Oxygen-induced hypercapnia: physiological mechanisms and clinical implications

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Abstract

Oxygen is probably the most commonly prescribed drug in the emergency setting and is a life-saving modality as well. However, like any other drug, oxygen therapy may also lead to various adverse effects. Patients with chronic obstructive pulmonary disease (COPD) may develop hypercapnia during supplemental oxygen therapy, particularly if uncontrolled. The risk of hypercapnia is not restricted to COPD only; it has also been reported in patients with morbid obesity, asthma, cystic fibrosis, chest wall skeletal deformities, bronchiectasis, chest wall deformities, or neuromuscular disorders. However, the risk of hypercapnia should not be a deterrent to oxygen therapy in hypoxemic patients with chronic lung diseases, as hypoxemia may lead to life-threatening cardiovascular complications. Various mechanisms

leading to the development of oxygen-induced hypercapnia are the abolition of 'hypoxic drive', loss of hypoxic vasoconstriction and absorption atelectasis leading to an increase in dead-space ventilation and Haldane effect. The international guideline recommends a target oxygen saturation of 88% to 92% in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and other chronic lung diseases at risk of hypercapnia. Oxygen should be administered only when oxygen saturation is below 88%. We searched PubMed, EMBASE, and the CINAHL from inception to June 2022. We used the following search terms: "Hypercapnia", "Oxygen therapy in COPD", "Oxygen-associated hypercapnia", "oxygen therapy", and "Hypoxic drive". All types of study are selected. This review will focus on the physiological mechanisms of oxygen-induced hypercapnia and its clinical implications.

Key words: Chronic obstructive pulmonary disease; Haldane effect; hypercapnia;, oxygen therapy.

Introduction

Oxygen is a drug; hence, it requires appropriate use and monitoring. Inappropriate or liberal use of oxygen in patients at risk of type-2 respiratory failure may cause hypercapnia, respiratory acidosis, organ dysfunction, and even coma [1]. COPD is the most common chronic lung disease associated with oxygen-induced hypercapnia [2]. However, there are other vulnerable patient groups also who are at risk of developing oxygen-induced hypercapnia e.g., morbid obesity, obstructive sleep apnea, obesity-hypoventilation syndrome (OHS), cystic fibrosis, neuromuscular disorders, restrictive chest wall deformities, severe asthma, and bronchiectasis [2,3]. Inappropriate use of oxygen in patients with AECOPD may be associated with increased mortality [4,5]. Other detrimental effects of high-flow oxygen during COPD exacerbations are prolonged hospital stays, greater requirement for ventilation, and more frequent admissions to high dependency units [6-10]. Therefore, controlled oxygen delivery targeting a pre-determined arterial oxygen saturation (SaO_2) goal should be the key approach to hypoxemia management in chronic lung disease

patients with a risk of hypercapnia. The goal of oxygen therapy in patients with a risk of hypercapnia is SaO_2 of 88–92% [2,11,13]. These patients should be observed closely following initiation of oxygen therapy for any signs of hypercapnia and carbon dioxide narcosis. Oxygen is a drug, hence, proper use is strongly recommended, particularly in patients who are at risk of hypercapnia. Detailed information should be provided by physicians regarding the delivery device, oxygen flow rate, and target oxygen saturation, with instructions on troubleshooting if these parameters are exceeded in either direction [11].

The development of hypercapnia due to liberal oxygen use is not a new phenomenon. It has been mentioned in literature even in the late 1930s. Barach in 1937 first reported that patients after inhalation of 50% oxygen developed temporary stupor and irrational behavior [14,15]. Few patients also developed lassitude, depression, and severe headache. He initially attributed these symptoms to a sudden change in cerebral oxygen tension [1]. However, others believed that these symptoms developed due to oxygen-induced carbon dioxide retention [16,17]. Subsequent paper in 1938, Barach recognized the link with the oxygen-induced elevation of partial pressure of carbon dioxide ($PaCO_2$) [15]. Barach also suggested the concept of controlled oxygen therapy by using oxygen at low concentrations and be escalated gradually if required [15]. Donald in 1949 similarly reported a case of carbon dioxide narcosis in a patient with severe emphysema and heart failure that developed 12 h after oxygen therapy. A $PaCO_2$ of 120 mm Hg was recorded at the time of coma and the condition improved rapidly following the withdrawal of oxygen therapy. According to Donald, hypercapnia developed due to reduced minute ventilation (V_E) resulting from the abolition of the hypoxic drive [17]. Davies and Mackinnon [18] in 1949 reported the harmful effects of oxygen therapy in two patients with chronic cor-pulmonale. The first patient developed myoclonic movements, profuse sweating, and fullness in the head after oxygen therapy, which resolved after the withdrawal of oxygen. The second patient had a diagnosis of congestive heart failure and COPD. He developed a coma two hours after administration of oxygen at about 6 liters/ minute and ultimately died. Further experimental studies by the same authors showed an increase in cerebrospinal fluid pressure when oxygen was applied in 50-100% concentration to patients with chronic cor

pulmonale compared to controls. They suggested that the adverse effect was due to carbon dioxide accumulation in the body. Comroe et al. [16] in 1950 published a series of 65 consecutive patients given oxygen therapy: 43 had emphysema and the rest had asthma, bronchiectasis, pulmonary vascular disease, and congenital heart disease. They demonstrated mental status changes in eight patients. All eight patients had emphysema and were characterized by a baseline $PaCO_2$ of greater than 50 mmHg and a baseline SaO2 of less than 90%. The rise in $PaCO_2$ by oxygen supplementation was between 10 to 52 mm of Hg. They proposed the following potential mechanisms of mental status changes; carbon dioxide narcosis, cerebral vasospasm, increased cerebrospinal fluid pressure, and reflex and direct depression of the cerebral cortex by high oxygen tension. They also suggested a low concentration of oxygen and frequent examination during the first three hours of oxygen therapy for signs of developing coma.

Westlake et al. [19] in 1955 described a case series of 16 patients who developed carbon dioxide narcosis following oxygen therapy during an acute respiratory disturbance. All of them had preexisting respiratory diseases and oxygen was given by tent with a FiO_2 varying between 40 and 50%. They reported a correlation between arterial carbon dioxide tension and symptoms development. The exact cutoff for $PaCO_2$ and pH that is dangerous is unclear. They reported normal mental clarity with a $PaCO_2$ below 80 mm of Hg and pH >7.3. However, a $PaCO_2$ of higher than 100 mm of Hg was associated with mental status changes and a $PaCO_2$ of more than 120 mm of Hg and pH <7.1 was associated with coma.

