Use of High-Flow Nasal Cannula Oxygen Therapy to Prevent Desaturation During Tracheal Intubation of Intensive Care Patients With Mild-to-Moderate Hypoxemia

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Objectives: Tracheal intubation of ICU patients is frequently associated with severe hypoxemia. Although noninvasive ventilation reduces desaturation during intubation of severely hypoxemic patients, it does not allow for per-procedure oxygenation and has not been evaluated in mild-to-moderate hypoxemic patients for whom high-flow nasal cannula oxygen may be an alternative. We sought to compare pre- and per-procedure oxygenation with either a nonrebreathing bag reservoir facemask or a high-flow nasal cannula oxygen during tracheal intubation of ICU patients.

Design: Prospective quasi-experimental before-after study (ClinicalTrials.gov: NCT01699880).

Setting: University hospital medico-surgical ICU.

Patients: All adult patients requiring tracheal intubation in the ICU were eligible.

Interventions: In the control (before) period, preoxygenation was performed with a nonrebreathing bag reservoir facemask and in the change of practice (after) period, with high-flow nasal cannula oxygen.

Measurements and Main Results: Primary outcome was median lowest Spo_2 during intubation, and secondary outcomes were Spo_2 after preoxygenation and number of patients with saturation less than 80%. One hundred one patients were included. Median lowest Spo_2 during intubation were 94% (83–98.5) with the nonrebreathing bag reservoir facemask versus 100% (95–100) with high-flow nasal cannula oxygen ($p < 0.0001$). Spo_2 values at the end of preoxygenation were higher with high-flow nasal cannula oxygen than with nonrebreathing bag reservoir facemask and were correlated with the lowest Spo_2 reached during the intubation procedure ($r = 0.38$, $p < 0.0001$). Patients in the nonrebreathing bag reservoir facemask group experienced more episodes of severe hypoxemia (2% vs 14%, $p = 0.03$). In the multivariate analysis, preoxygenation with high-flow nasal cannula oxygen was an independent protective factor of the occurrence of severe hypoxemia (odds ratio, 0.146; 95% CI, 0.01–0.90; $p = 0.037$).

Conclusions: High-flow nasal cannula oxygen significantly improved preoxygenation and reduced prevalence of severe hypoxemia compared with nonrebreathing bag reservoir facemask. Its use could improve patient safety during intubation. (*Crit Care Med* 2014; XX:00–00)

Key Words: hypoxemia; hypoxemic acute respiratory failure; oxygenation; patient safety; tracheal intubation

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Tracheal intubation is one of the most routinely performed invasive procedures in the ICU, but also one frequently associated with morbidity and, in some instances, mortality (1, 2). Almost one intubation out of three (28%) has been associated with at least one severe complication (3), and occurrence of severe hypoxemia was the complication the most often reported in this study (26%), which has been shown to increase mortality in specific populations (4, 5). Intubation is usually preceded by several minutes of preoxygenation through a nonrebreathing bag reservoir facemask (NRM) to delay desaturation. In healthy subjects such as in the anesthesia setting, preoxygenation allows for up to 9 minutes apnea without arterial desaturation below 90% (6). In the ICU however, preoxygenation is much less efficient, mainly due to patients' unstable cardiovascular or respiratory status (7). Alternative techniques have been proposed to reduce the prevalence of severe hypoxemia during intubation. A pivotal study by Baillard et al (8) convincingly showed that noninvasive ventilation (NIV) could reduce prevalence and magnitude of desaturation during intubation by enhancing preoxygenation. However, because this technique is interrupted during intubation (in order to allow laryngoscopy), there is no apneic oxygenation, and thus, serious desaturation may still occur, as evidenced by Baillard et al (8) in their study. In addition, patients with neurological impairment cannot benefit from this technique that requires patient's acceptance and cooperation. Finally, only a subset of ICU patients was evaluated in this study, those with profound hypoxemia. For all these reasons, an alternative technique that is more easily implemented and suitable for all patients including comatose ones merits investigation. High-flow nasal cannula oxygen (HFNC) is a device that allows the delivery of humidified and heated oxygen up to 60 L/min, with a modifiable inspired concentration of oxygen of up to 100%. It has become increasingly popular in the ICU to manage patients with acute hypoxemic respiratory failure (9–12) and may find other applications in ensuring oxygenation during invasive procedures (e.g., bronchoscopy [13, 14] or intubation). Indeed, HFNC has the advantage over the other techniques of preoxygenation (NIV and NRM) of being maintained during laryngoscopy and intubation allowing for apneic oxygenation. For these reasons, we believe that HFNC may improve the quality of pre- and per-intubation oxygenation. We thus conducted a prospective quasi-experimental before-after study to determine if HFNC is able to improve preoxygenation and reduce the prevalence of severe hypoxemia during intubation in comparison with NRM. We deemed that conducting a randomized trial would not be ethical due to obvious lack of equipoise between the two techniques.

PATIENTS AND METHODS

Study Design

This prospective quasi-experimental before-after study took place in the 12-bed medico-surgical ICU of Louis Mourier University Hospital, Colombes, France. It was conducted from March 2011 to November 2012. During the control period (March to December 2011), all patients were intubated with our standard preoxygenation procedure that used a NRM. In the "change of practice" period (January to November 2012), use of HFNC as a preoxygenation device was applied to all our patients requiring tracheal intubation.

The Ethics Committee of the French Society of Intensive Care approved the study protocol and waived the need for written informed consent of the participants, according to French law. A specific information letter was given to the patient and/or to the family, describing the purpose of the study and the nature of the data collected. In addition, as part of our general policy on information provided to the patients and relatives, a leaflet is given at admission to the ICU, explaining that data gathered for usual care purposes may be used for medical research and publication.

Description of the Intubation Procedure

Rapid sequence induction with a hypnotic agent and a short-acting neuromuscular blocking agent was performed systematically before intubation. In the absence of contraindication, succinylcholine and etomidate are, respectively, the neuromuscular blocking and the hypnotic agents used in our unit for rapid sequence intubation. Two operators are present for each intubation. A first laryngoscopy is systematically attempted by a resident, as part of our training policy (15). The senior physician takes control if the attempt failed. The initial ventilator settings are determined by the senior clinician in charge according to needs of the patients, usually with a F_{IO_2} of 1.0. A blood sample for arterial blood gas analysis is systematically performed less than 1 hour after intubation. During the control phase, preoxygenation was performed with a NRM for at least 3 minutes before intubation with 15 L/min oxygen flow. The mask was removed during the intubation itself. As routinely done in our ICU, oxygen with a 6 L/min flow was administered to patients through a nasopharyngeal catheter during the apnea period. During the second phase, preoxygenation was performed with HFNC for 3 minutes before intubation. Oxygen flow was set at 60 L/min and the F_{IO_2} at 1.0. The device was maintained during the intubation itself. All other steps of the procedure were similar during the two phases of the study.

