BJA

*British Journal of Anaesthesia*, 125 (1): e75–e80 (2020)

doi: 10.1016/j.bja.2020.02.023
Advance Access Publication Date: 31 March 2020
Clinical Investigation

CLINICAL INVESTIGATION

# High-flow nasal oxygen does not increase the volume of gastric secretions during spontaneous ventilation

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## Abstract

**Background:** High-flow, heated, and humidified nasal oxygen therapy (HFNO) is frequently used in critical care and perioperative settings for a range of clinical applications. Much of the benefit of HFNO is attributed to generation of modest levels of positive airway pressure. Concern has been raised that this positive airway pressure may cause gastric insufflation, potentially increasing the risk of regurgitation and aspiration in an unprotected airway.
**Methods:** A prospective, interventional, assessor-blinded study was undertaken to evaluate the effects of HFNO on gastric content and gastric distension in healthy fasted adult volunteers assessed by ultrasonography. The primary outcome was the volume of gastric secretions. The secondary outcomes were the incidence of gastric air insufflation and the distribution of gastric antral grades.
**Results:** Sixty subjects were enrolled. No subject was found to have air gastric distension either at baseline or after treatment with HFNO. All subjects had either a Grade 0 or Grade 1 antrum, with similar distribution of antral grades and similar volume of gastric secretions before and after treatment with HFNO.
**Conclusions:** There was no evidence that treatment with HFNO at flow rates of up to 70 L $min^{-1}$ for 30 min resulted in gastric distension or an increase in gastric secretions in healthy individuals breathing spontaneously. The generalisability of these findings to subjects under anaesthesia and patients with incompetence of the lower oesophageal sphincter or impaired gastric emptying requires further investigation.
**Clinical trial registration:** NCT03134937.

**Keywords:** airway management; gastric volume; high-flow nasal oxygen; oxygen inhalation therapy; pulmonary aspiration; stomach; ultrasonography

### Editor's key points

- High-flow, heated, and humidified nasal oxygen therapy (HFNO) is now an established treatment method, but one possible complication with its use is insufflation of oxygen into the stomach, leading to pulmonary aspiration of gastric contents.
- This study in volunteers indicates that HFNO has little risk of gastric insufflation in patients who are breathing spontaneously.

**Received:** 20 September 2019; **Accepted:** 27 February 2020

High-flow heated and humidified nasal oxygen therapy (HFNO) is frequently used in critical care settings to manage patients with acute hypoxaemic respiratory failure,[1–4] and to optimise pre-oxygenation before tracheal intubation in patients with mild-to-moderate hypoxaemia.[5] The use of HFNO has been recently described in the perioperative setting for a diverse range of clinical applications, including preoxygenation, facilitation of awake fibreoptic tracheal intubation and 'tubeless anaesthesia' using apnoeic oxygenation.[6,7] The basic concept of apnoeic oxygenation is certainly not new. Oxygen flows of up to 15 L $min^{-1}$ via a nasal cannula were previously used to extend apnoea time and minimise oxygen desaturation during emergency intubation.[6,8] What is new about HFNO is the ability to administer higher nasal flows than previously feasible up to 70 L $min^{-1}$, control oxygen concentration, and use a humidified mixture heated to body temperature via a specialised nasal cannula. Patel and Nouraei[7] used the acronym 'THRIVE' (transnasal humidified rapid insufflation ventilatory exchange) to describe apnoeic oxygenation with heated and humidified high-flow oxygen via a nasal cannula.

Extrapolating from vast clinical experience with methods of noninvasive positive pressure ventilation such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP), there is a concern that low levels of positive airway pressure associated with HFNO could potentially lead to gastric insufflation, higher volumes of gastric secretions and a higher risk of aspiration in an unprotected airway.[9–11] Distension of the gastric antrum triggers a parasympathetic reflex that results in increased secretions of gastric acid, pepsinogens and mucus.[12,13] The clinical concern of gastric distension from HFNO has not been systematically or prospectively studied previously.

With these considerations in mind, a prospective interventional, assessor-blinded study was undertaken in order to systematically evaluate the possible effects of HFNO on gastric content and gastric distension in healthy fasted adult volunteers. The primary outcome was the volume of gastric secretions. The study hypothesis was that HFNO administration for 30 min would result in a 50% increase in the volume of gastric secretions. The secondary outcomes were the incidence of gastric air insufflation and the distribution of antral grades.

