Carbon Dioxide Changes during High-flow Nasal Oxygenation in Apneic Patients: A Single-center Randomized Controlled Noninferiority Trial

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ANESTHESIOLOGY 2022; 136:82–92

EDITOR’S PERSPECTIVE

What We Already Know about This Topic

• Apneic oxygenation during surgery may be required to facilitate surgical interventions involving the airway or may occur during intubation or emergence
• Controversy over the past 60 yr remains about the rate of rise of carbon dioxide during apneic oxygenation
• Initial studies with high-flow humidified nasal oxygen therapy reported lesser than historical carbon dioxide increases during apnea, suggesting a ventilatory effect on carbon dioxide elimination
• Subsequent randomized data in pediatric patients disputed these observations

What This Article Tells Us That Is New

• Adults undergoing elective surgery underwent preoxygenation, standardized anesthetic induction, and randomization to 15 min of apneic oxygenation via endotracheal tube (0.25 l/min), or high-flow nasal oxygen (2 to 70 l/min) with jaw thrust or with laryngoscopy
• The primary outcome was the linear rate of increase of arterial carbon dioxide, with a predetermined noninferiority margin of 0.3 mmHg · min⁻¹ between groups
• All groups met the noninferiority criteria and with comparable arterial partial pressures of carbon dioxide

ABSTRACT

Background: Anesthesia studies using high-flow, humidified, heated oxygen delivered via nasal cannula at flow rates of more than 50 l · min⁻¹ postulated a ventilatory effect because carbon dioxide increased at lower levels as reported earlier. This study investigated the increase of arterial partial pressure of carbon dioxide between different flow rates of 100% oxygen in elective anesthetized and paralyzed surgical adults before intubation.

Methods: After preoxygenation and standardized anesthesia induction with nondepolarizing neuromuscular blockade, all patients received 100% oxygen (via high-flow nasal oxygenation system or circuit of the anesthesia machine), and continuous jaw thrust/laryngoscopy was applied throughout the 15-min period. In this single-center noninferiority trial, 25 patients each, were randomized to five groups: (1) minimal flow: 0.25 l · min⁻¹, endotracheal tube; (2) low flow: 2 l · min⁻¹, continuous jaw thrust; (3) medium flow: 10 l · min⁻¹, continuous jaw thrust; (4) high flow: 70 l · min⁻¹, continuous jaw thrust; and (5) control: 70 l · min⁻¹, continuous laryngoscopy. Immediately after anesthesia induction, the 15-min apnea period started with oxygen delivered according to the randomized flow rate. Serial arterial blood gas analyses were drawn every 2 min. The study was terminated if either oxygen saturation measured by pulse oximetry was less than 92%, transcutaneous carbon dioxide was greater than 100 mmHg, pH was less than 7.1, potassium level was greater than 6 mmol · l⁻¹, or apnea time was 15 min. The primary outcome was the linear rate of mean increase of arterial carbon dioxide during the 15-min apnea period computed from linear regressions.

Results: In total, 125 patients completed the study. Noninferiority with a predefined noninferiority margin of 0.3 mmHg · min⁻¹ could be declared for all treatments with the following mean and 95% CI for the mean differences in the linear rate of arterial partial pressure of carbon dioxide with associated P values regarding noninferiority: high flow versus control, −0.0 mmHg · min⁻¹ (−0.3, 0.3 mmHg · min⁻¹, P = 0.030); medium flow versus control, −0.1 mmHg · min⁻¹ (−0.4, 0.2 mmHg · min⁻¹, P = 0.002); low flow versus control, −0.1 mmHg · min⁻¹ (−0.4, 0.2 mmHg · min⁻¹, P = 0.003); and minimal flow versus control, −0.1 mmHg · min⁻¹ (−0.4, 0.2 mmHg · min⁻¹, P = 0.004).

Conclusions: Widely differing flow rates of humidified 100% oxygen during apnea resulted in comparable increases of arterial partial pressure of carbon dioxide, which does not support an additional ventilatory effect of high-flow nasal oxygenation.