Patients

Adult patients admitted to our ICU and requiring endotracheal intubation were eligible. Noninclusion criteria were age under 18 years, intubation for cardiac arrest, severe hypoxemia (defined as Sp_{O_2} < 95% under a NRM with an oxygen flow of 15 L/min), patients already receiving HFNC, and patients under NIV. Although the final decision to intubate was left at the clinician's discretion, our ICU follows accepted indications for intubation, which include respiratory arrest, respiratory pauses with loss of consciousness, psychomotor agitation making nursing care impossible and requiring sedation, hemodynamic instability despite vasopressor administration and with systolic arterial pressure below 70 mm Hg, partial pressure of arterial oxygen below 45 mm Hg, loss of consciousness, or worsening encephalopathy (16).

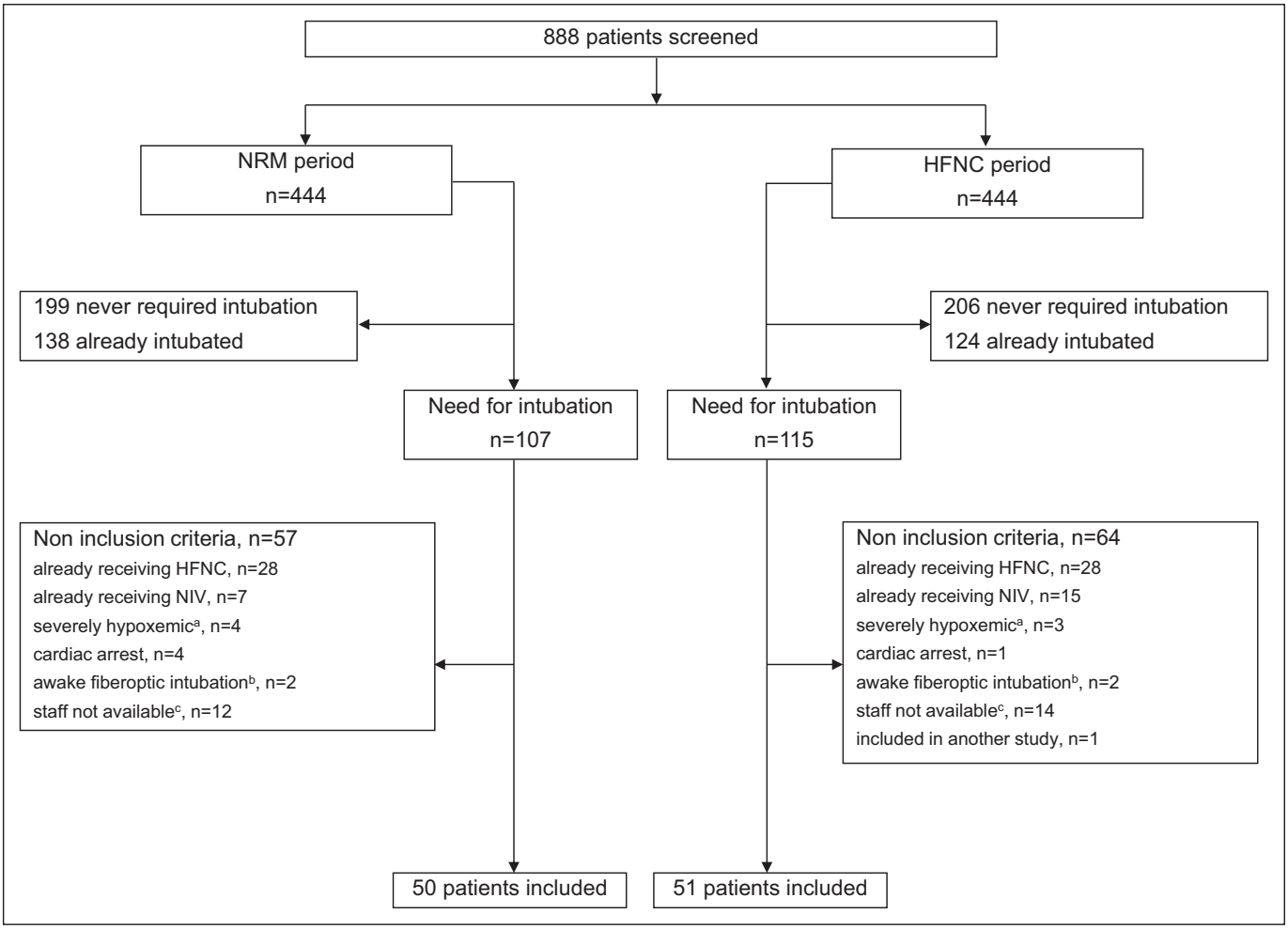

Figure 1. Patient flow chart indicating numbers of patients screened for eligibility, intubated in the ICU and finally analyzed in the study. HFNC = high-flow nasal cannula oxygen, NIV = noninvasive ventilation, NRM = nonrebreathing bag reservoir facemask. [a]Spo_2 below 95% while receiving 15 L/min oxygen through a NRM. [b]Awake fiberoptic intubation for planned difficult intubation. [c]Refers to a situation of intense activity in the ICU with work overload that precluded the physician from including the patient in the study.

Device Description

The HFNC device (Optiflow; Fisher & Paykel, Auckland, New Zealand) consists of an air-oxygen blender with adjustable Fio_2 (0.21–1.0) that delivers a modifiable gas flow (≤ 60 L/min) to a heated chamber (MR 850 passover humidifier; Fisher & Paykel) where the gas is heated and humidified. The gas mixture is then routed through a high-performance circuit (RT 310; Fisher & Paykel) to be delivered to the patient via short, wide bore nasal prongs at 37°C and containing 44 mg H_2O/L.

Conventional oxygen was given through a high Fio_2 NRM (Intersurgical, Wokingham, United Kingdom).

Collected Data

We recorded baseline demographic and clinical data. Vital signs, with a particular attention to Spo_2, were monitored before and after preoxygenation, during the whole procedure, and until 30 minutes after intubation. Arterial blood gas analyses preceding and following intubation were collected when available. Difficulty of intubation was assessed with the following variables: Cormack score (17), duration of the procedure (from drug injection to connection to the respirator), number of attempts, use of specific devices for difficult airway management, and success or failure of intubation by the resident. The following adverse events were recorded: occurrence of arrhythmia, cardiac arrest, and death during or immediately following the procedure. A portable chest radiograph was systemically performed after intubation to confirm adequate position of the tube. Presence of gastric distension was also checked on the radiograph.

Endpoints and Statistical Analysis

The primary endpoint of the present study was the lowest Spo_2 value observed in each patient. Secondary endpoints were median Spo_2 obtained during intubation, after preoxygenation, and after intubation and prevalence of life-threatening hypoxemia (defined by a Spo_2 below 80%) during the procedure. Other prespecified outcome measures were the prevalence of serious adverse events (cardiac arrest, sustained arrhythmia, and hemodynamic instability).

For all the analyses, the main independent variable was the group membership (HFNC or NRM) and was included in all multivariate models.