## Methods

A prospective, interventional, observer-blinded study was carried out in healthy non-pregnant adult subjects. The project was approved by the institutional research ethics board (UHN REB #17–5152; May 23, 2017), and written informed consent was obtained from each participant. The study was registered at clinicaltrials.gov (NCT03134937; May 1, 2017). Subjects were enrolled at Toronto Western Hospital in Toronto, Canada between November 2017 and March 2019. Inclusion criteria were: ASA physical status classification 1 or 2, age 17–80 yr and height of 145 cm or greater. Subjects were excluded if they had conditions associated with increased baseline gastric volume (pregnancy, diabetes, gastro-oesophageal reflux disease, current opioid use), any major upper gastrointestinal disease, lung disease or body mass index greater than 35 kg $m^{-2}$. Recruitment was by self-referral through advertisements in the Toronto area.

Subjects were asked to fast from solids for a minimum of 8 h and clear fluids for 2 h following current perioperative fasting recommendations.[14] Subjects had two gastric ultrasound examinations, one at baseline and a second one after 30 min of HFNO administration. The sonograms were performed by two independent anaesthesiologists with a minimum experience of 50 previous gastric ultrasound examinations and they were asked to do a baseline or post-treatment examination at random. The anaesthesiologists were blinded to this allocation. A low frequency (2–5 MHz) curvilinear array transducer and a Sonosite Edge system (FUJIFILM Sonosite, Bothell, WA, USA), with image-compounding technology were used. The examinations were performed in both supine and right lateral decubitus positions following a previously described protocol.[10–15] Specifically, the gastric antrum was identified in the sagittal plane in the epigastrium, between the left lobe of the liver and the pancreas at the level of the abdominal aorta (Fig 1). The antrum was classified using a 3-point grading system, where Grade 0 refers to an antrum with no fluid visible in either supine or right lateral decubitus position, a Grade 1 antrum has gastric fluid visible only in the right lateral decubitus, and a Grade 2 antrum has clear fluid apparent in both scanning positions. Gastric fluid appears as hypoechoic content. This

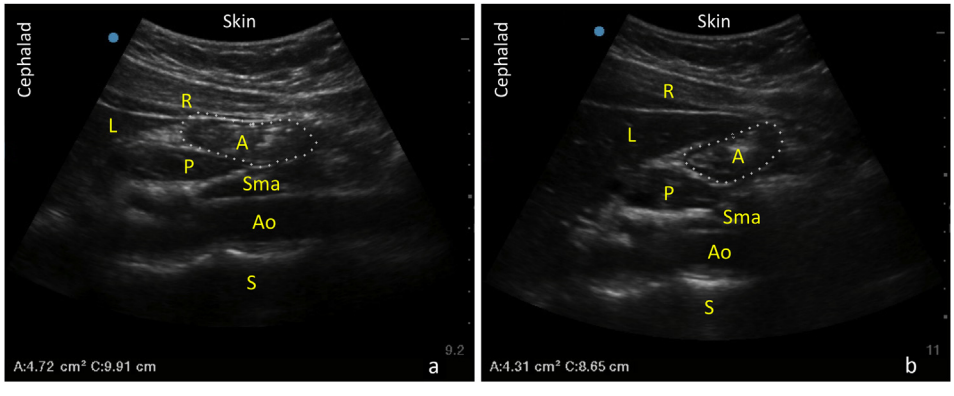


Fig 1. Ultrasonography images in the right lateral decubitus position before (a) and after (b) treatment with high-flow nasal oxygen therapy. A, antrum; Ao, aorta; L, liver; P, pancreas; R, rectus abdominis muscle; S, spine; Sma, superior mesenteric artery.

simple grading system has been shown to correlate closely with gastric fluid volume.[15–21] A cross-sectional area of the gastric antrum was measured in the right lateral decubitus at the level of the aorta, between peristaltic contractions, using a free-tracing method and the unit internal caliper, including the full thickness of the gastric wall (i.e. from serosa to serosa). Following standard practice and to minimise measurement error, an average of three measurements was used. The total gastric fluid volume was then estimated based on the antral cross-sectional area in the right lateral decubitus and the following validated model:

$$\text{Volume (ml)} = 27.0 + [14.6 \times \text{RLD-CSA (cm}^2) - 1.28 \times \text{age (yr)}]$$ [15]

The presence of air in the antrum was also documented. Significant gastric distension with air would appear as a hyperechoic lumen, with air collecting along the anterior wall of the antrum, blurring the posterior wall and posterior abdominal structures.

