High flow nasal oxygen during sedation in the cardiac catheterisation laboratory: A randomized controlled trial

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### Abstract

**Background**

High flow nasal oxygen (HFNO) permits flows of heated, humidified gas via nasal prongs at up to 70L/min. Delivering oxygen at such high flow-rates has multiple physiological effects that may better support the vulnerable breathing state of patients during procedural sedation. The objective of this study was to investigate the effects of HFNO in comparison to standard facemask oxygen during cardiac implantable electronic device (CIED) procedures performed with procedural sedation.

**Methods** A randomized controlled trial design was used with participants randomized in a 1:1 ratio to receive oxygen supplementation through a facemask as per usual practice or to receive HFNO during procedural sedation administered Anesthesia Assistants under the supervision of an Anesthesiologist. HFNO was delivered at 50L/min with a 50:50 oxygen to air ratio. The oxygen flow-rate for partcipants randomized to facemask oxygen was ≥ 10L/min. Ventilation status was measured continuously using a transcutaneous carbon dioxide monitor. Peak TcCO2 was the primary outcome and we pre-specified that a difference of more than 4 mmHg would be clinically significant. Oxygenation was assessed using a composite measure comprising the incidence, depth, and duration of oxygen desaturation events below SpO2 90%. Adverse sedation events were assessed using the Tracking and Reporting Outcomes of Procedural Sedation (TROOPS) tool. Satisfaction with sedation was measured using the Iowa Satisfaction with Anesthesia Scale (ISAS). Patient comfort with the oxygen device and Anesthesia Assistant ratings for difficulty using the oxygen supplementation device and maintaining oxygenation were measured using ordinal scales. Outcomes were analysed using Bayesian statistical models.

**Results**

The difference in peak TcCO2 between groups was 0.0mmHg (95% CI = -1.34 to 1.38). The estimated effect did not exceed 4 mmHg in either direction with high probability and there was no discernable trend observed in how the effect varied with procedure time. There is a high probability that the difference in satisfaction with sedation between groups is minimal (95% CI = -0.33 to 0.23). The probability that patients are more likely to rate comfort with the oxygen supplementation device higher with HFNO compared to the facemask is 0.70. The odds of Anesthesia Assistants being more likely to rate the use of the oxygen supplementation device as more easy to use in the facemask group was 3 times that of the HFNO group (95% CI = 1 to 7 times). The odds of Anesthesia Assistants being more likely to rate their ability to maintain oxygen saturations as easy in the facemask group was 10 times that of the HFNO group (95% CI = 3 to 20 times). Minor adverse sedation events related to airway and breathing were 6.4 times more likely to occur in the HFNO group, but this estimate is imprecise (1.3 times to 43 times more likely). A similar number of participants in the HFNO group (n=8; 12%) experienced an oxygen desaturation event in comparison with the facemask oxygen group (n=7; 11%). (1.2; 95% CI = 0.37 to 3.75). The probabity that oxygen desaturations were more severe in the HFNO group was 0.83.

**Conclusion**

We investigated the effects of using HFNO with the flow-rate and oxygen to air ratio set to deliver a FiO2 approximately equivalent to that achieved from standard practice with facemask oxygen. There was no clear advantage for using HFNO in preference to standard facemask oxygen during CIED procedures performed with sedation.

**Trial registration number:** NCT03858257

## Introduction

Cardiac implantable electronic device (CIED) procedures are commonly performed with procedural sedation.1 Oxygen supplementation is administered to reduce hypoxemia from sedation-induced hypoventilation.2,3 High flow nasal oxygen (HFNO) is a promising device for oxygen supplementation.4 HFNO allows for heated, humidified gas with a titratable oxygen:air ratio to be administered via nasal prongs at up to 70L/min. Delivering oxygen supplementation at such high flow-rates has physiological effects that may support the vulnerable breathing state of patients during procedural sedation. In particular, one of the proposed physiological effects of HFNO is that it facilitates active gas exchange during times of apnea due to turbulent supraglottic flow vortices.5 The effects of the potential disadvantages of using HFNO during sedation should also be evaluated. It is possible that the potential gains arising from the HFNO device may be offset by reduced ability to monitor ventilation from capnography waveforms when it is being used, as exhaled carbon dioxide concentrations are “washed out” by the high gas flow. Guidelines from the American Society of Anesthesiology have stated that there is insufficient evidence regarding which supplemental oxygen device (e.g., nasal cannula, face mask, or specialized devices such as HFNO) is most effective.6 The objective of this study was to investigate the effects of HFNO in comparison to facemask oxygen during CIED procedures performed with procedural sedation.

## Methods

### Design

A randomized controlled trial design was used with participants 1:1 randomized to:

1. Facemask oxygen; or
2. High flow nasal oxygen.

Informed consent was obtained, and the study protocol conforms to the 1975 Declaration of Helsinki as reflected by the hospital research ethics board approval (18-6343). The trial was prospectively registered (NCT03858257).

### Participants

Adults undergoing an elective CIED procedure with sedation administered by an Anesthesia Assistant were included.