TABLE 1. Baseline Characteristics, Intubation Conditions, and Reasons for Intubation of Study Patients

Variable	Nonrebreathing Bag Reservoir Facemask *n* = 50	High-Flow Nasal Cannula Oxygen *n* = 51	*p*
Age, yr, median (IQR)	61 (36–74)	59 (52–74)	0.90[a]
Gender, male/female, *n*	33/17	32/19	0.73[b]
Comorbidities, *n* (%)			
Chronic obstructive pulmonary disease	7 (14)	6 (12)	0.74[b]
Sleep apnea	2 (4)	0 (0)	0.24[c]
Chronic heart failure	5 (10)	3 (6)	0.70[b]
Coronary heart disease	6 (12)	4 (8)	0.71[b]
Hypertension	22 (44)	16 (31)	0.19[b]
Diabetes	4 (8)	10 (20)	0.09[b]
Atrial fibrillation	3 (6)	8 (16)	0.12[b]
Chronic renal failure	2 (4)	1 (2)	0.62[b]
Cancer	3 (6)	3 (6)	1.00[b]
Cirrhosis	10 (20)	11 (22)	0.85[b]
HIV	0 (0)	1 (2)	1.0[b]
Smoking	22 (44)	18 (35)	0.37[b]
Alcohol abuse	18 (36)	20 (39)	0.74[b]
Simplified Acute Physiology Score II, median (IQR)	44 (35–61.5)	47 (32–57)	0.77[a]
Difficulty of intubation			
Cormack 3–4, *n* (%)[d]	7 (14)	2 (4)	0.15[b]
Intubation duration, min, median (IQR)	2 (2–4)	2 (2–3)	0.21[a]
Use of Eschmann tracheal tube introducer, *n* (%)	11 (22)	6 (12)	0.17[b]
Success of intubation by a junior resident, *n* (%)	28 (56)	37 (72.5)	0.08[b]
Oxygenation variables (IQR)			
Spo_2, median	100 (98–100)	100 (100–100)	0.02[a]
O_2 nasal flow, median	3.5 (2–9)	5 (2–10)	0.58[a]
Reason for intubation, *n* (%)			
Shock	15 (30)	20 (39)	0.22[c]
Altered consciousness	12 (24)	19 (37)	
Acute respiratory failure	14 (28)	7 (14)	
Status epilepticus	6 (12)	3 (6)	
Acute-on-chronic respiratory failure	3 (6)	2 (4)	

IQR = interquartile range.
[a]Wilcoxon rank-sum test.
[b]Pearson chi-square test.
[c]Fisher exact test.
[d]Versus Cormack score 2–3.

TABLE 2. Oxygenation Variables, Adverse Events During and After Intubation, and ICU Mortality

Variable	Nonrebreathing Bag Reservoir Facemask *n* = 50	High-Flow Nasal Cannula Oxygen *n* = 51	*p*
Spo_2 after preoxygenation, %, median (IQR)	100 (98–100)	100 (100–100)	0.01[a]
Lowest Spo_2, median (IQR)	94 (83–98)	100 (95–100)	< 0.0001[b]
Adjusted lowest Spo_2, %, median[c]	94	99.2	0.007
Spo_2 upon respirator connection, %, median (IQR)	98 (92.5–100)	100 (99–100)	0.0004[b]
Spo_2 5 min after intubation, %, median (IQR)	100 (98.8–100)	100 (100–100)	0.002[b]
Spo_2 30 min after intubation, %, median (IQR)	100 (99–100)	100 (100–100)	0.024[b]
Spo_2 < 80%, *n* (%)	7 (14)	1 (2)	0.03[a]
Pao_2 after intubation, mm Hg, median (IQR)	280 (143–359)	239 (128–440)	0.59[b]
Sustained arrhythmia during intubation, *n* (%)	1 (2)	0 (0)	0.31[a]
Cardiac arrest during intubation, *n* (%)	1 (2)	0 (0)	0.31[a]
Death in ICU, *n* (%)	8 (16)	7 (14)	0.75[a]

IQR = interquartile range.

[a]Pearson chi-square test.

[b]Wilcoxon rank-sum test.

[c]Lowest Spo_2 was adjusted for the following variables (quantile regression of the median): study phase, baseline Spo_2, diabetes, difficulty of intubation (use of an Eschmann tube introducer, Cormack score 3 or 4, and success of intubation by a junior resident), and reason for intubation. See supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/B139) for details.

Results are expressed as median (25–75%) or frequencies and percentages (%), as appropriate. Categorical variables were compared by chi-square or Fisher exact test, and continuous variables were compared by Student *t* test or Wilcoxon rank-sum test, as appropriate.

Between-groups difference in lowest Spo_2 was adjusted for baseline covariates significantly associated with lowest Spo_2 or with the group membership ($p < 0.2$). As lowest Spo_2 was not normally distributed, univariate analysis of lowest Spo_2 was performed using Wilcoxon rank-sum test (for median comparisons) or Kendall correlation coefficient, and multivariate analysis used quantile regression of the median (18). Quantile regression differs from standard linear regression: quantile regression models the relation between a set of explicative variables and specific percentiles (e.g., the 50th percentile, i.e., the median) of the response variable, whereas linear regression models the mean of the response variable. Unlike linear regression, quantile median regression does not assume a normal error distribution, but it has a similar interpretation: it quantifies change in a central measure (the median) of the response variable (lower Spo_2) as a function of other predicators.

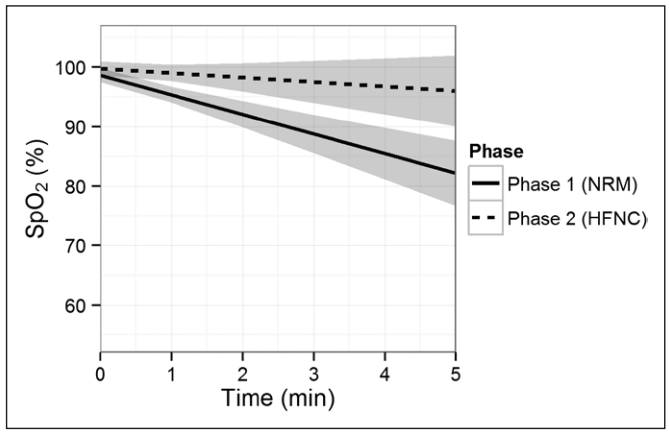

Figure 2. Predicted Spo_2 during the first 5 min of intubation. The two *black lines* represent the predicted Spo_2 during the first 5 min of intubation, using a linear mixed-effect model for each group (nonrebreathing bag reservoir facemask [NRM] and high-flow nasal cannula oxygen [HFNC]). For each prediction, the CI is figured by the gray region. There was a statistical difference for predicted Spo_2 drop between the two groups. Modeling took into account all the measures before the success of intubation (maximal duration of 10 min), but only the first 5 min of the predicted Spo_2 is represented (as the intubation procedure lasted < 5 min for 90% of patients). Variables of the mixed-effect model are presented in supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/B139).

