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

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Authors' contributions

Debendra K Tripathy was involved in conception and design, acquisition of data, analysis, and interpretation of data, manuscript editing, and review. Mridul Dhar was involved with the design, acquisition of data, analysis, and interpretation of data, manuscript preparation, editing, and review. Bharat B Bhardwaj helped in conception and design, manuscript editing, and review. K Hemanthkumar
performed acquisition of data, analysis, and interpretation of data, and final approval of the manuscript. Praveen Talawar helped in conception and design, manuscript editing, and final approval. Shalinee Rao helped in concept, design, data acquisition, and final approval. All the above are guarantors for the integrity of the work done.

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Declaration

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Key Points

-Question: Can a high-fidelity physiology modeled human patient simulator be used for performing apnea research comparing different strategies of high flow nasal oxygen?

-Findings: Data from simulation experiments correlated with prior similar human experiments and pre and para oxygenation had longer desaturation times compared to no or only apnea oxygenation.
-Meaning: Only apnea oxygenation without pre-oxygenation added no added benefit and human patient simulators can be used for similar future studies where patient safety is a concern.
Use of human patient simulator for apnea studies: a preliminary in vitro trial

Running title: Use of human patient simulator for apnea studies
Abstract

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

Methods: An experimental simulation study was planned on an HPS (CAE healthcare™) after approval from the institutional review board. The HPS responses were based on real-time physiological modeled responses to external gasses like oxygen (O₂). Apnea experiments were performed each at different physiological settings like shunt fraction (5%) and O₂ consumption (250, 500, and 750 ml/min). The 4 experiments were apnea with: no oxygenation (NO), only apnea oxygenation (AO), only pre-oxygenation (PO), and lastly para-oxygenation (PAO). Time to desaturate to 92%, 75%, and 50% was recorded. Alveolar and arterial gas levels were recorded till 50% SPO₂.

Results: At 250 ml/min PO (1121 sec) and PAO (1274.5 sec) had significantly (400% increase), longer desaturation times to 50% SPO₂ compared to NO (222.5 sec) and AO (239 sec). A similar trend could be observed for mean desaturation time to 92% and 75% as well. At higher O₂ consumption rates more rapid desaturation times were observed.

Conclusions: Apnea trends in the HPS correlated well with similar prior human experiments. Only apnea oxygenation without pre-oxygenation had no added benefit. Giving high flow O₂ via nasal cannula prolonged desaturating time, para-oxygenation more than only pre-oxygenation. HPS can be used for similar future studies where patient safety is a concern.

Keywords: Human patient simulator, Apnea, Hypoxia, Apnea oxygenation, Pre-oxygenation, High flow nasal cannula.
Key Points

-Question: Can a high-fidelity, physiology-modeled human patient simulator be used for performing apnea research comparing different strategies of high flow nasal oxygen?

-Findings: Data from simulation experiments correlated with prior similar human experiments and pre and para-oxygenation had longer desaturation times compared to no or only apnea oxygenation.

-Meaning: Only apnea oxygenation without pre-oxygenation added no added benefit and human patient simulators can be used for similar future studies where patient safety is a concern.
Introduction

The use of simulation in medical practice is an exciting new sub-specialty and is being widely used for teaching, especially to simulate rare events and to prepare students for real-life emergency scenarios. It has found utility in procedural training, with mannequins replacing real patients. This avoids the exposure of patients to novice students for learning [1,2]. The use of simulation in research is still limited to statistical models and a few experimental studies; although there is a lot of unexplored potential for its use [2,3].

The role of simulators in anesthesia has expanded to an advanced level with the availability of human patient simulator (HPS) machines which can simulate various physiological and pathological conditions precisely through input from a computer-based software [4]. Newer types of HPS are based on physio-pharmacological models which include real-time monitoring and feedback while performing interventions on the simulator. This makes it ideal to simulate complex critical scenarios and thus an appropriate tool, even for clinical research based on such scenarios.