*Exclusion criteria*

1. Under 16 years.
2. Underlying condition requiring chronic oxygen supplementation.
3. Diagnosed respiratory condition with current hypercapnia defined as PaCO2 during admission over 45mmHg.
4. Pre-existing untreated pneumothorax.
5. Planned transesophageal echocardiography.
6. Active nasal-bleeding.
7. Complete nasal obstruction.
8. Recent upper-airway surgery or base of skull fracture.
9. Previous participation.

### Interventions

**Facemask oxygen supplementation**

Supplemental oxygen through a facemask with the flow-rate chosen by the Anaesthesia Assistant as per their standard practice.

**High flow nasal oxygen**

The Optiflow device (Fisher and Paykel Healthcare, Auckland, New Zealand), heated breathing tube and chamber, and nasal cannula was used. This system is a humidifier with an integrated flow generator, able to humidify respiratory gases and deliver them down a heated breathing tube and through the nasal cannula interface. The gas temperature was set to the ‘High’ setting (ranges 30-32º Celsius) and titrated downwards if the patient complained of irritation. The gas flow-rate was commenced at 30L/min prior to sedation administration and titrated up to 50L/min as tolerated by the patient after sedative medication was administered. The fraction of oxygen in the gas was commenced at 50% but could be titrated according to patient requirements.

**Concomitant care**

There were no restrictions on concomitant care. Anesthesia Assistants were permitted to use whichever devices for physiological monitoring that they deemed were required and titrate sedation according to their usual practice. Concomiitant care most relevant to this trial was the use of capnography. Anesthesia Assistants elected to use capnography regardless of whether supplemental oxygen was delivered via HFNO or facemask. The facemask had an integrated CO2 sampling line. For participants randomized to HFNO, Anesthesia Assistants were used the CO2 sampling adapter integrated with the latest model of the HFNO nasal cannula for the majority of participants (all those recruited after September 2019). Prior to this model becoming available, Anesthesia Assistants placed a facemask with an integrated CO2 sampling line over the HFNO nasal cannula. Oxygen supplementation was delivered through the HFNO nasal cannula and CO2 was sampled from the sampling line integrated into the facemask.

### Outcomes

Ooutcome selection was informed by recommendations from the Sedation Consortium on Endpoints and Procedures for Treatment, Education and Research (SCEPTER).7,8 The primary outcome was peak transcutaneous carbon dioxide (TcCO2) concentration. Secondary outcomes were:

1. Mean TcCO2.
2. Trajectory of TcCO2 as a function of time.
3. Area under the curve of oxygen desaturation (AUCDESAT). This is the difference between the threshold (90%) and actual oxygen saturation (SpO2) summed every minute during which oxygen saturation was below the threshold.
4. Adverse sedation events, measured using the Tracking and reporting outcomes of procedural sedation (TROOPS) tool.
5. Patient satisfaction with sedation.
6. Comfort of the oxygen delivery device.
7. Anesthesia Assistant rating of difficulty maintaining oxygenation status.
8. Anesthesia Assistant rating of difficulty using oxygen delivery device.

### Data collection

#### Instruments

TcCO2 was measured continuously using the Sentec Digital Monitoring system with VSign 2 sensor. TcCO2 monitoring provides continuous, accurate and precise estimates of PaCO2.9 TcCO2 monitoring may provide even more precise estimates of changes in PaCO2 (mean bias 0.03 mmHg, 95% limits of agreement -0.44 to 0.38 mmHg).10 The Sentec VSign 2 sensor was attached to the forehead. Once the TcCO2 stabilized, the monitor was covered with a drape so that it was not visible to research staff or clinicians. The monitor was not used by the clinicians to guide treatment. TcCO2 was sampled at a frequency of one measurement per second. The recorded SpO2 was extracted from the Drug Reconciliation and Electronic Monitoring System at a frequency of one measurement per minute. Adverse sedation events were measured using the tracking and reporting outcomes of procedural sedation (TROOPS) tool.11 Satisfaction with sedation was measured using the Iowa Satisfaction with Anesthesia Scale (ISAS).12,13 Participants were asked to rate comfort with the oxygen delivery device and Anaesthesia Assistants were asked to rate their: 1) perceived level of difficulty in maintaining oxygenation; and 2) perceived level of difficulty using the oxygen delivery device, using a 6-level rating scale.

### Sample size calculation

We estimated based on our prior work2 that the peak TcCO2 level in the control group would be 47 mmHg and standard deviation would be 7 mmHg. Assuming a type I error rate of 5%, a sample of 130 participants would achieve 90% power to detect a reduction in mean TcCO2 levels of 4 mmHg in the intervention period. A difference in TcCO2 levels of 4 mmHg was selected for this sample size calculation because it was used to power previous trials.14,15 Differences in CO2 levels of a similar magnitude have been detected in previous trials evaluating the efficacy of interventions to improve sedation safety.16–20

### Statistical analyses

Bayesian statistical models were used. Data and code is available [here](https://hfnosedrct.netlify.app/flexdashboard). A detailed summary of the statistical models is presented in the Appendix. Prior distributions were chosen to be weakly informative, which is appropriate in the absence of information concerning the likely values of model parameters.21 Covariate adjustments were made for the stratification variables obstructive sleep apnea (OSA) status and whether or not the procedure was a cardiac resynchronization therapy (CRT) device implant as well as for baseline TcCO2 concentration, which was modelled using splines.22 Continuous outcomes were analyzed using robust regression models. A functional analysis of variance (ANOVA) model was used to investigate how mean TcCO2 concentration levels differ between groups as a function of procedure time23. Logistic regression was used for dichotomous outcomes. Proportional-odds models were used for ordinal outcomes. Analysis was performed only on those participants whose SPO2 was observed to fall below the 90% threshold for the AUCDESAT outcome.