(ANESTHESIOLOGY 2022; 136:82–92)
apnea period and a slower increase of carbon dioxide than previously described. This approach was named trans-nasal humidified rapid insufflation ventilatory exchange (THRIVE). The ventilatory effect obtained was reproduced by another research group, and simulation models supported the concept of improved carbon dioxide clearance during high-flow apneic oxygenation. A computer simulation showed that a cascade vortex flow produced by turbulence continuously flowing down the trachea into the alveoli under high-flow nasal oxygenation with an open mouth might lead to a carbon dioxide washout, explaining the ventilatory effect initially described. Carbon dioxide clearance is important, as increased arterial partial pressure of carbon dioxide (PaCO_2) causes acidosis and increases blood pressure, heart rate, and/or cerebral blood flow. Over time, increased carbon dioxide levels limit apneic oxygenation. During the first minute of apnea, PaCO_2 increases rapidly by 12.0 to 13.0 mmHg; thereafter, it increases by ~3.0 to 5.0 mmHg/min. Studies investigating THRIVE showed an end-expiratory carbon dioxide increase of ~1.1 to 1.8 mmHg/min during apnea, much lower than the historic controls investigating the increase in carbon dioxide during apnea.

Studies in pediatric patients described similar rates of carbon dioxide increase during apneic oxygenation using high-flow nasal oxygenation but with different flow rates, thus questioning the impact of flow on carbon dioxide clearance in children. The null hypothesis of this randomized controlled noninferiority trial was that there is a detectable difference in the linear rates of mean increase of arterial carbon dioxide between different flow rates (0.25/2/10 and 70 L/min) during the apneic period after induction of general anesthesia and neuromuscular blockade in adults computed by a linear regression.

Materials and Methods

With approval from the Cantonal Ethics Committee of Bern (2018-00293) and registration at ClinicalTrials.gov (NCT NCT03478774, primary investigator: Lorenz Theiler, date of registration: March 27, 2018), we performed this five-armed single-center randomized controlled non-inferiority trial in the Department of Anaesthesiology and Pain Medicine at the Bern University Hospital, University of Bern, Bern, Switzerland, between March 2018 and December 2019. The methods for this project have been published; however, some changes were necessary after its publication, which are explained in detail below.

Study Participants

Eligible adult patients scheduled for elective surgery under general anesthesia were identified from operating room lists. After screening for inclusion and exclusion criteria, the patients were recruited during the standard preadmission clinic visit, and written informed consent was obtained by the research team.

Inclusion criteria were age more than 18 and less than 80 yr of age and had American Society of Anesthesiologists (ASA) physical status of I to III, the ability to speak German or French, and the ability to understand the purpose of the study. Exclusion criteria were the need for flexible optic intubation, expected difficult mask ventilation, known coronary heart disease, known heart failure with New York Heart Association classification of 2 or higher, arrhythmias requiring antiarrhythmic therapy (e.g., implanted cardioverter defibrillator), peripheral occlusive arterial disease with a clinical classification higher than Fontaine 2b, treatment with β-receptor antagonists, known stenosis of the (common or internal) carotid or vertebral arteries, body mass index of more than 35 kg/m^2 or less than 16 kg/m^2, hyperkalemia (potassium level greater than 5.5 mmol/L), chronic obstructive pulmonary disease Gold classification of 2 or higher, known systolic pulmonary artery pressure greater than 35 mmHg, known obstructive sleep apnea syndrome requiring therapy, high risk of aspiration requiring rapid sequence intubation, known increased intracranial pressure, neurosurgical patients scheduled for intracranial surgery, anaemia with hemoglobin less than 100 g/L, pregnancy (a pregnancy test was performed in all fertile female patients before anesthesia), known neuromuscular disorders, known or suspected cervical spine instability, nasal obstruction with impossibility of nasal ventilation (both nares had to be patent), and allergies to or contraindications to use of one or more of the anesthesia agents used in the study protocol.

Study Procedures

After arriving in the operating room, the patients were monitored according to the local standard of care, including electrocardiogram, peripheral oxygen saturation (SpO_2), noninvasive blood pressure, end-tidal carbon dioxide (ETCO_2), and train of four (TOF-Watch; Organon Ltd., Ireland). Intravenous and ultrasound-guided intravascular access was established. Additionally, two monitors for transcutaneous measurement of carbon dioxide and oxygen (transcutaneous measurement monitors 4 and 5; both from Radiometer, Germany) were attached to the right anterior thorax at the third intercostal space. Furthermore, thoracic electrical impedance tomography (PulmoVista 500; Draeger, Germany) was used to monitor atelectasis formation and absence of diaphragmatic movements. To measure the depth of anesthesia during the apneic period, we recorded processed frontal electroencephalography (Narcotrend, Germany).

