Use of a human patient simulator for apnea studies: a preliminary in vitro trial

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Background: Modern human patient simulators (HPSs) could be used for researching critical scenarios such as apnea oxygenation. We aimed to study the use of a high-fidelity HPS to assess prolonged apnea using various oxygenation strategies with a simple high-flow nasal cannula (15 L/min).

Methods: An experimental simulation study using an HPS (CAE Healthcare™) was conducted after obtaining approval from the Institutional Review Board. The HPS responded according to real-time physiologically modeled responses to external gases, such as oxygen (O₂). Apnea experiments were performed with different physiological settings, such as shunt fraction (5%) and O₂ consumption (250, 500, and 750 ml/min). The following four apnea experiments were conducted: no oxygenation (NO), apnea oxygenation alone (AO), preoxygenation alone (PO), and para-oxygenation (PAO). The time to 92%, 75%, and 50% saturation was recorded. Alveolar and arterial gas levels were recorded till 50% saturation.

Results: At 250 ml/min, PO (1121 s) and PAO (1274.5 s) had a significantly longer time to 50% saturation (400% increase) compared to NO (222.5 s) and AO (239 s). A similar trend was observed for the time to 92% and 75% saturation. At higher O₂ consumption rates, a shorter time to desaturation was observed.

Conclusions: Apnea trends in the HPS correlated with similar prior human experiments. AO without preoxygenation was found to provide no additional benefit. Preoxygenation with high-flow O₂ via nasal cannula prolonged the time to desaturation in the PAO more than PO scenario. Therefore, HPSs can be used in future studies where patient safety is a concern.

Keywords: Apnea; Hypoxia; Nasal cannula; Oxygen inhalation therapy; Oxygen saturation; Patient simulation.

Introduction

The use of simulations in medical practice is an exciting new sub-specialty that is being widely used for teaching, especially to simulate rare events and prepare students for real-life emergency scenarios. Simulations have been used effectively for procedural training, with mannequins replacing real patients, to avoid exposing novice students to patients for learning [1,2]. The use of simulations in research is still limited to statistical models and a few experimental studies, although there are many unexplored potential applications [2,3].
With the availability of human patient simulator (HPS) machines that can precisely simulate various physiological and pathological conditions through input from computer-based software, the role of simulators in anesthesia has expanded to an advanced level [4]. Newer types of HPSs are based on physio-pharmacological models, which include real-time monitoring and feedback while interventions are performed on the simulator. HPSs are therefore ideal for complex critical scenarios and, thus, an appropriate tool for clinical research based on such scenarios.

Preoxygenation and apnea oxygenation are established techniques for prolonging the duration of apnea during intubation attempts in operation rooms and intensive care units [5–8], but most studies have been performed only on certain oxygen (O₂) saturation levels because of ethical issues related to exposing patients to apnea and potential hypoxia [9–11]. Recent literature has documented the efficacy of high-flow O₂ administered through a nasal cannula to provide longer periods of apnea in operation rooms and to maintain oxygenation in patients with pulmonary pathologies [12–17].

Through this experimental study, we aimed to investigate the effect of O₂ therapy on prolonged apnea using a high-fidelity HPS. This allowed for longer periods of apnea to be studied and analyzed without risking patient safety. The primary objective of our study was to assess the utility of an HPS for apnea simulation and O₂ therapy research, and the validity of extrapolating the data to human patients. The secondary objective was to compare the efficacy of different oxygenation strategies using a simple nasal cannula during apnea in terms of the time to desaturation.

Materials and Methods

Setup

After approval from the Institutional Review Board (IRB no. 261/IEC/IM/NF/2019), an experimental simulation study using an HPS was planned over four months. The HPS (CAE Healthcare™, USA) is equipped to detect delivered O₂ and is used along with an anesthesia workstation and monitor with hemodynamic and oxygenation parameters.

Functioning of the HPS

The study object was a high-fidelity HPS. The basic components of this HPS are a mannequin attached to a central control unit or lab rack (Fig. 1A) through an umbilical assembly (Fig. 1B). The lab rack is driven by various gases, such as O₂, nitrogen (N₂), carbon dioxide (CO₂), and compressed air. A specific software (Müse, CAE Healthcare™, USA) is used to control the functioning of the HPS (Fig. 1C). Circulation and respiration are simulated through the lab rack. Two bellows inside the lab rack serve the function of the lungs (Fig. 1A). Gas monitoring sensors are present at the level of the lab rack even though sampling is performed on the mannequin (Fig. 1D). Simulated hemodynamic measurements, such as non-invasive blood pressure, pulse oximetry for O₂ saturation (SpO₂), and electrocardiography, can also be obtained from the mannequin using actual monitors.