In 1960, EJM Campbell reinforced the concept of controlled oxygen therapy and suggested that fraction of inspired oxygen (FiO_2) of 24 to 35% would relieve hypoxemia without the risk of severe hypercapnia [20]. He measured the response in four patients with AECOPD (Mean $PaCO_2$ and PaO_2 of 79 mmHg and 23 mmHg respectively) to varying concentrations of inspired oxygen and demonstrated that the PaO_2 of patients with severe respiratory failure was very sensitive to even small degrees of oxygen enrichment. He proposed continuous oxygen therapy at an FiO2 of 24 to 35% as intermittent therapy may cause significant hypoxemia. In a subsequent paper, EJM Campbell highlighted the issues of wide variations in VE with existing oxygen delivery devices and described a new oxygen delivery mask

based on venturi principle and is popularly known as venturi mask, which delivers a fixed FiO_2 [21].

In the J Burns Amberson Lecture in 1967, EJM Campbell described three types of outcomes in COPD patients following uncontrolled oxygen therapy. In 10% of cases, there was an improvement or no change in the clinical state and $PaCO_2$ level. In 60% of cases, patients became drowsy but arousable. Their $PaCO_2$ slowly rises in about 12 hours by up to 20 mm of Hg and then stabilizes. However, in 30% of cases of hypercapnic acute respiratory failure in patients with COPD, narcosis developed. The patients deteriorated rapidly, and the PaCO2 escalated at a rate of ≥30 mm of Hg per hour [22]. Eldridge and Gherman studied the effects of controlled oxygen in patients during acute exacerbations of COPD and who had hypoxemia and hypercapnia while breathing room air. They administered oxygen by nasal cannula or plastic oronasal mask at flow rates ranging from 2 to 6 liters/min for periods of from 10 to 180 min to 19 patients with AECOPD. The majority of patients had a rise in $PaCO_2$ levels following the administration of oxygen therapy. However, the $PaCO_2$ response to a given PaO2 is highly variable from patient to patient. They observed that a 10 mm of Hg rise in the PaO_2 level increases the $PaCO_2$ level by 1 to 5 mm of Hg [23]. The risks of oxygen-induced hypercapnia can occur not only during AECOPD but even in stable COPD. Some patients may show a rapid and marked increase in $PaCO_2$ level within 60 minutes [5]. However, patients treated with low concentration oxygen may also develop hypercapnia and acidosis [23,24]. Uncontrolled oxygen therapy in pre-hospital and hospital emergency setting among patients with AECOPD may be associated with a poor prognosis. In a prospective audit of 101 admissions of AECOPD, those who had received a FiO_2 of 0.28, developed severe acidosis and had higher in-hospital mortality (14%) compared to patients who had received a FiO_2 of ≤28% (2%) [6]. Therefore, paramedics and emergency physicians should be educated regarding the management of AECOPD with low and the target oxygen saturation goal.

Other conditions associated with oxygen-induced hypercapnia

Neuromuscular disease (NMD)

Hypoventilation is the main mechanism that explains hypercapnia in patients with neuromuscular disease and diaphragmatic dysfunction [25]. Patient with NMD with

diaphragmatic involvement is at risk of worsening hypercapnia, even with the administration of low-flow oxygen [26,27]. In a retrospective study, Gay and Edmonds analyzed arterial blood gas studies before and after the administration of low-flow oxygen (0.5 to 2 Liters/min) in eight patients with NMD and diaphragmatic dysfunction and demonstrated a mean increase in carbon dioxide of 28.2 ± 23.3 mm of Hg with oxygen therapy [26]. Supplemental oxygen, even low flow in patients with NMD and diaphragmatic dysfunction, should ideally be monitored frequently, particularly if the baseline carbon dioxide level is elevated. Similarly, Chiou et al. [27]. reported a rise in $PaCO_2$ of 52.1 ± 42.0 mm of Hg over a mean of 17.4 h in NMD patients.

Obesity-hypoventilation syndrome (OHS)

Obesity hypoventilation syndrome (OHS) is characterized by obesity, chronic hypercapnia due to alveolar hypoventilation, and severe sleep-disordered breathing. Similar to COPD patients, patients with OHS also show a rise in hypercapnia and acidemia following oxygen therapy. Wijesinghe et al. [28] in a double-blind, randomized, controlled, crossover trial, studied the effect of 100% oxygen or room air for 20 minutes on two separate days in 24 outpatients with newly diagnosed OHS. They measured the transcutaneous partial pressure of carbon dioxide ($PtCO_2$), V_E, and dead space/tidal volume (V_D/V_T) ratio at baseline and after 20 minutes. They reported worsening hypercapnia following breathing 100% oxygen. The PtCO2 and V_D/V_T ratio increased by 5.0 mm of Hg (95% CI, 3.1-6.8; $p<0.001$) and 0.067 (95% CI, 0.035-0.10; $p<0.001$) respectively with oxygen compared with room air, whereas the V_E was decreased by 1.4 L/min (95% CI, 0.11-2.6 L/min; $p=0.03$). Therefore, 100% oxygen administration causes worsening hypercapnia in stable patients with OHS similar to COPD. Moreover, OAH patients with marked baseline hypoxemia are at the greatest risk of oxygen-induced worsened hypercapnia. Said et al. [29] observed an increase in $PaCO_2$ from 51 to 68 mm of Hg after breathing 100% oxygen for 20 to 30 minutes. Similar to COPD patients, the rise in $PaCO_2$ occurs within a short period. Obese patients with marked baseline hypoxemia are at a greater risk of oxygen therapy-associated hypercapnia. Wijisinghe et al. [28] reported that for every 1% fall in baseline SaO_2, the transcutaneous carbon dioxide rises by 0.5 mm of Hg. It can be explained by the fact that obese patients

with a low baseline SaO_2 are more likely to receive a high concentration of oxygen. Hollier et al. [30] in a randomized crossover study evaluated the effect of FiO_2 0.28 and 0.50, each for 20 minutes on $PaCO_2$, pH, V_E, and V_D/V_T among people with stable untreated OHS, in comparison to healthy controls and reported a worsened hypercapnia and induced acidaemia due to hypoventilation and a worsening of V_D/V_T ratio.

Asthma

The causes of hypercapnia during asthma exacerbation are related to severe disease, leading to respiratory muscle fatigue and increased dead space. Uncontrolled oxygen therapy may also be detrimental in older patients with asthma [31]. Field, in 1967, evaluated the effects of 100% oxygen administered for 20 minutes, posture, isoproterenol, and atropine on ventilation-perfusion relationships in acute severe asthma [32]. Twenty-six asthmatics were studied during an acute exacerbation. There was a statistically significant increase in V_D/V_T on breathing oxygen and an increase in mean $PaCO_2$, which occurred despite an increase in minute ventilation. The results remained the same despite the change in posture indicating that the changes in pulmonary artery pressure were unlikely to contribute to V_D/V_T increases. He explained the increase in V_D/V_T due to the abolition of HPV [32].