Posterior inference for all models except the functional ANOVA model was performed using Hamiltonian Monte Carlo through the brms package24, version 2.12.0. For this set of models, 2000 posterior samples were obtained from 4 independent chains of 2000 samples, where the first 1000 warm-up samples were discarded. Posterior inference for the functional ANOVA model was performed using the Integrated Nested Laplacian Approximation25 through the INLA package, version 20.5.12. The marginal posterior distribution of parameters were summarized by their mean and a 95% credible interval defined by the interval spanning the 2.5% and 97.5% percentiles of their distributions. The clinical significance of treatment effects relating to TcCO2 concentration were evaluated by computing the posterior probability that an effect exceeds 4 mmHg in either direction. When the proportion of missing data was large and the missing completely at random (MCAR) assumption was unlikely to be satisfied, a sensitivity analysis was performed to investigate the robustness of the conclusions of the complete-case analysis.

## Results

### Participants

From August 2019 to March 2020, we screened 270 patients undergoing CIED procedures (Figure 1). A total of 130 participants were randomized. One participant was excluded because the procedure was cancelled. One participant, who was randomized to the HFNO group, had their procedure rescheduled to a time that the Research Assistant was not available. As such, this participant received oxygen via standard face mask and TcCO2 data were not collected. For two participants, the TcCO2 sensor failed to callibrate prior to commencement of the procedure. Most (n=29; 45%) Anesthesia Assistants reported having used HFNO between 2-5 times.

Participant characteristics are presented in Table 1. The sample was mostly elder and male. Anesthesia Assistants’ rated the ASA Physical Classification Status as either III or IV. Obstructive sleep apnea was common. About 20% of procedures were for cardiac resnchronisation therapy.

### Comparisons between groups

#### Primary outcome

Results are presented in Table 2. The effect of HFNO on the peak TcCO2 was estimated to be 0.0mmHg (95% CI = -1.34 to 1.38). The probability that it exceeds the 4 mmHg clinical significance threshold of 4mmHg in either direction is 0.

#### Secondary outcomes

The effect of HFNO on the mean TcCO2 concentration was estimated to be -0.1 mmHg (-1.36, 1.17). The probability that it exceeds the 4 mmHg clinical significance threshold is 0 in either direction. TcCO2 concentrations for all patients throughout procedures are displayed in Figure 2, with the longest procedure highlighted as a reference. The estimated effect did not exceed the 4 mmHg clinical significance threshold in either direction with probability greater than 0.95. There is no discernable trend observed in how the effect varies with procedure time. Precision decreases as time increases, reflecting the shrinking number of participants.

The effect of HFNO on ISAS score was estimated to be 0.0 (95% CI = -0.33 to 0.23). The probability that patients are more likely to rate comfort with the oxygen supplementation device higher with HFNO compared to the facemask is 0.70.

The odds ratio for Anesthesia Assistant ratings of difficulty maintaining oxygenation status and difficulty using the oxygen delivery device as estimated using a complete-case analysis are 0.1 (95% CI = 0.05 to 0.31) and 0.3 (95% CI = 0.14 to 0.83), where a value less than 1 indicates a greater level of difficulty for respondents in the HFNO group. It may be simpler for interpretation to reverse the terms. For example, the odds of Anesthesia Assistants being more likely to rate the use of the oxygen supplementation device as more easy to use (i.e., “extremely” or “very easy” versus “easy”) in the facemask group was estimated to be 3 times [i.e., 1/0.33] that of the HFNO group. The odds of Anesthesia Assistants being more likely to rate their ability to maintain oxygen saturations as easy in the facemask group was 10 times [i.e., 1/0.1] that of the HFNO group. It should be noted, however, that the Anesthesia Assistant ratings of difficulty using the oxygen device and difficulty maintaining oxygenation were missing 45 and 46 responses, respectively, likely due to the survey being voluntary. It is unlikely that missingness among these ratings occurred completely at random, so a best- and worst-case imputation approach was used to investigate the impact that the missing data could have on the results in extreme cases. The best- and worst-case sensitivity analysis gave estimates ranging between 0.0 (95% CI = 0.01 to 0.08) and 3.3 (95% CI = 1.72 to 6.62) for difficulty maintaining oxygenation status and from 0.1 (95% CI = 0.04 to 0.18) and 5.0 (95% CI = 2.49 to 9.79) for difficulty using the oxygen delivery device. These estimates suggest the directionality of the effect could be positive or negative with high probability, so conclusions of the complete-case analysis are not robust to assumptions about the values for the missing data.

