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High flow nasal oxygen during procedural sedation for cardiac implantable electronic devices: A randomized controlled trial

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Abstract:	Background High flow nasal oxygen may better support the vulnerable breathing state of patients during procedural sedation. Objective The objective of this study was to investigate the effects of high flow nasal oxygen in comparison to facemask oxygen on ventilation during cardiac implantable electronic device procedures performed with procedural sedation. Design Randomized controlled trial. Setting The study was conducted at one academic teaching hospital in Canada. Participants Adults undergoing elective cardiac implantable electronic device procedures with sedation administered by an Anesthesia Assistant (supervised by an Anesthesiologist) from August 2019 to March 2020. Interventions Participants were 1:1 randomized to facemask (≥ 8L/min) or high flow nasal oxygen (50L/min and 50:50 oxygen to air ratio). Main outcome measures The primary outcome was peak transcutaneous carbon dioxide. Outcomes were analysed using Bayesian statistics. Results

	The 129 participants who were randomized and received sedation were included. The difference in peak transcutaneous carbon dioxide was 0.0mmHg (95% CI = -1.3 to 1.37). Minor adverse sedation events were 6.4 times more likely to occur in the high flow nasal oxygen group. This estimate is imprecise (95% CI = 1.34 to 42.99). The odds ratio for oxygen desaturation for the high flow nasal oxygen group compared with the facemask group was 1.2 (95% CI = 0.37 to 3.75). The difference in satisfaction with sedation scores between groups was 0.0 (95% CI = -0.33 to 0.23). Conclusions Ventilation, as measured by TcCO2, is highly unlikely to differ by a clinically important amount between high flow nasal oxygen at 50L/min or facemask oxygen at 8L/min. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio when using high flow nasal oxygen during cardiac implantable electronic device procedures performed with sedation.
Response to Reviewers:	Please see the attached cover letter with detailed responses to the reviewers' comments.

High flow nasal oxygen during procedural sedation for cardiac implantable electronic devices: A randomized controlled trial

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Running head: High flow nasal oxygen during sedation

Abstract

Background

High flow nasal oxygen may better support the vulnerable breathing state of patients during procedural sedation.

Objective

The objective of this study was to investigate the effects of high flow nasal oxygen in comparison to facemask oxygen on ventilation during cardiac implantable electronic device procedures performed with procedural sedation.

Design

Randomized controlled trial.

Setting

The study was conducted at one academic teaching hospital in Canada.

Participants

Adults undergoing elective cardiac implantable electronic device procedures with sedation administered by an Anesthesia Assistant (supervised by an Anesthesiologist) from August 2019 to March 2020.

Interventions

Participants were 1:1 randomized to facemask (≥ 8L/min) or high flow nasal oxygen (50L/min and 50:50 oxygen to air ratio).

Main outcome measures

The primary outcome was peak transcutaneous carbon dioxide. Outcomes were analysed using Bayesian statistics.

Results

The 129 participants who were randomized and received sedation were included. The difference in peak transcutaneous carbon dioxide was 0.0mmHg (95% CI = -1.3 to 1.37). Minor adverse sedation events were 6.4 times more likely to occur in the high flow nasal oxygen group. This estimate is imprecise (95% CI = 1.34 to 42.99). The odds ratio for oxygen desaturation for the high flow nasal oxygen group compared with the facemask group was 1.2 (95% CI = 0.37 to 3.75). The difference in satisfaction with sedation scores between groups was 0.0 (95% CI = -0.33 to 0.23).

Conclusions

Ventilation, as measured by $TcCO_2$, is highly unlikely to differ by a clinically important amount between high flow nasal oxygen at 50L/min or facemask oxygen at 8L/min. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio when using high flow nasal oxygen during cardiac implantable electronic device 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 the 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 on ventilation during CIED procedures performed with procedural sedation.

Methods

Design

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

- Facemask oxygen; or
- High flow nasal oxygen.

Informed consent was obtained. The study protocol conforms to the 1975 Declaration of Helsinki. Ethical approval for this study (Ethical Committee Number: 18-6343) was provided by the University Health Network Research Ethics Board, Toronto, Canada (Co-chair Morris Sherman) on June 21 2019. The trial was prospectively registered (NCT03858257).

Participants

Adults undergoing an elective CIED procedure with sedation administered by an Anesthesia Assistant at one large academic teaching hospital in Canada were included.

Exclusion criteria

- <16 years.
- Underlying condition requiring chronic oxygen supplementation.
- Diagnosed respiratory condition with current hypercapnia defined as $PaCO_2$ during admission over 45mmHg.
- Pre-existing untreated pneumothorax.
- Planned transesophageal echocardiography.

- Active nasal-bleeding.
- Complete nasal obstruction.
- Recent upper-airway surgery or base of skull fracture.
- Previous participation.

Sedation

The model of sedation at the site where this trial was conducted follows recommendations from the Canadian Anesthesiologists' Society.[7] Sedation was provided by a team that included a sedation supervisor (Anesthesiologist) and an approved and credentialed sedation assistant (Anesthesia Assistant) who is delegated tasks of providing sedation and monitoring the patient. The Anesthesia Assistant remains in constant attendance with the patient, providing continuous monitoring and immediately informing the sedation supervisor of any concerns. The sedation supervisor (Anesthesiologist in this case) retains responsibility for the patient. It is standard practice at this site for a combination of midazolam, fentanyl and propofol administered as bolus doses to be used. There were no additional restrictions on the type or dose of sedation used by Anesthesia Assistants imposed for participants enrolled in the trial. The actual doses of sedation used for participants in the trial were recorded.

Interventions

Facemask oxygen supplementation

Supplemental oxygen was delivered using a standard facemask with an integrated exhaled CO2 sampling line. The flow-rate chosen by the Anaesthesia Assistant as per their standard practice, which was mostly ≥8L/min.

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). 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. A Research Assistant who was trained in the use of the HFNO device was present during all procedures to assist Anesthesia Assistants with set-up, application and trouble-shooting if required.

Concomitant care

There were no restrictions on concomitant care. Anesthesia Assistants were permitted to use standard physioligcal monitoring devices, as dictated by the Canadian Anesthesiologists' Society (CAS), and to titrate sedation according to their usual practice.[7] Concomitant 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, as this is a requirement from the

Canadian Anesthesiologist Society anytime procedural sedation is being administered.[7] The facemask had an integrated CO_2 sampling line. For participants randomized to HFNO, Anesthesia Assistants 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 - recruitment started in August 2019). Prior to this model becoming available, Anesthesia Assistants placed a facemask with an integrated CO_2 sampling line over the HFNO nasal cannula. Oxygen supplementation was delivered through the HFNO nasal cannula and CO_2 was sampled from the sampling line integrated into the facemask.

Outcomes

Outcome selection was informed by recommendations from the Sedation Consortium on Endpoints and Procedures for Treatment, Education and Research (SCEPTER).[8] The primary outcome was peak transcutaneous carbon dioxide ($TcCO_2$) concentration. Secondary outcomes were:

- Mean $TcCO_2$.
- Trajectory of $TcCO_2$ as a function of time.
- Area under the curve of oxygen desaturation (AUC_{DESAT}). This is the difference between the threshold (90%) and actual oxygen saturation (SpO_2) summed every minute during which oxygen saturation was below the threshold.
- Adverse sedation events, measured using the Tracking and reporting outcomes of procedural sedation (TROOPS) tool.
- Patient satisfaction with sedation.

