Oxyhemoglobin desaturation as a function of age and hypercapnia from ventilatory pump failure (VPF)

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ABSTRACT

Background: Supplemental O2 is often administered without knowledge of CO2 levels for patients with ventilatory pump failure (VPF). This can render oximetry ineffective as a gauge of alveolar ventilation, airway secretions, and lung disease. We have noted that diurnal hyperventilation with hypercapnia tends to be symptomatic when O2 saturation levels decrease below 95% and patients extend sleep noninvasive ventilatory support (NVS) into daytime hours. We also noted that with advancing age, less hypercapnia results in desaturation. This study was designed to explore oxyhemoglobin desaturations (O2: desats) as a function of age and hypercapnia for patients with VPF.

Methods: A retrospective analysis of 8933 consecutive patient visits for whom end-tidal CO2 and O2 sats were measured. O2: sats < 95% at CO2 levels of 45, 50, and 60 cmH2O were correlated with 10 years age intervals to age 80.

Results: Of 8933 visits, 8642 had complete data. Outcomes for CO2 levels > 50 cmH2O were the most significant including for visit-ages < 30 and ≥ 30 years. There was a statistically significant 4% decrease in the odds of O2 desat for every one-year increase in age to age 30 (OR = 0.96, 95% CI=[0.93, 0.99], p=0.02) and for visit-ages ≥ 30 a significant 30% increase in the odds of O2 desat for every 10-year increase in age (OR 1.3, 95% CI=[1.1,1.6], p=0.006). Relationship for ages ≥ 30 years were also significant for CO2 levels over 45 mmHg also. 40% of the time when CO2 was greater than 45 mmHg O2: sat was low.

Discussion: This study demonstrated a significantly lower risk of O2 desat occurring at EtCO2 levels ≥ 50 mmHg for patients from 10 to 20 years of age than those younger than 10 and a significantly greater risk of O2 desat for 10 years intervals after age 20. Thus, with age, less hypercapnia results in desats and dyspnea with patients tending to extend NVS into daytime hours. This may be due to increases in physiological shunting, decreased pulmonary elasticity, and worsening ventilation/perfusion ratios with age.

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1 Introduction

Over the course of 8642 visits of patients with ventilatory pump failure (VPF), most of whom with neuromuscular diseases (NMDs), older patients appeared to develop oxyhemoglobin saturation (O₂ sat) below 95% at lower levels of hypercapnia. It also became apparent that symptoms of hypoventilation and resort to daytime noninvasive ventilatory support (NVS), paralleled decreases in O₂ sat below 95% irrespective of extent of daytime hypercapnia. We undertook this study to determine age related O₂ desat as a function of end-tidal CO₂ levels (EtCO₂).

2 Materials and methods

We performed a retrospective review of all visits of patients with VPF for whom end-tidal CO₂ and O₂ sat were measured simultaneously and the data taken from the database of patient visits to a NMD clinic. All CO₂ and O₂ sat measurements were obtained by the same therapist over a 35 year period. The highest observed EtCO₂ was recorded. For patients with very shallow tidal volumes, an abdominal thrust was applied at end expiratory to obtain an end-tidal sample. Since all patients had normal PetCO₂ and O₂ sat levels while using NVS, their data did not contribute to the analyses in this study. No patients received supplemental O₂. All measurements were made with the patients sitting and at routine out-patient visits.

We excluded patients for whom EtCO₂, O₂ sat, or age were lacking. The maximum observed EtCO₂ and maximum and minimum visit O₂ sat data were recorded with the minimum O₂ sat used for this analysis. The minimum O₂ sat data were then segregated as a function of age in 10 year groupings for EtCO₂ levels of 45, 50, and 60 mmHg. The database for this study terminated in July 2017 when all medical records were mandated to be input into a standard electronic medical records system from which the data were no longer readily accessible electronically.

We screened for the following symptoms of hypoventilation: fatigue, daytime drowsiness, morning headaches, respiratory orthopnea, difficulty concentrating, and others [1], diagnosis, and for extent of use of NVS. When symptoms were associated with vital capacities (VC) diminished by 30% or more from predicted normal levels or by hypercapnia (EtCO₂ > 45 mmHg) with or without O₂ sat < 95%, sleep NVS was offered at full NVS settings to optimally rest respiratory muscles and provide NVS as needed rather than use “NIV”, that is, noninvasive ventilation or bi-level positive airway pressure at less than NVS settings [1]. The subsequent effects on daytime O₂ sat and CO₂ were observed. Patients were encouraged to use sleep NVS only if their symptoms were relieved by it otherwise they would be reevaluated at future visits.

