Short Communication

Happy Hypoxia and Conscious Prone Position Ventilation

Ethiya N[1], Kalpana Rani U[2], Nalini S[3]

[1] Professor, Department of Physiology, Government Theni Medical College, Theni, [2]Assistant Professor, Department of Physiology, Government Theni Medical College, Theni, [3]Associate Professor, Department of Physiology, Government Theni Medical College, Theni

Abstract

The traditional supine position suggested to patients lying in hospital beds has long been known to be detrimental to their underlying pulmonary function. Many asthmatic/COPD patients adopt leaning forward in sitting position than recline or supine positions. We were taught and we teach students to put patients with hypotension in trendlenberg position or to elevate foot end. Many of us are not aware that prone positioning improves both respiratory and cardiac functions significantly to the extent of saving lives. In the ongoing pandemic of COVID-19, 15% develop respiratory symptoms, 2-4% develop Hypocapnic Hypoxia, lethal Hypoxia without dyspnoea known as Happy Hypoxia/Silent Hypoxia, 6% develop Adult Respiratory Distress Syndrome (ARDS)and>3% die as even mechanical ventilation fail to rescue these patients. Understanding pathophysiology to pick up patients who may need medical careearly and finding treatment modalities that will reduce sudden deaths due to Happy Hypoxia, ICU care & Ventilator usage becomes paramount important and knowledge on these needs to be spread far &wide. Prone position ventilation has been proved to be advantageous to the extent of bringing down mortality. Conscious ventilation with high FiO_2beingactive ventilation with respiratory muscles functioning leads to production of CO_2 that maintains the sensitivity of carotid body chemo receptors to hypoxia. Pathophysiology of Happy Hypoxia &physiological factors that facilitate respiration and improve cardiac function when patient is nursed in prone position are discussed in this article.

Key words: ARDS, COVID-19, Happy Hypoxia, Prone position ventilation,

Corresponding Author
Dr S Nalini, Associate Professor, Department of Physiology, Government Theni Medical College, Theni Mobile No: 7667140494; E mail: nalini.santhalingam@gmail.com

Introduction

We are aware of the fact that ventilation & perfusion in the upright position declines in a linear fashion from the bases to the apices of the lungsresulting in abnormal V_A/Q of 2.5 times of ideal value at the top & 0.6 in the bottom of lungs resulting in physiological dead space and physiologic shunt respectively and Foot end elevation &trendlenberg position improves venous return, all due to the effect of gravity[1,2]. But we know little about the physiological effects&advantages of prone position & reverse trendlenberg position on V_A/Q and venous return.

As early as 1960s, when the knowledge base for Adult Respiratory Distress Syndrome consisted of descriptive case series, the need for effective therapies was readily apparent. Early investigators noted reduced pulmonary compliance and increased atelectasis that characterize the disease and suggested applying positive end-expiratory pressure (PEEP) to improve oxygenation. To reduce further atelectasis in injured lungs, Bryan proposed prone positioning, theorizing that prone positioning would reduce pleural pressure gradients and restore aeration to dorsal lung segments. Clinical case series supported this concept, documenting significant improvement in oxygenation with prone positioning.

The recent COVID-19 pandemic has seen the critical care community treating increasing number of patients with ARDS over recent weeks, with one Chinese study reporting the prevalence of hypoxic respiratory failure in these patients at around 19%. Approximately 5% of all COVID-19 patients will require mechanical ventilation on an intensive care unit, with a further 14% requiring oxygen therapy[3].

Internationally, observations of critical care clinicians treating these patients in critical care have reported that patients with moderate to severe ARDS appear to have responded well to invasive ventilation in the prone position, leading to prone ventilation being recommended in international guidelines for the management of COVID-19[4]. This corroborates well with the findings of a recent meta-analysis, a Cochrane Systematic review and randomised controlled trial on 466 patients with severe ARDS all of which support the early application of prone ventilation for at least 16 hours a day in patients with moderate to severe ARDS in improving oxygenation and reducing mortality when compared with conventional supine ventilation[5].

