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Mini-Review

Happy hypoxia in COVID-19 patients associated with hypoxic ventilatory depression

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Objective: Acute exposure to hypoxia generally increase the ventilation. However, some of COVID-19 patients who suffer from pneumonia are characterized by hypoxic ventilatory depression with loss of dyspnea which is called as happy hypoxia. This report describes the background and the clinical issues of happy hypoxia.
Methods: The mechanisms to increase ventilation and dyspnea under hypoxia are explained. Further, clinical issues and characteristics in COVID-19 are reviewed.
Results: Genetic factors are definitely concerned with chemosensitivity to hypoxia. Further disease factors including COVID-19 infection could influence the attenuation of the chemosensitivity. This can be attributed to either ventilatory depression due to the modulation of metabolic substrate, adenosine in the brain, or autonomic neuropathy including the dysfunction of the carotid body.
Conclusions: COVID-19 patients must be carefully treated and/or monitored to avoid hypoxic ventilator depression. The clinical application of aminophylline will be an issue to be considered.

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Key words: COVID-19, hypoxia, dyspnea, ventilation, chemosensitivity, carotid body

The clinical characteristics of COVID-19 infection have been reported, but little is known about the pathophysiology on hypoxia associated loss of dyspneic sensation[1]. Happy hypoxia observed in COVID-19 patients provides old but new important topics. In COVID-19 patients, hypoxia progresses in an acute or subacute course in accordance with pneumonia. Hypoxemia generally augments ventilator drive to maintain homeostasis and arterial oxygen pressure. However, some patients suffer from hypoxemia, so called happy hypoxia[2] or silent hypoxia, without dyspneic sensation, occasionally resulting in unexpected death. When patients fall into happy hypoxia phenomenon, they do not feel dyspnea associated with the decrease in ventilatory drives, i.e., hypoxic ventilatory depression (HVD). Ventilatory response to hypoxia is mediated through the increased inputs from the peripheral chemoreceptors, mainly the carotid body, through the carotid sinus nerves, impinging on the respiratory center complex that modulates respiratory output in brain stem[3]. On the other hand, hypoxemia itself suppresses the ventilator drive in the central nervous system (CNS), mainly caused by the accumulation of suppressive mediators in the brain. Actual ventilatory drive is elicited by the integrated summation of the excitatory inputs from the carotid body and inhibitory effects of the brain. Happy hypoxia phenomenon is presumably considered

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to occur by suppressing total output of ventilation due to hypoxia. It can be produced by not only attenuated afferent inputs via the carotid body but also central respiratory depression including the respiratory center complex. The former can be caused by the carotid body dysfunction and abnormal afferent inputs from the carotid body as a result of autonomic neuropathy. The latter can be attributed to central depression due to the modulation of metabolic substrate. HVD is attenuated by aminophylline, suggesting the contribution of adenosine in the mechanism[4]. Moreover, increase in central blood flow might take part in this mechanism resulting from central hypocapnia[5]. Chemosensitivity to hypoxia was clarified to be strongly influenced by genetic factors compared to that to hypercapnia[6]. Analysis among individuals revealed that chemosensitivity to hypoxia are widely distributed from non-responders to strong responders. Once the subjects of non-responders suffer from acute hypoxic condition, it is likely that they easily fall into severe hypoxic depression. The genetic factor is maintained to aged period, and the attenuated hypoxic chemosensitivity is associated with hypoxia-related life-threatening conditions such as near fetal asthma[7]. Blunted hypoxic chemosensitivity was reported to easily cause acute mountain sickness and pulmonary edema at high altitude, representing that the higher chemosensitivity to hypoxia, the higher physical performance at high altitude[8]. Environmental or disease factors also influence the attenuation of the chemosensitivity. It is recognized that COVID-19 causes systemic inflammation including CNS dysfunctions as well as pneumonia[9]. Also, it is shown that COVID-19 causes the deterioration of not only the CNS but also the peripheral nerves[10] including the carotid sinus nerve, both of which potentially cause HVD. Based on issues mentioned, the question arises why happy hypoxia in COVID-19 patients is found only in limited patients of COVID-19. So far, the answer is unknown. It has been clarified that the damage to the CNS is caused by the direct pathogenic effect of COVID-19 infection in the CNS neurons[9]. So, it is possible that COVID-19 causes the dysfunction in the regions responsible for central respiratory depression in the CNS. Another possibility is that autonomic neuropathy selectively occurs in the carotid body and/or afferent pathways surrounding glossopharyngeal nerve regions. The other is that the involvement of the susceptibility to hypoxic events, i.e., a certain subjects who show reduced innate hypoxic chemosensitivity are likely to develop happy hypoxia without dyspnea even with a minor degree of autonomic dysfunction. Pursuing the physiological mechanism of happy hypoxia is of scientifical importance. Needless to say, however, hypoxic loading on humans is ethically unrealistic. Elucidation of the pathophysiology underlining the mechanisms will be awaited by using safe methods such as a single O_2 breath test proposed by Dejours[11] for evaluating hypoxic chemosensitivity in humans. Furthermore, the neuropathological investigation will be needed on the involvement in central and peripheral nervous systems in COVID-19 patients who died of COVID-19 associated with happy hypoxia. From clinically important points of view, diabetes mellitus is well known to cause autonomic and peripheral neuropathy, especially in thin fibers of afferent nerves. Indeed, attenuated ventilatory response to hypoxia is observed in patients with diabetes mellitus[12, 13]. Inadequate hemodynamic compensatory responses to hypoxia which cause tissue hypoxia but not hypoxemia might be involved[14]. COVID-19 patients in particular with diabetes mellitus must be carefully treated to avoid HVD. The clinical application of aminophylline to HVD will be an issue to be considered.

Declaration of conflicting interest

The author declare that there is no conflict of interest.

No figure, No Table

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