Chien et al. [33] assessed the effects of uncontrolled oxygen on $PaCO_2$ and forced expiratory volume in 1 second (FEV_1). Following admission to the emergency department, 37 asthmatic subject s(FEV_1) 49 ± 3.6% predicted] were administered 100% oxygen *via* a non-rebreathing face mask for 20 minutes. There was carbon dioxide retention in 67.6% of patients and the risk was greatest in patients with the most severe airway obstructions. Twenty-five patients had a rise in $PaCO_2$ ranging from 1 to 10 mm of Hg (mean 4.1 ± 0.6 mm of Hg). Therefore, patients with asthma should be administered supplemental oxygen in a controlled fashion.

The safe limit of the FiO_2 is not clear. However, Rudolf et al. [34] had shown that a FiO_2 of 60% is a safe approach to manage hypoxemia in acute asthma. Perrin et al. [35] studied the effect of high concentration oxygen therapy in 106 patients with severe exacerbations of asthma and measured the proportion of patients with a rise in $PtCO_2$ ≥4 mm of Hg at 60 minutes. Patients were randomized to receive either high concentration oxygen at 8 Liter/minute *via* simple facemask or titrated oxygen to achieve a target saturation of 93–95%

for 60 minutes. The $PtCO_2$ was raised significantly in the high concentration oxygen group versus the controlled group [44% *versus* 19%, RR 2.3 (95% CI 1.2 to 4.4, p<0.006)]. Therefore, oxygen should be administered in a controlled fashion in patients with severe asthma, when presenting with severe exacerbations, as uncontrolled oxygen therapy can cause hypercapnia similar to COPD. The mechanism of oxygen-induced hypercapnia in asthmatics may be due to a worsening V/Q mismatch following the abolition of HVC and the resulting increase in physiological dead space. Rodrigo et al. [36] in a randomized controlled trial compared 28% oxygen via a standard face mask with 100% oxygen via a non-rebreathe facemask administered for 20 minutes among 74 asthmatics presented in the emergency. The liberal oxygen group was significantly associated with more severe respiratory acidosis and hypercapnia as compared with the 28% oxygen group and the magnitude of the increase was seen, particularly in those patients with raised baseline $PaCO_2$. Therefore, liberal oxygen therapy may cause a rise in $PaCO_2$ levels and this rise is greatest in the patients with the most abnormal baseline condition (Increase airway obstructions and baseline $PaCO_2$).

Community-acquired pneumonia

Wijesinghe et al. [37] in a randomized controlled trial had shown that high concentration oxygen therapy administered to 150 patients presenting to an emergency department with suspected community-acquired pneumonia resulted in a significant increase in $PtCO_2$. About 50.0% of patients in the high concentration oxygen group had a rise in $PtCO_2$ ≥4 mm of Hg at 60 minutes compared to 14.7% in the titrated oxygen group (RR 3.4, 95% CI 1.9 to 6.2, p<0.001). Similarly, 15.3% of patients in the high concentration oxygen group had a $PtCO_2$ ≥8 mm of Hg versus 2.7% in the controlled group, (RR 5.7, 95% CI 1.3 to 25.0, p=0.007). Table 1 is showing various studies related to oxygen-induced hypercapnia.

Mechanisms of oxygen-induced hypercapnia

The development of hypercapnia following uncontrolled oxygen therapy is a well-recognised complication in patients with acute exacerbations and stable COPD. [38] It has also been detected in other lung conditions such as asthma, pneumonia, obesity-

hypoventilation syndrome, and neuromuscular diseases. However, it should be remembered that not all patients with COPD develop oxygen-induced hypercapnia, and correction of hypoxemia is equally important, as it has arrhythmogenic potential.

Multiple mechanisms have been proposed to explain the mechanisms of oxygen-induced hypercapnia. These include hypoventilation, increased dead-space ventilation, and the Haldane effect (Figure 1). However, the most plausible theory is the worsened ventilation-perfusion mismatch [39]. The response to high-flow oxygen in a healthy individual is different compared to patients with chronic respiratory diseases. Administration of high-flow oxygen increases V_E and decreases end-tidal carbon dioxide concentration. Becker et al. [40] had shown that breathing oxygen-enriched air in an isocapnic situation increases the V_E in a dose-dependent manner in healthy individuals. When the end-tidal $PaCO_2$ was not controlled, hyperoxia increases V_E by 16% and decreases both the end-tidal PCO_2 and $PaCO_2$.

Blunted hypoxic ventilatory response

The conventional hypothesis is the hyperoxia-induced abolition of the hypoxic drive leading to diminished V_E and a subsequent rise in $PaCO_2$. Campbell in 1960 first proposed the hypoxic drive hypothesis in chronically hypercapnic COPD patients [20]. According to this hypothesis, COPD patients with chronic hypercapnia depend primarily on the hypoxic respiratory drive to breathe as the hypercapnic respiratory drive is depressed. It may be explained by either mechanical limitations imposed by the disease process itself (called "can't breathe") or by reduced sensitivity of the respiratory centers to the carbon dioxide stimulus (termed "won't breathe") [41]. The blunted response to carbon dioxide stimulus can be due to the metabolic adaptations to chronic hypercapnia. Goldring et al. [42] showed that the increased bicarbonate pool for a given change in $PaCO_2$ provides a mechanism for the observed alterations in respiratory responsiveness. A high bicarbonate level may result in an increased buffering capacity around the respiratory centers, and subsequently, a reduced hydrogen ion concentration in the vicinity of the respiratory center, resulting in a reduced ventilatory response to carbon dioxide. Therefore, overzealous oxygen therapy in these patients by blunting the hypoxic drive will cause alveolar

hypoventilation, resulting increase in $PaCO_2$ level. Moreover, there may be a role of genetics in determining individual susceptibility to carbon dioxide retention which needs to be studied [43].