Given the improvement in mechanically ventilated patients,it has been postulated that adopting the prone position for conscious COVID-19 patients requiring basic respiratory support, may also benefit them in terms of improving oxygenation, reducing the need for invasive ventilation and potentially even reducing mortality. Conscious ventilation increases pCO_2due to active work of breathing and is advantageous in Happy Hypoxia or Silent hypoxia(severe hypoxemia without dyspnea).It ishypocapnic hypoxia;the alveolar pCO_2 is at lower than normal values though there is Hypoxemia.This is because diffusion of $CO_2$is 20 times that of O_2andanatomical dead space is minimal.The normal responseto hypoxemia is to increase minute ventilation, primarilyby increasing the tidal volume (up to 15–20 ml/kg), which is associated with a more negative intrathoracic inspiratory pressure. The near normal compliance in some of these patients, however, explains why they (2-4 out of 15% symptomatic COVID-19) present without dyspneaas they are able to inhale the volume they expect. This increase in minute ventilation leads to a decrease in $paCO_2$[7]. Work of breathing isinfluenced by Dead space, Lung compliance & Airway resistance and most strongly affected by the drive to clear CO_2. Hence these patients don't feel difficulty in breathing or are not dyspneicas work of breathing is not much increased and fail to seek treatment early, collapsing within a few hours when pO_2 falls below 50mmHg depressing CNS.

Happy Hypoxemia

This may result from any lung disease which causes a limited amount of shunt, while preserving the remainder of the lung (e.g., lobar consolidation or atelectasis).[9]

It occurs in COVID-19 patients in early phase of lung involvement when the patient is in L (Low elastance) phenotype of respiratory pathology or early in the disease process.The reasons have beenhypothesized based on detailed observation of several cases anddiscussions with his colleagues treating COVID-19 patients[7]. These patients have

1. Low elastance (Normal &high compliance).
2. Low ventilation-to-perfusion Ratio signifying right to left shunt as degree ofhypoxic vasoconstriction regulating perfusion when there is alveolar hypoxia varies with individuals and it is less in these patients developing Silent Ischemia.
3. Low lung weight – with no or with minimal lung edemaand
4. Low alveolar recruitability on Positive End Expiratory Pressure (PEEP) ventilation& Continuous Positive Alveolar Pressure (CPAP) ventilation meaning atelectatic or collapsed alveoli are less.

Happy Hypoxemia is Lethal

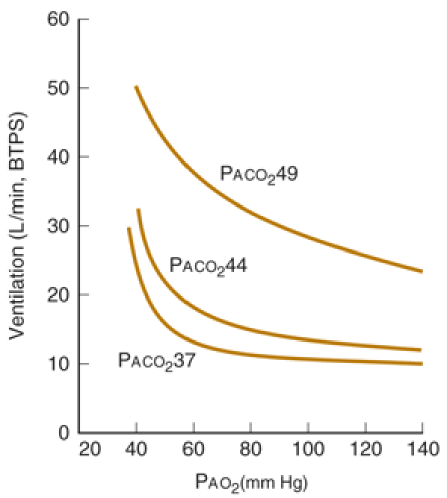
The L Type patients may remain unchanging for a period and then improve or worsen[7]. The possible key featurewhich determines the evolution of the disease, other than the severity of the disease itself, is the depth of the negative intrathoracic pressure associated with the increased tidal volume in spontaneous breathing. Indeed, the combination of a negative inspiratory intrathoracic pressure and increased lung permeability due to inflammationresults in interstitial lung edema. This phenomenon, initially described by Barach and Mascheroni in an experimental setting, has been recently recognized as the leading cause of Patient Self-Inflicted Lung Injury (P-SILI). Over time, the increased edema increases lung weight, superimposed pressureand dependent atelectasis; when lung edema reaches a certain magnitude the gas volume in the lung decreasesand the tidal volumes generated for a given inspiratory pressure decrease. At this stage, dyspnea developswhich in turn leads to worsening P-SILI. The transition from Type L to Type H (High Compliance) may be due to the evolution ofthe COVID-19 pneumonia on one hand and the injury attributable to high-stress ventilation on the other.

