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<td>Mishima, Gaku; Sanuki, Takuro; Revie, James; Pinkham, Max; Watanabe, Toshihiro; Kurata, Shinji; Tatkov, Stanislav; Ayuse, Takao</td>
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Nasal high flow improves ventilation during propofol sedation: A randomized cross-over study in healthy volunteers

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ABSTRACT

Objective: Hypoventilation and carbon dioxide (CO2) retention are common during sedation. The current study investigated the ventilation responses to nasal high flow (NHF) during sedation with propofol.

Methods: NHF of 30 L/min and 60 L/min with room air was applied during wakefulness and sedation in 10 male volunteers. Ventilation was monitored by respiratory inductance plethysmography, transcutaneous partial pressure of CO2 (TcCO2), and SpO2.

Results: During sedation, NHF of 30 L/min and 60 L/min reduced the TcCO2 by 2.9±2.7 mmHg (p = 0.025) and by 3.6±3.4 mmHg (p = 0.024) without affecting SpO2 and reduced the mean respiratory rate by 3±3 breaths/min (p = 0.011) and by 4±3 breaths/min (p = 0.003), respectively.

Conclusion: During sedation with propofol, NHF without supplemental oxygen attenuated CO2 retention and reduced the respiratory rate. The findings show that NHF can improve ventilation during sedation, which may reduce the risk of complications related to hypoventilation.
2. Materials and methods

2.1. Subjects

Ten healthy male volunteers (age 30.5 ± 5.1 years, weight 66.2 ± 6.6 kg, height 169.2 ± 6.1 cm, BMI 23.2 ± 2.8 kg/m²) were recruited and considered eligible if they had no abnormalities during physical examination, no respiratory or heart disease, and no history of any allergy. The study was approved by the International Review Board of Nagasaki University Graduate School of Biomedical Sciences [No. 1395 (Revision 1)] and was performed according to the latest version of the Declaration of Helsinki, whereby written informed consent was obtained for each subject.

2.2. Study design

Each participant was ordered not to eat for at least 8 h and not to drink for at least 2 h before the experiment in accordance with the sedation guideline; they did not receive any premedication. NHF was generated using an integrated blower-humidifier (AIRVO™ 2, Fisher & Paykel Healthcare, Auckland, New Zealand) and delivered via nasal cannula (Optiflow™, Fisher & Paykel Healthcare, Auckland, New Zealand). The study involved three separate visits for each subject and had a cross-over design. The study consisted of three groups: 1) sedation without NHF, 2) sedation + NHF, and 3) wakefulness + NHF. During each visit there were three 5-minute periods of recording; between each intervention there was a 10-minute washout period. The first recording period was a baseline when no NHF was applied. During the second and third recording periods, NHF of 30L/min or NHF of 60L/min was applied in random order (see Table 1 for an outline of the study protocol).

In six of the participants, the ventilation parameters during propofol sedation and no NHF were measured; (1) sedation without NHF, (2) sedation + NHF, and (3) wakefulness + NHF. During each visit there were three 5-minute periods of recording; between each intervention there was a 10-minute washout period. The first recording period was a baseline when no NHF was applied. During the second and third recording periods, NHF of 30L/min or NHF of 60L/min was applied in random order (see Fig. 1 for an outline of the study protocol).

In six of the participants, the ventilation parameters during propofol sedation and no NHF were measured; (1) sedation without NHF, i.e. time control. The average duration of sedation was 39 ± 7 min.

2.3. Experimental protocol

Each participant was maintained in the supine position for the experiment. In the wakefulness + NHF group, the subject remained awake and did not receive propofol sedation. In the two sedation groups, propofol was administered intravenously via the target-controlled-infusion (TCI) system. The dose of propofol was adjusted to achieve a moderate depth of sedation (Bispectral Index (BIS) value of 60–80; response to verbal or tactile stimulation) (see Table 1). Ventilation was monitored using respiratory inductance plethysmography (RIP), (Respitrace QDC; Viasys Services, USA). RIP was performed with one belt placed at the nipple line and one at the level of the umbilicus. Prior to all experiments and before sedation, the subject maintained natural breathing for at least 5 min to assist Respitrace QDC self-calibration (Sackner et al., 1989). Oxygen saturation (SpO2), pulse rate, and the TeCO2 were measured in all subjects (TCM400, Radiometer, Denmark). In only the experiments for propofol sedation, BIS value was measured to determine the depth of sedation. The sensor strip of BIS monitor was placed on the participant’s forehead.