Pre-oxygenation and apnea oxygenation are established techniques to prolong apnea durations during intubation attempts in the operation theatre and intensive care units [5-8], but most of the studies have been performed only to certain oxygen (O_2) saturation levels due to ethical issues related to exposing patients to apnea and potential hypoxia [9-11]. Recent literature has documented the efficacy of high flow O_2 given through nasal cannula for providing longer apnea periods in operation theatres and also to maintain oxygenation in sick patients with pulmonary pathologies [12-17].

Through this experimental study, we intended to study the effect of O_2 therapy in prolonged apnea using a high-fidelity HPS. This would allow us to study and analyze longer apnea periods without risking patient safety. Thus, experiments on a high-fidelity human simulator will help us extrapolate
data to human patients and analyze the utility of our study interventions. The primary objective of our study was to assess the utility of an HPS to research apnea simulation and O₂ therapy. The secondary objective was to compare the effectiveness of different oxygenation strategies using a simple nasal cannula during apnea in terms of time to desaturate.
Materials and Methods

Setup: An experimental simulation study was planned on an HPS after approval from the institutional review board (261/IEC/IM/NF/2019), over 4 months. The HPS (CAE healthcare™) is equipped with detecting delivered O₂ and is used along with an anesthesia workstation and monitor with hemodynamic and oxygenation parameters.

Functioning of HPS: A high fidelity HPS was the study object. Its basic components include the mannequin (Figure 1d) attached to a central control unit or lab rack through an umbilical assembly (Figure 1b). The lab rack is driven by various gasses such as O₂, nitrogen (N₂), carbon dioxide (CO₂), and compressed air. The functioning is controlled through a specific software. The simulation of circulation and respiration is controlled from the lab rack. There are 2 bellows inside the lab rack which serve the function of the lungs (Figure 1a). Gas monitoring sensors are present at the level of the lab rack even though the sampling is done at the mannequin. Simulated hemodynamic measurements can also be taken from the mannequin such as non-invasive blood pressure, pulse oximetry, and electrocardiogram using actual monitors.

Software: The software related to the HPS (Figure 1c) allows 2 modes of functioning: in the first, the response of HPS is controlled by the operator at the computer interface; the second is a modeled response based on normal adult physiology. The normal physiology is based on setting several parameters such as for lungs: shunt fraction (set at 5% for this study), O₂ consumption, lung volume, respiratory quotient, etc. A list of all parameters which were set at default values is given in Table 1 [4]. The clinical hemodynamic parameters along with blood gas parameters such as partial pressure of alveolar (PA), arterial (Pa), and venous (Pv) O₂ and CO₂, etc. are visible on a separate screen, which can either be a fixed expected response based on the experiment or setting applied in the software; or it
could a modeled response after synchronizing the monitors with the HPS mannequin. Once in the modeled mode the HPS behaves like an independent unit from the fixed software and responds physiologically to real-time interventions like external O\textsubscript{2} or anesthetic agents. For this particular study, we were specifically interested in the functioning of the respiratory system, simulation of lung function, and gas sensing mechanisms. In the gas monitoring, alveolar O\textsubscript{2} and CO\textsubscript{2} were the values being sensed at the level of the lab rack; and all other arterial parameters including pulse oximetry were derived based on set physiological parameters. Figure 1 depicts a schematic diagram of the components and functioning of the HPS system.

Experiments: Apnea setting was applied from baseline values and changes in hemodynamic and blood gas parameters (PAO\textsubscript{2}, PaO\textsubscript{2}, PACO\textsubscript{2}, PaCO\textsubscript{2}, SPO\textsubscript{2}, pH) were recorded across time till the end of the experiment which was 50% O\textsubscript{2} saturation. 4 experiments were conducted with apnea; 1) No oxygenation (NO): only apnea setting applied, 2) Only apnea oxygenation (AO): Simple nasal cannula 15L/min O\textsubscript{2} given after applying apnea setting, 3) Only pre-oxygenation (PO): O\textsubscript{2} given till PAO\textsubscript{2} of 400 mmHg, then apnea was applied with no O\textsubscript{2} given during apnea and 4) Para-oxygenation (PAO): Preoxygenation till PAO\textsubscript{2} of 400 mm Hg followed by applying apnea and giving 15L/min O\textsubscript{2} via a simple nasal cannula through the apnea. Alveolar and arterial gas levels were noted every 1 min from the beginning of the apnea period. Time to desaturation was noted for 92%, 75%, and 50% O\textsubscript{2} saturation.