Software

The HPS software, allows for two modes of functioning (Fig. 1C). In the first mode, the HPS response is controlled by an operator at the computer interface, whereas with the second mode, responses are modeled based on normal adult physiology. Several parameters are set for normal adult physiology, such as the shunt fraction (set at 5% for this study), O₂ consumption, lung volume, and respiratory quotient, among others. Table 1 shows a list of all the parameters that were set using the default values [4]. The clinical hemodynamic and blood gas parameters, such as partial pressure of alveolar (PA), arterial (Pa), and venous (Pv) O₂ and CO₂, are visible on a separate screen, which can either be a fixed expected response based on the experiment, a setting that is applied in the software, or a modeled response after synchronizing the monitors with the HPS mannequin. Once in the modeled mode,
Table 1. List of Respiratory Parameters That Can Be Adjusted in the Software

| Basic parameters | Additional parameters |
|------------------|-----------------------|
| Tidal volume     | Chest wall compliance factor |
| Tidal volume factor | Functional residual capacity |
| pH shift         | Lung compliance factor: left |
| PEEP             | Lung compliance factor: right |
| Chest tube       | Venous CO₂ shift |
| Chest tube flow  | Bronchial resistance factor: left |
| Chest tube air leak | Bronchial resistance factor: right |
| O₂ consumption  | Alveolar enflurane |
| CO₂ production factor | Fraction of inspired enflurane |
| PaCO₂ set-point | Alveolar halothane |
| PaO₂ set-point   | Fraction of inspired halothane |
| I to E ratio (1:X) | Alveolar isoflurane |
| PetCO₂-PaCO₂ factor | Fraction of inspired isoflurane |
| Respiratory gain factor | Alveolar nitrous oxide |
| Respiratory quotient | Fraction of inspired nitrous oxide |
| Volume/rate control factor | Alveolar sevoflurane |
| Chest wall capacity | Fraction of inspired sevoflurane |

SpO₂: oxygen saturation, NMB: neuromuscular block, ETCO₂: end-tidal carbon dioxide, PETCO₂: partial pressure of end-tidal carbon dioxide, PaO₂: partial pressure of oxygen in arterial blood.

Results

Fig. 2 shows a comparison of the desaturation time to 50%, 75%, and 92% SpO₂ among the four experimental settings at O₂ consumption rates of 250, 500, and 750 ml/min. At 250 ml/min, NO (222.5 s) and AO (239 s) had a similar desaturation time to 50% SpO₂. PAO (1274.5 s) had a longer desaturation time to 50% SpO₂ than PO (1121 s), which was a 400% increase compared to NO. At higher O₂ consumption rates, the desaturation times were shorter. At 500 ml/min, the desaturation time to 50% SpO₂ for NO and AO were 97 s and 98 s, respectively. Compared with NO, the desaturation time to 50% SpO₂ for PO and PAO was 300 s and 316 s, respectively, which was an increase of approximately 200%. Similar comparative trends were observed for the desaturation time to 92% and 75% SpO₂ (Fig. 2).

Fig. 3 shows a graphical trend of the partial pressure of O₂ in...
Time to 50%, 75%, and 92% saturation among all four oxygenation strategies was achieved at 250 ml/min NO, 500 ml/min AO, and 750 ml/min PO. Experiments at higher consumption rates also had lower pH values compared to 250 ml/min oxygenation. Lower pH values were observed with NO and PAO (75.1 mmHg), which allowed for longer apnea times and higher PaCO₂ values (75 mmHg). A similar study would be very difficult to perform in modern research settings due to the ethical issues of subjecting patients to such high levels of respiratory acidosis and CO₂. In the current study, a normal physiologically modeled HPS was used to study various oxygenation strategies during apnea to an extent that would not be feasible for real subjects (50% SpO₂). The lowest pH reached was 7.18 and the highest PaCO₂ value was 75 mmHg (250 ml/min O₂ consumption) at 50% SpO₂.