Although hypercapnia may occur secondary to worsening respiratory failure, oxygen therapy is responsible for the highest level of $PaCO_2$. Respiratory failure per se cannot explain a $PaCO_2$ level above 100 mm of Hg [5,9]. Following abolition of hypoxic drive and subsequent alveolar hypoventilation, hypercapnia occurs via the following two mechanisms. First, hypoventilation-induced hypercapnia does not stimulate ventilation. Moreover, loss of pulmonary HVC by oxygen therapy further leads to ventilation/perfusion mismatch and a rise in $PaCO_2$ level [44]. Rudolf et al. [44] also suggested that even with ventilation/perfusion mismatch, it is imperative to have a loss of carbon dioxide sensitivity. However, the "blunted hypoxic drive" theory has been disapproved later on as the sole cause of oxygen-induced hypercapnia by subsequent studies [45,46]. In a prospective study involving 20 patients with COPD in acute respiratory failure (mean PaO_2 of 37.6 mmHg and a mean $PaCO_2$ of 61 mmHg at baseline) and 11 normal controls, Aubier et al. [45] administered supplemental oxygen at 5 L/min for 30 minutes and measured the arterial blood gas (ABG) before and at the end of oxygen supplementation. They demonstrated a rise in $PaCO_2$ from 61 mm Hg to 68 mm Hg, with a mean increase of 10 mmHg. The fall in V_E was not due to a change in tidal volume, but due to a small decrease in respiratory rate. The respiratory drive (P0.1) was significantly elevated while breathing room air with a mean of 8.3 cm of H_2O compared to 1.7 cm of H_2O in normal controls. Although the central drive was decreased in COPD patients, it is still higher than in normal controls. After recovery, the P0.1 of COPD patients while breathing room air and controls were 3.9 ± 0.4 cm of H_20 and 1.7 ± 0.2 cm of H_20 respectively. The decrease in respiratory drive translated into a 14% decrease in V_E, comprised a reduced respiratory frequency but a preserved tidal volume. The authors noted that the overall magnitude of change in minute ventilation was insufficient to explain the observed rise in $PaCO_2$. This study indicates that the oxygen-induced hypercapnia in COPD is not predominantly due to hypoventilation. Aubier et al. [46] in the second study examined the effects of breathing 100% oxygen for 15 minutes on V_E and ABG in 22 COPD patients during acute respiratory failure. They measured the $PaCO_2$

response to oxygen, respiratory frequency, tidal volume, minute ventilation, and V_D/V_T ratios. Initially, a transient decrease in V_E (mean fall of 18 ± 2%) occurred in all patients, and the nadir developed between 20 and 180 seconds (mean, 71 ± 9 seconds) from the onset of oxygen inhalation. Subsequently, the V_E slowly increased and reached 93% of the baseline after about 12 minutes of oxygen inhalation. The increase in $PaCO_2$ was on an average of 23 mm of Hg after 15 minutes of oxygen inhalation. Although the V_E decreased transiently, it was inadequate to explain the 35% rise in $PaCO_2$. The decreased V_E could explain ~5 mm of Hg of the total observed rise in $PaCO_2$, indicating that other factors may be responsible for hypercapnia. However, the authors noted a significant rise in V_D/V_T ratio and this was likely to be the most important mechanism of hypercapnia. The increased V_D/V_T ratio was due to an increased V/Q mismatching within the lungs, possibly due to the reversal of hypoxic vasoconstriction. Rialp et al. [47] had shown that during weaning from mechanical ventilation in normoxic subjects with COPD exacerbation, hyperoxia does not seem to modify significantly the central respiratory drive or the ventilatory response to hypercapnia. Sassoon et al. [48] evaluated the mechanism of hyperoxic-induced hypercapnia in 17 stable patients with moderate-to-severe COPD. They measured the ventilatory and mouth occlusion pressure (P0.i) responses to hypercapnia and hypoxia. They reported a small but significant increase in Ptco2 following high levels of inspired oxygen use in patients with stable COPD. They reported a concomitant decrease in both V_E and carbon dioxide production (VCO_2) clearly refuting the role of reduced V_E in causing hypercapnia. The authors proposed that an increased V_D/V_T component as the primary mechanism of hypercapnia development is responsible for approximately 80% of the changes in $PaCO_2$. There was a correlation between the degree of hyperoxic-induced hypercapnia and the severity of airway obstruction. Therefore, a low FEV_1 appears to be a risk factor in the development of hyperoxic-induced hypercapnia. Since they did not find any effect of oxygen administration on V_T, it explains the role of worsening V/Q mismatch as the mechanism of increased V_D/V_T.

HVC enhances pulmonary gas exchange by reducing venous admixture or physiological shunt. HVC does it by redistribution of blood flow from poorly ventilated to better-ventilated areas. Moreover, it reduces dead space [49]. Oxygen by releasing the HVC in low V/Q areas

diverts perfusion from the well-ventilated areas, resulting in high V/Q areas. Gomersall et al. [50] argued that the absence of hypercapnic drive and dependence on the hypoxic drive will lead to chronic and irreversible hypercapnia. However, two studies had reported reversibility of hypercapnia in acute exacerbation of COPD in 40% to 54% of patients [51,52]. This goes against the abolition of the hypoxic drive theory. Tardif et al. [53] had shown that carbon dioxide drive was a major determinant of respiratory stimulation in many COPD patients with acute respiratory failure. Lee et al. [54] estimated the extent of the reflex hypoxic respiratory drive in a group of patients who were hypoxaemic because of chronic bronchitis. The fractional fall in ventilation depends on the degree of baseline hypoxemia. The most severely hypoxaemic patient (PaO_2 45 mmHg) had a fall in ventilation of 27%, indicating that at least 27% of his resting ventilation resulted from hypoxic stimulation of the peripheral chemoreceptors. At what level of PaO_2 will abolish the hypoxic drive is not clear. However, Dejours reported that the PaO_2 must be raised to a level of 172.5 mmHg before complete abolition of hypoxic respiratory drive occurs [55].

Increased dead-space ventilation

The dead space ventilation contributed to a $PaCO_2$ rise of 11 mm of Hg (48%). HVC is an important defense mechanism that tries to balance the ventilation, and perfusion in poorly ventilated pulmonary regions of COPD patients. Administering of high concentration of oxygen may release HPV in poorly ventilated regions of the lung and subsequently, results in a significant ventilation-perfusion mismatch and an increase in physiological dead-space. [56] Another mechanism of dead space creation is the phenomenon of absorption atelectasis that occurs due to the administration of high concentration oxygen and subsequent alveolar denitrogenation. A high concentration of oxygen facilitates absorption atelectasis of lung units with very low ventilation-perfusion ratios as the oxygen is taken up into the pulmonary circulation faster than it is delivered by the reduced ventilation. [57] Absorption atelectasis can develop at FiO_2 as low as 30–50%.[58] It will cause an increased V/Q mismatch. The worsening of ventilation/perfusion mismatch leading to increased dead space is the major reason for oxygen-induced hypercapnia in COPD patients.