2.4. Sample size analysis

The sample size estimation was calculated to determine how much difference in the RR was of clinical significance. The authors established the standard effect size (0.513 to 0.594) based on data showing that 20 L/min NHF reduced RR of 15.3 ± 9.1 % in healthy volunteers and 22 ± 11.3 % in patients with Chronic Obstructive Pulmonary Disease (COPD) (Braunlich et al., 2013). Six subjects were needed to detect a difference in RR with a type 1 error of 0.05 and a power of 0.8 for a two-tailed paired t-test. Ten subjects were enrolled in the study to account for possible drop-out or failure to obtain measurement.

2.5. Data analysis

The primary outcome was RR and secondary endpoints were inspiratory effort, SpO2, pulse rate, and the TeCO2. The RR was calculated from the peak analysis of the RIP signal. The amplitude of the RIP signal represented the inspiratory effort in volts (V). The QDC calibration of the RIP signal sets 0.40 V as the baseline amplitude for the inspiratory effort in each individual, which was performed prior to sedation. Analog signals were digitized using an ADI PowerLab (ADInstruments, New Zealand), recorded, and then analyzed using LabChart V8.1.13 software (ADInstruments, New Zealand). Two independent anesthesiologists (M. G. and T. S.) performed the experiment and the recordings were sent to blinded researchers who did not know the presence or absence of sedation and level of NHF intervention (J. R., M. P.) for analysis.

3. Statistical analysis

Results are expressed as the mean ± SD unless otherwise stated. GraphPad Prism V8.2.1 (GraphPad Software, USA) was used to perform the statistical analysis. For the time-control study, the effects of time on ventilation were examined using a repeated-measures one-way ANOVA with a Bonferroni post-hoc test. Effects of NHF and difference between sedation vs. awake were examined by repeated measures two-way ANOVA with a Bonferroni post-hoc test. To compare the amplitude of the RIP signal to the calibrated level of 0.4 V, a repeated measures one-way ANOVA with a Dunnet’s post-hoc test was used. The threshold for statistical significance was set at p < 0.05.

<table>
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<th>Table 1</th>
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<td>Changes in effect-site concentration of propofol and BIS values during the three 5-minute intervals when recordings were analyzed. Values recorded during each of the three recording periods.</td>
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<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
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<tr>
<td>No NHF Effect-site concentration of propofol (μg/ mL)</td>
<td>2.1 ± 0.6</td>
<td>2.0 ± 0.7</td>
</tr>
<tr>
<td>BIS values</td>
<td>78 ± 2</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>+ NHF Effect-site concentration of propofol (μg/ mL)</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>BIS values</td>
<td>77 ± 2</td>
<td>76 ± 2</td>
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† Indicates significant difference between time 3 and time 2, P < 0.05. Data is mean ± SD.
4. Results

4.1. Ventilation parameters during sedation

RR, inspiratory effort, TcCO2, and SpO2 remained stable during sedation; however, the heart rate decreased over time by an average of 5 beats/min, \( p = 0.017 \). During sedation, the inspiratory effort was significantly reduced from the pre-sedation QDC-calibrated level of 0.4 V, \( p < 0.05 \). Data is mean ± SD.

4.2. Ventilatory responses to NHF during wakefulness and sedation

The TcCO2 in 7 out of the 10 participants was greater during sedation compared to wakefulness with a mean difference of 3.3 mmHg, \( p = 0.12 \) (see Table 2). In the sedation group, the application of NHF reduced TcCO2 by 3–4 mmHg. The findings suggest that NHF therapy improves ventilation during sedation even in the presence of a decrease in the respiratory rate.

Respiratory depression is common during sedation and can result in hypoxemia and CO2 retention, particularly during prolonged exposure, higher doses of sedative, or in patients with existing airway disease or obesity (Kleinschmidt et al., 1999; Pasero, 2012). In the present study, the ventilation parameters during the propofol sedation were characterized. The individual TcCO2 values remained stable during sedation and were 43–57 mmHg and the inspiratory effort was reduced, consistent with hypoventilation in healthy males (range; 43–57 mmHg).

In response to NHF during sedation, the inspiratory effort increased so that it was no longer different from the pre-sedation QDC calibrated level of 0.4 V. There was a weak correlation between the change in the

5. Discussion

The current study is the first to present the effects of NHF on ventilation during sedation. It shows that during sedation with propofol, NHF without supplemental oxygen attenuates an increase in the partial pressure of transcutaneous CO2. The findings suggest that NHF can improve ventilation during sedation even in the presence of a decrease in the respiratory rate.