TABLE 3. Risk Factors for Severe Hypoxemia (Spo_2 < 80%)

Variable	Spo_2 > 80% *n* = 93	Spo_2 < 80% *n* = 8
Age, yr, median (IQR)	60 (49–74)	47 (33.5–66)
Male sex, *n* (%)	60 (65)	5 (62)
Chronic obstructive pulmonary disease, *n* (%)	11 (12)	2 (25)
Chronic heart failure, *n* (%)	7 (8)	1 (12)
Coronary heart disease, *n* (%)	8 (9)	2 (25)
Hypertension, *n* (%)	34 (37)	4 (50)
Sleep apnea, *n* (%)	1 (1)	1 (12)
Diabetes, *n* (%)	13 (14)	1 (12)
Atrial fibrillation, *n* (%)	10 (11)	1 (12)
Chronic renal failure, *n* (%)	3 (3)	0 (0)
Cancer, *n* (%)	6 (6)	0 (0)
Cirrhosis, *n* (%)	21 (23)	0 (0)
HIV, *n* (%)	1 (1)	0 (0)
Smoking, *n* (%)	37 (40)	3 (38)
Alcohol abuse, *n* (%)	36 (39)	2 (25)
Eschmann tracheal tube introducer requirement, *n* (%)	15 (16)	2 (25)
Cormack 3–4, *n* (%)[e]	8 (9)	1 (12)
Success of intubation by a resident, *n* (%)	62 (67)	3 (38)
Duration of intubation, median (IQR)	2 (2–3)	3.5 (2.75–4.25)
Baseline O_2 nasal flow, median (IQR)	5 (2–12)	2.5 (2–3)
Baseline Pao_2, median (IQR)	102 (81–154)	88 (77–96)
Baseline Spo_2, median (IQR)	100 (99–100)	98.5 (97.5–100)
Preoxygenation with high-flow nasal cannula oxygen, *n* (%)	50 (54)	1 (12)

IQR = interquartile range, NA = not applicable.

[a]Wilcoxon rank-sum test.

[b]Fisher exact test.

[c]Adjustment on "sleep apnea" was not possible because there were only two patients with sleep apnea both belonging to the nonrebreathing bag reservoir facemask group. A multivariate model with the same variables excluding these two patients did not change the conclusion.

[d]Pearson chi-square test.

[e]Versus Cormack score 2–3.

Evolution of Spo_2 during the intubation procedure was analyzed through a linear mixed-effects model to take into account the existence of a correlation between repeated measurements (for a complete description of the model, see **supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/B139).

Multivariate analysis of the occurrence of a desaturation (< 80%) was performed using logistic regression. Variables associated ($p < 0.10$) with outcome or with the group membership were introduced into the multivariate model. Odds ratios (and their 95% CI) are provided. Significance was defined as p values of less than 0.05. Statistical analyses were performed using R 3.0.1 (http://www.R-project.org).

RESULTS

Patient flow chart is shown in **Figure 1**. Eight hundred and eighty-eight patients were admitted to our ICU during the two study periods. Two hundred and sixty-two were already intubated and 405 never required endotracheal intubation. Finally, 101 patients (50 during the first phase and 51 during the second phase) were included in the study and analyzed.

Baseline characteristics of the studied patients are reported in **Table 1**. The two study groups were similar in terms of age, sex, underlying comorbidities, and the Simplified Acute Physiology Score (19). Arterial blood gases were not systematically drawn prior intubation. When available, these samples were classified according to the time of

Univariate Analysis			Multivariate Analysis		
Odds Ratio	95% CI	*p*	Odd Ratio	95% CI	*p*
0.98	0.94–1.01	0.21[a]			
1.09	0.21–4.73	1.0[b]			
2.49	0.34–12.45	0.27[b]			
1.76	0.09–12.11	0.50[b]			
3.54	0.47–18.65	0.18[b]			
1.74	0.39–7.77	0.71[b]			
13.14	0.49–357.70	0.15[b,c]			
0.88	0.045–5.55	1.0[b]	2.74	0.12–30.26	0.46
1.19	0.06–7.71	1.0[b]			
NA	NA	1.0[b]			
NA	NA	1.0[b]			
NA	NA	0.20[b]			
NA	NA	1.0[b]			
0.91	0.18–3.93	1.0[d]			
0.53	0.08–2.44	0.70[d]			
1.73	0.24–8.40	0.62[b]			
1.52	0.08–10.22	0.54[b]			
0.3	0.06–1.30	0.13[b]	0.26	0.04–1.32	0.10
1.20	0.87–1.58	0.035[a]			
0.80	0.55–0.99	0.07[a]	0.77	0.50–0.98	0.026
0.99	0.96–1.00	0.17[a]			
0.83	0.64–1.13	0.06[a]			
0.12	0.006–0.73	0.06[d]	0.14	0.01–0.90	0.037

sampling (within 2 hr of intubation, between 2 and 4 hr, and > 4 hr). There was no significant difference in Pao_2 at any of the different time points between the two groups (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B139). Oxygen flow delivered before inclusion was not different between the two groups. Initial Spo_2 was 100% (100–100) in the NRM versus 100% (98–100) in the HFNC ($p = 0.01$). Both groups were similar in term of indication for intubation, duration and difficulty of intubation, and organ failure at baseline (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B139).

Changes in Spo_2 during intubation are shown in **Table 2** and **Figure 2**. The decrease in Spo_2 during intubation was greater in the NRM group as evidenced by the lowest values of Spo_2 reached in each group (NRM, 94% [83–98.5] vs HFNC, 100% [95–100]; $p < 0.0001$). After adjustment for significant ($p < 0.2$ with outcome and/or group status) baseline covariates (baseline Spo_2, diabetes, difficulty of intubation [use of an Eschmann tube introducer, Cormack score 3 or 4, and success of intubation by a junior resident], reason for intubation, atrial fibrillation, sex, chronic pulmonary failure, and coronary heart disease), the difference remained significant (94 vs 99; difference 5% [1–9], $p = 0.007$). The decrease in the Spo_2 during the intubation procedure was analyzed with a linear mixed-effects model to adjust for the effect of time. The difference was statistically significant (Fig. 2), although

this analysis should be interpreted with caution because of the heterogeneity of individual Spo_2 profiles. The prevalence of severe hypoxemia, defined by a Spo_2 less than 80% during the procedure, was significantly lower in the HFNC group (2% vs 14%, $p = 0.03$). One cardiac arrest was recorded in the NRM group, and it was due to severe hypoxemia. Postintubation chest radiograph revealed no episode of gastric distension during the study period.

The variables associated with the occurrence of severe hypoxemia in univariate and multivariate analysis are shown in **Table 3**. In the multivariate analysis, preoxygenation with HFNC was an independent protective factor of the occurrence of severe hypoxemia (odds ratio, 0.14; 95% CI, 0.01–0.90; $p = 0.037$). Spo_2 values at the end of preoxygenation were correlated with the lowest Spo_2 reached during the intubation procedure ($r = 0.38$; $p < 0.0001$).