After standard preoxygenation (to end-tidal oxygen greater than 90%), anesthesia was induced using a target-controlled infusion of propofol (plasma concentration, 2.5 to 4.0 μg/mL) and remifentanil (plasma concentration, 2.5 to 6.5 ng/mL). The depth of anesthesia was targeted to...
Narcotrend index values between 35 and 55. Rocuronium (0.6 to 0.9 mg · kg⁻¹) was used for neuromuscular blockade; adequacy was verified with a train-of-four value of 0 before the onset of apnea and every 5 min throughout the procedure and by visual absence of diaphragmatic movements in the electrical impedance tomography. Hypotension (defined as reduction of 20% from the baseline value, measured pre-operatively on the ward) due to anesthetic drugs was counteracted with a continuous infusion of norepinephrine.

After successful facemask ventilation was established, a sealed opaque envelope was opened. Patients were randomly allocated to one of five study groups, and the apneic period was started. Randomization was computer generated (www.randomization.com, accessed October 7, 2021), and patients were stratified in blocks of five according to body mass index (16 to 25 kg · m⁻², 25.1 to 30 kg · m⁻², and 30.1 to 35 kg · m⁻²) and smoking status (nonsmoker, former smoker, daily smoker 40 yr of age or less, and daily smoker of greater than 40 yr of age). Patients were blinded to their group allocation; blinding of study personnel was not feasible due to the study setup. Randomization was kept in sequentially numbered opaque envelopes, which were opened just before anesthesia induction by the research team.

Inspired oxygen concentration was 1.0 in all patients. High-flow humidified oxygen was delivered via a high-flow nasal cannula of adequate size (small to large, occlusion of maximum 50% of nostrils; Optiflow MR 850 system, Fisher & Paykel, New Zealand). The medium-flow and low-flow humidified oxygen was delivered using Aquapak Hudson RCI (Teleflex, USA) and a flow-meter (Carbamed digiflow, Switzerland) using a standard nasal cannula (O₂-Star curved nasal cannula, Dräger, Germany). We delivered minimal-flow oxygen via a standard endotracheal tube, using the circuit of a Dräger Primus anesthesia machine to ensure the delivery of exactly 0.25 l · min⁻¹.

The five study groups included four experimental groups and one control group:

(i) Minimal-flow group: 0.25 l · min⁻¹ oxygen via endotracheal tube (additional study arm, which was added after publication of the initial study protocol)
(ii) Low-flow group: 2 l · min⁻¹ oxygen + continuous jaw thrust
(iii) Medium-flow group: 10 l · min⁻¹ oxygen + continuous jaw thrust
(iv) High-flow group: 70 l · min⁻¹ oxygen + continuous jaw thrust
(v) Control group: 70 l · min⁻¹ oxygen + continuous laryngoscopy with a McGrath MAC video laryngoscope (Medtronic, Ireland)

Upper airway patency was visually confirmed using a nasopharyngeal fiberscope (EF-N slim, Acutronic, Switzerland) directly after the start of apnea and at 7 min and 14 min into the apnea period. If airway patency was not achieved, an oropharyngeal tube (Guedel airway, Intersurgical, United Kingdom) was inserted. If airway patency still was not achieved, the study intervention would have been terminated.

The predefined study termination criteria were: Spo₂ less than 92%, transcutaneous carbon dioxide greater than 100 mmHg, pH less than 7.1, potassium greater than 6 mmol · l⁻¹, and apnic period reaching 15 min. If any of these criteria were attained, apnea was terminated (termination of study period), and bag-mask ventilation was commenced. Airway management was then performed according to the discretion of the attending anesthesiologist. After intubation, a standardized manual airway recruitment maneuver was performed. The recruitment maneuver consisted of sustained manual inflations of the anesthesia reservoir bag to a peak inspiratory pressure of 40 cm H₂O for 15 s.

Throughout the study, serial arterial blood samples for blood gas analysis (ABL 800, Radiometer) were drawn and analyzed in our central laboratory: awake, immediately after apnea start and 1 min later, then every 2 min, and 10 min after the end of the study period. A safety interview was conducted on the first postoperative day to evaluate side effects and possible injuries during airway management.

Measurements

The recorded patient baseline characteristics included sex, age, height, weight, body mass index, smoking status (smoker, ex-smoker, pack years), ASA physical status, dental prosthesis, and the surgical discipline (visceral, orthopedics, thoracic/neuro). Vital signs (invasive continuous blood pressure, heart rate, Spo₂, ETco₂, transcutaneous carbon dioxide, and blood gas parameters (pH, Paco₂, Pao₂, and potassium) were recorded. The amount of the drug delivered was recorded, as well as any side effects (e.g., sore throat, hoarseness, pain, postoperative nausea and vomiting) on the first postoperative day.