- Comfort of the oxygen delivery device.
- Anesthesia Assistant rating of difficulty maintaining oxygenation status.
- Anesthesia Assistant rating of difficulty using oxygen delivery device.

Data collection

Instruments

$TcCO_2$ was measured continuously using the Sentec Digital Monitoring system with VSign 2 sensor. $TcCO_2$ monitoring provides continuous, accurate and precise estimates of $PaCO_2$.[9] $TcCO_2$ monitoring may provide even more precise estimates of changes in $PaCO_2$ (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 $TcCO_2$ 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. $TcCO_2$ was sampled at a frequency of one measurement per second. The recorded SpO_2 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] Participants were asked to rate comfort with the oxygen delivery device and Anesthesia Assistants were asked to rate their: 1) perceived level of difficulty in maintaining oxygenation; and 2) perceived level of difficulty in using the oxygen delivery device, using a 6-level rating scale.

Sample size calculation

We estimated based on our prior work[2] that the peak $TcCO_2$ 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 $TcCO_2$ levels of 4 mmHg in the intervention period. A difference in $TcCO_2$ levels of 4 mmHg was selected for this sample size calculation because it was deemed of potential clinical relevance and was used to power previous trials.[13] Differences in CO_2 level of a similar magnitude have been detected in previous trials evaluating the efficacy of interventions to improve sedation safety.[14,15]

Random sequence generation and concealment

A stratified (by diagnosis of obstructive sleep apnea and type of procedure – cardiac resynchronization therapy device implant), block randomized sequence was generated and concealed using the web-based randomization feature in REDCap™. The RA retrieved the allocation for each consecutive participant in REDCap™ prior to the procedure.

Statistical analyses

Bayesian statistical models were used. Data and code are available here and is archived here. 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.[16] 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 $TcCO_2$ concentration, which was modelled using splines.[17] Continuous outcomes were analyzed using robust regression models. A functional analysis of variance (ANOVA) model was used to investigate how mean $TcCO_2$ concentration levels differ between groups as a function of procedure time[18]. Logistic regression was used for dichotomous outcomes. Proportional-odds models were used for ordinal outcomes. Analysis was performed only on those participants whose SPO_2 was observed to fall below the 90% threshold for the AUC_{DESAT} outcome.

Posterior inference for all models except the functional ANOVA model was performed using Hamiltonian Monte Carlo through the brms package[19], 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 Approximation[20] through the INLA package, version 20.5.12. The marginal posterior distribution of parameters was 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 $TcCO_2$ 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. The procedure for one participant, who was randomized to the HFNO group, was rescheduled to a time that the Research Assistant was not available. As such, this participant received oxygen via standard face mask and $TcCO_2$ data were not collected. For two participants, the $TcCO_2$ sensor failed to calibrate 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 resynchronisation therapy. Table 2 presents a comparison of the total doses of sedation. The difference in doses was not statistically different for midazolam, fentanyl or propofol.

Comparisons between groups

Primary outcome

Results are presented in Table 3. The effect of HFNO on the peak $TcCO_2$ was estimated to be 0.0mmHg (95% CI = -1.3 to 1.37). The probability that it exceeds the 4mmHg clinical significance threshold of 4mmHg in either direction is 0.

Secondary outcomes

The effect of HFNO on the mean $TcCO_2$ concentration was estimated to be -0.1 mmHg (-1.31, 1.14). The probability that it exceeds the 4mmHg clinical significance threshold is 0 in either direction. $TcCO_2$ 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 4mmHg 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 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 should be noted, however, that the Anesthesia Assistants' 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.

The odds ratio for a minor adverse sedation event related to airway or breathing for the HFNO group compared with the facemask group was 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 AUC_{DESAT} was imprecise, spanning from 5 minutes.% higher in the face mask group to 24 minutes.% higher in the HFNO group. The probability that AUC_{DESAT} is higher with HFNO is 0.83. A visualization of the SpO_2 trajectories for patients whose SpO_2 was below 90% is available here.

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 ≥8L/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 the quality of the capnography waveform was not sufficient while the HFNO device was in use.

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 in comparison with standard facemask oxygen at ≥8L/min. A prior physiological modeling study of apneic oxygenation identified a mechanism by which HFNO promotes carbon dioxide clearance.[5] We did not observe a significant reduction in peak TcCO2 concentration. 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).[21] 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).[22] 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.

Another commonly proposed physiological effect of HFNO, which has been observed in a study of healthy volunteers, is increased pressure in the upper airways.[23] However, more recent data from a clinical population of apneic patients undergoing general anesthesia for elective surgery found that airway pressure increases were negligible

during HFNO with an open mouth and remained below 10 cmH2O with closed mouths and flow rates up to 80L/min.[24] We neither directly measured airway pressure or imposed strict restrictions in regard to maintaining a closed mouth during HFNO administration. Therefore, it is unknown whether mouth positioning (closed or open) influenced our results.

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. There are two plausible mechanisms that may explain this result. It is possible that the 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 ≥8L/min of 100% O_2. 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. Capnography is widely considered to be an essential aspect of physiological monitoring during sedation.[25–27] The concern about reduced ability to monitor capnography waveforms when HFNO is used potentially increasing the risk of more prolonged, undetected episodes of hypoventilation during sedation has been raised previously in the literaure.[28] However, it should be noted that if undetected episodes of hypoventilation were considerably more frequent and prolonged when HFNO was used in our study, presumably, we would have observed higher $TcCO_2$

concentrations in this group. We did not observe higher $TcCO_2$ concentrations in the HFNO group for the peak measurement or at any particular time-point during procedures.

In our study, a new HFNO cannula with an integrated CO2 sampling line was used for the majority of patients. According to manufacturer instructions, the CO2 sampling line in these cannulas was positioned at the entrance of a nostril or the mouth. There have been no studies published reporting on a comparison in the quality of the capnography waveform produced from this new cannula and alternative ways to monitor capnography during HFNO therapy. Capnography monitoring for the subset of patients enrolled in the first two months of our trial who were randomized to HFNO was achieved by placing a facemask with an integrated CO2 sampling line (the same mask used for the control group) over the HFNO cannula. Although we did not perform a formal comparison, anecdotally, the quality of the capnography waveform produced using this method was not worse or better than that achieved with the new HFNO cannula. This is likely due to the fact that both methods involve CO2 sampling from an unsealed airway in the presence of very high flows of gas from the HFNO device. Novel airway management devices that provide a sealed airway with separate channels for ventilation, oxygenation and EtCO2 sampling may be a potential solution.[29] A potential consequence of using a (unsealed) facemask superimposed over the HFNO cannula is that it could mimic the airway conditions achieved with a closed mouth even when it is opened. Due to the small number of patients who received capnography monitoring in this fashion, it is unlikely to have impacted our results to a significant degree.

The evidence base for the effects of HFNO therapy for procedural sedation in other clinical contexts is limited. One large[30] and three small randomized controlled trials were published in 2019, with several more on-going trials registered.[31] The primary outcomes for all the trials to date have focused on investigating the impact of HFNO on oxygenation with inconsistent results. One of the small trials randomized 60 participants undergoing bronchoscopy to receive HFNO at 50L/min with 100% oxygen or oxygen at 10-15L/min through a facemask.[32] 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 SpO_2 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.[33] Again, there was no difference in the primary outcome of oxygen desaturation (SpO_2 < 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.[34] 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).[30] This result is likely explained by the large difference in FiO_2 that was delivered between the two groups. In the HFNO group participants received 60L/min of 100% oxygen and in the control group participants received just 2L/min of oxygen.