DISCUSSION

The results of this study strongly suggest that HFNC significantly improved oxygenation during intubation in our patients and prevented life-threatening hypoxemia compared with NRM. Given the high rate of severe hypoxemia during intubation in the ICU, our results have major clinical consequences, directly applicable in the ICU worldwide.

Life-threatening hypoxemia is the most frequently reported complication of intubation in the ICU (3). These desaturations occur despite preoxygenation. Numerous reasons concur to limit efficiency of preoxygenation in ICU patients: cardiopulmonary underlying disease, anemia, low cardiac output, hypermetabolic states, ventilation/perfusion mismatch, obesity, pain, etc (6, 7, 20). Finally, the rate of difficult intubation is greater in the ICU, and a subset of patients require more than two attempts, prolonging duration of apnea and obviously risk of desaturation. Improving preoxygenation is a crucial issue to reduce morbidity of urgent tracheal intubation in the ICU. Efforts to improve preoxygenation through optimized conventional facemask oxygenation and ventilation were found to be only marginally effective to prevent desaturation (7). Thus, other oxygenation administration techniques are required. NIV has proven to be among the most successful, as clearly shown by Baillard et al (8) in their compelling study comparing conventional facemask preoxygenation and NIV. They showed that NIV reduced profound desaturation (≤ 80%) from 46% to 7%. Despite these impressive results, it seems that NIV has not been widely adopted as a preoxygenation device. To the best of our knowledge, these results were not confirmed by another team apart from the particular case of obese patients' intubation in the operating room (21, 22). In the authors' own ICUs, a subsequent study indicated that NIV was "spontaneously" used in only 42% of the patients requiring urgent intubation (23). NIV has inherent limitations; the main one is the necessary acceptance and cooperation of the patient, excluding all the patients with neurological impairment; and the removal of the positive pressure to allow for laryngoscopy, thus preventing any oxygen delivery during attempts.

Our positive results with HFNC over conventional oxygen are consistent with the data reported in patients with acute hypoxemic respiratory failure and are related to the high Fio_2 delivered with the device (due to the absence of oxygen dilution), the pharyngeal dead-space washout, the optimal conditioning of inspired gases, and a certain amount of positive pressure (10, 11, 24–27). The extent to which the moderate positive pressure generated with HFNC (28) contributed significantly to the improved preoxygenation cannot be assessed, but these moderate levels of pressure have been shown to result in alveolar recruitment (29). Obviously, these levels are much smaller than those delivered during NIV (around 12 cm H_2O in the study by Baillard et al [8]) but may be sufficient in less hypoxemic patients. An important feature of HFNC and potential advantage over NIV is the possibility to pursue oxygenation during laryngoscopy, a technique known as "apneic oxygenation." Oxygen diffusion from the alveoli to the capillaries decreases alveolar pressure, generating a flow of air from the pharynx to the distal airway. Increasing pharyngeal oxygen content thus enhances apneic oxygenation, which has been shown to further delay desaturation (30–32). It is clear that features of HFNC make it ideal for apneic oxygenation. The respective contribution of each of them to the beneficial effect observed in the present study is difficult to establish.

A high Fio_2 NRM was used during the control period because it is the device used in our ICU for several years to provide preoxygenation. A recent study (33) compared bagvalve masks and NRM for preoxygenation and found that use of a NRM resulted in the same level of denitrogenation than the bagvalve mask. In addition, a greater difficulty to breathe through the bagvalve mask than through the NRM was reported in this study, and $Etco_2$ at the end of preoxygenation was higher with the bagvalve consistent with a certain level of rebreathing.

Limits and Strength of the Study

Our study has several limitations. First, it was not a randomized controlled trial (RCT). We believe that the choice of such a design would have been questionable for ethical reasons. Indeed, the prerequisite for performing an RCT is the high probability of clinical equipoise (which is supposed to be reached if most physicians agree they cannot decide a priori on the superiority of one arm over the other). In the present case, it is difficult to consider that equipoise exists for several reasons: by essence, HFNC was designed to deliver greater Fio_2 than NRM, and bench test evaluation provides clear evidence of this superiority (34), confirmed in several clinical studies unequivocally and systematically showing greater improvement in oxygenation with HFNC than with NRM in ICU patients (11, 24, 25, 29, 35). Our study was made ethically acceptable by the fact that we compared a period when limited availability of HFNC restricted its use to the sickest patients (which were not included in

this study) with another period when availability enabled to expand its use in all patients. In addition, as advocated by Concato et al (36), observational studies may provide valid results similar to RCT. We therefore believe that our results provide evidence supporting the use of HFNC for preoxygenation before intubation in the ICU. Second, inspired and end-tidal oxygen concentrations that may help determine optimal preoxygenation were not monitored in our study. Contrary to the operating room, they are seldom used in the ICU, and we failed to find a device that could adapt satisfactorily to the high-flow cannulas. Third, one may question the clinical significance of the difference in Spo_2 found in our study given that the SD of the pulse oximeter reading as a predictor of Hbo_2% is ± 2%. Figure 2 illustrates the prediction of Spo_2 evolution over time in the two groups. Although modest differences in Spo_2 exist initially, these become considerable over time and greater than the imprecision of Spo_2 reading with regard to Hbo_2. In addition, we deliberately chose other, more relevant outcome measures such as Spo_2 less than 80%. As such, and because we restricted inclusions to mild to moderately hypoxemic patients, desaturation less than 80% happened in only eight patients. Strengths of our study lie in the number of patients included (twice as many as in the study by Baillard et al [8]); the capture of real-life setting (all kinds of patients were studied, including patients with neurological impairment); and most importantly, the fact that we were able to show a significant decrease in prevalence of severe hypoxemia in a study patient population where the sickest patients were not included. Intuitively, one could infer that those patients would benefit even more from this technique.

CONCLUSION

In conclusion, use of HFNC for preoxygenation significantly reduced the prevalence of severe hypoxemia during intubation compared with NRM. We believe that the use of HFNC during intubations in the ICU represents a major advance in patient safety during these potentially high-risk procedures.