Settings and analysis: Each apnea experiment was repeated 3 times (in different sittings) and the mean values of the three recordings were taken for comparative analysis. Each set of 4 experiments was performed on different days to allow the machine to restart and equilibrate to baseline physiological values. This allowed us to keep a quality check on the data and avoid erroneous readings. All the experiments were then performed again at O\textsubscript{2} consumption rates of 500 and 750 ml/min. Comparisons
of apnea trends were made between all experiments NO, AO, PO, and PAO. Time to desaturation was compared between experiments and also between different O₂ consumption rates.
Results

Figure 2 shows the comparison of time taken to desaturate to 50%, 75%, and 92% O2 saturation in all four experimental settings at O2 consumption of 250 ml/min, 500 ml/min, and 750 ml/min. At 250 ml/min NO (222.5 sec) and AO (239 sec) had similar desaturation times to 50% SPO2. PAO (1274.5 sec) had longer desaturation times compared to PO (1121 sec). PO and PAO produced around a 400% increase in desaturation time compared to NO. At higher O2 consumption rates more rapid desaturation times were observed. At 500 ml/min NO was 97 sec and AO was 98 sec till 50% SPO2. PO was 300 sec and PAO was 316 sec, which was an increase of around 200% compared to NO. A similar trend was observed for desaturation time to 92% and 75% as well (Figure 2).

Figure 3 shows the graphical trend of partial pressure of O2 in the alveoli (dashed line) and arterial blood (solid line) in all four experiments across time till the end of the experiment (50% O2 saturation). Results are shown at all three O2 consumption rates (250 ml/min, 500 ml/min, and 750 ml/min).

Table 2 shows the end experiment values of partial pressure of CO2 and pH in all four experiments at different O2 consumption rates. At 250 ml/min O2 consumption, because of the shorter duration of desaturation to 50% SPO2 in NO and AO, the maximum PCO2 achieved was less (52.13 vs 52.90 mmHg) compared to 72.5 mmHg in PO and 75.1 mmHg in PAO which allowed longer apnea times and higher PCO2 values (Table 2). Thus, lower pH values were observed in PO (7.2) and PAO (7.12) owing primarily to respiratory acidosis. Similarly, experiments at higher O2 consumption rates also had lower PCO2 and higher pH values compared to 250 ml/min experiments due to shorter desaturation times (Table 2).
Discussion

Recently, there has been a growing interest in simulation/mannequin-related research studies. Such in vitro studies offer the advantage of being able to perform research on complex clinical scenarios which are rarely encountered in practice, or studies that potentially put the patient at a health risk [2,3]. One such scenario is apnea oxygenation. Also described as “apneic diffusion oxygenation”, this technique primarily involves drawing ambient O₂ “en masse” into the lungs by providing a continuous flow through the airways [18]. Devices like nasal cannula have conventionally been used which have evolved into higher flow devices like THRIVE (transnasal humidified rapid-insufflation ventilatory exchange) which have allowed tolerating of longer apnea times in clinical situations [16].

Apnea oxygenation has been studied since 1959, in humans. One of the first few studies includes one by Frumin et al where patients undergoing elective surgeries under general anesthesia with neuromuscular blockade were subjected to prolonged apnea following a period of pre-oxygenation and denitrogenation. Although the apnea termination point was not fixed, periods of apnea ranged from 15–55 minutes with monitoring of arterial samples for blood gas analysis and catecholamine levels. The lowest O₂ saturation levels reached were 98%, the lowest pH was 6.88 and the highest PaCO₂ was 250 mm Hg [18]. Such a study may be very difficult to perform in modern research settings, in terms of ethical issues of subjecting patients to such levels of respiratory acidosis and CO₂ levels. In the current study, we have used a normal physiology modeled HPS to study various oxygenation strategies during apnea to an extent (50 % O₂ saturation) that would not be feasible in real subjects. The lowest pH reached was 7.18 with the highest PCO₂ value of 75 mmHg (250ml/min O₂ consumption) at the endpoint of 50% O₂ saturation.
Another in vitro study by Struys et al, compared the time course of inhaled anesthetic drug delivery between two types of anesthesia machine circuits using test lungs [3]. Different combinations of settings like flows were applied; to observe various patterns of anesthetic delivery and end-tidal concentrations. Such studies can also be performed using HPS and would be more accurate than a test lung due to the more advanced real-time gas sensing mechanisms once synchronized to the modeled mode. A substantial quantum of anesthesia-related simulation research has been in the field of airway management, with various studies involving airway techniques and devices being performed regularly [2]. Although there is criticism that such studies are seldom followed up by patient-based studies to validate the simulation data, scenarios like apnea oxygenation in actual patients will be possible only to a certain ethical level of acceptable desaturation. Such experimental simulation-based studies should offer insight into the study of mechanisms and a preliminary understanding of new interventions.