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 Anesthesia Assistant 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

The primary outcome was peak $TcCO_2$ and we accounted for the correlation between baseline and peak measurements by including the baseline measurements as a covariate in the model. However, a potential limitation is that results may be sensitive to how the baseline and peak measurements were chosen. We did not blind participants or clinicians to group assignment. The small dropout and cross-over rate are 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.[35] 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.[1,3] Results from our trial cannot be directly generalized to other clinical settings where desaturation is more severe and occurs more often. Considering Anaesthesia Assistants had limited prior use of HFNO for sedation, results may not reflect the use of this device by more experienced users. We

did not use a validated sedation scale to measure level of sedation. Although doses of the medications used for sedation were similar between groups, dosage does not necessarily reflect sedation depth. As such, it is possible that differences in sedation depth between groups could have influenced the results. The direction or magnitude of this potential effect is unknown. It should also be noted that, when planning the trial, we anticipated that an initial setting for the oxygen to air ratio of 50% for the HFNO would achieve and FiO2 approximately similar to what was achieved with standard practice in the facemask group (typically ~8L/min). Results for the secondary outcomes related to oxygenation and minor adverse sedation events suggest this may not have been the case. We chose the settings for the oxygen to air ratio because we were primarily interested in the effect of HFNO on ventilation, not the effect of increasing FiO2 on oxygenation. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio.

Conclusion

We compared HFNO with the flow-rate set to L/min and a 50:50 oxygen to air ratio for the majority of time during sedation compared with facemask oxygen at ≥ 8 liters per minute. The main finding from our primary outcome is that ventilation, as measured by TcCO2, is highly unlikely to differ by a clinically important amount. Results from secondary outcomes yielded some important additional insights. 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 at 50 liters per minute and a 50:50 oxygen to air ratio compared with facemask oxygen at ≥ 8 liters per minute. Further research is required for confirmation, however, this result suggests that

an oxygen to air ratio setting higher than 50% may be required for HFNO to achieve oxygenation status similar or superior to standard practice with facemask oxygen ≥ 8 liters per minute in the population we studied. Finally, 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.

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- Conflicts of interest: none.

- Presentation: none.

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Figure legend

Fig. 1 CONSORT Flow Diagram

Fig. 2 Transcutaneous carbon dioxide measurements throughout procedures

Fig. 3 Oxygen flow-rates

Table 1. Participant characteristics

Characteristic	High Flow nasal oxygen, N = 64[1]	Face mask oxygen, N = 65[1]
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%)
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 Continuous Positive Airway Pressure therapy for sleep apnea	9 (14%)	12 (18%)
Admission source		
Day surgery	45 (70%)	44 (68%)
Ward	17 (27%)	18 (28%)
Cardiovascular Intensive Care Unit	2 (3.1%)	3 (4.6%)
American Society of Anesthesiology classification status		
I	0 (0%)	0 (0%)
II	0 (0%)	0 (0%)
III	21 (33%)	16 (25%)
IV	43 (67%)	49 (75%)
Body mass index	28.5 (5.1)	28.8 (6.7)
Procedure		
Implantable cardioverter defibrillator	19 (30%)	13 (20%)
Permanent pacemaker insertion	11 (17%)	17 (26%)
Implantable cardioverter defibrillator generator change	10 (16%)	13 (20%)
Cardiac resynchronisation therapy with defibrillator	11 (17%)	11 (17%)
Permanent pacemaker generator change	6 (9.4%)	7 (11%)
Cardiac resynchronisation therapy with pacing	2 (3.1%)	2 (3.1%)
Other	3 (4.7%)	1 (1.5%)

Characteristic	High Flow nasal oxygen, N = 64[1]	Face mask oxygen, N = 65[1]
Implantable cardioverter defibrillator lead revision	2 (3.1%)	0 (0%)
Permanent pacemaker lead revision	0 (0%)	1 (1.5%)
Charlson Comorbidity Index	4.46 (2.14)	5.15 (2.51)

[1]Statistics presented: mean (SD); n (%)

Table 2. Participant characteristics

Characteristic	High Flow nasal oxygen, N = 64[1]	Face mask oxygen, N = 65[1]	p-value[2]
Total dose of midazolam (mg)	1.58 (0.84)	1.45 (0.71)	0.3
Total dose of propofol (mg)	100 (126)	88 (104)	0.6
Total dose of fentanyl (mcg)	71 (28)	76 (56)	0.5

[1]Statistics presented: mean (SD)

[2]Statistical tests performed: t-test

Table 3. Results

Outcome	Summary value	Randomization		Effect type	Estimated treatment effect (95% CI)*
		High flow nasal oxygen	Face mask oxygen		
Peak $TcCO_2$	N	61	65		
	Mean (sd)	47.8 mmHg (9.7)	49.0 mmHg (6.9)	Absolute difference	0.0 mmHg (-1.3, 1.37)
Mean $TcCO_2$	N	61	65		
	Mean (sd)	42.7 mmHg (7.2)	44.3 mmHg (5.9)	Absolute difference	-0.1 mmHg (-1.31, 1.14)
SpO_2	N	64	65		
	SpO_2 <90% event	8 (12%)	7 (11%)	Odds ratio	1.2 (0.37, 3.75)
	Median (IQR) Area under SpO_2 desaturation curve	9.5 (5.75, 25.25)	8 (3.5, 9.5)	Absolute difference	5.6 % minute (-5.39, 24.24)
ISAS score	N	63	63		
	Mean (sd)	2.0 (1.0)	2.1 (0.9)	Absolute difference	0.0 (-0.33, 0.23)
Patient comfort	N	63	65		
	Maximal comfort	9	17	Odds ratio	1.2 (0.64, 2.17)
	Very comfortable	26	13		
	Comfortable	22	22		
	Uncomfortable	3	10		
	Very uncomfortable	2	2		
	Maximal discomfort	1	1		
Difficulty maintaining oxygenation status	N	52	31		

Outcome	Summary value	Randomization		Effect type	Estimated treatment effect (95% CI)*
		High flow nasal oxygen	Face mask oxygen		
	Extremely easy	9	17	Odds ratio	0.1 (0.05, 0.31)
	Very easy	14	10		
	Easy	17	4		
	Difficult	6			
	Very difficult	4			
	Extremely difficult	2			
Difficulty using oxygen delivery device	N	52	32		
	Extremely easy	15	17	Odds ratio	0.3 (0.14, 0.83)
	Very easy	17	9		
	Easy	20	6		
Minor airway or breathing event	N	64	65		
	Yes	9	2	Odds ratio	6.4 (1.34, 42.99)
	No	55	63		

*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
$TcCO_2$ = Transcutaneous carbon dioxide concentration
SpO_2 = Percentage of hemoglobin saturate with oxygen
ISAS = Iowa Satisfaction with Anesthesia Scale
95% CI = 95% credible intervals