The odds ratio for a minor adverse sedation event related to airway or breathing, as measured by the TROOPS tool, for the HFNO group compared with the facemask group was estimated to be 6.4. This effect estimate is very imprecise due to the small number of events (95% CI 1.3 to 43). A similar number of participants in the HFNO group (n=8; 12%) experienced an oxygen desaturation event in comparison with the facemask oxygen group (n=7; 11%). (1.2; 95% CI = 0.37 to 3.75). The effect estimate for the absolute difference in the AUCDESAT was imprecise, spanning from 5 minutes.% higher in the face mask group to 24 minutes.% higher in the HFNO group. The probabity that AUCDESAT is higher with HFNO is 0.83. A visualization of the SpO2 trajectories for patients whose SpO2 was below 90% is available [here](https://hfnosedrct.netlify.app/flexdashboard).

#### Oxygen flow-rates

Most participants randomized to the HFNO group had the flow-rate set at 50L/min (Figure 3). Most participants randomized to the facemask group received oxygen at ≥10L/min. Two participants who were randomized to HFNO did not receive this intervention at all and four participants who were randomized to HFNO stopped receiving this intervention at a certain timepoint during procedures at the discretion of the Anesthesia Assistant, with the rationale that capnography monitoring was not sufficient with the HFNO device.

## Discussion

We found that HFNO at 50L/min for patients undergoing elective CIED procedures with sedation is highly unlikely to *decrease* or *increase* peak TcCO2 concentration by a clinically important amount. Although a prior physiological modeling study identified a mechanism by which HFNO promotes carbon dioxide clearance,5 it seems the magnitude of any such effect is insufficient to produce an important difference in ventilation status during procedural sedation. This result is consistent with prior clinical research in the non-sedation context. The difference in PaCO2 observed between HFNO (5.81 kPa; sd=1.1) and facemask oxygen (5.6 kPa; sd=1.0) from a randomized trial of 20 patients who were receiving pre-oxygenation for induction of anesthesia prior to emergency surgery was not significant (p=0.631).26 Likewise, in a larger trial of pre-oxygenation with 80 patients, the end-tidal CO2 in the first breath after intubation was not significantly different between HFNO (5.0 kPa; sd=0.8) and standard facemask (5.3 kPa sd=1.0) oxygen supplementation (p=0.18).27 Importantly, in contrast to these trials where ventilation status was assessed at one specific point in time with either PaCO2 or ETCO2 samples, we used continuous TcCO2 monitoring so that we could estimate differences in ventilation between groups over the whole duration of procedures. There was no discernible trend observed in how the effect varied over time, lending strength to the assertion that ventilation status is not impacted by the use of HFNO.

The probability that minor adverse sedation events related to airway and breathing are more likely to occur with HFNO is 0.99. The suspected etiology noted for these events by the Anesthesia Assistants in the TROOPS tool was oxygen desaturation. This finding is consistent with the difference observed between groups in the AUCDESAT outcome. The probability that AUCDESAT is higher with HFNO is 0.83. There are two plausible mechanisms that may explain these findings. First, it is possible that the flow-rate (50 liters/minute) and oxygen:air blend (50:50) used in the HFNO group was simply not equivalent to the amount of oxygen supplementation received in the facemask group. Most participants in the facemask group received >10L/min of 100% O2. Further research with a larger sample size would be useful to determine the optimal oxygen:air ratio for HFNO during sedation for CIED procedures, with a focus on adverse sedation events or hypoxemia as the primary outcome.

Another plausible mechanism is that the ability to monitor capnography waveforms was diminished with HFNO. As a consequence, clinicians may not able to detect episodes of hypoventilation as easily when HFNO is used leading to delayed initiation of interventions to support respiratory status or titration of medications. Capnography is widely considered to be an essential aspect of physiological monitoring during sedation.28–30 The concern about reduced ability to monitor capnography waveforms when HFNO is used potentially increasing risk of more prolonged, undetected episodes of hypoventilation during sedation has been raised previously in the literaure.31 However, it should be noted that if undetected episodes of hypoventilation were considerably more frequent and prolonged when HFNO was used, presumably, we would have observed higher TcCO2 concentrations in this group. We did not observe higher TcCO2 concentrations in the HFNO group for the peak measurement or at any particular timepoint during procedures.

The evidence base for the effects of HFNO therapy for procedural sedation in other clinical contexts is limited. One large32 and three small randomized controlled trials of HFNO during procedural sedation have been published in 2019, with several more on-going trials registered.33 The primary outcomes for all the trials to date have focused on investigating the imapact of HFNO on oxygenation. Results have been inconsistent. One of the small trials randomized 60 participants undergoing bronchoscopy to receive HFNO at 50L/min with 100% oxygen or to receive oxygen at 10-15L/min through a facemask.34 There was no difference observed between the treatment groups for the primary outcome, which was the proportion of patients who experienced oxygen desaturation (defined as SpO2 90%). Another trial randomized 59 morbidly obese patients undergoing endoscopy to receive a fraction of inspired oxygen concentration of 0.36 either via HFNO at a flow-rate of 60L/min or via nasal cannula at 4L/min.35 Again, there was no difference in the primary outcome of oxygen desaturation (SpO2 90%). The third study randomized 30 participants undergoing dental sedation into three groups to receive a fraction of inspired oxygen concentration of 0.4 either via HFNO at a flow-rate of 50L/min, via HFNO at a flow-rate of 30L/min or via nasal cannula at 5L/min.36 Participants randomized to the HFNO groups had higher nadir blood oxygen levels recorded than the low flow oxygen group. In contrast, a large trial of 1994 participants undergoing gastroscopy with propofol sedation reported a large reduction in risk of hypoxemia (8.4% in the control group and 0% in the HFNO group).32 This resuslt is likely explained by the large difference in FiO2 that was delivered between the two groups. In the HFNO group participants received 60 liters of 100% oxygen per minute and in the control group participants received just 2 liters of oxygen per minute.