Patient studies involving apnea oxygenation have been performed primarily in operative, emergency departments, and critical care settings [7,8,10]. Outcome parameters range from time to desaturation, the incidence of desaturation, lowest mean saturation reached during intubation, mean saturation in respiratory failure, etc [7, 9-11,13,14,17]. A study on apneic oxygenation comparing trans nasal humidified O₂ therapy versus conventional nasal oxygenation by Rajan et al found a longer desaturation time to 90% in the transnasal humidified group (796 seconds versus 444 seconds) [16]. Similar desaturation times (to 92%) were observed in the present simulation study at 250 ml/min O₂ consumption (915 sec for PO, 1087 sec for PAO) using a nasal cannula at 15L/min. Other studies based on lower apnea oxygenation flows of 5-10L/min had desaturation times (92-95%) ranging from 408 sec to 587 sec [19-21]. Assuming that the O₂ consumption/ pulmonary shunt fraction will be slightly more than ideal in real patients and the differences in flow rates used, the experimental HPS data correlated well with patient data from previous human apnea oxygenation studies.
In the present study, we have compared different nasal oxygenation strategies on the HPS mannequin, varying from no oxygenation, only apnea oxygenation to para-oxygenation to assess the time to desaturate to different time points (92%, 75%, and 50% O₂ saturation). Across all settings, no oxygenation and oxygenation only during apnea had similar desaturation times, and para-oxygenation produced marginally longer desaturation times compared to only pre-oxygenation; both of which were significantly longer than in the earlier 2 settings. The above findings highlight that, without preoxygenation giving only apnea oxygenation does not achieve any additional benefit and 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 consumption settings which can further be extrapolated to varied O₂ demand situations. Comparative findings were similar across all consumption rates. In the current study, only the shunt fraction and O₂ consumption rate were manipulated, but there is scope to simulate complex pulmonary pathologies by adjusting various other physiological parameters to estimate how the actual patient might behave under various conditions like anesthesia and surgery [4]. For example, chest wall compliance factor and bronchial resistance factors can be used to simulate restrictive and obstructive lung pathologies respectively. Different flow rates of nasal oxygenation can also be compared on the HPS similar to what was proposed in the protocol by Theiler et al [22].

**Conclusion**

In the current study, apnea trends in the HPS correlated well with similar prior human experiments, encouraging future use in similar research. Through the simulation experiments, we could deduce that only apnea oxygenation without pre-oxygenation has no added benefit compared to giving no O₂.
Giving high flow O₂ via nasal cannula prolonged desaturating time, in para-oxygenation (PAO) experiment more than only pre-oxygenation (PO). Complex, rare, and potentially dangerous scenarios such as apnea oxygenation can be easily performed in HPS to study patterns of various new interventions without the ethical concerns of exposing real patients.
References


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Table 1: List of respiratory parameters which can be adjusted in the software.