Following baseline gastric ultrasound assessment, HFNO was administered to each subject via a disposable nasal cannula and the Optiflow™ system (Fisher & Paykel Healthcare, Auckland, New Zealand) as per the manufacturer's specifications. Optiflow consists of an air-oxygen blender with adjustable inspired oxygen concentration (0.21–1.0), delivering a modifiable gas flow (≤70 L $min^{-1}$) to a heated chamber (MR 810 pass-over humidifier; Fisher & Paykel Healthcare) where the gas is humidified and heated to 37°C. The gas mixture is then routed through a high-performance circuit (AA 400; Fisher & Paykel Healthcare) to be delivered to the patient via a short, wide-bore nasal cannula at a temperature of 37°C containing 44 mg $H_2O$ $L^{-1}$. The size of the nasal cannula (medium or large) was chosen for each subject to ensure a snug fit into the nostrils for optimal equipment function. Although the system used had a blender with the capacity to deliver different oxygen concentrations, 100% oxygen was used to mimic perioperative use. An initial flow rate of 30 L $min^{-1}$ was administered and increased by 10 L $min^{-1}$ every 2 min until a flow rate of 70 L $min^{-1}$ was reached for a total 'treatment' time of 30 min. For greater clarity, 30 L $min^{-1}$ were administered for 2 min, 40 L $min^{-1}$ for a second interval of 2 min, 50 L $min^{-1}$ for a third 2 min interval, 60 L $min^{-1}$ for a fourth interval of 2 min and the maximum 70 L $min^{-1}$ was administered for the remaining 22 min of 'treatment'. This graded approach is used to enhance tolerance of high flows. Subjects were asked to keep their mouths closed during the study period.

### Sample size estimate and statistical analysis

Based on results of previous investigations using gastric sonography, we know that baseline gastric volume is higher than previously appreciated.[21–25] The mean baseline gastric volume can vary from 0.4 to 1.0 mL $kg^{-1}$ with a standard deviation (SD) of 0.6 mL $kg^{-1}$ in healthy fasting adults.[21–25] The threshold of gastric volume that increases aspiration risk under general anaesthesia is not yet well defined, and risk is likely multifactorial. We used a pragmatic approach and considered a minimum clinically significant difference a 50% increase in the volume of gastric secretions, from a baseline mean of 1.0 mL $kg^{-1}$ to a post-treatment value of 1.5 mL $kg^{-1}$. This latter volume represents the upper end of normal values and volumes greater than 1.5 mL $kg^{-1}$ are often considered a marker of a 'full stomach'.[15,18,19] Based on the above premises, it was estimated that 56 subjects would be required to reject the null hypothesis with a type I error of 0.05 and power of 80%.[26] To account for possible withdrawals or incomplete data, 60 subjects were enrolled.

Clinical and demographic variables were described with means and SDs for continuous variables, and frequencies and percentages for categorical variables. Antral grades at baseline and after treatment were compared with McNemar test for paired binary data. Values of antral cross-sectional area, volume and volume per weight were expressed as means (SD) and compared with paired *t*-test and paired Wilcoxon nonparametric test as appropriate. The difference between the post-test and pre-test values was reported along with 95% confidence interval of this difference. A *P*-value <0.05 was considered significant. R version 3.3.3. was used for statistical analysis.

## Results

Sixty subjects were enrolled in the study. Participant characteristics are summarised in Table 1. All 60 subjects completed the study and tolerated maximum delivery rates of HFNO. The gastric antrum and body were identified in all participants. No subject was found to have air gastric distension either at baseline or after treatment with HFNO. All subjects had either a Grade 0 or Grade 1 antrum, compatible with an 'empty stomach' or fasting state in both baseline and post-treatment examinations. The distribution of antral grades was similar at baseline and post-treatment with no evidence of higher grades after treatment (Table 2). The antral cross-sectional area in the right lateral decubitus and gastric volume remained unchanged from baseline after HFNO administration (Table 3 and Fig 2). There was no evidence of increase in the volume of gastric secretions.