In our published methods article, we defined the increase in transcutaneous carbon dioxide as the primary outcome parameter and Paco₂ as a secondary outcome parameter. However, very early in the experiment, we realized that there were discrepancies in the values of transcutaneous carbon dioxide measurements. This was confirmed when we installed a second system for transcutaneous measurement, distributed by the same manufacturer. Because it was impossible to determine which transcutaneous measurement was the correct one, we decided to rely on Paco₂ measurements instead, using them as the primary outcome. The results of the transcutaneous carbon dioxide values are provided in the Supplemental Digital Content (http://links.lww.com/ALN/C735).

The primary outcome parameter was therefore the mean increase in Paco₂ in mmHg · min⁻¹ during the 15-min apnea period. Secondary outcomes were the number of patients who desaturated before the end of the predefined apnea period and the time (in minutes) until desaturation from Spo₂ 100 to 92% (measured by pulse oximetry).
Statistical Analysis

The linear increase in $\text{Paco}_2$ over 15 min (mmHg $\cdot$ min$^{-1}$) was computed via linear regression for each patient, resulting in a distribution for the linear $\text{Paco}_2$ increase for each treatment group. For the noninferiority test, the null hypothesis stated that the difference of mean linear increase of $\text{Paco}_2$ between any of the four experimental groups and the control group rates of 100% oxygen in apneic, anesthetized, and paralyzed adults after induction of anesthesia before intubation was at least $\delta = 0.3$ mmHg $\cdot$ min$^{-1}$ (non-inferiority margin).

Data from published literature suggest that patients in the control group should have a low linear increase in $\text{Paco}_2$ of 0.9 mmHg $\cdot$ min$^{-1}$. A value of 0.3 mmHg $\cdot$ min$^{-1}$ would result in a total increase of 4.5 mmHg over a 15-min apnea period. We defined this as clinically acceptable, because the normal range of $\text{Paco}_2$ is 35.0 to 46.0 mmHg.

To test the noninferiority hypothesis, a 0.025 $\alpha$-level was used, which corresponds to a two-sided 95% ($100 \times (1 - 2\alpha)$) CI. We declared noninferiority if the upper limit of the 95% CI of the difference in mean linear increase of $\text{Paco}_2$ was below the predefined noninferiority margin of $\delta = 0.3$ mmHg $\cdot$ min$^{-1}$. Normality of the individual linear rates in $\text{Paco}_2$ was assessed using a Shapiro–Wilk test. To account for multiple testing across the four noninferiority tests for each comparison of a treatment group with the control group, the noninferiority declarations and the associated $P$ values were based on simultaneous CI computed with the single-step Dunnett procedure.$^{15}$

Three sensitivity tests to assess the robustness and dependence of the declaration of noninferiority on the underlying blood sample measurements were performed. The reference case is denoted as “raw data” and includes missing blood sample measurements for some patients at varying time points. The “complete data” sensitivity test considers only those patients for whom blood sample measurements are available for each time point. The sensitivity test denoted as “imputed data” is based on imputed missing values computed with the predictive mean matching as imputation method. To allow for an adjustment period after the induction of apnea, the sensitivity test “complete data + adjustment” considers only blood sample measurements from the second half of the apnea period (minutes 7 to 15).

The Supplemental Digital Content (http://links.lww.com/ALN/C735) shows the detailed analysis as outlined in the published study protocol using a linear mixed-effect model and the outcome parameter of transcutaneous carbon dioxide for transcutaneous measurement monitors 4 and 5 (Supplemental Digital Content figs. I through VI and tables I through VIII, http://links.lww.com/ALN/C735).

To calculate the necessary sample size, a difference in linear group means a $\text{Paco}_2$ of 3 mmHg $\cdot$ min$^{-1}$ was necessary; assuming a SD of 0.353 mmHg $\cdot$ min$^{-1}$, 22 patients were required per group (based on a one-sided $\alpha$-value of 0.025 and a power of 80%). We therefore decided to include 25 patients/group.

The data are reported as means $\pm$ SD or percentage; a probability of less than 0.05 was considered significant. All statistical analyses were performed with R (R Core Team, R Foundation for Statistical Computing, Austria).

Results

All patients were included in the analysis. The apnea period of 15 min was completed by 95% of all patients, irrespective of the treatment group. Baseline characteristics of the 125 participants were comparable (25 per group) and are summarized in table 1. Figure 1 shows the study consort flow diagram.

### Table 1. Patient Baseline Characteristics

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<tr>
<td>Female, n (%)</td>
<td>10 (40)</td>
<td>10 (40)</td>
<td>14 (56)</td>
<td>9 (36)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>46 $\pm$ 15</td>
<td>47 $\pm$ 17</td>
<td>48 $\pm$ 19</td>
<td>48 $\pm$ 19</td>
<td>46 $\pm$ 18</td>
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<td>Height, cm</td>
<td>174 $\pm$ 7</td>
<td>172 $\pm$ 9</td>
<td>170 $\pm$ 8</td>
<td>173 $\pm$ 10</td>
<td>170 $\pm$ 8</td>
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<tr>
<td>Weight, kg</td>
<td>78 $\pm$ 13</td>
<td>76 $\pm$ 14</td>
<td>71 $\pm$ 14</td>
<td>75 $\pm$ 18</td>
<td>70 $\pm$ 12</td>
</tr>
<tr>
<td>Body mass index, kg $\cdot$ m$^{-2}$</td>
<td>26 $\pm$ 3.5</td>
<td>25 $\pm$ 3.3</td>
<td>24 $\pm$ 3.3</td>
<td>25 $\pm$ 4.5</td>
<td>24 $\pm$ 3.7</td>
</tr>
<tr>
<td>Smoking status*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>8 (32)</td>
<td>11 (44)</td>
<td>6 (24)</td>
<td>6 (24)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1 (4)</td>
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<tr>
<td>Pack years, yr</td>
<td>18 $\pm$ 3</td>
<td>23 $\pm$ 15</td>
<td>9 $\pm$ 7</td>
<td>2</td>
<td>15 $\pm$ 20</td>
</tr>
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<td>ASA physical status, n (%)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (42)</td>
<td>6 (24)</td>
<td>3 (12)</td>
<td>6 (24)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>II</td>
<td>13 (54)</td>
<td>16 (64)</td>
<td>21 (84)</td>
<td>18 (72)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>III</td>
<td>1 (4)</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>3 (12)</td>
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<tr>
<td>Dental prosthesis, n (%)</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

The values are number (proportion) or mean $\pm$ SD.

*Smoking status, missing for two patients in the medium-flow group.

ASA, American Society of Anesthesiologists.
Figure 2A shows the trajectories of Paco2 for all study groups. Figure 2B shows the mean rate of changes in Paco2 over the observation period. Absolute Paco2 increases over time (means ± SD), and associated linear increase rates were: minimal flow, 32.0 ± 5.6 mmHg (2.0 ± 0.3 mmHg min⁻¹); low flow, 31.2 ± 5.5 mmHg (2.0±0.4 mmHg min⁻¹); medium flow, 29.6 ± 5.8 mmHg (2.0 ± 0.4 mmHg min⁻¹); high flow, 32.0 ± 7.6 mmHg (2.1 ± 0.5 mmHg min⁻¹); and high flow (control), 33.2 ± 7.0 mmHg (2.1 ± 0.4 mmHg min⁻¹). The Supplemental Digital Content table XII (http://links.lww.com/ALN/C735) shows the sensitivity testing of the linear rates of changes in arterial carbon dioxide.

Figure 3 shows the noninferiority of all four experimental groups compared to the control group. The upper limit of a two-sided 95% CI for the mean difference in the linear rate of Paco2 increase was below the predefined noninferiority margin of 0.3 mmHg · min⁻¹ in all experimental groups. Means and 95% CIs for the mean differences in the linear rate of Paco2 with associated P values regarding noninferiority are as follows: high flow versus control, –0.0 mmHg · min⁻¹ (–0.3, 0.3 mmHg · min⁻¹, P = 0.030); medium flow versus control, –0.1 mmHg · min⁻¹ (–0.4, 0.2 mmHg · min⁻¹, P = 0.002); low flow versus control, –0.1 mmHg · min⁻¹ (–0.4, 0.2 mmHg · min⁻¹, P = 0.003); and minimal flow versus control, –0.1 mmHg · min⁻¹ (–0.4, 0.2 mmHg · min⁻¹, P = 0.004).

Three sensitivity tests assessed and confirmed the overall noninferiority of the four experimental groups compared to the control group. All but one upper limit of the two-sided
95% CI for the mean difference in the linear rate of \( \text{Paco}_2 \) in all sensitivity tests over all group comparisons was below the predefined noninferiority margin of 0.3 mmHg ∙ min^{-1}. Only when high flow was compared with the control did the 95% CI of the sensitivity analysis using the complete data + adjustment exceed the noninferiority margin by 0.0 mmHg ∙ min^{-1} (\( P = 0.060 \)). The complete data + adjustment approach considers only blood sample measurements from the second half of the apnea period (minutes 7 to 15) to allow for an adjustment period after the induction of apnea. It is noteworthy that the additional constraints on data availability in these sensitivity tests may reduce the number of available patients, which reduces the power to detect a statistically significant noninferiority difference.

As a further sensitivity test, the entire noninferiority analysis was additionally computed with a mixed-effects regression model. The same conclusions regarding the non-inferiority were found, which highlights the robustness of our findings (compare Supplemental Digital Content figs. I through VI and tables I through VII, http://links.lww.com/ALN/C735).

Table 2 shows the means ± SD linear rates of increase in transcutaneous measurement of carbon dioxide over time with transcutaneous measurement monitor 4, and table 3 shows the results with transcutaneous measurement monitor 5. No one met the study termination criterion of an increase in transcutaneous carbon dioxide above 100 mmHg. In six patients (5%), the \( \text{Spo}_2 \) level decreased less than 92% (one in...
the minimal-flow group, two in the low-flow group, one in the medium-flow group, and two in the high-flow (control) group. One patient in the minimal-flow group and one in the high-flow (control) group desaturated after 7 min. The two patients in the low-flow group desaturated after 9 min, while one patient in the medium-flow group and one patient in the high-flow (control) group desaturated after 13 min. In patients who met a termination criterion, bag-mask ventilation was commenced immediately. All patients reached an SpO2 level of greater than 92% before airway management.

There was no difference in the incidence of hoarseness, sore throat, headache, or nausea and vomiting between the treatment groups. The next day, 21 patients reported a dry nose (minimal flow, 1; low flow, 5; medium flow, 1; high flow, 4; and high flow [control], 10).

During the postoperative safety interview, one patient reported suffering from eye lacrimation and nasal irritation caused by inadvertent drying of water in the humidifying systems. The symptoms disappeared within 3 days after surgery. No other adverse events were recorded.

**Discussion**

This single-center randomized controlled noninferiority trial demonstrates that the rate of carbon dioxide increase during apneic oxygenation is noninferior to high-flow nasal oxygenation at 70 l·min⁻¹ flow with continuous laryngoscopy to ensure a patent airway. Flow rates for 100% oxygen varied between 0.25 and 70 l·min⁻¹, and carbon dioxide accumulation was comparable in all conditions; therefore, our results suggest the absence of an additional ventilatory effect attributed to high-flow nasal oxygenation in adults.

There was a marked discrepancy between the values measured with the two transcutaneous carbon dioxide monitoring devices of the same manufacturer. This made it difficult to decide which monitor would provide the correct data. To base our primary outcome (rate of carbon dioxide increase) on solid, verifiable measurements, only the analyses of PaCO2 increase (measured every 2 min by arterial sampling) were used in the model calculations.
High-flow nasal oxygenation is an established method used to improve alveolar oxygen concentration during intubation,\textsuperscript{16–19} preoxygenation,\textsuperscript{17,20} awake flexible optic intubation,\textsuperscript{18} intubation of morbidly obese patients,\textsuperscript{19} and endoscopic airway surgery in adults.\textsuperscript{21} Additionally, high-flow nasal oxygenation was successfully used during pediatric airway surgery where an endotracheal tube would have blocked the surgical field\textsuperscript{22} and during induction of anesthesia for healthy children.\textsuperscript{23}

The main limitation of apneic oxygenation is carbon dioxide accumulation, which causes cardiovascular complications and respiratory acidosis caused by hypercapnia.\textsuperscript{7,24} Previous studies reported a carbon dioxide increase of 1.1 to 3.4 mmHg ∙ min\textsuperscript{−1} during apneic oxygenation under general anesthesia.\textsuperscript{1,7,10,24} Another group reported a high mean increase in Paco\textsubscript{2} of 12 mmHg in the first minute and after that a slower increase of 3.4 mmHg ∙ min\textsuperscript{−1} in the ensuing 5 min.\textsuperscript{10} Others observed a transcutaneous carbon dioxide rise of 2.3 mmHg ∙ min\textsuperscript{−1} during apneic oxygenation using buccal oxygen with flows of 10 l ∙ min\textsuperscript{−1}.\textsuperscript{25}

Upon first publication of the concept of high-flow nasal oxygenation, the study authors reported an increase of only 1.1 mmHg ∙ min\textsuperscript{−1} for ETco\textsubscript{2} with high-flow nasal oxygenation—only one third of the rate observed with historical controls. Therefore, the study authors postulated that high-flow nasal oxygenation has a ventilatory effect and created the acronym THRIVE.\textsuperscript{1}

Further studies have shown improved carbon dioxide elimination in adults.\textsuperscript{3,26} In apneic patients undergoing laryngeal surgery, one research group reported an increase of 0.9 mmHg ∙ min\textsuperscript{−1} in ETco\textsubscript{2} using the same method; however, the same study showed an increase in Paco\textsubscript{2} of 1.8 mmHg ∙ min\textsuperscript{−1}.\textsuperscript{1,3} In the initial study of the concept of high-flow nasal oxygenation, the rise in ETco\textsubscript{2} was compared to the rise in the Paco\textsubscript{2} of historical controls.\textsuperscript{1} It may not account for the increasing arterial-to-alveolar gradient with progressive apnea.\textsuperscript{27}

A further potential reason that our results differ might be that the authors used historical controls from the 1950s rather than performing a prospective randomized controlled trial. The effects of high carbon dioxide levels on the sympathetic nervous system was hard to control in early studies. We therefore meticulously followed a protocol to keep blood pressure, heart rate, and depth of anesthesia in a tight range of values. That way, we tried to rule out the influence of different levels of depth of anesthesia resulting in different activation of the sympathetic system. Our results showed a mean increase in Paco\textsubscript{2} between 2.0 and 2.1 mmHg ∙ min\textsuperscript{−1} for all study groups, well within the difference of our predefined noninferiority margin. These values are comparable to the 1.8 mmHg ∙ min\textsuperscript{−1} reported previously.\textsuperscript{3} One possible explanation that these values are lower than those of earlier reports is that modern anesthesia might reduce metabolism substantially, resulting in far less carbon dioxide production, which in turn results in less carbon dioxide increase, leading

### Table 2. Linear Rates in Increase of Transcutaneous Carbon Dioxide per Minute with Transcutaneous Measurement Monitor 4

<table>
<thead>
<tr>
<th>Data</th>
<th>Minimal Flow (n = 23)</th>
<th>Low Flow (n = 24)</th>
<th>Medium Flow (n = 23)</th>
<th>High Flow (n = 22)</th>
<th>High Flow (Control; n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw data</td>
<td>2.1 ± 0.5</td>
<td>1.9 ± 0.5</td>
<td>1.6 ± 0.4</td>
<td>1.9 ± 0.7</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>Complete data</td>
<td>2.1 ± 0.5</td>
<td>1.9 ± 0.5</td>
<td>1.6 ± 0.4</td>
<td>1.9 ± 0.7</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Complete data + adjustment</td>
<td>1.9 ± 0.4</td>
<td>1.7 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.7 ± 0.7</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Imputed data</td>
<td>2.0 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>1.6 ± 0.4</td>
<td>1.9 ± 0.7</td>
<td>1.9 ± 0.5</td>
</tr>
</tbody>
</table>

The data are means ± SD. The units are in mmHg ∙ min\textsuperscript{−1}. The number of patients in each group may differ across the sensitivity tests due to missing data measurements. The reference case is denoted as raw data and includes missing blood sample measurements for some patients at varying time points. The complete data sensitivity test considers only those patients for whom blood sample measurements are available for each time point. The sensitivity test denoted as imputed data is based on imputed missing values computed with the predictive mean matching as imputation method. To allow for an adjustment period after the induction of apnea, the sensitivity test complete data + adjustment considers only blood sample measurements from the second half of the apnea period (minutes 7 to 15). (Transcutaneous measurement monitor 4 [Radiometer, Germany].)

### Table 3. Linear Rates in Increase of Transcutaneous Carbon Dioxide per Minute with Transcutaneous Measurement Monitor 5

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Raw data</td>
<td>1.7 ± 0.8</td>
<td>1.7 ± 0.4</td>
<td>1.4 ± 0.5</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Complete data</td>
<td>1.7 ± 0.8</td>
<td>1.7 ± 0.3</td>
<td>1.4 ± 0.5</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Complete data + adjustment</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.4</td>
<td>1.3 ± 0.5</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Imputed data</td>
<td>1.7 ± 0.8</td>
<td>1.5 ± 0.6</td>
<td>1.4 ± 0.5</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.5</td>
</tr>
</tbody>
</table>

The data are means ± SD. The units are in mmHg ∙ min\textsuperscript{−1}. The number of patients in each group may differ across the sensitivity tests due to missing data measurements. The reference case is denoted as raw data and includes missing blood sample measurements for some patients at varying time points. Please refer to table 2 for a detailed description of the three sensitivity studies (complete data, complete data + adjustment, and imputed data). (Transcutaneous measurement monitor 5 [Radiometer, Germany].)
to a substantially prolonged apneic oxygenation period. However, future studies need to confirm this.

None of these high-flow nasal oxygenation studies compared different flow rates. Our study compared an increase in carbon dioxide at different flow rates, thus showing the absence of a relevant ventilatory effect caused by a higher flow of nasal oxygen. Because there was no significant difference between the high-, medium-, low-, and minimal-flow study groups, a ventilatory carbon dioxide clearance caused by the high flow of high-flow nasal oxygenation can be excluded.

Only three randomized controlled trials on high-flow nasal oxygenation report PaCO₂ or transcutaneous carbon dioxide measurements, and they are all pediatric studies. One study found no difference with or without high-flow nasal oxygenation and reported an increase in carbon dioxide of 2.4 (range, 0.2 to 3.9) mmHg/min for both groups.28 Another study reported a comparable carbon dioxide rate increase of 4.3 (interquartile range, 3.8 to 4.7) mmHg/min without and 4.1 (interquartile range, 3.2 to 4.6) mmHg/min with high-flow nasal oxygenation.23 These studies also failed to show a flow-dependent ventilatory effect at flow rates of up to 2 l·kg⁻¹·min⁻¹.23,28 In response to criticism that 2 l·kg⁻¹·min⁻¹ might be not equivalent to the adult rate of 70 l·kg⁻¹ considered to be high flow, a recent study even confirmed the absence of a flow-dependent ventilatory effect of high-flow nasal oxygenation in small children at flow rates of 4 l·kg⁻¹·min⁻¹.23,41

The lungs are oxygenated during apnea, when oxygen reaches the alveoli after passing through the upper airways. There is a ventilatory mass flow of oxygen from the unobstructed upper airways in the direction of the alveoli generated by higher alveolar oxygen extraction from the alveoli and lower carbon dioxide diffusion into the alveoli. This creates a subatmospheric alveolar pressure that triggers the oxygen flow into the alveoli. This leads to the substantially prolonged safe apnea period observed by the application of high-flow nasal oxygenation. Applying humidified instead of dry oxygen over longer apneic periods preserves the integrity and function of the respiratory mucosa.29,30

When a mouth is open, the turbulent supraglottic gas flow of high-flow nasal oxygenation loops around the soft palate, exits the mouth, and is responsible for a continuous flushing of the oral and pharyngeal cavity with fresh oxygen from the cannula. A recently published study by our research group dismissed the purported mechanism of positive airway pressure generation by high-flow nasal oxygenation in the trachea and bronchi when the mouth is open.31 Cardiogenic oscillations remain the only physiologic mechanism explaining carbon dioxide elimination during apneic oxygenation. Cardiac contractions in the thoracic cavity compress and expand the small airways, causing these cardiogenic oscillations with a gas movement of 10 to ~30 ml/heartbeat.32,33 This bidirectional air movement is responsible for minor gas transport; it is independent of nasal oxygen flow rates.

Limitations

The post hoc change of the primary outcome parameter (as explained under “Materials and Methods”) could be regarded as a limitation of our study; however, the Supplemental Digital Content (http://links.lww.com/ ALN/C735) shows the results of this originally planned analysis. Other limitations are the single-center study design and the inability to blind the study team to the intervention, although it seems difficult to imagine how this could have influenced patients’ PaCO₂ levels. Another limitation of this study is the extensive exclusion criteria, which need to be considered while judging our results and their transferability to other patients and/or settings.

Conclusions

This study provides evidence that the increase in PaCO₂ in apneic, anesthetized, and paralyzed adults during apneic oxygenation with 100% oxygen is similar using different flow rates between 0.25 and 70 l·min⁻¹. All experimental groups were noninferior to the accepted standard technique of high-flow nasal oxygenation with a flow of 70 l·min⁻¹ and continuous laryngoscopy. This study demonstrates the absence of the proposed ventilatory effect of high gas flows while performing nasal apneic oxygenation.

Acknowledgments

The authors thank the following (both from the Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland): Sabine Nabecker, anesthesia study nurse, for her help in conducting the study and Jeannie Wurz, B.A., research assistant, for review of the English in the article.

Research Support

Supported by a departmental research grant from the Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.

Competing Interests

Dr. Riedel holds a consultancy contract with the company Sentec AG, Landquart, Switzerland, and has received a grant from the Swiss Foundation for Research on Muscle Diseases, Colombier, Switzerland, for a different research project. Both have no association with the current research project. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: sabine.nabecker@insel.ch. Raw data available at: sabine.nabecker@insel.ch.
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