Figure 1

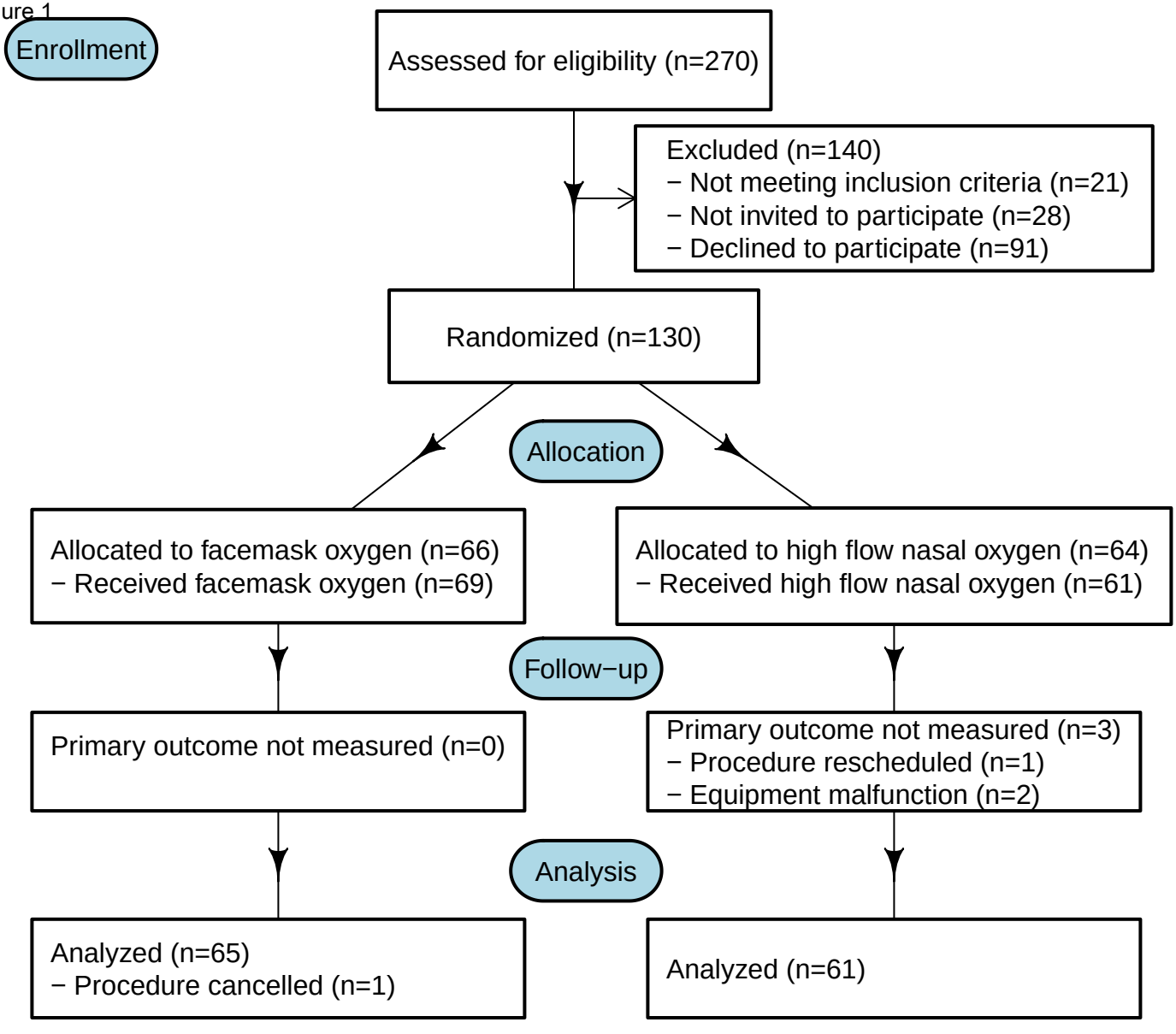
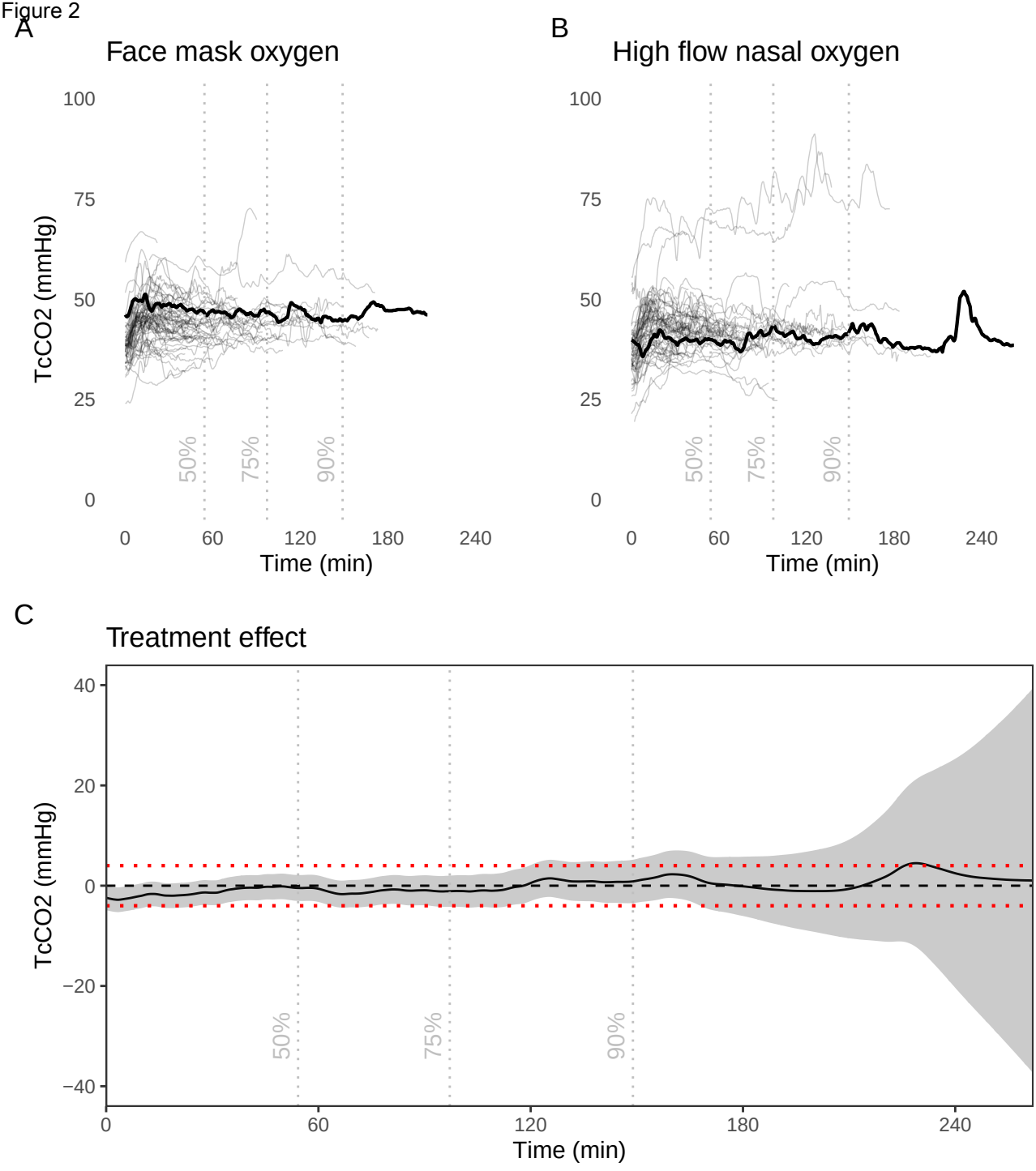
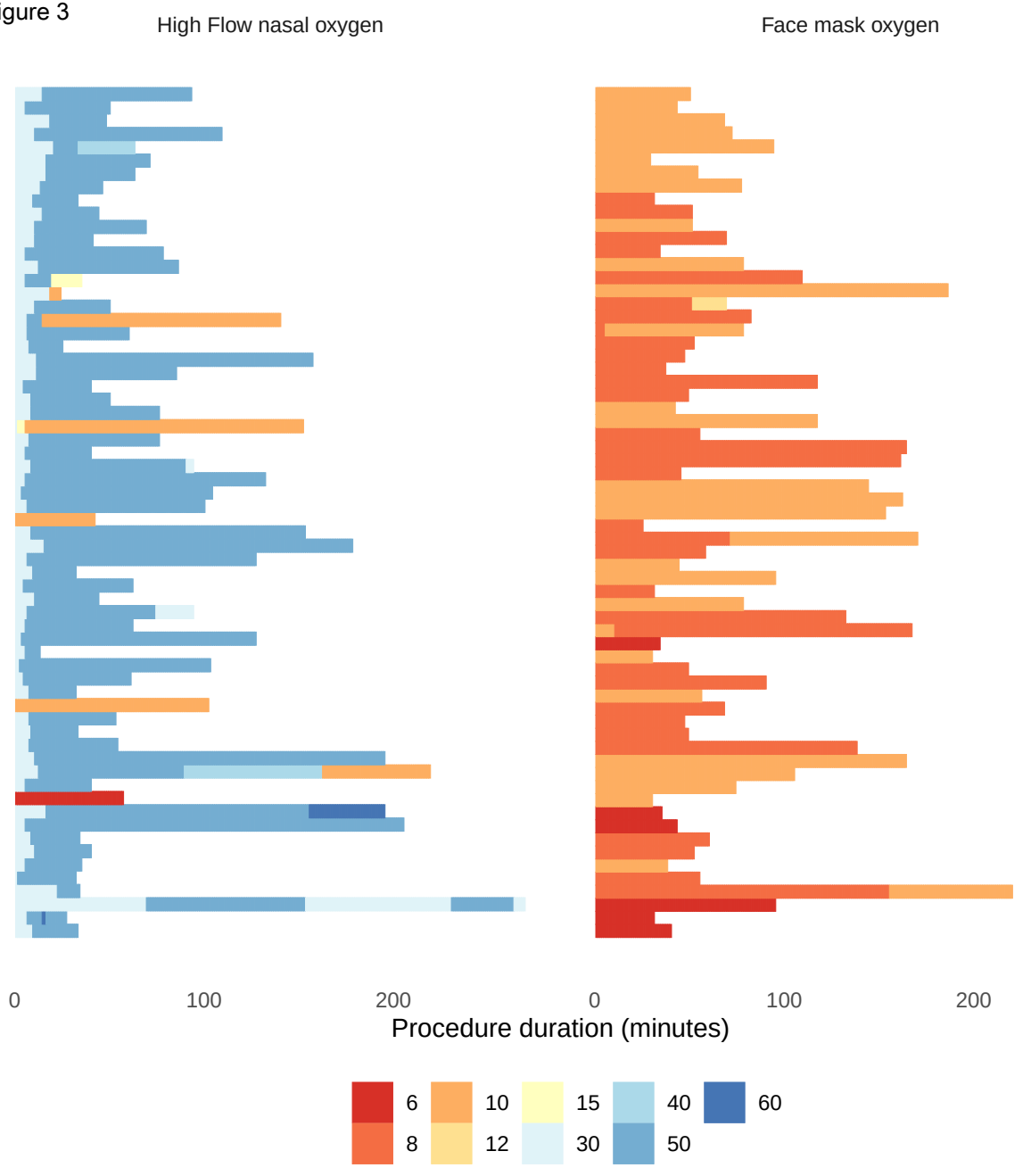