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Original Article

Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways

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Summary

Emergency and difficult tracheal intubations are hazardous undertakings where successive laryngoscopy–hypoxaemia–re-oxygenation cycles can escalate to airway loss and the 'can't intubate, can't ventilate' scenario. Between 2013 and 2014, we extended the apnoea times of 25 patients with difficult airways who were undergoing general anaesthesia for hypopharyngeal or laryngotracheal surgery. This was achieved through continuous delivery of transnasal high-flow humidified oxygen, initially to provide pre-oxygenation, and continuing as post-oxygenation during intravenous induction of anaesthesia and neuromuscular blockade until a definitive airway was secured. Apnoea time commenced at administration of neuromuscular blockade and ended with commencement of jet ventilation, positive-pressure ventilation or recommencement of spontaneous ventilation. During this time, upper airway patency was maintained with jaw-thrust. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) was used in 15 males and 10 females. Mean (SD [range]) age at treatment was 49 (15 [25–81]) years. The median (IQR [range]) Mallampati grade was 3 (2–3 [2–4]) and direct laryngoscopy grade was 3 (3–3 [2–4]). There were 12 obese patients and nine patients were stridulous. The median (IQR [range]) apnoea time was 14 (9–19 [5–65]) min. No patient experienced arterial desaturation < 90%. Mean (SD [range]) post-apnoea end-tidal (and in four patients, arterial) carbon dioxide level was 7.8 (2.4 [4.9–15.3]) kPa. The rate of increase in end-tidal carbon dioxide was 0.15 kPa.min^{-1}. We conclude that THRIVE combines the benefits of 'classical' apnoeic oxygenation with continuous positive airway pressure and gaseous exchange through flow-dependent deadspace flushing. It has the potential to transform the practice of anaesthesia by changing the nature of securing a definitive airway in emergency and difficult intubations from a pressured stop–start process to a smooth and unhurried undertaking.

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Introduction

The principal objective of airway management during anaesthesia is maintenance of oxygenation. As the patient transitions from wakefulness to anaesthesia and receives neuromuscular blockade, the anaesthetist is afforded a finite time ('apnoeic window') during which to secure a definitive airway. Failure to do so normally results in recommencement of facemask ventilation, re-oxygenation and a further attempt at securing a definitive airway. In some patients, the combination of

unfavourable pharyngolaryngeal anatomy and reduced apnoea time due to cardiorespiratory decompensation makes this stop-start approach hazardous. Multiple attempts at difficult laryngoscopy increase the risk of airway trauma, which in turn makes subsequent attempts at laryngoscopy and facemask ventilation more difficult [1]. This can deleteriously impact on human factors that are intrinsic to a highly pressured clinical scenario [2], and can readily cascade into a 'cannot intubate, cannot ventilate' scenario with significant attending morbidity and mortality [3, 4].

The mainstay method of increasing the apnoeic window is through pre-oxygenation, which entails spontaneous facemask ventilation with 100% oxygen [5]. Pre-oxygenation denitrogenises the lungs and creates an alveolar oxygen reservoir [6]. The size of this reservoir can be increased by reducing dependent atelectasis through head-up patient positioning [7] and raising mean airway pressure [8] but ultimately, the size of the oxygen reservoir is fixed at the end of pre-oxygenation and once apnoea begins, it does not get replenished.

Aventilatory mass flow (AVMF) [9] is a physiological phenomenon in which, provided that a patent air passageway exists between the lungs and the exterior, the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH_2O [10] that drives oxygen into the lungs [9, 11–16]. The clinical application of this phenomenon is known in modern anaesthetic practice as apnoeic oxygenation (i.e. AVFM and apnoeic oxygenation are synonymous). Apnoeic oxygenation has been used both experimentally and clinically as a strategy to extend the apnoeic window by providing a pharyngeal oxygen reservoir [9, 11–14, 16, 17]. We report our early experience with OptiFlow™, a commercial transnasal humidified oxygen delivery system (Fisher and Paykel Healthcare Limited, Panmure, Auckland, New Zealand) to increase apnoea time in difficult airway patients undergoing general anaesthesia.

Methods

Between 2013 and 2014, 25 adult patients presenting for surgery, in whom the presence of a difficult airway was known based on previous anaesthetics or strongly anticipated based on unfavourable pharyngolaryngeal anatomy, and whose BMI or underlying cardiorespiratory disease made rapid arterial oxygen desaturation at induction of anaesthesia likely, were clinically judged as likely to benefit from using the Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) technique. Patients were undergoing surgery for laryngotracheal stenosis, vocal fold pathology and obstructive sleep apnoea, and benign and malignant hypopharyngeal obstruction.

All patients were pre-oxygenated at 40 degrees of head-up inclination with the OptiFlow nasal cannula (Fig. 1) at a rate of 70 $l.min^{-1}$ for 10 min. Intravenous induction of anaesthesia then commenced with boluses of 2–3 $mg.kg^{-1}$ propofol, 1–2 $\mu g.kg^{-1}$ fentanyl, and 0.5 $mg.kg^{-1}$ rocuronium, followed by a peripheral infusion of propofol at a rate of 0.2–0.3 $mg.kg^{-1}.min^{-1}$. Jaw-thrust was performed immediately the patient became unconscious and was maintained throughout the apnoeic period, to ensure upper airway patency. Facemask ventilation was confirmed and discontinued. The patient's angle of inclination was reduced to 20 degrees for laryngoscopy. The first attempt at laryngoscopy was with a standard metal Macintosh laryngoscope and if this was unsuccessful, an A.P. Advance™ videolaryngoscope (Venner Medical Deutschland GmbH, Dänischenhagen, Germany) with a Macintosh blade was used. If this also proved unsuccessful, an A.P. Advance difficult airway blade was used. Meticulous care was taken in all laryngoscopies not to traumatise the airway. Nasal oxygenation was maintained at the same rate of 70 $l.min^{-1}$ until the definitive airway was secured. Apnoea time referred to the time between administration of neuromuscular blockade and commencement of jet ventilation, positive-pressure ventilation or recommencement of spontaneous ventilation.

Information about patients' age, sex, ASA grade, burden of general morbidities (which was quantified using the Charlson co-morbidity score [18]), BMI, indication for and the nature of the procedure undertaken, and Mallampati [19] and Cormack-Lehane direct laryngoscopy grades [20] were recorded. Duration of apnoea was determined by clinical need in all cases and the nature of the airway placed at the end of the apnoeic period and procedure were recorded. Maximum heart rate and minimum oxygen saturations during apnoea, and end-tidal carbon dioxide levels

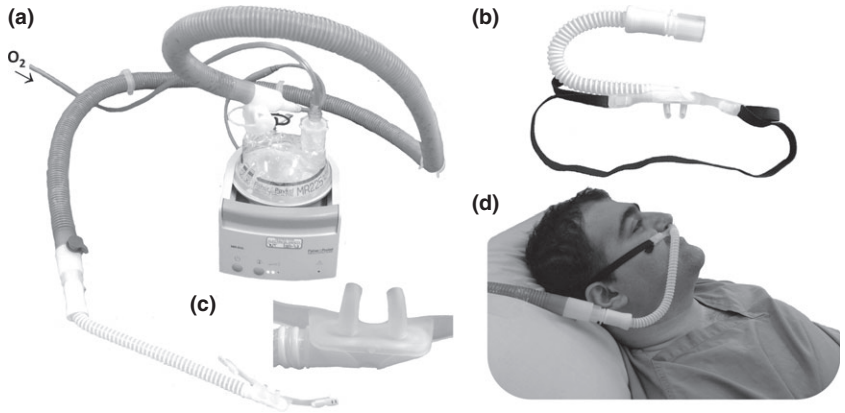

Figure 1 The OptiFlow high-flow humidified oxygen delivery system. The oxygen humidification unit (a) receives oxygen from a standard oxygen regulator and delivers humidified oxygen to a custom-built transnasal oxygen cannula (b and c) like a standard nasal oxygen cannula (d).

once a definitive airway had been placed, were recorded from the anaesthetic record. In four patients with longer apnoea times and in whom arterial cannulation had been required, arterial blood gases were also measured. The correlation between carbon dioxide levels at the end of apnoea and apnoea time was assessed with simple correlation. Data were analysed using MedCalc (MedCalc Software bvba, Ostend, Belgium). As data were collected as part of delivering standard care following introduction of a new technique into clinical practice, formal ethical committee approval was not sought. However, we consulted the Caldicott guardian for approval to analyse the data and present the study.