Robinson et al. [8] studied the mechanisms of oxygen-induced hypercapnia in 22 patients during an acute exacerbation of COPD by using the multiple inert gas elimination technique (MIGET). They measured ventilation, cardiac output, and the distribution of ventilation-perfusion ratios during breathing air and then 100% oxygen through a nose mask. The 12 retainers had a rise in $PaCO_2$ level by more than 3 mm of Hg (mean rise of 8.3 mm of Hg) while the 10 non-retainers of carbon dioxide showed a $PaCO_2$ change of an average of −1.3 mmHg while breathing 100% oxygen for at least 20 min. Patients who retained carbon dioxide in response to 100% oxygen showed a significant fall in ventilation of 20% (from 9.0 ± 1.5 to 7.2 ± 1.2 L/min, p=0.007). However, the non-retainers group did not show any change in ventilation (mean 9.8-9.9 liter/min). The retainer group showed a significantly lower PaO_2 at baseline compared to the non-retainer group (54.5 ± 7.5 mm Hg versus 62.7 ± 10.0 mm Hg). The pulmonary blood flow increased significantly in both groups, indicating the release of HVC. However, the log SD ˙V (a measure of the dispersion of ventilation) on 100% oxygen was significantly greater in the retainer group than in the non-retainer group, indicating a rise in alveolar dead space. The alveolar dead space increased by 24% in the carbon dioxide retainer group. One mechanism of a high V/Q ratio is hypercapnia-induced bronchodilatation. [59] Therefore, the major differentiating features between the retainer group and non-retainer group are hypoventilation and an increase in alveolar dead space. Subsequent modeling analysis showed relative contributions to hypercapnia in the retainer group by various mechanisms; 46% due to hypoventilation, 43% by an increase in alveolar dead space, 6% by the Haldane effect and 5% by a change in cardiac output. [60] Hanson et al. [49] in a computer-based study reported that the Haldane effect and abolition of HVC are the main mechanisms responsible for oxygen-induced hypercapnia.

Haldane effect

Haldane and his colleagues described the Haldane effect in 1914 [61]. Haldane effect encompasses the release of carbon dioxide from hemoglobin when deoxyhemoglobin converts to oxyhemoglobin. This is because of the more avid binding affinity of oxygen to

hemoglobin compared to that of carbon dioxide. Therefore, if a hypoxaemic patient is administered oxygen, arterial oxygen will dislodge carbon dioxide from the haemoglobin binding site and the PaCO2 will rise. The effect on $PaCO_2$ is usually transient [62]. Haldane effect explained an additional 7 mm of Hg (30 percent) rise in $PaCO_2$ [63]. Oxygen has a greater affinity to bind with hemoglobin than carbon dioxide and displaces carbon dioxide from hemoglobin, thereby increasing the amount of dissolved CO_2 and subsequently $PaCO_2$ [64]. The Haldane effect is most pronounced on the steep part of the oxygen-hemoglobin dissociation curve and a PaO_2 of 20 and 60 mm of Hg [65].

Higher density of oxygen

Johnson et al. [66] evaluated the effect of high FiO_2 on forced expiratory flow in individuals with 18 patients with moderately severe COPD. In a randomized double-blind study, they compared patients breathing air, 100% oxygen, or a four-gas mixture (oxygen 21.0%, argon 48.6%, nitrogen 19.3%, and helium 11.1%). Patients breathing oxygen had an FEV_1 reduction of 4.9% at 1 minute and 6.3% at 5 minutes. They concluded that the high density and viscosity of oxygen relative to air reduced the FEV_1 in patients with airflow obstruction. Among the various mechanisms of oxygen-induced hypercapnia, abolition of the hypoxic pulmonary vasoconstriction is responsible for the largest increase of oxygen-induced hypercapnia [67].

Clinical features

Carbon dioxide narcosis usually develops gradually; however, few patients may progress to coma within a few minutes of the administration of oxygen [19]. The neurological effects of carbon dioxide are protean. Patients may develop asterixis, which is characterized by the inability to maintain sustained posture with subsequent brief, shock-like, involuntary movements [68]. Asterixis is negative myoclonus characterized by muscular inhibition. Other neurological effects include confusion, mania, headache, sweating, muscle twitching, raised intracranial pressure, papilloedema, and drowsiness to a profound coma. Carbon dioxide, by causing cerebral vasodilatation may raise the intracranial pressure and leads to the development of headache and papilloedema [19]. The risk of oxygen-induced

hypercapnia has been reported both in stable patients with COPD and in exacerbation states [69]. However, the risk of hypercapnia is more in patients with AECOPD than in stable condition and in COPD patients with persistent hypercapnia [70,71]. Few patients with COPD develop oxygen-induced hypercapnia rapidly. Campbell in 1967 reported that uncontrolled oxygen therapy in patients with AECOPD caused a 20 mm Hg rise in $PaCO_2$ over 12 hours in 60% of patients and 30% cases, a more than 30 mm Hg rise occurred in one hour and the patients became rapidly unconscious [22]. Bone et al. reported that 26% of acutely ill patients became stuporous while on controlled oxygen therapy and required mechanical ventilation. They also demonstrated that hypoxemia and acidosis are more predictive for "carbon dioxide narcosis" than hypercapnia [72]. Murphy et al. [5] reported that a low concentration of oxygen can also cause hypercapnia, however, high concentration of oxygen has a greater potential to cause carbon dioxide retention. The magnitude of the change in $PaCO_2$ following oxygen therapy is not known. However, patients with prior history of hypercapnia during a previous COPD exacerbation are at greater risk of carbon dioxide narcosis [22,72]. High levels of carbon dioxide may have a deleterious effect on humans by causing depression of neurological and cardiorespiratory function. However, unlike hypoxemia, these effects do not occur quickly [72].

Prognosis of oxygen-induced hypercapnia

The development of oxygen-induced hypercapnia carries a poor prognosis. Plant et al. [9] in a large one-year prospective study involving patients with COPD aged 45–79 years estimated the prevalence of respiratory acidosis and its relationship with oxygenation. Approximately, 46.7% developed hypercapnia, and 20.4% developed respiratory acidosis. Development of acidosis portends a poor risk for subsequent intensive care unit (ICU) admission as the OR was 6.10 (95% CI 1.19 to 31.11) with a pH<7.25, and 8.73 (95% CI 2.11 to 36.06) with a pH of 7.25–7.30. Moreover, more than 50% of hypercapnic patients were acidotic if the PaO2 was greater than 75 mm Hg. Therefore, the higher the concentration of oxygen, the greater would be the carbon dioxide retention and acidosis. On reducing the FiO_2, pH was normalised in the majority of the patients. Joosten et al. [7] in a retrospective analysis of 65 patients admitted with AECOPD showed that a majority of