Enrollment
Assessed for eligibility (n=270)
Excluded (n=140)
− Not meeting inclusion criteria (n=21)
− Not invited to participate (n=28)
− Declined to participate (n=91)
Randomized (n=130)
Allocation
Allocated to facemask oxygen (n=66)
− Received facemask oxygen (n=69)
Allocated to high flow nasal oxygen (n=64)
− Received high flow nasal oxygen (n=61)
Follow−up
Primary outcome not measured (n=0)
Primary outcome not measured (n=3)
− Procedure rescheduled (n=1)
− Equipment malfunction (n=2)
Analysis
Analyzed (n=65)
− Procedure cancelled (n=1)
Analyzed (n=61)

Figure 2



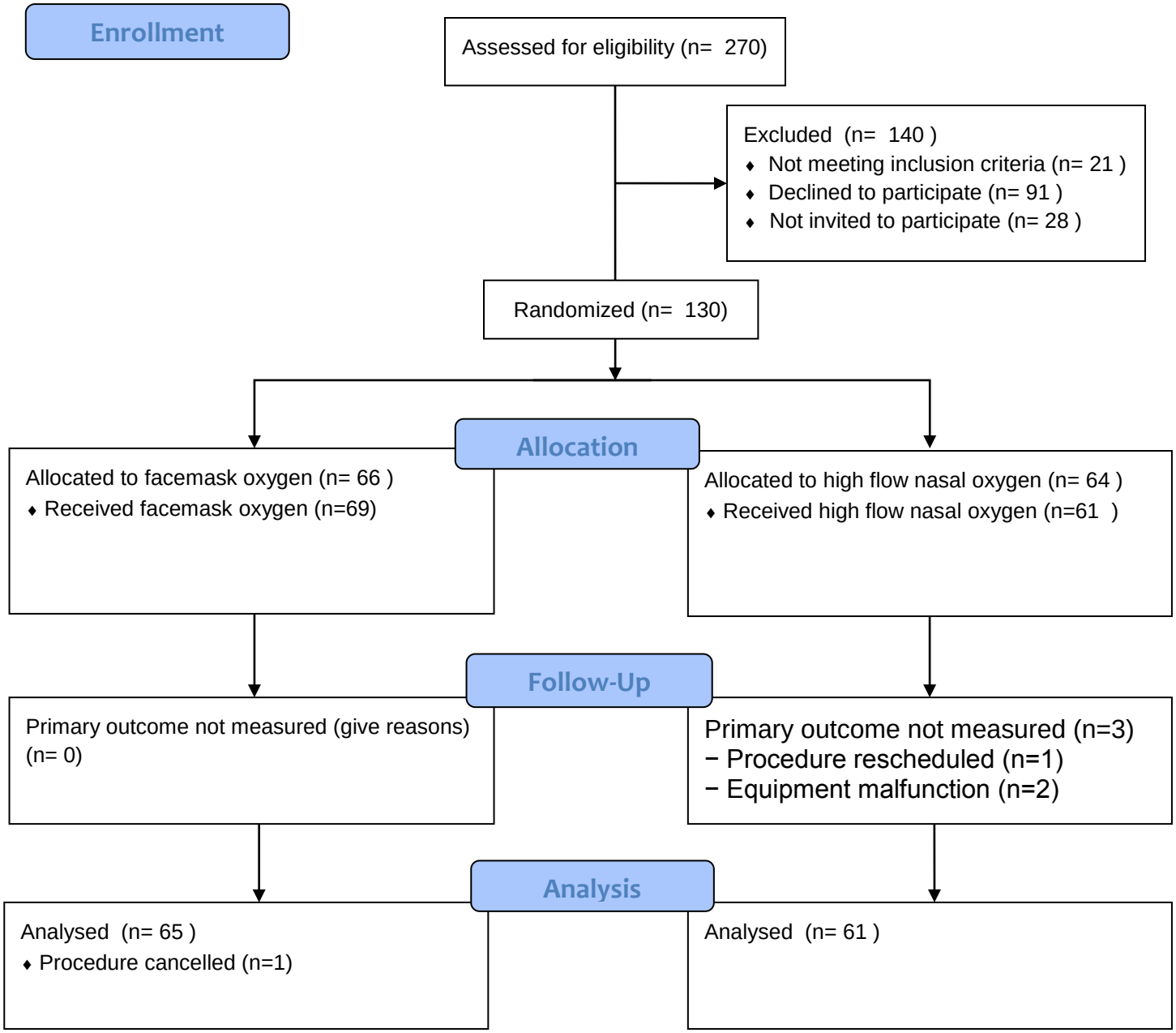
Longest procedures highlighted as a reference in A and B