The NVS settings were typically volume preset assist-control range 700 to 1500 ml and rate 12–14 as per patient preference. Over 80% of NVS users chose to use 1200 to 1300 ml volumes. The NVS users were typically switched to pressure assist/control settings of 17–25 cmH₂O if abdominal distention became a problem. Patients with morbid obesity, however, typically used sleep as well as at least some daytime NVS at positive inspiratory pressures (PIPs) between 25 and 55 cmH₂O. The NVS settings were intended to optimize respiratory muscle rest and maintain normal CO₂ and O₂ sat levels during sleep and as normal as possible when not using NVS during daytime hours. O₂ sat and CO₂ levels were always normal while using NVS during daytime hours such as for continuous noninvasive ventilatory support (CNVS) users with little or no ventilator free breathing ability.

We used generalized estimating equations
with a logistic link and binomial distribution to model the relationship between age groups and O₂ values < 95%. The robust “sandwich” estimator, shown to be sufficient in larger studies, was used to estimate the standard error [2]. We stratified the analysis on patient age and estimated the trend in the proportion of O₂ values falling short of 95% (O₂95) as a function of age for CO₂ exceeding 45, 50, and 60 mmHg. Results are presented as odds ratios (OR) and 95% confidence intervals (CI). A 95% CI that excludes the value 1.0 is equivalent to a p-value < 0.05 (statistical significance).

3 Results

Of 8833 patient visits, 4968 from males, 3865 females, 8642 had demographic data and measurements of O₂ sat and EtCO₂. Incomplete data resulted in the exclusion of 133 additional data points. There were 1453 points of data with EtCO₂ ≥ 45 mmHg and 583 of these with O₂ sat < 95%. Fig. 1 is a patient flow diagram. The 8509 studied data points were from 3095 patients with the following diagnoses: Duchenne muscular dystrophy (DMD), 279; non-DMD myopathies, 289; spinal muscular atrophy (SMA) type 1, 235; other SMAs, 327; amyotrophic lateral sclerosis/motor neuron disease (ALS), 569; myotonic dystrophy, 177; other NMDs (OMD), 1301; high level spinal cord injury (SCI), 80; severe chest wall deformity/coliosis, 47; morbid obesity, 27; other neurological disease (OND) including multiple sclerosis, cerebral palsy, and traumatic brain injury, 80. The number of data points per patient ranged from 1 to 23 with 60% of subjects contributing 1, and 15% 2 points. Thirty-six percent of the points were from subjects aged 30 years or younger at first visit. There were 1483 data points for CO₂ ≥ 45 mmHg. All patients other than the majority of ALS patients used only NVS rather than tracheostomies for ventilatory support.

Considering the three CO₂ values of 45, 50, and 60 mmHg and the relationship between age and SpO₂ < 95% for 10-year age intervals below and above ages 20 and 30 (Table 1) the only statistically significant relationship for the intervals below age 30 was for O₂ desaturation occurring for EtCO₂ ≥ 50 mmHg (p < 0.02). However, for the 10-year age intervals greater than age 20, O₂ desaturation below 95% was very significantly more likely for the intervals when EtCO₂ ≥ 45 mmHg, as well as ≥ 50 mmHg (Table 1). Restricting the analysis to subjects with all CO₂ values exceeding 50 mmHg for visit-ages < 30 and ≥ 30 years, there was a statistically significant 4% decrease in the odds of O₂ desat for every 1-year increase in age to age 30 (OR = 0.96, 95% CI = [0.93, 0.99], p = 0.02) and for visit-ages ≥ 30 there was a significant 30% increase in the odds of O₂ desat for every 10-year increase in age (OR 1.3, 95% CI = [1.1, 1.6], p = 0.006).

Restricting the analysis to subjects with all CO₂ values exceeding 60 mmHg, there was no significant change in the odds of O₂ desat for either age-visit groups but for age < 30, for every one-year increase in age, there is a 7% not statistically significant decline in O₂ desat (p = 0.08, OR = 0.93, 95% CI = [0.86, 1.001]). For persons aged ≥ 30

Fig. 1 Respiratory data flow diagram.
years, there is a not statistically significant 2% decrease in the odds of O₂ desat for every 10-year increase in age \( (p = 0.94, \text{OR} = 0.98, \text{95% CI} = [0.63, 1.54]) \).

Table 2 demonstrates the numbers of patients with minimum daytime O₂ sat levels below 95% for 10-year age intervals through age 80 for EtCO₂ levels \( \geq 45, 50, \) and 60 mmHg, respectively. Tables 1 and 2 and Fig. 2 demonstrate the tendencies to have O₂ desaturation occur with hypercapnia of 45, 50, and 60 mmHg for 10-year age intervals.