Another in vitro study conducted by Struys et al. [3] compared the time course of inhaled anesthetic drug delivery between two types of anesthesia machine circuits using test lungs. Different combinations of settings (e.g., flow) were applied to observe various patterns of anesthetic delivery and end-tidal concentrations. Such studies can also be performed using an HPS and would even be more accurate than a test lung due to its more advanced real-time gas-sensing mechanisms once synchronized to the modeled mode. A substantial amount of anesthesia-related simulation research has been conducted in the field of airway management, with various studies involving airway techniques and devices [2]. Although such studies are criticized for seldom following up with
Fig. 3. Graphical trend of partial pressure of oxygen in the alveoli and arterial blood among all four experiments across time until 50% SpO₂, at oxygen consumption rates of 250, 500, and 750 ml/min. NO: no oxygenation, AO: apnea oxygenation alone, PO: pre-oxygenation alone, PAO: para-oxygenation, alv: alveolar, art: arterial.
In the present study, we compared different nasal oxygenation strategies on an HPS mannequin that varied from no oxygenation to apnea oxygenation alone to para-oxygenation, to assess the time to 92%, 75%, and 50% SpO₂. Across all settings, no oxygenation and oxygenation only during apnea showed similar times to desaturation, and para-oxygenation produced marginally longer times to desaturation compared to preoxygenation alone, both of which were significantly longer than those in the earlier two settings. The above findings highlight that, without preoxygenation, apnea oxygenation alone does not provide any additional benefit, and that para-oxygenation can be used to maximize the duration of safe apnea.

The four experimental settings were also applied at O₂ consumption rates of 250, 500, and 750 ml/min to evaluate the performance of the HPS at different O₂ settings, which can be further extrapolated to varied O₂ demand situations. The comparative findings were similar across all consumption rates. In the current study, only the shunt fraction and O₂ consumption rate were manipulated; however, complex pulmonary pathologies may be simulated by adjusting various physiological parameters to estimate how an actual patient might behave under various conditions, such as anesthesia and surgery [4]. For example, chest wall compliance and bronchial resistance factors can be used to simulate restrictive and obstructive lung pathologies, respectively. Different flow rates of nasal oxygenation could also be compared on the HPS, similar to the protocol proposed by Theiler et al. [22].

The major and obvious limitation of the study is that the results obtained with any simulator experiment cannot with absolute certainty be compared to human data. Only its proximity to reality, as much as possible, can be ascertained, as was done in the present study. Another limitation is that the full spectrum of the software modifiable physiological factors could not be explored in the present study. This can be planned in future projects.

In conclusion, apnea trends in the HPS in the current study correlated well with similar prior human experiments, providing support for the use of HPS in similar future research and extrapolation of data to human patients. Through simulation experiments, we deduced that AO alone without preoxygenation provides no additional benefit to NO. High-flow O₂ via nasal cannula prolonged the time to desaturation in the PAO scenario more than in the PO scenario. Complex, rare, and potentially dangerous scenarios, such as apnea oxygenation, can be easily performed using HPS to study the patterns of various new interventions without the ethical concerns of exposing real patients.

Table 2. Maximum Values of Measured Parameters at the End of the Experiments (50% Saturation)

| Experiment | NO | AO | PO | PAO |
|------------|----|----|----|-----|
| PaCO₂* (mmHg) |
| 250 ml/min | 52.13 | 52.90 | 72.50 | 75.10 |
| 500 ml/min | 50.67 | 50.77 | 62.10 | 63.17 |
| 750 ml/min | 51.87 | 50.97 | 64.57 | 63.90 |
| pH* |
| 250 ml/min | 7.35 | 7.34 | 7.20 | 7.18 |
| 500 ml/min | 7.36 | 7.36 | 7.28 | 7.27 |
| 750 ml/min | 7.35 | 7.36 | 7.26 | 7.26 |

*Mean of 3 readings. NO: no oxygenation, AO: apnea oxygenation alone, PO: pre-oxygenation alone, PAO: para-oxygenation, PaCO₂: partial pressure of arterial carbon dioxide.

Patient-based studies to validate the simulation data, apnea oxygenation scenarios can only be ethically conducted to a certain level of acceptable desaturation in actual patients. Such experimental simulation-based studies should offer insights into the mechanisms and a preliminary understanding of new interventions.

Patient studies involving apnea oxygenation have been performed primarily in the operative, emergency, and critical care settings [7,8,10]. Outcome parameters range from time to desaturation, incidence of desaturation, lowest mean saturation reached during intubation, and mean saturation in respiratory failure, among others [7,9–11,13,14,17]. A study on apneic oxygenation comparing trans nasal humidified O₂ therapy versus conventional nasal oxygenation conducted by Rajan et al. [16] found a longer time to 90% desaturation in the transnasal humidified group (796 s vs. 444 s). Similar time to desaturation (to 92%) was observed in the present simulation study at 250 ml/min O₂ consumption (915 s for PO, 1087 s for PAO) using a nasal cannula at 15 L/min. Other studies based on lower apnea oxygenation flows of 5–10 L/min had times to desaturation (92–95%) ranging from 408 s to 587 s [19–21]. Assuming that the O₂ consumption/pulmonary shunt fraction will be slightly more than ideal in real patients and considering the differences in flow rates used, the experimental HPS data correlated well with patient data from previous human apnea oxygenation studies.

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## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.
Author Contributions

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