Figure 3


High Flow nasal oxygen
Face mask oxygen
0
100
200
0
100
200
Procedure duration (minutes)
6
8
10
12
15
30
40
50
60

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	10-11
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12-13
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-15 Table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-15
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18-19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19
Other information			
Registration	23	Registration number and name of trial registry	NCT03858257
Protocol	24	Where the full trial protocol can be accessed, if available	https://www.aaronconway.info/HFNO/Protocol.html
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Cover Letter

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8 October 2020

European Journal of Anaesthesiology
Editorial Board

To the editor,

Thank you for allowing us to revise our manuscript for further consideration for publication. Please find our responses to the comments from the reviewers in the table attached below.

Regards,

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Reviewer 1	
Comment	Response
Thank you for giving me the opportunity to review this paper by Conway et al. The authors conducted a prospective study comparing NON(?)-rebreathing facemasks with high-flow nasal cannula therapy (HFNCT) using an FiO2 of 0.5. The study reveals some interesting (negative) results that mandate a few comments.	Thank you for reviewing our manuscript. We have revised our paper and provided responses to each of your comments below.
Methods	
Page 6, line 41: how many patients complained of a too high temperature? It seems odd that this were an issue for patients.	We stipulated in our protocol that the temperature could have been titrated down if required but this was not needed for any patients. As such we have removed that part of the sentence. It now reads: "The gas temperature was set to the 'High' setting (ranges 30-32º Celsius)." (page 7 line 23)
It remains unclear what kind of facemasks were used. Non-rebreathing?	A standard facemask was used to deliver oxygen in the control group. Non-rebreathing masks were not used. To clarify, we have changed the section to read: "Supplemental oxygen was delivered using a standard facemask with an integrated exhaled CO_2 sampling line. The flow-rate chosen by the Anaesthesia Assistant as per their standard practice." (page 7 line 4)

According to the clinical trials entry, the FiO2 in the HFNCT group was titrated "according to requirements". Likewise, the flow was titrated. This is imprecise and could easily explain the difference in saturation between the groups as well as the lack of (superior) effect. A flow of 30L/min does not meet peak inspiratory flow (>40L/min). The oxygen concentration therefore is lower than 50% at an FiO2 of 0.5. Additionally, the benefit of CPAP is not maintained at these relatively low flows. It seems not logical to use a method (HFNCT) that could increase the advantage of PEEP with additional O2 (up to an FiO2 of 1.0) and then not use it to its full advantage. If I was to spend extra money on a device, I would make sure I would get the full benefit - and THEN evaluate whether this was better compared to my cheaper standard of care. Why cripple the expensive device and then wonder why it does not perform better? The fact that more than 10% of the patients desaturated during the intervention is simply alarming and I would be very unhappy about this as head of the department - why not use an FiO2 of 1.0? Please comment on these thoughts.	The flow-rate in the HFNO was *commenced* at 30L/min before patients received sedation, as this is consistent with the manufacturers' recommendations for flow rate prior to induction of anesthesia. The flow rate was *increased to 50L/min as soon as sedation was administered*. This was stated in the methods, re-iterated in results section (Oxygen flow-rates) and displayed graphically in Figure 3. As the flow rate was 50L/min (and consequently higher than peak inspiratory flow) for the majority of time after sedation was administered, we disagree that the FiO_2 would have been less than 50% in the HFNO (for the majority of time - as shown in Figure 3). We share your surprise that more patients in the HFNO group had minor adverse events due to brief and minor desaturations, but we do not believe this was related to the *flow rate*. In planning for the trial, we anticipated that setting the oxygen to air ratio for the HFNO at 50% would be similar to what was achieved with standard practice in the facemask group (typically ~8L/min). It seems that an oxygen to air ratio of 50% in the HFNO group was not sufficient to produce similar oxygenation status in the patients in this study. That said, it is worth emphasising that *oxygen desaturations was not the primary outcome for this study*. For this reason, we have changed the conclusion in the abstract to more specifically highlight the result of the primary outcome and clarify that additional research would be required to determine the optimal oxygen:air ratio when using HFNO during sedation for CIED procedures: "Ventilation, as measured by TcCO~2~, is highly unlikely to differ by a clinically important amount between high flow nasal oxygen at 50L/min or facemask oxygen at 8L/min. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio when using high flow nasal oxygen during cardiac implantable electronic device procedures performed with sedation." (page 3) We also added this to the limitations section: "It should also be noted that, when planning the trial, we anticipated that an initial setting for the oxygen to air ratio of 50% for the HFNO would achieve and FiO2 approximately similar to what was achieved with standard practice in the facemask group (typically ~8L/min). Results for the secondary outcomes related to oxygenation and minor adverse sedation events suggest this may not have been the case. We chose the settings for the oxygen to air ratio because we were primarily interested in the effect of HFNO on ventilation, not the effect of increasing FiO2 on oxygenation. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio." (page 20 lines 14-34)
Statistics	
What program(s) was used for the statistical calculations? r only?	R was used for all analyses. Data and code required to completely reproduce the analyses is available.
Results	

Page 11, line 35. It is unfortunate that the anaesthesia assistants were unfamiliar with the HNFCT device. Who were errors in the applications detected?	We agree that the Anesthesia Assistants' experience with using the device is an important consideration, and it is for this reason that we collected data and reported on the extent of their experience. We do not suspect that there were errors in applications of the device though, as we had a Research Assistant present during all procedures. We have added the sentence below to clarify this point: "A Research Assistant who was trained in the use of the HFNO device was present during all procedures to assist Anesthesia Assistants with set-up, application and trouble-shooting if required." (page 7, line 35-40) Notwithstanding the presence of the RA, the limited experience of the Anesthesia Assistants is important. To highlight this, we added the sentence below to the limitations section: "Considering Anaesthesia Assistants had limited prior use of HFNO for sedation, results may not reflect the use of this device by more experienced users." (page 19 line 58)
The unfamiliarity with the device might explain the difference in comfort as well. It seems very peculiar that patients preferred a face mask of dry oxygen instead of a less invasive nasal cannula. In daily clinical practice, it is the other way around. Please comment on this.	The reviewer may have misread the results for this particular outcome. Results suggest patients may rate comfort *higher* with HFNO, although the effect estimate is imprecise (the estimated treatment effect as an odds ratio is presented in table 2: OR 1.2; 95% CI = 0.64 to 2.17) . The advantage of using Bayesian statistics is that we can estimate the probability that patients who receive HFNO will rate their comfort higher than facemask oxygen. We stated in the original manuscript that the probability that patients are more likely to rate comfort with the oxygen supplementation device higher with HFNO compared to the facemask is 0.7. Perhaps the confusion was due to our reporting of the probability as a proportion instead of percent? With this in mind, we have changed the sentence in the results section to: "The probability that patients are more likely to rate comfort with the oxygen supplementation device higher with HFNO compared to the facemask is 70%." (page 13 line 30)
Table 1: the difference in the dosage of medications should be statistically evaluated. Unlike the demographic characteristics, the medication was not part of the randomization. In fact, the interventionist and the anaesthetists naturally were not blinded to the procedure. Please provide p-values for midazolam, propofol and fentanyl and determine the influence of the dose on the likelihood of a negative outcome and if there were differences between the groups.	We have removed the medication comparison from Table 1 and created a new table 2 with a comparison of medications with a column for p-values. There were no statistically significant differences between the groups. We have also added this sentence to the text in the results: "Table 2 presents a comparison of the total doses of sedation. The difference in doses was not statistically different for midazolam, fentanyl or propofol." (page 12 line 40-45)