All 3095 patients eventually began requiring sleep NVS with or without having normal daytime blood gases. Initially, except for five morbidly obese patients, the daytime O₂ sat and EtCO₂ were completely normalized by sleep NVS. Over 1000 of these patients including all 279 with DMD, 45% of those with ALS/MND, all with SMA type 1, over 100 with congenital myopathies, 5 high level SCI patients and 15 with morbid obesity eventually became CNVS dependent with little or no ventilator free breathing ability. Nine of the SMA type 1 patients are now over 20 years of age with VCs as little as 0 and CNVS dependent from as

| CO₂ values (mmHg) | Number of visits | Under 20 years of age* | OR (95% CI) | p-value | 20 years of age and older** | OR (95% CI) | p-value |
|-------------------|-----------------|------------------------|-------------|---------|----------------------------|-------------|---------|
| \( \geq 45 \)     | 1453            | 0.96 (0.91, 1.01)      | 0.11        |         | 1.34 (1.2, 1.5)            | < 0.0001    |         |
| \( \geq 50 \)     | 664             | 0.97 (0.92, 1.02)      | 0.26        |         | 1.41 (1.2, 1.6)            | < 0.0001    |         |
| \( \geq 60 \)     | 121             | 0.91 (0.81, 1.02)      | 0.09        |         | 1.2 (0.8, 1.8)             | 0.39        |         |

| CO₂ values (mmHg) | Number of visits | Under 30 years of age* | OR (95% CI) | p-value | 30 years of age and older** | OR (95% CI) | p-value |
|-------------------|-----------------|------------------------|-------------|---------|----------------------------|-------------|---------|
| \( \geq 45 \)     | 1453            | 0.98 (0.94, 1.01)      | 0.18        |         | 1.22 (1.03, 1.45)          | 0.02        |         |
| \( \geq 50 \)     | 664             | 0.96 (0.93, 0.99)      | 0.02        |         | 1.3 (1.1, 1.6)             | 0.006       |         |
| \( \geq 60 \)     | 121             | 0.93 (0.86, 1.01)      | 0.08        |         | 0.98 (0.63, 1.54)          | 0.94        |         |

OR, odds ratio.

* OR associated with a 1-year increase in age; ** OR associated with a 10-year increase in age.

| CO₂ values (mmHg) | 45 mmHg | 50 mmHg | 60 mmHg |
|-------------------|---------|---------|---------|
| Sat O₂ < 95%      | 28 (41.2%) | 52 (23.3%) | 73 (37.6%) |
|                   | 61 (26.1%) | 38 (27.3%) | 26 (26.6%) |
|                   | 111 (43.7%) | 111 (43.7%) | 97 (57.1%) |
|                   | 97 (43.9%) | 60 (37.3%) | 12 (66.7%) |
|                   | 82 (51.3%) | 62 (57.2%) | 10 (66.7%) |
|                   | 55 (73.3%) | 33 (84.6%) | 33 (84.6%) |
|                   | 583 (41.1%) | 380 (57.2%) | 99 (81.8%) |

| CO₂ values (mmHg) | Overall |
|-------------------|---------|
|                   | 983 (40.1%) |

| CO₂ values (mmHg) | Overall |
|-------------------|---------|
|                   | 583 (40.1%) |

| CO₂ values (mmHg) | Overall |
|-------------------|---------|
|                   | 380 (57.2%) |

| CO₂ values (mmHg) | Overall |
|-------------------|---------|
|                   | 99 (81.8%) |

| CO₂ values (mmHg) | Overall |
|-------------------|---------|
|                   | 99 (81.8%) |

Table 2: O₂ saturation levels less than 95% for patients with end-tidal CO₂ levels greater than or equal to 45, 50, and 60 mmHg.
young as 4 months of age but all these and all the other patients including all with morbid obesity maintained normal CO2 and O2 sat levels while actually using NVS/CNVS, that is, end-tidal CO2 ≤ 42 mmHg and O2 sat ≥ 95% in ambient air.

4 Discussion

This study demonstrated a significantly lower risk of O2 desat occurring at EtCO2 levels ≥ 50 mmHg for patients from 10 to 20 years of age than for patients younger than age 10 and a significantly greater risk of increasingly severe O2 desat occurring after 20 years of age for patients with EtCO2 ≥ 45, and ≥ 50 mmHg. Specifically, O2 desat occurred for significantly fewer patients at CO2 levels of 50 mmHg for the second 10-year interval (ages 10 to 20) than the first interval and then occurred for an increasingly higher percentage of patients at 45 and 50 cmH2O for every 10-year interval subsequently. EtCO2 is reported to reflect PaCO2 levels to an accuracy of 1 to 2 mmHg [3].

We observed that virtually all of the patients using sleep NVS who extended it into daytime hours did so only after daytime hypercapnia was associated with dips in O2:sat below 95%. Subsequently patients required NVS increasingly into daytime hours, in many cases to become CNVS dependent with little to no ventilator free breathing ability. Over 250 of these patients also required extubation back to CNVS during intercurrent episodes of acute respiratory failure (ARF) and thereby avoided tracheotomies [4, 5]. There is no comparable medical literature on this subject.