Satisfaction with sedation is very likely to be similar between HFNO and facemask oxygen. The probability that patients are more likely to rate comfort with the oxygen supplementation device higher with HFNO was 0.70. In contrast, we identified that the HFNO device was rated as more difficult for Anesthesia Assistants to use compared with the standard facemask. None of the Anesthesia Assistants rated the HFNO device as *difficult* to use and most had very limited experience using the device. Also, most participants reported they had used HFNO between 2 and 5 times. Experience with HFNO is likely to influence clinicians’ perceptions about the difficulty using the device.

### Limitations

Ventilation was measured using TcCO2 monitoring, which is not a perfect substitute for PaCO2. The primary outcome was peak TcCO2 and we accounted for the correlation between baseline and peak measurements by including the baseline measurements as a covariate in the model. However, an inherent problem with this approach is that it is potentially sensitive to how the baseline and peak measurements were chosen. We chose the TcCO2 concentration at the time sedation was first administered as the baseline measurement and the maximum TcCO2 observed over the whole procedure as the peak. We did not blind participants or clinicians to group assignment. The small dropout and cross-over rate is unlikely to have exerted a major impact on the effect estimates. Participants received propofol, midazolam and fentanyl, which is a common and recommended approach for CIED procedures.37 Severe oxygen desaturation is not a common event when oxygen supplementation is delivered at flow-rates between 6-10L/min through a face mask during procedures performed with sedation in the cardiac catheterisation laboratory.1,3 Results from our trial can not be directly generalised to other clinical settings where desaturation is more severe and occurs more often.

### Conclusion

We investigated the effects of using HFNO with the flow-rate and oxygen to air ratio set to deliver a FiO2 approximately equivalent to that achieved from standard practice with facemask oxygen. Ventilation, as measured by TcCO2, is highly unlikely to differ by a clinically important amount. The probability that minor adverse sedation events were more likely to occur in the HFNO group was high and the severity of oxygen desaturations is probably worse with HFNO. There is a higher probability that patients will be more comfortable during procedures with HFNO in comparison to the facemask, but overall patient satisfaction with sedation is likely to be similar. Overall, there was no clear advantage identified for using HFNO in place of facemask oxygen.