patients who achieved a PaO_2 of ≥74.5 mmHg had a significantly longer hospital stay (p=0.029), greater use of non-invasive ventilation (NIV) on admission (p=0.0124); and more frequent admission to the high-dependence unit (p=0.0124) compared to those with a PaO_2 <74.5 mmHg. Moreover, 95% of patients who were carbon dioxide retainers had received oxygen at a flow rate greater than 2 L/minute. Controlled oxygen treatment in pre-hospital settings reduces mortality, acidosis, and hypercarbia in patients with acute exacerbation of chronic obstructive pulmonary disease. Austin et al. [73] in a randomized controlled trial conducted on 405 patients with AECOPD in the prehospital setting found that controlled oxygen with a target range of 88–92% (delivered *via* nasal prongs to achieve a SpO_2) compared with high-flow oxygen (delivered via a non-rebreather mask at 8–10 L/min) in patients with AECOPD had a significantly lower risk of death (2% versus 9% respectively). The mortality with controlled oxygen was 78% lower for confirmed COPD patients (RR 0.22, 95% CI 0.05 to 0.91; p=0.04) compared with high-flow oxygen. However, the mortality benefit was obtained only on intention-to-treat analysis and no statistically significant difference in mortality was observed per protocol analysis. Controlled oxygen therapy during AECOPD also caused significantly lower respiratory acidosis (mean difference in pH 0.12; p=0.01) and hypercapnia (mean difference in $PaCO_2$−33.6 mm Hg; p=0.02) compared with high-flow oxygen therapy. The number needed to harm (NNH) with high-flow oxygen therapy in COPD was 14. Therefore, all patients with COPD exacerbation and hypoxemia should only receive titrated oxygen treatment. Controlled oxygen delivery is the correct approach to oxygen therapy in COPD and other chronic lung disease patients who are at high risk of hypercapnic respiratory acidosis. Causes of increased mortality may be due to hypercapnia, hyperoxemia-induced reduced coronary blood flow or myocardial reperfusion injury, rebound hypoxia in case of the abrupt stoppage of oxygen therapy [74]. Echevarria et al. [75] in an observational study of 2645 patients admitted in six United Kingdom hospitals with COPD exacerbation assessed the impact of admission oxygen saturation level and baseline carbon dioxide on inpatient mortality. They reported the lowest in-hospital mortality among patients with admission oxygen saturations between 88 and 92%. The adjusted risk of death in the 97-100% group was 2.97 (95% CI 1.58 to 5.58, p=0.001). with oxygen saturations 97-100%. Patients with normocapnia also showed the

same effect. They recommended that all patients with COPD receiving supplemental oxygen should have an oxygen saturation target of 88-92% independent of the presence of hypercapnia.

Acute oxygen use in hospitalized patients with COPD is often guideline-discordant [76]. Despite all the international guidelines recommending controlled oxygen therapy, over-oxygenation is common during the management of AECOPD. Anderson et al. [77] in a retrospective Australian study examined oxygen use in 111 patients admitted with an exacerbation of COPD and hypercapnia and observed a significantly higher over-oxygenation in non-respiratory ward admissions compared to respiratory ward admissions (76% *vs* 57%, p=0.03). Overall, over-oxygenation was reported in 62% of admission. Wijesinghe et al. [10] had reported that pre-hospital administration of a high concentration of oxygen in patients during AECOPD carries a poor prognosis. An increased oxygen flow had an odds ratio (OR) of 1.2 (95% CI 1.0–1.4) for an increased risk of mortality, requirement of assisted ventilation or respiratory failure for every 1 L/minute oxygen flow. The predictors of poor outcome were home oxygen (OR 2.8, 95% CI 1.5–5.1), previous respiratory failure (OR 2.6, 95% CI 1.5–4.6), previous ventilation (OR 3.2, 95% CI 1.7–5.9) and home nebulizer use (OR 2.4, 95% CI 1.4–4.3).

Oxygen therapy in patients with chronic lung diseases

Use of oxygen supplementation in high concentration is a well-established risk of hypercapnia in patients with COPD during stable and acute exacerbation [9,21,44,78], and patients with other conditions who are at risk for developing hypercapnia (e.g., obesity hypoventilation syndrome [28], bronchiectasis, cystic fibrosis [79], neuromuscular disease, asthma, and chest wall deformities such as severe kyphoscoliosis) [13]. Major international guidelines have recommended controlled oxygen therapy for the management of hypoxemia during AECOPD [80-82]. The concept of controlled oxygen therapy was first introduced by Barach. He suggested that hypoxemic patients should be exposed to gradually increasing concentration of continuous oxygen therapy, otherwise the patients may become stuporous [15]. Beasley et al. [13] suggested that controlled oxygen delivery is the delivery of 0.5–2.0 L/min oxygen and is indicated for hypoxemia in patients with

exacerbations. International guidelines recommend that patients with COPD or other diseases at risk for hypercapnic respiratory failures such as morbid obesity, cystic fibrosis, chest wall deformities or neuromuscular disorders, or fixed airflow obstruction associated with bronchiectasis, should target a saturation goal ranging between 88% and 92% [2,13]. This goal should be achieved with a controlled oxygen delivery system. However, in acutely ill patients not at risk of hypercapnic respiratory failure, a higher target saturation of 94–98% should be considered [2]. Austin et al. [73] in a randomized controlled trial first confirmed the benefit of controlled oxygen therapy. Patients on controlled oxygen had a significantly lower risk of hypercapnia and a 78% reduction in risk of mortality compared with high concentration oxygen therapy.

The recommended delivery of controlled oxygen is via a Venturi mask or nasal cannulae. The ABG should be checked within 60 minutes of initiating oxygen therapy and a change in FiO_2. The FiO_2 subsequently should be increased only if the effect of pH is modest [83]. Automated oxygen delivery system may also have a potential role in patients with acute respiratory failure as it helps in controlled oxygen delivery [84]. Agusti et al. [85] in a small randomized crossover study involving 18 hospitalised COPD patients with acute respiratory failure demonstrated improvement of oxygen tension by venturi masks and nasal prongs to the same extent, without any significant effect upon hypercarbia. Moreover, nasal prongs were significantly associated with a longer time of SpO_2<90% over a 24 hours compared to the venturi mask (5.4 *vs* 3.7 hours over a 24 hours). Therefore, venturi mask is preferable in the management of COPD with acute respiratory failure.

