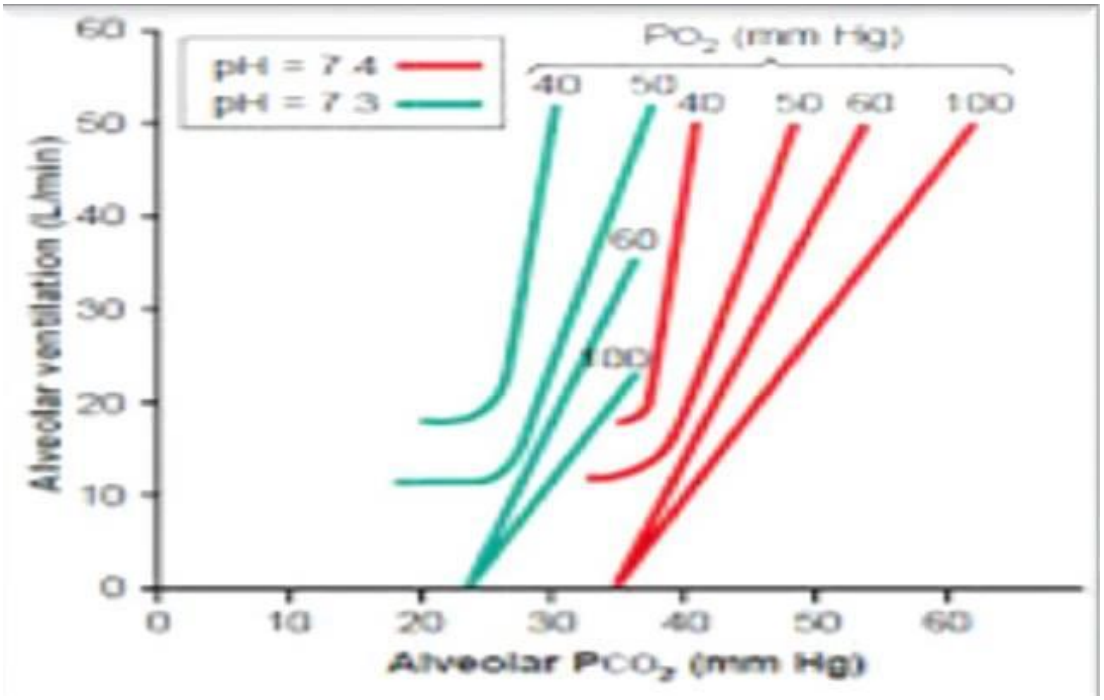
Another important physiological consideration that needs attention is the fact that carbon dioxide can cross the biological membrane with ease when compared to oxygen as the diffusing capacity of the former is 400-450 ml/min/ mm Hg whereas it is 20-25 ml/min/ mm Hg for the latter [21]. Thus any impairment in the diffusion would produce hypoxia much earlier than hypercapnia [22]. This is the basic mechanism in acute respiratory distress syndrome (ARDS). In the initial stages of ARDS, hypoxia prevails due to increased thickness of the respiratory membrane because of inflammatory changes [23] resulting in minimal or no dyspnoea. Hypercapnia sets later in the course due to pump failure, which also alters the pH, thus hypoxia in the presence of hypercapnia and acidosis result in strong stimulation of respiration resulting in dyspnoea [22].

Role of hypercapnia in pulmonary edema- recent findings

The conventional teaching in respiratory physiology talks about the role of Starling's forces of pulmonary circulation and lymphatics in the lungs in keeping the alveoli dry. Recent research has shed light on the role of respiratory epithelium in the prevention of pulmonary

edema. An intact fully functional respiratory epithelium is pivotal for maintaining optimal fluid balance and gas exchange in the lung [24]. The Epithelial sodium channels (ENaC) of the alveolar epithelial cells (AEC) pump the sodium from the alveolus into the AECs from where it is pumped into the interstitium by the basolateral Na^+ K^+ pump that creates the driving force for movement of water through the paracellular pathway. Hypercapnia downregulates these ENaCs of AECs by CO_2-induced and ERK-, AMPK-, and JNK-mediated signaling pathway, which promotes phosphorylation of both β-ENaC and Nedd4-2, leading to ubiquitination of β-ENaC and subsequent internalization of the α/β-ENaC complex [25].

Figure - 2: Effect of falling pO_2 level on ventilation in the presence of acidosis and hypercapnia (Courtesy: Guyton & Hall. Textbook of Medical Physiology).



Summary

Happy hypoxemia is a clinical condition increasingly recognized in severe COVID 19 patients. Physicians are baffled to find patients with severe hypoxemia with minimal or no dyspnoea. Dyspnoea, like pain, is a subjective symptom that has many interrelated mechanisms. It is important to understand the basic physiologic concepts explained in chemical regulation of respiration that helps to understand this paradoxical phenomenon.

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