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# Figure legend

Fig. 1 CONSORT Flow Diagram

Fig. 2 Transcutaneous carbon dioxide measurements throughout procedures

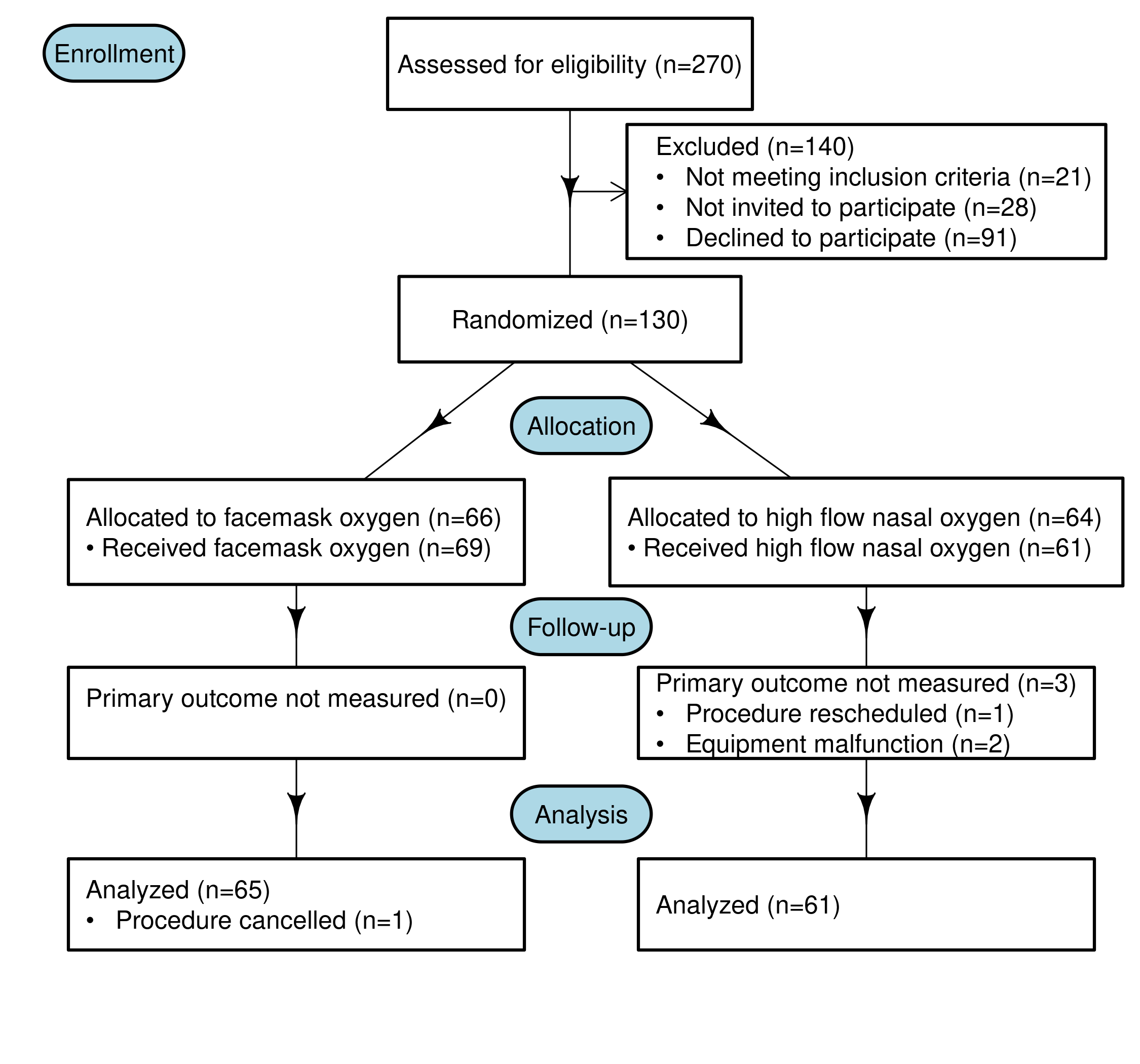


Figure : CONSORT flow diagram

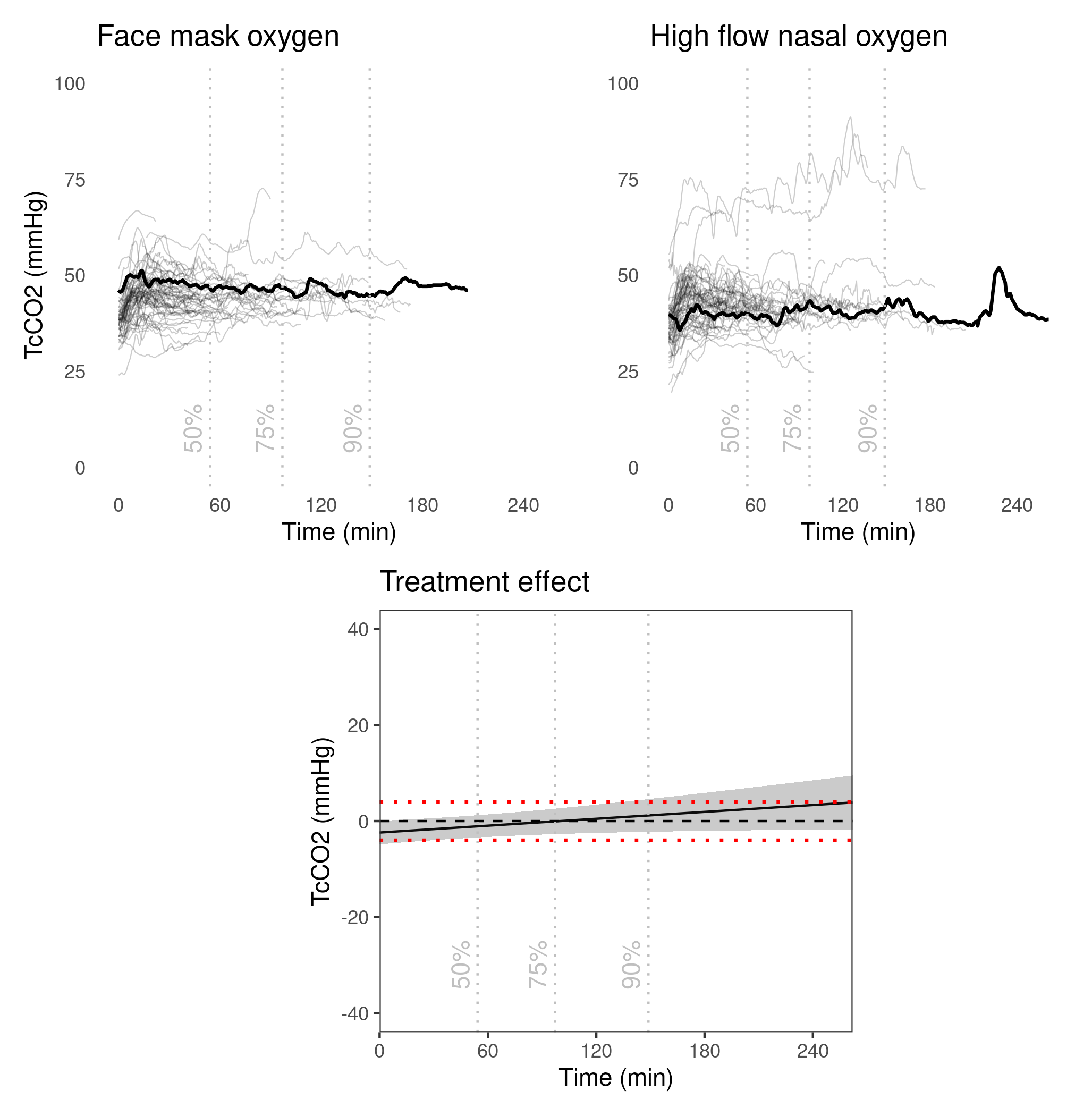


Figure : Transcutaneous carbon dioxide measurements throughout procedures



Figure : Oxygen flow-rates

## Table 1. Participant characteristics

| Characteristic | High Flow nasal oxygen, N = 641 | Face mask oxygen, N = 651 |
| --- | --- | --- |
| *Age (years)* | 67 (14) | 70 (13) |
| *Gender* |  |  |
| Female | 19 (30%) | 17 (26%) |
| Male | 45 (70%) | 47 (72%) |
| Prefer not to say | 0 (0%) | 1 (1.5%) |
| Other | 0 (0%) | 0 (0%) |
| *Smoking history* |  |  |
| Never | 23 (36%) | 25 (38%) |
| Current | 7 (11%) | 7 (11%) |
| Past | 34 (53%) | 33 (51%) |
| *Obstructive sleep apnea* | 17 (27%) | 18 (28%) |
| *Uses CPAP* | 9 (14%) | 12 (18%) |
| *Admission source* |  |  |
| Ward | 17 (27%) | 18 (28%) |
| Day surgery | 45 (70%) | 44 (68%) |
| CVICU | 2 (3.1%) | 3 (4.6%) |
| CICU | 0 (0%) | 0 (0%) |
| *ASA classification status* |  |  |
| I | 0 (0%) | 0 (0%) |
| II | 0 (0%) | 0 (0%) |
| III | 21 (33%) | 16 (25%) |
| IV | 43 (67%) | 49 (75%) |
| *Procedure* |  |  |
| PPM | 11 (17%) | 17 (26%) |
| PPM generator change | 6 (9.4%) | 7 (11%) |
| PPM lead revision | 0 (0%) | 1 (1.5%) |
| ICD | 19 (30%) | 13 (20%) |
| ICD generator change | 10 (16%) | 13 (20%) |
| ICD lead revision | 2 (3.1%) | 0 (0%) |
| CRT-D | 11 (17%) | 11 (17%) |
| CRT-P | 2 (3.1%) | 2 (3.1%) |
| Wound revision | 0 (0%) | 0 (0%) |
| Other | 3 (4.7%) | 1 (1.5%) |
| *Charlson Comorbidity Index* | 4.46 (2.14) | 5.15 (2.51) |
| *Total dose of midazolam (mg)* | 1.58 (0.84) | 1.45 (0.71) |
| *Total dose of propofol (mg)* | 100 (126) | 88 (104) |
| *Total dose of fentanyl (mcg)* | 71 (28) | 76 (56) |
| 1Statistics presented: mean (SD); n (%) | | |

## Table 2. Results

|  | | Randomization | |  | |
| --- | --- | --- | --- | --- | --- |