Respiratory depression is common during sedation and can result in hypoxemia and CO2 retention, particularly during prolonged exposure, higher doses of sedative, or in patients with existing airway disease or obesity (Kleinschmidt et al., 1999; Pasero, 2012). In the present study, the ventilation parameters during the propofol sedation were characterized. The individual TcCO2 values remained stable during sedation and were 43–57 mmHg and the inspiratory effort was reduced, consistent with hypoventilation in healthy males during moderate sedation with propofol. The application of NHF with room air only and no supplemental oxygen during the propofol sedation reduced the tissue CO2 by 3–4 mmHg. The findings suggest that NHF therapy improves ventilation and attenuates CO2 retention during sedation.

Goodman et al. reported that mild sedation with propofol induced a 30 % decrease in the minute ventilation, which was mediated by a reduction in the tidal volume (Goodman et al., 1987). The suppressed inspiratory effort during sedation can increase the ratio of dead-space ventilation. It is possible that the reduction in dead-space ventilation is available for gas exchange per breath (Pinkham et al., 2019). In addition, NHF during sedation was observed to decrease the RR and increase the inspiratory effort, which further reduces the dead-space ventilation.
respiratory rate by 3 breaths/min (SD 3) during 30 L/min and 4 breaths/min (SD 3) during 60 L/min. In clinical practice, the RR may be used as a measurement of ventilation. However, the RR may not always correlate with the minute ventilation (Holley et al., 2016). The authors analyzed the relationship between the change in the RR and tissue CO2 in response to NHF; the correlations were weak and the coefficient of determination, R², values ranged between 0.005 and 0.153. The current findings suggest that during NHF a decrease in the RR can occur in the presence of improved ventilation, as measured by a decrease in tissue CO2. Therefore, the changes in RR in response to NHF should be considered carefully in the context of the respiratory support mechanisms.

Prior to the study, it was unknown whether the ventilatory responses to NHF during sedation would be similar to wakefulness or sleep. In the present study, the ventilation responses to NHF during sedation and wakefulness were similar. Mündel et al. investigated the ventilatory responses to NHF during awake and natural sleep in healthy volunteers (Mundel et al., 2013). During wakefulness, NHF led to a reduction in the RR, an increase in the tidal volume, and no change in the minute ventilation, similar to the responses observed in the current study. However, during wakefulness the tissue CO2 was unaltered in response to NHF whereas during sedation the tissue CO2 was reduced. It is unclear how NHF induces different ventilation responses during sedation when compared to wakefulness.

Sedation and natural non-REM sleep are consistent in terms of a loss of consciousness. However, there are major differences in brain functional connectivity between propofol sedation and natural sleep (Güldenmund et al., 2017). A recent study using EEG concluded that propofol sedation does not produce physiological sleep (Akeju and Brown, 2017). The precise mechanism for the difference between the ventilatory responses to NHF during natural sleep and sedation has not been examined. To determine this, the effect of NHF on the ventilatory responses during sedation using other sedative agents which resemble natural sleep, such as Dexmedetomidine, should be investigated.

5.1. Strengths and limitations

The main strength of the current study is the experimental design which investigated the ventilatory responses to NHF during both propofol sedation and during wakefulness in same the subject. The cross-over design of the study reduced the influence of natural variation in physiological responses to NHF that may be observed between different individuals and in different contexts. The main limitation of this study is that the subjects were young, healthy volunteers and the level of sedation was mild. Therefore, the results may not apply to other populations such as subjects with respiratory disease or a different sedation level. Another limitation was that the RIP signal was un-calibrated and the breathing volumes were unknown. Further research using calibrated RIP will better determine the effects of NHF during various sedatives.

5.2. Conclusion

The current study shows that during sedation with propofol, NHF without supplemental oxygen attenuates CO2 retention and reduces the respiratory rate. The findings suggest that NHF can improve ventilation during sedation, which may reduce the risk of complications related to hypventilation.

Authors’ contributions

(Gaku Mishima and Takuro Sanuki equally contributed to this study.)

Study design: G. M., T. A., T. A.
Data collection: G. M., T. S., T. W., S. K.
Data analysis: J. R., M. P., S. T.
Statistical analysis and advice: J. R., M. P., S. T., T. A.

Writing up the draft of the manuscript: G. M., T. S., J. R., M. P., S. T., T. A.


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Declaration of Competing Interest

J. R., M. P., and S. T. are employees of Fisher & Paykel Healthcare Ltd, the manufacturers of the nasal high flow (NHF) devices used in the study. T. A. has received funding and support from Fisher & Paykel Healthcare Ltd. G. M., T. S., T. W., and S. K. have no declaration of interest.

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