Table 2: please report a sedation score and comment on this if there were differences.	Unfortunately at the centre where this trial was conducted it is not standard practice for Anesthesia Assistants to routinely document a sedation score. For this reason we are not able to provide a sedation score. We have added this sentence to the limitations: "We did not use a validated sedation scale measure level of sedation. Although doses of the medications used for sedation were similar between groups, dosage does not necessarily reflect sedation depth. As such,it is possible that differences in sedation depth between groups could have influenced the results. The direction or magnitude of this potential effect is unknown." (page 20 line 4-14)
Reviewer 2	
The paper by Conway and colleagues covers an interesting topic, with use of HFNO during procedural sedation compared to face mask on transcutaneous CO2 detection main endpoint. The topic is relevant, but not so original.	Thank you for reviewing our manuscript. We have revised our paper and provided responses to each of your comments below.
English needs some review to improve readability.	We have revised the paper for readability.
Page 4 line 28: the issue of HFNO generating CPAP and allowing passive ventilation has recently been questioned. See Riva T, Meyer J, Theiler L, et al. Measurement of airway pressure during high-flow nasal therapy in apnoeic oxygenation: a randomised controlled crossover trial [published online ahead of print, 2020 Aug 10]. Anaesthesia. 2020;10.1111/anae.15224. doi:10.1111/anae.15224. This point may be discussed either here and better in the discussion section.	Thank you for directing us to this new evidence. We have added the paragraph to the discussion citing this work: "Another commonly proposed physiological effect of HFNO, which has been observed in a study of healthy volunteers, is increased pressure in the upper airways.[23] However, more recent data from a clinical population of apneic patients undergoing general anesthesia for elective surgery found that airway pressure increases were negligible during HFNO with an open mouth and remained below 10 cmH2O with closed mouths and flow rates up to 80L/min.[24] We neither directly measured airway pressure or imposed strict restrictions in regard to maintaining a closed mouth during HFNO administration. Therefore, it is unknown whether mouth positioning (closed or open) influenced our results." (page 15 line 53)

Consider also that a modified HFNO cannula with CO2 detection has been proposed for clinical use. The model of HFNO cannula used is a bit unclear, as it seems that both the original and the CO2-embedded one were used. Further discussion and data may be added for the CO2 washout point (see also Sorbello M, Pulvirenti GS, Pluchino D, Skinner M. State of the Art in Airway Management During GI Endoscopy: The Missing Pieces. Dig Dis Sci. 2017;62(5):1385-1387. doi:10.1007/s10620-017-4494-1). This issue seems of some importance also for those patients in which a facemask was applied over HFNO for CO2 detection. This may result in 1) imprecise CO2 reading; 2) alteration (or biasing) of CPAP effect, as the applied mask may work as a "closed mouth"; 3) interference with study protocol (I guess no oxygen was delivered via the superimposed facemask). Please clarify.	You are correct that both the original HFNO cannula (without integrated CO_2 sampling line) and new HFNO cannula model with the integrated CO_2 sampling line was used in this study. The majority of patients used the new cannula with integrated CO_2 line, which became available within the first 2 months of study recruitment (total recruitment was 8 months). We have clarified this further a statement in the 'Concomitant care' section: "For participants randomized to HFNO, Anesthesia Assistants used the CO_2 sampling adapter integrated with the latest model of the HFNO nasal cannula for the majority of participants (all those recruited after September 2019 - recruitment started in August 2019)." (page 8 line 7-14) As stated in our protocol, we did not impose restrictions on 'concomitant' care, including the approaches used for monitoring ventilation with capnography by the Anesthesia Assistants. We have added a paragraph to our discussion regarding "Co_2 washout" to highlight the reference you provided that suggests novel airway management devices that seal the airway and provide separate channels for $EtCO_2$ sampling may assist with this issue: "In our study, a new HFNO cannula with an integrated CO2 sampling line was used for the majority of patients. According to manufacturer instructions, the CO2 sampling line in these cannulas was positioned at the entrance of a nostril or the mouth. There have been no studies published reporting on a comparison in the quality of the capnography waveform produced from this new cannula and alternative ways to monitor capnography during HFNO therapy. Capnography monitoring for the subset of patients enrolled in the first two months of our trial who were randomized to HFNO was achieved by placing a facemask with an integrated CO2 sampling line (the same mask used for the control group) over the HFNO cannula. Although we did not perform a formal comparison, anecdotally, the quality of the capnography waveform produced using this method was not worse or better than that achieved with the new HFNO cannula. This is likely due to the fact that both methods involve CO2 sampling from an unsealed airway in the presence of very high flows of gas from the HFNO device. Novel airway management devices that provide a sealed airway with separate channels for ventilation, oxygenation and EtCO2 sampling may be a potential solution.[29] A potential consequence of using a (unsealed) facemask superimposed over the HFNO cannula is that it could mimic the airway conditions achieved with a closed mouth even when it is opened. Due to the small number of patients who received capnography monitoring in this fashion, it is unlikely to have impacted our results to a significant degree." (page 17 para 2)
I would have recommended and included predicted difficult airway management between exclusion criteria, given that any trouble during the procedure might have resulted in critical airway management. Given its implication on airway patency, obesity and sleep apnea syndrome should have been considered as exclusion factor.	Although we did not exclude these patients who may have been considered at 'increased' risk of critical airway management, we did use a standardized and recommended approach to capturing such events by using the TROOPS tool. No severe adverse events related to airway occurred in either group, as was reported in the results section.

BMI is not recorded or presented in table I.	We have added body mass index to Table 1.
Sleep apnea is mentioned in the random sequence generation section and also page 11 line 43 "sleep apnea was common". Please clarify. An incidence of sleep apnea around 25-30% may represent a biasing factor, given that almost 15% on both arms was already on CPAP, indicating a certain disease severity. Similarly, I would have excluded smokers from study (almost 40% in both arms of the study), as history of smoking widens the gap between PCO2 and PaCO2.	Using a randomized controlled trial design minimized the risk of bias from confounding factors such as those you have mentioned (OSA, smoking). We documented the incidence of these risk factors to allow for comprehensive description of the participant characteristics.
Finally, no upper age limit was considered.	To the authors knowledge, there are no specific upper age limits noted in the literature as contraindications for use of HFNO during sedation.
Considering the primary endpoint of tCO2, and considering that PaCO2 depends on alveolar partial pressure, ventilation may affect such values. As a consequence, I strongly believe that oxygen flow on the facemask should have been standardized, and in any case fixed above or around the minute ventilation of the patient, rather than left at "flow-rate chosen by the Anaesthesia Assistant as per their standard practice".	The primary outcome for this study was $TcCO_2$ because we were interested in determining the effect of HFNO on *ventilation* during sedation, because of the previous evidence which suggested that the high flow rate can promote carbon dioxide clearance during apnea. In order to more closely reflect how HFNO would be used in practice during sedation, we elected to not impose a strict standardized flow-rate for either group, allowing for the clinicians to titrate according to patient requirements. However, we believe that for the vast majority of patients, the flow rate for the HFNO group was applied at a sufficient rate (i.e. ≥50L/min, which is reported in the results section of the text and shown in Figure 3).