Before starting oxygen therapy in chronic lung disease patients, an assessment of the risk of hypercapnic respiratory failure should be done. Following conditions are associated with an increased risk of developing hypercapnic respiratory failure; moderate-to-severe COPD (especially with previous respiratory failure or on long-term oxygen therapy), asthma, severe obesity, obesity-hypoventilation syndrome, neuro-muscular disease, severe chest wall or spinal disease (e.g. Kyphoscoliosis), cystic fibrosis, bronchiectasis or previously unrecognized COPD. [2] Patients with risk of hypercapnic respiratory failure should be advised controlled oxygen therapy with a target saturation of 88 to 92%. The initial oxygen level should be 24% or 28% venture masks or 1-2 Liters/minute *via* nasal cannula. If patients

develop respiratory acidosis and hypercapnia, consider NIV support or ICU admission. Figure 2 is showing flowchart of oxygen administration in patients with COPD and other chronic diseases with risk of hypercapnia.

Controlled oxygen *versus* intermittent oxygen

In the early 1960s, there was a debate on the two modes of oxygen delivery systems in COPD patients with hypercapnia: intermittent and continuous with a gradual increase in FiO_2. Few authors suggested that intermittent oxygen delivery will reduce the risk of alveolar hypoventilation and at the same time, will increase the partial pressure of oxygen in the blood [86,87]. Cohn et al. [86] suggested that a FiO_2 of 40% was adequate and safe concentration to administer oxygen and it should be administered intermittently with at least hourly oxygen-free environment. Massaro et al. [24] studied the effects of two oxygen delivery methods (continuous with graded increase and intermittent) in patients with COPD and hypercapnia and demonstrated that intermittent oxygen therapy resulted in more pronounced hypoxemia without any benefit on blood carbon dioxide levels. Campbell in 1965 also suggested a controlled approach of hypoxemia initiating with a FiO_2 of 24.5% or 28% [88]. Therefore, controlled oxygen should be used in patients with chronic respiratory diseases and who are at risk of developing hypercapnia in order to ensure the correction of the dangerous level of hypoxia while minimizing the risk of hypercapnia. Liberal oxygen therapy may lead to the development or worsening of existing hypercapnia and portend a poor prognosis. Prompt and appropriate treatment for hypercapnia is required as it may ensure correction of even extreme levels of hypercapnia as high as 31.05 kPa (232.89 mm of Hg) [89]. Despite all the guidelines, uncontrolled oxygen therapy is not infrequent, especially in pre-hospital settings. Ringbaek et al. [90] in a retrospective study analysed the impact of uncontrolled oxygen therapy in the pre-hospital settings involving 405 consecutive patients with AECOPD. Approximately 88.7% of patients had received inappropriate high-dose oxygen therapy in the ambulance. The Thoracic Society of Australia and New Zealand oxygen guideline for acute oxygen use in adults recommends a SpO_2 target of 88 to 92% in exacerbations of COPD and other conditions associated with chronic respiratory failure (such as obesity hypoventilation syndrome, bronchiectasis, cystic fibrosis,

neuromuscular disease and chest wall deformities such as severe kyphoscoliosis) [13]. Strict monitoring is also required. [91] Hypoxemic patients at risk of hypercapnia should be considered for ABG measurement. Initially, controlled oxygen should be administered via nasal cannula at 1 to 2 L/min or Venturi mask at 2 to 4 L/mi (FiO_2 24% or 28%). Oxygen-driven nebulization should be avoided and air-driven nebuliser or metered dose inhalation should be used. The ABG should be monitored to detect hypercapnia. Consider non-invasive ventilation (NIV) or invasive ventilation support if patients become acidosis (pH <7.35) and hypercapnic ($PaCO_2$>45 mm Hg). However, for the fear of aggravating hypercapnia by the oxygen therapy, we should not show laxity in hypoxemia management. The clinician should always focus on the patient's PaO_2 rather than $PaCO_2$ level [92] as improper management of hypoxemia can pose danger to patients' life, although it should be done in a controlled way. Other management options such as bronchodilators, secretions clearance and ventilatory support should also be focused upon. The exact levels of hypoxemia and hypercapnia that can cause clinical harm is unclear. Murphy et al. [5] published that a PaO_2 of less than 50 mm of Hg and $PaCO_2$ of greater than 80 mm of Hg is likely to be harmful. The $PaCO_2$ danger level of greater than 80 mm of Hg rarely occurs in COPD while breathing room air and always occurs as a consequence of oxygen therapy [93,94]. Chu et al. [95] in the Oxygen Therapy in Acute-illness (IOTA) systematic review and meta-analysis pooled the results of 25 RCTs compared conservative vs. liberal oxygen strategy in 16,037 acutely ill adult patients 25 randomized controlled trials enrolled 16 037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, cardiac arrest, and patients who had emergency surgery reported a significantly higher in-hospital mortality of patients receiving the liberal oxygen strategy (RR 1.21 [95% CI 1.03–1.43], I2= 0%, high quality),at 30 days and at longest follow-up. They also suggested a "safe" upper-limit of SpO2 between 94 and 96%. Allardet-Servent et al. [96] proposed that oxygen therapy should be started when SpO2 falls below 89% in patients at risk of oxygen-induced hypercapnia or below 93% for other patients. Similarly, in patients with the risk of oxygen-induced hypercapnia, the upper limit of SpO2 should be 92% and for other categories of patients, it should be 96%. The Global Strategy for Prevention, Diagnosis and Management of COPD (GOLD) guideline similarly suggested a target saturation goal of 88-92%. After

initiation of oxygen therapy, ABG should be performed frequently to ensure satisfactory oxygenation without carbon dioxide retention and/or worsening acidosis. If $PaCO_2$ becomes ≥45 mm of Hg with a pH ≤7.35, NIV support should be initiated [12]. Figure 2 is showing flowchart of oxygen administration in patients with COPD and other chronic diseases with risk of hypercapnia.

Nebulization in COPD

Air-driven nebulization is preferable in patients with AECOPD as oxygen-driven nebulization may lead to an increase in PtCO2 in exacerbations of COPD. Bardsley et al. [97] in a randomised controlled trial compared nebulization of salbutamol 2.5 mg delivered by air or oxygen at 8 Liters/minute and demonstrated a significantly higher mean (standard deviation) change in $PtCO_2$ at 35 min was 3.4 (1.9) mm of Hg and 0.1 (1.4) mm of Hg in the oxygen and air groups respectively [difference and 95% CI; 3.3 mmHg (2.7 to 3.9), $p<0.001$]. Overall, 40% of patients in the oxygen-driven groups had a $PtCO_2$ change ≥4 mmHg compared to none in the air-driven nebulization groups.

Oxygen alert cards

Oxygen alert cards should be given to patients who are at risk of hypercapnic respiratory failure. The oxygen alert cards may facilitate controlled oxygen therapy by the treating clinicians and paramedics, particularly in the ambulance and emergency [98].