<table>
<thead>
<tr>
<th>Basic Parameters</th>
<th>Additional Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen Tongue</td>
<td>Respiratory Rate</td>
</tr>
<tr>
<td>Shunt Fraction</td>
<td>Chest Wall Compliance Factor</td>
</tr>
<tr>
<td>Airway Occluder</td>
<td>Tidal Volume</td>
</tr>
<tr>
<td>SpO2</td>
<td>Distended Chest Wall Compliance Factor</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Functional Residual Capacity</td>
</tr>
<tr>
<td>NMB</td>
<td>Lung Compliance Factor: Left</td>
</tr>
<tr>
<td>Needle Decompression</td>
<td>Lung Compliance Factor: Right</td>
</tr>
<tr>
<td>Intrapleural Volume: Left</td>
<td>Venous CO2 Shift</td>
</tr>
<tr>
<td>Bronchial Occlusion (Left and Right)</td>
<td>Bronchial Resistance Factor: Left</td>
</tr>
<tr>
<td>Respiratory Rate Factor</td>
<td>Bronchial Resistance Factor: Right</td>
</tr>
<tr>
<td>Intrapleural Volume: Right</td>
<td>Alveolar Enflurane</td>
</tr>
<tr>
<td>ETCO2</td>
<td>CO2 Production Factor</td>
</tr>
<tr>
<td></td>
<td>Fraction of Inspired Enflurane</td>
</tr>
<tr>
<td></td>
<td>PaCO2 Set-point</td>
</tr>
<tr>
<td></td>
<td>Alveolar Halothane</td>
</tr>
<tr>
<td></td>
<td>PaO2 Set-point</td>
</tr>
<tr>
<td></td>
<td>Fraction of Inspired Halothane</td>
</tr>
<tr>
<td></td>
<td>I to E Ratio (1:X)</td>
</tr>
<tr>
<td></td>
<td>Alveolar Isoflurane</td>
</tr>
<tr>
<td></td>
<td>PetCO2-PaCO2 Factor</td>
</tr>
<tr>
<td></td>
<td>Fraction of Inspired Isoflurane</td>
</tr>
<tr>
<td></td>
<td>Respiratory Gain Factor</td>
</tr>
<tr>
<td></td>
<td>Alveolar Nitrous Oxide</td>
</tr>
<tr>
<td></td>
<td>Respiratory Quotient</td>
</tr>
<tr>
<td></td>
<td>Fraction of Inspired Nitrous Oxide</td>
</tr>
<tr>
<td></td>
<td>Volume/Rate Control Factor</td>
</tr>
<tr>
<td></td>
<td>Alveolar Sevoflurane</td>
</tr>
<tr>
<td></td>
<td>Chest Wall Capacity</td>
</tr>
<tr>
<td></td>
<td>Fraction of Inspired Sevoflurane</td>
</tr>
</tbody>
</table>
Table 2: Maximum values of measured parameters at the end of the experiments (fall of saturation to 50%)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>No oxygenation</th>
<th>Only apnea oxygenation</th>
<th>Only pre-oxygenation</th>
<th>Para-oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO2* (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250ml/min</td>
<td>52.13</td>
<td>52.90</td>
<td>72.50</td>
<td>75.10</td>
</tr>
<tr>
<td>500 ml/min</td>
<td>50.67</td>
<td>50.77</td>
<td>62.10</td>
<td>63.17</td>
</tr>
<tr>
<td>750 ml/min</td>
<td>51.87</td>
<td>50.97</td>
<td>64.57</td>
<td>63.90</td>
</tr>
<tr>
<td>pH*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250ml/min</td>
<td>7.35</td>
<td>7.34</td>
<td>7.20</td>
<td>7.18</td>
</tr>
<tr>
<td>500 ml/min</td>
<td>7.36</td>
<td>7.36</td>
<td>7.28</td>
<td>7.27</td>
</tr>
<tr>
<td>750 ml/min</td>
<td>7.35</td>
<td>7.36</td>
<td>7.26</td>
<td>7.26</td>
</tr>
</tbody>
</table>

*Mean of 3 readings
Figure 1: a) Bellows inside the lab rack, b) Umbilical assembly, c) Software for HPS, d) HPS Mannequin
Figure 2: Time to desaturate to 50%, 75%, and 92% oxygen saturation in all four experimental settings at oxygen consumption of 250 ml/min, 500ml/min, and 750 ml/min.
Figure 3: Graphical trend of partial pressure of oxygen in the alveoli and arterial blood in all four experiments across time till 50 % SPO₂, at oxygen consumption rates of 250 ml/min, 500ml/min, and 750 ml/min.