| Outcome | Summary value | Face mask oxygen | High flow nasal oxygen | Effect type | Estimated treatment effect (95% CI)\* |
| Peak TcCO2 | N | 65 | 61 |  |  |
|  | Mean (sd) | 49.0 mmHg (6.9) | 47.8 mmHg (9.7) | Absolute difference | 0.0 mmHg (-1.34, 1.38) |
| Mean TcCO2 | N | 65 | 61 |  |  |
|  | Mean (sd) | 44.3 mmHg (5.9) | 42.7 mmHg (7.2) | Absolute difference | -0.1 mmHg (-1.36, 1.17) |
| SpO2 | N | 65 | 64 |  |  |
|  | SpO2 <90% event | 7 (11%) | 8 (12%) | Odds ratio | 1.2 (0.37, 3.75) |
|  | Median (IQR) Area under SpO2 desaturation curve | 8 (3.5, 9.5) | 9.5 (5.75, 25.25) | Absolute difference | 5.6 % minute (-5.39, 24.24) |
| ISAS score | N | 63 | 63 |  |  |
|  | Mean (sd) | 2.1 (0.9) | 2.0 (1.0) | Absolute difference | 0.0 (-0.33, 0.23) |
| Patient comfort | N | 65 | 63 |  |  |
|  | Maximal comfort | 17 | 9 | Odds ratio | 1.2 (0.64, 2.17) |
|  | Very comfortable | 13 | 26 |  |  |
|  | Comfortable | 22 | 22 |  |  |
|  | Uncomfortable | 10 | 3 |  |  |
|  | Very uncomfortable | 2 | 2 |  |  |
|  | Maximal discomfort | 1 | 1 |  |  |
| Difficulty maintaining oxygenation status | N | 31 | 52 |  |  |
|  | Extremely easy | 17 | 9 | Odds ratio | 0.1 (0.05, 0.31) |
|  | Very easy | 10 | 14 |  |  |
|  | Easy | 4 | 17 |  |  |
|  | Difficult |  | 6 |  |  |
|  | Very difficult |  | 4 |  |  |
|  | Extremely difficult |  | 2 |  |  |
| Difficulty using oxygen delivery device | N | 32 | 52 |  |  |
|  | Extremely easy | 17 | 15 | Odds ratio | 0.3 (0.14, 0.83) |
|  | Very easy | 9 | 17 |  |  |
|  | Easy | 6 | 20 |  |  |
| Minor airway or breathing event | N | 65 | 64 |  |  |
|  | Yes | 2 | 9 | Odds ratio | 6.4 (1.34, 42.99) |
|  | No | 63 | 55 |  |  |
| \*Adjusted for covariates | | | | | |
| Odds ratios are interpreted as the odds of the event occuring in the HFNO group compared with the odds of the event occuring in the facemask group | | | | | |
| TcCO2 = Transcutaneous carbon dioxide concentration | | | | | |
| SpO2 = Percentage of hemoglobin saturate with oxygen | | | | | |
| ISAS = Iowa Satisfaction with Anesthesia Scale | | | | | |
| 95% CI = 95% credible intervals | | | | | |