Results

Twenty-five patients underwent induction of anaesthesia using the THRIVE technique between 2013 and 2014. There were 15 males and 10 females and mean age (SD [range]) at treatment was 49 (15 [25–81]) years. The median (IQR [range]) ASA grade was 3 (2–3 [1–4]). The median (IQR [range]) BMI was 30 (23–36 [18–52]) $kg.m^{-2}$. The median (IQR [range]) age-adjusted Charlson co-morbidity index was 2 (0–4 [0–5]). Ten patients underwent treatment for benign laryngeal conditions, two patients had surgery for obstructive sleep apnoea and four patients had treatment for benign or malignant head and neck conditions. Nine patients had acute airway compromise with stridor on presentation. The median (IQR [range]) Mallampati grade was 3 (2–3 [2–4]) and direct laryngoscopy grade was 3 (3–3 [2–4]). The median (IQR [range]) apnoea time was 14 (9–19 [5–65]) min. No patient experienced arterial desaturation < 90% (Fig. 2).

The surgical procedures required different forms of definitive airway management: in 14 patients the definitive airway was suspension laryngoscopy and jet ventilation; and four patients were tracheally intubated. Furthermore, four patients had a laryngeal mask airway placed after THRIVE, one patient had a tracheostomy, and for two patients, THRIVE was the sole mode of ventilation throughout the procedure.

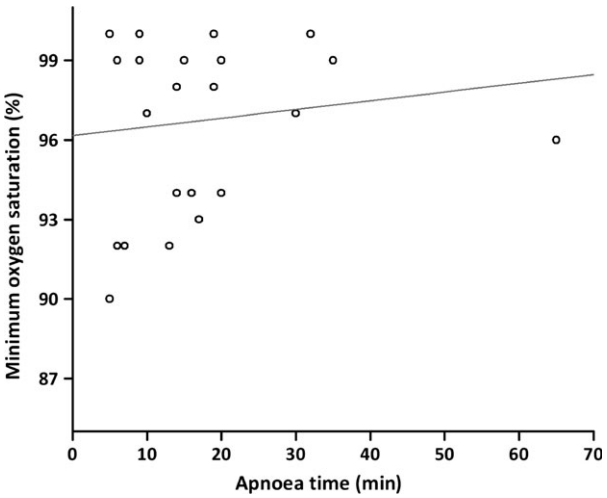

Figure 2 The relationship between apnoea time and oxygen saturation levels (n = 25). The line represents linear regression with r = 0.136 and p = 0.51.

Figure 3 illustrates the relationship between duration of apnoea and carbon dioxide levels at the end of the apnoeic period.

Discussion

We found deployment of THRIVE beneficial in extending apnoea time in our patients with difficult airways undergoing general anaesthesia [1, 21]. There were no desaturations below 90%, despite an average apnoea time of 17 min and none of the patients developed cardiac arrhythmias or other complications suggestive of carbon dioxide toxicity [13, 22].

High-flow nasal oxygenation has successfully been used, predominantly in intensive care [23] but also in emergency department [24] settings, to treat acute respiratory failure [25–29], to prevent postoperative atelectasis [30], and to alleviate dyspnoea in acute heart failure [31]. Interest is also emerging in the use of this technique to increase the apnoeic window in the context of tracheal intubation in the intensive care unit [32]. Our findings extend the application of this technique to managing patients with difficult airways undergoing general anaesthesia.

In 23 of 25 of our patients, termination of apnoea was planned and THRIVE made securing the definitive airway a smooth and unpressured undertaking. One

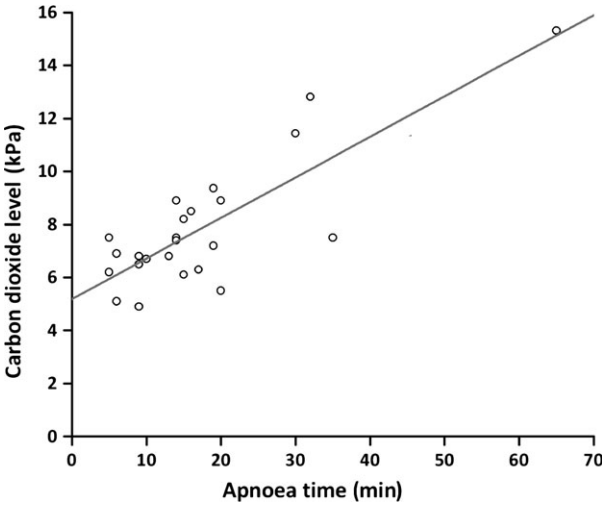

Figure 3 The relationship between apnoea time and end-tidal (and in four patients, arterial) carbon dioxide levels (n = 24). The line represents linear regression with r = 0.82 and p < 0.0001. The regression equation was $CO_2 = (5.2 \pm 0.5) + (0.15 \pm 0.02) \times$ apnoea time.

stridulous patient with acute airway compromise due to severe tracheobronchomalacia and a BMI of 34 $kg.m^{-2}$ desaturated to 92% at 7 min after induction and is likely to have done so sooner without THRIVE, and a second patient with spasmodic dysphonia and a BMI of 52 $kg.m^{-2}$ desaturated to 90% after 5 min of apnoea. In both of these cases, the modestly extended apnoeic window allowed suspension laryngoscopy and jet ventilation to be atraumatically established and saturations returned to 99% once jetting commenced. In two other patients, THRIVE was used throughout the procedure; these patients had apnoea times of 32 and 65 min, and this allowed pharyngolaryngeal surgery to be performed.

The physiological nomenclature for describing 'apnoeic oxygenation' has changed several times since the phenomenon was described by Volhard in 1908 [10]. It has been described as 'diffusion respiration' by Draper and Whitehead [33], as 'AVMF' by Bartlett et al. [9] and as 'apnoeic oxygenation' by Frumin et al. [13]. What all of these studies describe is oxygenation using only the difference in the rates of excretion of carbon dioxide and absorption of oxygen as the driver of gaseous flow. It was rapidly recognised that while apnoeic oxygenation alone could largely match the oxygen demands of the subject, it did not prevent a potentially rapid and dangerous rise in carbon dioxide concentration. In Frumin et al.'s experiments, two of eight human trials were prematurely terminated owing to development of ventricular arrhythmias [13], and in Draper et al.'s experiments, one of the 12 dogs died, most likely from carbon dioxide toxicity [11]. There were also early suggestions of patients' death and altered cerebral function following 'classical' apnoeic oxygenation [34, 35]. Joels and Samueloff demonstrated that classical apnoeic oxygenation causes a progressive respiratory acidosis that rapidly overwhelms the blood's buffering mechanisms and progresses into a mixed acidosis that proves fatal [36]. Death is principally due to limited tolerance of the myocardial contractile [37] and conductive [22] mechanisms to acidosis. Joels and Samueloff's experiments placed the upper limit of the 95% CI for occurrence of death due to acidosis at a pH of 6.9 [36].