**Table 1** Participant characteristics. Values are presented as range, *n* (%) and mean (standard deviation, SD) and reported as appropriate.

| | All subjects |
|---|---|
| *n* | 60 |
| Age (range), yr | 21–65 |
| Female sex, *n* (%) | 33 (55) |
| Weight (kg), mean (SD) | 69 (14) |
| Height (cm), mean (SD) | 170 (11) |
| BMI (kg $m^{-2}$), mean (SD) | 23.6 (3.1) |
| ASA physical status 1, *n* (%) | 56 (87) |

**Table 2** Distribution of antral grades at baseline and after treatment.

| | | After treatment (*n*) | |
|---|---|---|---|
| | | Grade 0 | Grade 1 |
| Baseline (*n*) | Grade 0 | 26 | 12 |
| | Grade 1 | 15 | 7 |

Table 3 Antral cross-sectional area and gastric fluid volume at baseline and after treatment. Values are expressed as mean and standard deviation (SD). The difference is the absolute change in the mean value after treatment compared with baseline and the 95% confidence interval (CI) of that difference. RLD-CSA, cross-sectional area of the gastric antrum measured in the right lateral decubitus.

| | Baseline | After treatment | Difference (95% CI) | P-value |
|---|---|---|---|---|
| RLD-CSA ($cm^2$) | 6.0 (2.3) | 5.7 (2.2) | −0.3 (i1.0 to 0.4) | 0.369 |
| Volume (ml) | 69 (35) | 64 (33) | −5 (−15 to 6) | 0.369 |
| Volume (ml $kg^{-1}$) | 1.0 (0.5) | 1.0 (0.5) | −0.1 (−0.2 to 0.1) | 0.433 |

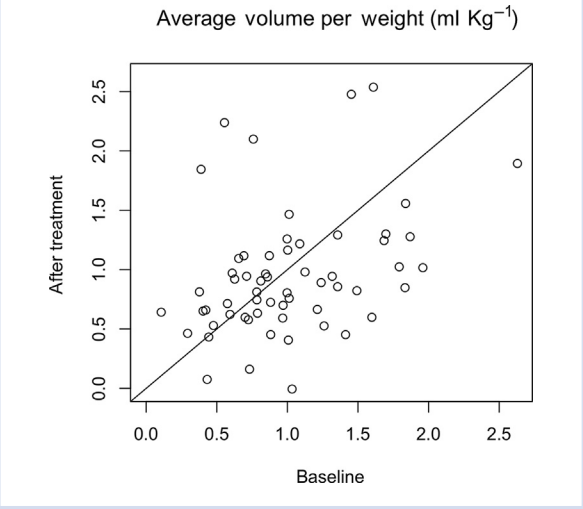


Fig 2. Distribution of values of gastric fluid volume (in ml $kg^{-1}$) at baseline and after treatment with high flow nasal oxygen therapy.

## Discussion

Based on our results, there is no evidence to suggest that treatment with HFNO at flow rates of 70 L $min^{-1}$ for 22 min and a total treatment time of 30 min results in gastric distension or an increase in the volume of gastric secretions in healthy subjects who are breathing spontaneously.

We chose the volume of gastric secretions as the primary outcome given that this is a continuous variable that is measurable noninvasively in an accurate and reliable manner. Air distension of the stomach, on the other hand, is more difficult to establish and it is often a dichotomous outcome based on subjective evaluation of ultrasound images. Our findings are consistent with those reported by Sud and colleagues,[27] who found no significant difference in the volume of gastric gas between standard preoxygenation and preoxygenation with HFNO in patients undergoing CT-guided interventional procedures under general tracheal anaesthesia.

The positive airway pressure associated with HFNO has raised the question of whether its use could result in gastric insufflation, increased production of gastric secretions and a higher risk of aspiration in an unprotected airway. This is an important question as aspiration is the leading cause of mortality in the setting of difficult airway management.[28] Gastric insufflation is a well-known complication of noninvasive positive pressure ventilation methods such as CPAP and BiPAP. It is thought to occur in up to 50% of all patients and to result in pulmonary aspiration in up to 5% of cases.[11] Severe gastric insufflation can have serious consequences including hypoxaemia, pulmonary aspiration, acute respiratory distress syndrome and death.[9,10] There are, however significant differences between noninvasive positive pressure ventilation systems and HFNO. The former relies on a closed circuit and the delivery of positive pressure into the airway is the primary mechanism of action. Positive pressure is applied continuously throughout the respiratory cycle with CPAP and at differing inspiratory and expiratory pressures with BiPAP. HFNO is essentially an open system resulting in only modest levels of positive pressure in the airway. Indeed, gastric insufflation has been correlated with high pressures of more than 25 cm $H_2O$ during noninvasive ventilation, whereas HFNO may only reach about 7 cm $H_2O$ at maximum flow, a level of pressure previously suggested to be safe.[29]

It is important to consider the anatomical and physiologic basis by which gastric insufflation and increased gastric secretions could occur during HFNO therapy.[30] Pharyngeal pressure during HFNO is affected by mouth opening or closing, delivered flow, and size of nasal cannula. In this study, the size of the nasal cannula (medium or large) was chosen for each subject to ensure a snug fit into the nostrils for optimal equipment function, and subjects were asked to keep their mouths closed during the study period. Used in this manner, the pressure generated by HFNO during expiration is higher than the mean airway pressure over the entire respiratory cycle.[30] It is conceivable that passage of air across the upper oesophageal sphincter (UOS) could occur with swallowing in awake patients, or passively in sedated or paralysed patients, with subsequent passage of air across the lower oesophageal sphincter (LOS) during transient periods of relaxation.[31] Anaesthesia and muscle paralysis may result in decreased oesophageal motility and lower oesophageal sphincter tone.[32,33] When the stomach is distended, a parasympathetic reflex leading to secretion of acetylcholine by enteric neurones is activated. The vagus nerve acts both as the afferent and efferent limbs in this reflex integrated in the brainstem.[34] Acetylcholine activates M3 receptors on the gastric wall leading to increased gastric acid and mucus secretion.[12,13] This reflex mechanism increases gastric acid output by up to 100% from baseline in animal models.[35] Retrograde passage of gastric content into the oesophagus could occur if intra-gastric pressure were to exceed the barrier pressure of the LOS, which is more likely to occur under anaesthesia.

The possible effects of HFNO on gastric distension have not been previously systematically studied and there is limited data to date. A retrospective cohort study of HFNO for preoxygenation before tracheal intubation in 51 intensive care patients did not report any cases of gastric distension. However, a post-intubation portable chest X-ray has a low sensitivity and may only detect severe cases of gastric distension.[5] A retrospective study of 298 infants (<24 months of age) did not report any cases of gastric distension.[36] However, these events are unlikely to be systematically captured in clinical

charts, and thus may be underreported. A single case report describes critical abdominal distension in a 21-month-old patient following HFNO therapy at 20 L $min^{-1}$ with a nasal airway.[37] In this case, it was retrospectively noticed that the 10 cm nasal airway was likely positioned into the oesophagus, directing the HFNO flow into the gastrointestinal tract.

The present study several limitations. It was conducted on healthy, awake subjects breathing spontaneously. Therefore, although the results may be applicable to the use of HFNO for the treatment of mild respiratory failure in awake subjects breathing spontaneously, they may not be easily extrapolated to the apnoeic, anaesthetised, and paralysed patient. In addition, the treatment study period with maximum flows of 70 L $min^{-1}$ lasted for 22 min. Although no evidence of gastric distension or increase in gastric secretions was found, this may not be immediately extrapolated to longer treatment periods of several hours. Finally, all subjects in the study had previously fasted following current perioperative recommendations. It is not possible to know whether these results are applicable to patients with a full stomach at baseline. Future research should aim to address some of these limitations, including investigating the effect of HFNO on gastric volume in anaesthetised and paralysed patients, and those exposed to HFNO therapy for longer periods of time.

In conclusion, this prospective study suggests that 30 min of HFNO therapy at increasing rates of up to 70 L $min^{-1}$ is not associated with an increase in the volume of gastric secretions in healthy fasting subjects who are breathing spontaneously. Further investigation is necessary to determine the generalisability of these findings to subjects under anaesthesia, muscle relaxation, or both, and patients exposed to HFNO therapy for longer periods.

## Authors' contributions

Performed blinded ultrasonography scans: EM, KL, AP
Data collection: EM, KL, DB
Data entry: DB
Maintained regulatory documents: DB
Protocol development: EB (contributor), AP (developer)
Logistical and personnel support: VC
Statistical analysis NM.
Principal investigator: AP.
Writing of the first draft of the manuscript: EM
Contribution to the manuscript: KL, EB, VC, AP
Review of the manuscript: KL, EB, VC, DB, NM, AP
All authors approved the final version of the manuscript.

## Declarations of interest

Elizabeth McLellan, Karen Lam, Didem Bozak, and Nicholas Mitsakakis—have no conflicts of interest to declare. Elizabeth Behringer—financial research support from Fisher & Paykel; speakers' bureau for Kart Storz Endoscopy America Inc. Vincent Chan—honorarium from Philips Healthcare. Anahi Perlas—equipment and grant support to the institution from Fisher & Paykel for this study.

## Funding

Research grant from Fisher & Paykel, New Zealand (grant number 108235)

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*Handling editor: Takashi Asai*