Any decline in arterial pO_2 below 100 mm Hg produces increased discharge in the nerves from the carotid and aortic chemoreceptors. Recent evidence indicates that additional chemoreceptors are located in the vicinity of the solitary tract nuclei, the locus ceruleus, and the hypothalamus[1].The stimulation by peripheral chemo receptors is slight when the pO_2 of the inspired air is more than 60 mm Hg and marked stimulation of respiration occurs only at lower pO_2 values (Figure 1). The stimulatory effects of hypoxia on ventilation are not clearly manifest until they become strong enough to override the counterbalancing inhibitory effects of a decline in arterial H^+ concentration and pCO_2[1].

When the alveolar pCO_2 is stabilized at a level 2 to 3 mm Hg above normal, there is an inverse relationship between ventilation and the alveolar pO_2 even in the 90 to 110 mm Hg range; but when the alveolar pCO_2 is fixed at lower than normal values, there is no stimulation of ventilation by hypoxia until the alveolar pO_2 falls below 60 mm Hg[1]and there is no stimulation of ventilation due to central mechanism too as central chemoreceptor response to hypoxia actually depresses ventilation, presumably by depressing oxidative metabolism in neural tissue[6] and central stimulation by pCO_2also is lost as it is lower than normal.This worsens patient's condition and may lead to sudden unwarranted death.Thus, conscious ventilation /Active breathingby increasing CO_2 levelmay aid in respiratory support when treating COVID-19 patients in addition to mitigating the problem of disuse atrophy of respiratory musclesfacilitating early weaning from assisted ventilation/mechanical ventilation if the patient worsens to H type.[6]

Figure: 1

Ventilation at various alveolar pO_2 values when pCO_2 is held constant at 49, 44 or 37 mm Hg



The Mystery of Sudden Death in Happy Hypoxia

Sudden death in ambulant COVID-19 patients with Happy Hypoxia may be due to following causes apart from extreme Hypoxia that depresses respiratory centers to the extent of not responding to stimulation by peripheral Chemo receptors

1. Pulmonary Embolism, Arrhythmias & massive MI[10].A research article published on 25th March 2020 in *JAMA Cardiology* documented heart damage in nearly 20% of patients out of 416 hospitalized for COVID-19 in Wuhan, China.
2. Up to 10% of COVID-19 patients suffer CNS symptoms including hyposmia, headaches, weakness, altered consciousness, Encephalitis with seizures and with a 'Sympathetic Storm' a hyper reaction of sympathetic system that causes seizure like symptoms, demyelination, neuropathy, and stroke suggests invasion and / or depression of the medullary cardio respiratory center that may contribute to the refractory respiratory failure too observed in critically-ill COVID-19 patients.[10,11]

'Cytokine Storm Syndrome' may directly or indirectly be responsible for the above conditions ,as a study done in Wuhan has found higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF-α in those who needed ICU care compared to those who were symptomatic but could be managed in non ICU ward[12].

Benefits of Prone Positioning

Physiologically, prone positioning when applied to all patients regardless of whether they are intubated or not will provide following potential benefits:

- Improved V_A/Q matching and reduced hypoxemia
- Reduced shunt
- Recruitment of the posterior lung segments due to reversal of atelectasis
- Improved secretion clearance
- Reduction in Ventilation Induced Lung Injury (VILI)
- Facilitation of venous return & easing of right ventricle function by reducing after load

In a multi-center prospective randomized controlled trial[4] done in patients with severe ARDS enrolled12-24 h after the onset of ARDS, the day 28 mortality in the supine group was 32.8%versus 16% in the prone group.

Prone Positioning and Gas Exchange

When a person is supine, the weight of the ventral lungs, heart, and abdominal viscera increase dorsal pleural pressure. This compression reduces transpulmonary pressure in the dorsal lung regions. The increased mass of the edematous ARDS lung further increases the ventral-dorsal pleural pressure gradient and reduces regional ventilation of dependent dorsal regions. The ventral heart is estimated to contribute approximately an additional 3 to 5 cm H_2O of pressure to the underlying lung tissue, with experimental studies showing improved ventilation of these infra cardiac lung regions in a prone position. In addition to the weight of the heart, intra-abdominalpressure is preferentially transmitted through the (often paralyzed and relaxed) diaphragm, further compressing dorsal regions. Although these factors tend to collapse dependent dorsal regions, the gravitational gradient in vascular pressures preferentially perfuse these regions, yielding a region of low ventilation and high perfusion, manifesting clinically as hypoxemia.