We provide further evidence that classical apnoeic oxygenation provides little clearance of carbon dioxide.

We have plotted the rate of rise of carbon dioxide in three studies of classical apnoeic oxygenation [13, 15, 16], along with one study by Stock et al., who measured the rate of increase in carbon dioxide during airway obstruction (Fig. 4) [38]. In all of these studies, the rate of rise of carbon dioxide levels was between 0.35 and 0.45 kPa.min^{-1}, suggesting that classical apnoeic oxygenation provides a similarly low level of carbon dioxide clearance to that if the airway was obstructed.

It seems, therefore, that 'apnoeic oxygenation', while almost certainly a contributor to oxygenation during THRIVE, is an incomplete description for the technique. Perhaps, there is a contribution from a high-flow pre-oxygenation element, since very high flows of oxygen before or at induction may reduce rebreathing and maximise oxygen stores [39]. Moreover, we believe that a better explanation for the physiology that is being clinically observed can be derived from Meltzer and Auer's 'respiration without respiratory movements' experiments [40]. They maintained prolonged ventilation, apparently without carbon dioxide toxicity, through continuous insufflation of oxygen into the trachea [40]. They chose the calibre of the cannula to be smaller than tracheal diameter to allow gases to be exchanged with the exterior. We believe that continuous insufflation is the critical component of THRIVE, which achieves a continuous positive airway pressure of approximately 7 cmH_2O [41] that splints the upper airways and reduces shunting [42, 43]. Continuous insufflation facilitates oxygenation [17, 44] and carbon dioxide clearance through gaseous mixing and flushing of the deadspace. Evidence for the existence of flow-dependent, non-rhythmic ventilatory exchange can be provided by comparing the increase in rise of carbon dioxide under different continuous insufflation apnoeic conditions. Rudolf and Hohenhorst [45] performed a study in which ventilation was achieved through an intratracheal catheter delivering oxygen at a rate of 0.5 l.min^{-1}. This achieved a rate of carbon dioxide increase of 0.24 kPa.min^{-1}. Watson et al. used a high-flow tracheal cannula at 45 l.min^{-1} and achieved a steady-state carbon dioxide level within 5 min of the start of apnoea [46]. With THRIVE, the rate of carbon dioxide increase was 0.15 kPa.min^{-1} (Fig. 3) and a steady-state carbon dioxide level was not reached.

Our study was limited by the fact that it was observational and cross-sectional, and we only maintained THRIVE until a definitive airway had been secured. Furthermore, we only recorded those measurements of oxygenation and carbon dioxide

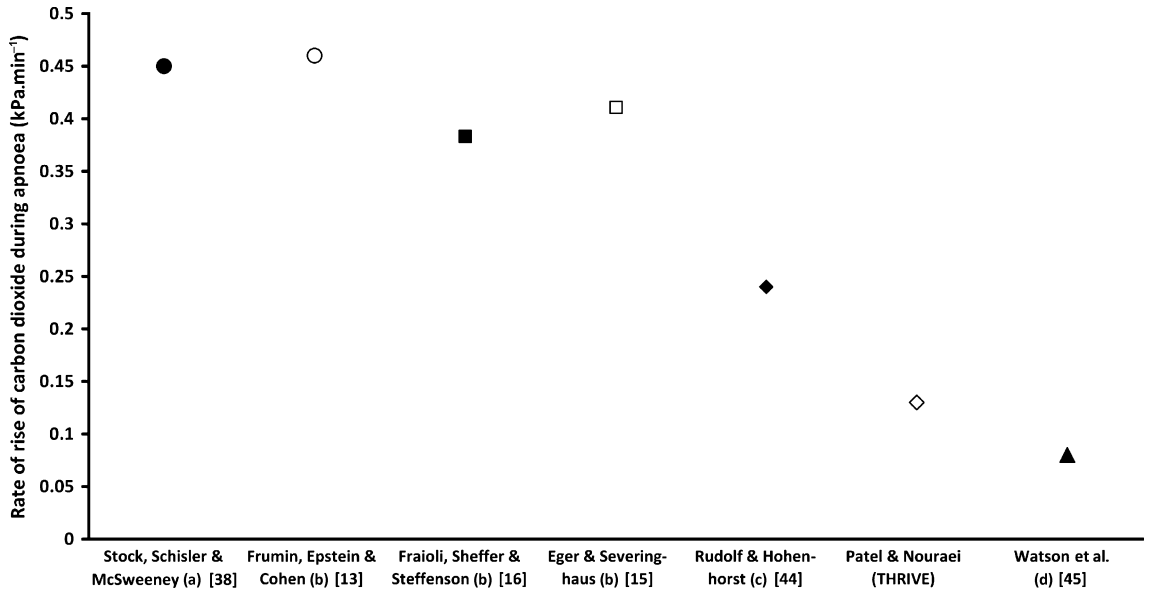

Figure 4 Rate of rise of carbon dioxide levels under different apnoea conditions undertaken within the study referred to: (a) airway obstruction; (b) classical apnoeic oxygenation; (c) low-flow intra-tracheal cannula and (d) high-flow intratracheal cannula.

excretion that were necessary as part of delivering routine clinical care. Furthermore, experimental studies are needed to characterise safe upper limits of THRIVE in different patient groups. We encountered two instances of desaturation, although not hypoxaemia. One case occurred in the presence of severe obesity and a second in the presence of severe tracheobronchomalacia and obesity. We are mindful of the fact that the apnoeic window, while extended through post-oxygenation compared with pre-oxygenation alone, is unlikely to be the same in obese as in non-obese patients. Based on our preliminary findings, the safe upper limit of apnoea in the presence of morbid obesity can be as low as 5 min, but this needs to be confirmed through an experimental human physiology study. It is also unlikely that THRIVE can readily rescue those patients who have total airway obstruction and its use in the presence of a known or suspected cranial base fracture is also not advised.

In conclusion, we have shown that THRIVE, as currently administered through a standard commercially available nasal high-flow oxygen delivery system, could maintain oxygen saturations after commencement of apnoea to levels that could change the nature of difficult intubations from a hurried stop-start, potentially traumatic undertaking, to a smooth event undertaken within an extended safe apnoeic window.

Competing interests

No external funding or competing interests declared. AP has contributed to the design of the A.P. Advance videolaryngoscopy system.

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