It also appears that the FiO2 is different, and unfairly favoring the facemask group.	We agree that the results for the *secondary* outcomes related to oxygenation and minor adverse sedation events, which occurred mostly due to *brief and minor* desaturations below 90%, could have been due to patients in the HFNO receiving an FiO_2 lower than the facemask group. We specifically discussed that in paragraph 2 of the discussion. To be clear, although identifying that there appeared to be differences in outcomes related to oxygenation between the two strategies is important, the fact that these were *secondary* outcomes should be emphasised. It is entirely logical that delivering a higher FiO_2 would improve oxygenation during sedation. In planning for the trial, we suspected that setting the oxygen to air ratio for the HFNO at 50% would be approximately similar to what was achieved with standard practice in the facemask group (typically ~8L/min). It seems that this was not the case. For this reason, we have changed the conclusion in the abstract to specifically highlight that additional research would be required to determine the optimal oxygen:air ratio when using HFNO during sedation for CIED procedures: "Ventilation, as measured by TcCO2, is highly unlikely to differ by a clinically important between high flow nasal oxygen at 50L/min or facemask oxygen at 8L/min. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio when using high flow nasal oxygen during cardiac implantable electronic device procedures performed with sedation." (page 3) We also added this to the limitations section: "It should also be noted that, when planning the trial, we anticipated that an initial setting for the oxygen to air ratio of 50% for the HFNO would achieve and FiO~2~ approximately similar to what was achieved with standard practice in the facemask group (typically ~8L/min). Results for the secondary outcomes related to oxygenation and minor adverse sedation events suggest this may not have been the case. Further research with a larger sample size would be required to determine the optimal oxygen:air ratio." (page 20 line 14-34)
Page 8, line 30 add manufacturer for Sentec monitor.	Sentec is the name of the manufacturer for the $TcCO_2$ monitor used for the study.
Page 11, line 25 "had their" should be "his" or "her", being a single case.	Changed to: "The procedure for one participant, who was randomized to the HFNO group, was rescheduled to a time that the Research Assistant was not available." (page 12 line 17-22)
Sample size calculation is someway unclear; if 130 participants were needed, this means you should have 130 participants each arm, correct? I see from consort diagram that from original 270 eligible cases, 130 were included and subsequently randomized in the two arms. Does this make the study underpowered? This is my feeling.	The sample size calculation estimated that 130 participants would be required in total. The study is not underpowered for the primary outcome.

When the Authors report that 20% of cases were resyncronizations, this means that no device was implanted? We normally provide deeper sedation for these procedures, including propofol bolus with apnea episode. How was sedation provided and monitored? Was the same protocol adopted for all patients? A descriptive section for these issues and the surgical procedures performed is missing in the methods section (though mentioned in table I).	Cardiac resynchronization therapy does involved implantation of a specific type of cardiac implantable electronic device where a lead is placed through the coronary sinus so that both the left and right ventricle can be paced. We have added a section on the sedation in the methods: "The model of sedation at the site where this trial was conducted follows recommendations from the Canadian Anesthesiologists' Society.[7] Sedation was provided by a team that included a sedation supervisor (Anesthesiologist) and an approved and credentialed sedation assistant (Anesthesia Assistant) who is delegated tasks of providing sedation and monitoring the patient. The Anesthesia Assistant remains in constant attendance with the patient, providing continuous monitoring and immediately informing the sedation supervisor of any concerns. The sedation supervisor (Anesthesiologist in this case) retains responsibility for the patient. It is standard practice at this site for a combination of midazolam, fentanyl and propofol administered as bolus doses to be used. There were no additional restrictions on the type or dose of sedation used by Anesthesia Assistants imposed for participants enrolled in the trial. The actual doses of sedation used for participants in the trial were recorded." (page 6 line 19-46)
Same table I, please expand all abbreviations.	Abbreviations have been removed and expanded in full in Table 1.
Table II: expand IQR, check CI "credible" for "confidence".	Response: As we have used Bayesian models for the statistical analysis, 'credible' is the correct term.
Figure 3 I would swap the two columns for coherence with other pictures presented (facemask on left).	Response: HFNO is on the left and facemask is on the right in all tables and figures now.
The Anesthesia rating section for oxygenation difficulty in results appears a little bit confusing, and the all section for outcomes in general. Probably because a technical language related to statistical methods is used. I would suggest to expand little bit to improve clarity.	We believe we have reported the results consistent with the approach used for the analyses (Bayesian statistical models). If there is a specific component of the results that required clarification we are happy to provide additional revisions.
Page 14 line 9-12 please clarify; capnography monitor is unclear.	Changed to: "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 the *quality of the capnography waveform was not sufficient while the HFNO device was in use*." (page 14 line 40-51)

Page 14. Lines 26-31: I would not be so dogmatic, and I basically disagree. The CO2 clearing effect of HFNO may be visible also in your results: given the sedation, patients may be prone to develop hypoventilation (and with 30% of OSAS patient this may easily happen) and turn hypoxemic and hypercapnic. Maintenance of stable CO2 values might mean the HFNO support works. I would not expect that HFNO may reduce CO2 in this setting.	We have revised this paragraph to portray the uncertainty as to whether CO_2 clearing was facilitated by HFNO and instead highlight that our results showing no difference in $TcCO_2$ was consistent with prior research in the non-sedation context: "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 in comparison with standard facemask oxygen at ≥8L/min. A prior physiological modeling study of apneic oxygenation identified a mechanism by which HFNO promotes carbon dioxide clearance.[5] We did not observe a significant reduction in peak TcCO2 concentration. 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).[21] 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).[22] 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." (page 15, para 1)
Page 17, lines 42-47 unclear: "HFNO with the flow rate.." something missing? Wasn't the HFNO set to 50% FiO2 and the facemask to 100%? If so, this may bias results and conclusions for desaturation.	We have revised the conclusion to more clearly emphasise the intervention and control conditions. It now reads: "We compared HFNO with the flow-rate set to L/min and a 50:50 oxygen to air ratio for the majority of time during sedation compared with facemask oxygen at ≥ 8 liters per minute. The main finding from our primary outcome is that ventilation, as measured by TcCO2, is highly unlikely to differ by a clinically important amount. Results from secondary outcomes yielded some important additional insights. 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 at 50 liters per minute and a 50:50 oxygen to air ratio compared with facemask oxygen at ≥ 8 liters per minute. Further research is required for confirmation, however, this result suggests that an oxygen to air ratio setting higher than 50% may be required for HFNO to achieve oxygenation status similar or superior to standard practice with facemask oxygen ≥ 8 liters per minute in the population we studied. Finally, 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." (page 20 line 40)
Acknowledgments, point c, "none"	Corrected the typo.

Please check references for format and updates. As a side remark, I notice 7 self-citations, which may be of some sense given the topic of research, but they may be reconsidered, representing almost ¼ of total references.	We believe the citations included from our prior work are relevant to the topic. We have added references to the other studies you referred to in your comments.