Figure 2illustrates the gravitational and geometric factors contributing to more uniform pulmonary aeration in the prone position.

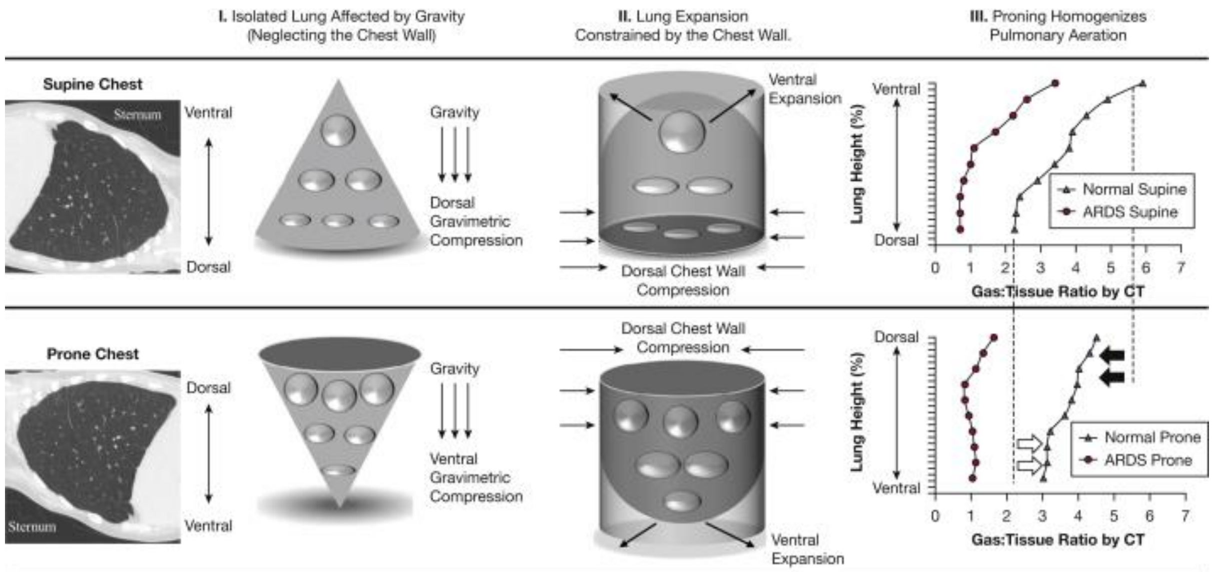


Figure 2:

Column I show an isolated lung (cone) and alveolar units (circles) removed from the chest wall. This illustrates how the unhindered lung contains more alveolar units in the dorsal regions than in the ventral regions. Column II illustrates the effects of compressing the native conical shape of the lungs into the rigid chest wall. While the patient is supine, the compressive effects of gravity are magnified by the chest wall, further compressing the dorsal segments while expanding the ventral segments. Conversely, when the patient is prone, the chest wall effects oppose gravimetric effects, leading to more homogeneous aeration. Column III displays experimental data supporting this model. The curves describe how pulmonary aeration (gas to tissue ratio on CT) varies as one move along the lung's vertical axis in human patients with ARDS. Note the marked asymmetry in aeration (and thus ventilation) along the ventral/dorsal axis when supine and a much more uniform gas to tissue ratio when prone. The white arrows signify recruitment of dependent regions, and the black arrows signify reduced regional hyperinflation in well-aerated lung.