Alveolar hypoventilation signaled by hypercapnia is a common cause of oxyhemoglobin desaturation in these patients. Airway secretion congestion and intrinsic lung disease also cause hypoxia but may not be associated with hypercapnia. Oxygen supplementation to treat hypoxia can severely exacerbate CO2 retention, it does not treat the underlining cause of the hypoxia and often results in ARF and intubation, so O2 supplementation should not be used as a substitute for NVS and mechanical insufflation (MIE) to clear airway secretions for these patients [6].

In this study, 59.9% of the time when EtCO2 was greater than 45 mmHg, O2: sat was normal. This included 18.2% of instances when EtCO2 was greater than 60 mmHg. While the association of hypoxia secondary to hypoventilation and hypercapnia is clear, and that O2 supplementation should be used for patients with CO2 levels greater than 45 mmHg.
exacerbates CO₂ retention via the Haldane effect and diminution of hypoxic ventilatory drive, the role of hypercapnia in the mechanism of hypoxemia is unclear. Apparently, tolerance of hypercapnia, 59.9% in the early years, decreases with age as shown in Fig. 2. Why this occurs is unclear. Age is linked to the development and growth of the lungs and cardiovascular system. The alveolarization stage, when new alveoli and bronchioles are forming, ends around age 3. Around that time alveolar microvasculature matures, decreasing the thickness of the alveolar walls [7–10]. Up to 8 years of age, alveoli increase in number and size and do so through age 18 [8]. In turn, pulmonary mechanics change. A new born child’s airway resistance can be 15 times greater than for adults [7, 8]. Vital capacity peaks at 19 to 20 years of age then decreases at 1% to 1.2% per year. Thus, at about 20 years of age the respiratory system is at its peak.

With age there are increases in physiological shunting, decreased pulmonary elasticity, and worsening ventilation/perfusion ratios. Respiratory muscle weakness increases residual volume, increases the alveolar arterial oxygen difference (DA-aO₂), and PaO₂ and VC also decrease with age [11–19]. Thus, for PaO₂ of 100 mmHg, pulse oximetry is normally above 95% and remains normal even if PaO₂ decreases by 20 mmHg or more for a physiological “cushion” for adolescents. However, with age the greater arterial-oxygen difference (DA-aO₂) decreases PaO₂ and milder hypercapnia results in O₂ desaturation. The greater the capacity to incorporate O₂ in hemoglobin, the greater the hypercapnia tolerated by the organism without the appearance of hypoxemia. Very young patients, whose lungs are still developing, and old patients have the least capacity to tolerate hypoventilation without producing hypoxemia. The process by which hypoventilation generates hypoxemia is dynamic and not only depends on increases in CO₂ but also on respiratory capacity and PaO₂ that changes with each stage of pulmonary development. Further study is needed to better understand these phenomena.

Another limitation stems from the fact that for normals, awake PetCO₂ differs from PaCO₂ by only 1 to 2 mmHg [3]. However, even for normal subjects, tidal volumes decrease during sleep, the ratio of dead space to tidal volume increases, and patients can exhale out of the mouth and thereby bypass the PetCO₂ sampling at the nostrils and render PetCO₂ falsely low. PetCO₂ is also less accurate in the presence of high PaCO₂ levels [20]. On the other hand, many studies have reported PetCO₂ to be accurate for conditions in which the exhaled gas can be sampled within or close to the airways such as for patients whose alveolar dead space is not very large and, if using NIV/NVS, for those whose sampling is at the prongs, as in these cases, rather than via larger interfaces that dilute the sample [21]. In a study of 39 subjects with NMD, while maximum transcutaneous (Ptc) CO₂ was 4 to 16 mmHg higher than EtCO₂s, mean PtcCO₂ was less than 1 mmHg to 7 mmHg greater [22]. This discrepancy could change the threshold in the correlation of O₂ desaturation as a function of age and CO₂ levels but it does not change the fact that the aging patient is more likely to have O₂ desaturation at lower levels of hypercapnia.

In conclusion, the mission of neurorestoratology includes maximizing the physical functioning of...
patients impaired by NMD whose activities of daily living are greatly restricted by dyspnea and the other neurological symptoms of hypercapnia. The use of NIVS can relieve these symptoms and, when extended to CNVS, permits lifetime ventilatory support without resort to invasive airway tubes and invasive mechanical ventilation. It can both extend life and preserve quality of life by restoring the patients’ ability to function to the level permitted by only their skeletal muscle, but not their respiratory muscle, impairment.

Conflict of interests

The authors declare no conflict of interests.

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