Non-invasive ventilatory (NIV) support

Bi-level NIV may be used for patients with acute respiratory failure to improve the acute and acute-on-chronic respiratory acidosis (pH ⩽7.35)including oxygen-induced hypercapnia in patients with chronic respiratory diseases [99]. NIV reduces the likelihood of mortality and endotracheal intubation in patients admitted with acute hypercapnic respiratory failure secondary to an AECOPD [100]. The European Respiratory Society (ERS) Task Force suggests that in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, long-term home non-invasive ventilation should be advised if hypercapnia persists following the episode [101]. NIV is

also an important and effective modality in patients with neuromuscular diseases and it should be used early in the course of respiratory muscle involvement in NMD patients (FVC <80% of predicted values in the presence of symptoms of respiratory impairment). It has positive impact on health-related quality of life and survival [102].

High flow nasal cannula (HFNC)

It delivers warmed and humidified oxygen at a flow rate of 30-60 L/min or more. The physiological effects of HFNC include flushing of anatomical dead space due to high gas flow, generation of positive airway pressure and a subsequent rise in functional residual capacity, improvement in alveolar recruitment, and enhanced mucociliary transport [103]. In a randomized controlled trial involving COPD patients with acute compensated hypercapnic respiratory failure, Li et al. randomized 320 patients to either the HFNC group (n=160) or the conventional oxygen therapy (COT) group (=160) and reported a significantly lower treatment failure during hospitalization in the HFNC group compared to the COT group (p=0.026). They also reported a significantly lower PaCO2 level 24 hours after recruitment in the HFNC group compared to the COT group (54.1 ± 9.79 mmHg *vs* 56.9 ± 10.1 mmHg, p=0.030) [104]. However, due to the lack of a well-designed, prospective, randomized and controlled multicenter trial and a medium-high risk of bias in existing studies, HFNO therapy can be administered in patients who cannot tolerate noninvasive mechanical ventilation [12,105].

Rebound hypoxemia

Although uncontrolled oxygen administration may lead to worsening hypercapnia, abrupt removal of high concentration oxygen in COPD may be detrimental as it may produce life-threatening hypoxemia which is more severe than the pre-oxygenated baseline level [2,20,106]. The fall in arterial PaO_2 may be precipitous and even may cause death though the $PaCO_2$ is stable or improving [107]. Therefore, oxygen therapy should be stepped down gradually [106].

Figure 2 is showing the alveolar gas equation.

$PAO_2 = FiO_2 (PB – PH_2O) – (PaCO_2 \div RQ)$

PAO_2 = Alveolar partial pressure of oxygen

FiO_2 = Fraction of inspired oxygen

PB = Barometric pressure

PH_2O= water vapour pressure

$PaCO_2$= Arterial partial pressure of carbon dioxide

RQ=Respiratory quotient

The high partial pressure of carbon dioxide within the alveoli competes with oxygen for space and a fall in oxygen level due to sudden stoppage of oxygen will cause further reduction in partial pressure of oxygen within the alveoli and subsequently within the arterial system. Therefore, in patients with oxygen-associated hypercapnia, oxygen should not be abruptly withdrawn but in a controlled gradual manner [100].

Conclusion

Controlled oxygen therapy has several beneficial effects in patients with COPD and other chronic lung diseases who are at high risk of hypercapnia. Controlled oxygen therapy reduces mortality, risk of hypercapnia, and risk of severe acidosis. The conventional theory that explains the development of oxygen-induced hypercapnia is the blunting of hypoxic drive. However, several studies had argued against the hypothesis. Evidences are now supporting that the increase in dead space due to oxygen-mediated removal of hypoxic pulmonary vasoconstriction and absorpsion atelectasis is responsible for a largest increase of oxygen-induced hypercapnia. Therefore, a controlled oxygen therapy targeting saturations of 88% to 92% is the safest way to correct hypoxemia and prevent hypercapnia in patients at risk of oxygen-induced hypercapnia.

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Figure 1. Mechanism of oxygen-induced hypercapnia.

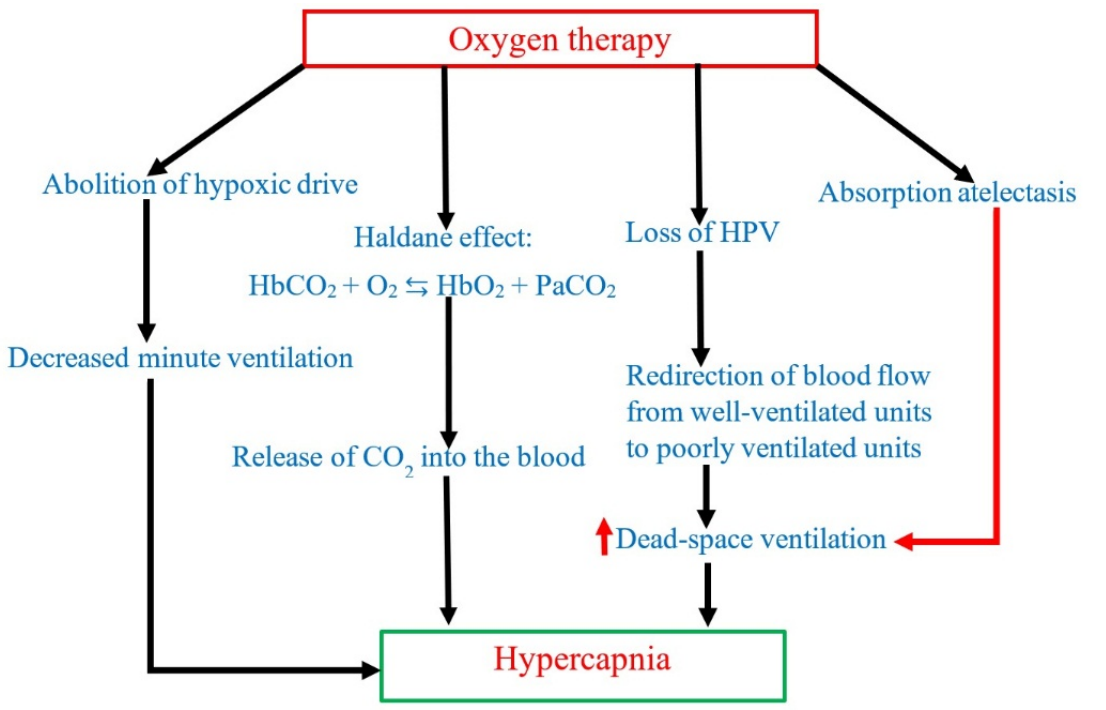

Figure 2. Flowchart of oxygen administration in patients with COPD and other chronic diseases with risk of hypercapnia.