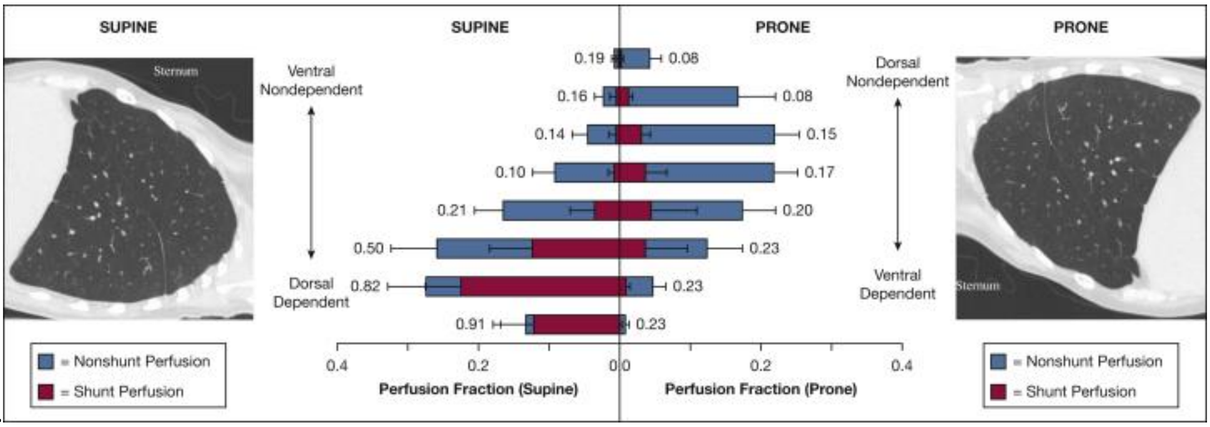


Figure 3:

In a sheep model, pulmonary perfusion along a lung-height axis is displayed for both the supine (left side of graph) and prone (right side) positions. The total length of each of the eight bars along the x-axis represents the relative perfusion of each of the eight stacked coronal planes. The red shading within each bar represents the fraction of perfusion that is shunt perfusion, whereas the blue colouring is the nonshunt perfusion. The number adjacent to the bar is the precise value of the shunt fraction for that plane. For example, in the supine position, the most dorsal (dependent) plane receives approximately 13% of total perfusion (x-intercept) and of that perfusion, 91% of it is shunt perfusion. Note that prone positioning does not significantly change the distribution of perfusion but it does markedly reduce the total shunt fraction.

Unlike its effects on dorsal lung aeration, the prone position does not have a major impact on regional distribution of pulmonary blood flow. In both the supine and prone positions, pulmonary blood flow is directed dorsally in normal and injured lungs (Fig 2). Thus, regional perfusion distribution is dictated in large part by non-gravitational factors like lung/heart geometry, airspace compression of vessels, reduction in the dorsal region's hypoxic vasoconstriction, and so on. With perfusion patterns relatively constant, and a marked improvement in ventilatory homogeneity in the prone position, the shunt fraction would be expected to fall substantially on placing the person in a prone position. Many animal and human studies confirm this hypothesis; on average, in a prone position, the relative shunt fraction in injured lungs is reduced by about 30%.Thus, in most patients, decreased shunting when in the prone position leads to clinically significant improvements in oxygenation

Lung Protection

The prone position generally improves oxygenation, but its ability to attenuate mechanical lung injury may be more important mechanism of clinical benefit.Comparing the supine and prone aeration curves in Figure 2, column III, suggests a mechanism. First, note how the prone position improves dependent aeration, effectively recruiting parenchyma (white arrows). Second, the nondependent lung regions show dramatic reduction in hyperinflation with the prone position (black arrows). The net effect is more homogenous lung aeration, which reduces regional shear strain, leading to less VILI.

In ARDS, increased PEEP is known to prevent alveolar derecruitment but may deleteriously promote over distension of previously well-ventilated alveoli. The prone position may help mitigate these deleterious effects of PEEP.Adding prone positioning to high-PEEP ventilation

(1) Increases lung aeration

(2) Reduces regional hyperinflation

(3) Decreasessmall airway opening/closing events during the respiratory cycle decreasing barotrauma and atelectrauma and thereby protect against Ventilator Induced Lung Injury. In humans both serum and broncho-alveolar lavage inflammatory markers are reduced by prone positioning, which may reflect less VILI.

(4) Reduces infectious complications: While prone, gravity can assist secretion drainage along the general dorsal lung to ventral trachea drainage vector. This enhanced drainage may explain observations that a prone position (1) improves secretion clearance, (2) causes opacities to migrate ventrally on imaging while improving overall aeration, and (3) may decrease rates of ventilator-associated pneumonia.

On Extra pulmonary Organ Systems

In addition to its lung-protective effects, a prone position impacts cardiac and abdominal pressures. In general, total cardiac output is unchanged when patients with ARDS are placed in a prone position. However, while prone, the right atrium moves ventrally so that venous return is now aided by gravity. Thus, preload responsive patients like those suffering from hypovolemia hypotension may augment their cardiac output by being placed in a prone position. Additionally, right ventricular afterload typically falls, likely due to relief of hypoxic pulmonary vasoconstriction. This effect may be most clinically relevant in populations with severe ARDS, as the prone position reduces the right ventricular dilatation and septal dysfunction that accompanies this disease.The prone position also affects chest/abdominal interactions.

Disadvantages of Prone Position Ventilation

In obese humans with ARDS, the prone position may worsen intra-abdominal hypertension and lead to subsequent renal and hepatic dysfunction. To mitigate this, intra-abdominal pressure should be monitored while the patient is in a prone position and consider using an air mattress or a suspended abdomen if abdominal pressures become excessive.

Conclusion

Knowing & understanding simple postural / positional changes in health and diseased conditions can be lifesaving if applied in a proper way to the right patients suffering from respiratory, cardiac illnesses, conditions of Hypotension& during anesthesia. COVID-19 has reminded us the advantages of prone position ventilation; though we teach students about the effects of Intra-abdominalpressures on respiration, gravitational effects of ventral lung & Heart on aeration of dorsal/dependent lung alveoli aeration is basic concept that needs to be taught. We are teaching students to place persons suffering from hypotension due to various reasons in lying down position with foot end elevated; with its advantages of better V/Q and venous return we should advocate prone positioning hereafter if there are no injuries that will preclude. Vital Capacity measurement in prone position in addition to sitting & standing position shall be included in I MBBS practical exercises.

Happy hypoxemia has existed forever, but these patients presented only occasionally. COVID-19has forced us to re-think this physiology and calls for teaching recording of SO_2 as a vital sign by using simple technique of Pulse Oximetry and significance of fall in it, which can save thousands of lives.

Acknowledgements: Nil

Conflict of interest: Nil

References

1. Kim E Barrett, Scott Boitano, Susan M Barman, Heddwen L Brooks. Respiratory Physiology; Ganong's review of Medical Physiology; 23rd Ed; P 603.
2. Arthur C Guyton, John E Hall. Physical Principles of Gas Exchange; Diffusion of Oxygen and Carbon Dioxide; Unit VII, Chapter 39; 11th Ed; P 500.
3. Peter Bamford, Andrew Bentley, Jane Dean, David Whitmore and Norman Wilson-Baig; ICS Guidance for Prone Positioning of the Conscious COVID Patient 2020; Intensive care society
4. Claude Guerin C, Reignier J, Richard JC, et al. Prone positioning in Severe Acute Respiratory Distress Syndrome. CurrOpinCrit Care. 2014;20(1):92-7.
5. Eric L. Scholten, Jeremy R. Beitler, MPH, G. Kim Prisk, and Atul Malhotra. Treatment of ARDS With Prone Positioning: Chest. 2017;151(1):215–224.
6. Pittman RNChapter 5, Chemical Regulation of Respiration; Regulation of Tissue Oxygenation. Unit IV; Integrated Systems Physiology; San Rafael (CA): Morgan & Claypool Life Sciences; 2011; www.ncbi.nlm.nih.gov/books/NBK54106; colloquium lecture series.
7. Luciano Gattinoni, DavideChiumello, Pietro Caironi, MattiaBusana, Federica Romitti, Luca Brazziand Luigi Camphorate. COVID‑19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med; https://doi.org/10.1007/s00134-020-06033-2© 2020.
8. Oxygen Flow Rate and FiO2: Understanding the Relationship. online CPD articles; asumed.com. published on 14th April.
9. Josh Farkas, Understanding happy hypoxemia physiology: how COVID taught me to treat pneumococcus; PulmCrit – April 15, 2020.
10. Meredith Wadman, Jennifer Couzin-Frankel, Jocelyn Kaiser, Catherine Matacic; How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toesApr. 17, 2020 , 6:45 PM.
11. V. Montalvana, J. Leea, T. Buesoa, J. De Toledoa, K. Rivasb: Neurological manifestations of COVID-19 and other coronavirus infections:A systematic review.
12. Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu et al, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.