# Appendix

## Robust regression

A robust regression model is used for the analysis of continuous outcomes peak TcCO2, mean TcCO2, log SPO2 AUC, and average ISAS score. Let be the value of the continuous response for the th patient, be a baseline covariate, and be an indicator variables which is nonzero if the patient belonged to the HFNO treatment group. Associated with each patient are additional stratification indicator variables for OSA status and CRT status . We supress the patient index on patient covariates to simplify the notation.

The likelihood of the robust regression model is where is the response value of the th patient, is a generalized Student’s t-distribution with degrees of freedom , location parameter and scale parameter . The location parameter for the th patient is assumed to depend on their covariates as

where is a non-linear continuous function of a continuous covariate and , are regression coeficients. For peak and mean TcCO2, is taken as the first recorded value of TcCO2 of the patient during their procedure. For average SPO and average ISAS score there is no corresponding baseline covariate and so is omitted. Prior distributions of model parameters are chosen to be diffuse in the absence of information about their likely values. In the following list of prior specifications, denotes a normal distribution with mean and standard deviation .

* : The function are estimated using a thin-plate spline basis and the random-effect formulation used in brms [cite]. The spline basis dimension is 20 and the standard deviation parameter governing the random-effect distribution is given a prior.
* : intercept coefficient is given a prior, where the location parameter is set equal to the mean value of the response.
* : coefficients of indicator variables are given a prior.
* : degrees of freedom parameter is given a prior proposed for such parameters in the absence of any information (cite).
* : scale parameter is given a prior.

## Logistic and proportional odds regression

A logistic regression models are used for both the adverse affect “patient experienced at least one minor respiratory event” and the event “patient experienced at least one desaturation event”. A proportional-odds model with logit link is used for ordinal outcomes patient comfort of oxygen delivery, and Anesthesia Assistant rating of difficulty maintaining oxygenation status and rating of difficulty using oxygen delivery device. The link function in each model is written as a function of covariates in the same way as in the robust regression case (). The coeficients are given a prior distributions in the absence of information about their likely values.

## Functional analysis of variance

The functional observations are taken to be the vector of TcCO2 measurements of the th patient belonging to randomization group measured at 1 second intervals from the procedure’s start until the procedure’s end. The group variable indicates membership to the face mask oxygen group and indicates membership to the HFNO group. Associated with each patient are stratification indicator variables for their OSA status and CRT status . All functional observations are aligned to have time occur at the start of each procedure. The time resolution of observations is reduced to measurements every 30 seconds to reduce the computational burden of model fitting.

The one-way functional ANOVA model assumes that the TcCO2 measurments for the th patient has the likelihood function where is the mean vector and is a covariance matrix. The mean vector is assumed to have the form where is the baseline functional effect common to all patients, is the th treatment group functional effect, and are effects for OSA status and CRT status, respectively. A normally-distributed random intercept is included to account for different average levels in TcCO2 observed between patients. The baseline constraint parameterization of is used to ensure that the model is identifiable. Under this parameterization, is the mean level of TcCO2 of the face mask oxygen group and is the mean level of TcCO2 of the HFNO group.

The set of TcCO2 measurements from a patient form a time-series that is inadequately modelled by assuming independent and identically distributed normal errors in (3). Mis-specification of the covariance structure can lead to credible intervals for the treatment effect that are artificially narrow. To better model the error structure of the data, the covariance matrix is assumed to have the form of an autoregressive process of order 1 with the same set of correlation and variance parameters for every patient, denoted and , respectively.

The model is scaled to have generalized variance of 1 to aid in prior specification38. The prior distrbutions of model parameters are chosen to be diffuse in the absence of information about their likely values. They are as follows:

* : functional effects are estimated using a smoothing spline approach by specifying a random-walk prior of order 2 on the 2nd-order differences of the vector components [BRINLA]. The standard deviation parameter hyper-parameter of the random walk processeses is given a prior distribution.
* , : regression coeficients are given a prior distribution.
* standard deviation of the random intercept is given a prior distribution.
* prior distributions for the parameters of the covariance matrix are specified according to their internal parameterization in INLA: