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High flow nasal oxygen during sedation for cardiac implantable electronic device procedures: A randomized controlled trial

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Abstract:	Introduction High flow nasal oxygen (HFNO) 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 facemask oxygen during cardiac implantable electronic device (CIED) procedures performed with procedural sedation. Methods A randomized controlled trial was conducted. Participants were 1:1 randomized to facemask (≥ 8L/min) or HFNO (50L/min with a 50:50 oxygen to air ratio) during procedural sedation administered by Anesthesia Assistants (supervised by an Anesthesiologist). The primary outcome was peak transcutaneous carbon dioxide ($TcCO_2$). Outcomes were analysed using Bayesian statistical models. Results The 129 participants who were randomized and received a CIED with sedation were included. The difference in peak $TcCO_2$ was 0.0mmHg (95% CI = -1.3 to 1.37). Minor adverse sedation events were 6.4 times more likely to occur in the HFNO group. This estimate is imprecise (95% CI = 1.34 to 42.99). The odds ratio for oxygen desaturation was 1.2 (95% CI = 0.37 to 3.75). Anesthesia assistants rated the HFNO device as harder to use. 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. Conclusion We investigated the effects of using HFNO with oxygen to air ratio settings estimated to deliver a FiO_2 approximately equivalent to that achieved from standard practice with facemask oxygen. There was no clear advantage for using HFNO in preference to facemask oxygen during CIED procedures performed with sedation.
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Editorial Board

To the editor,

Please find enclosed our manuscript 'High flow nasal oxygen during sedation for cardiac implantable electronic device procedures: A randomized controlled trial'.

Regards,

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Highlights

- High flow nasal oxygen at 50L/min for patients undergoing elective CIED procedures with sedation is highly unlikely to *decrease* or *increase* peak $TcCO_2$ concentration by a clinically important amount.

- There was no discernable trend observed in how the difference in peak $TcCO_2$ varied with procedure time.

- Satisfaction with sedation is very likely to be similar between high flow nasal oxygen and facemask oxygen.

- The high flow nasal oxygen device was rated as more difficult for Anesthesia Assistants to use, although none rated the HFNO device as *difficult*.

Abstract

Introduction

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Trial registration number: NCT03858257

High flow nasal oxygen during sedation for cardiac implantable electronic device procedures: A randomized controlled trial

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Conflicts of interest: The authors declare no competing interests.

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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 during CIED procedures performed with procedural sedation.

Methods

Design

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

a. Facemask oxygen; or

b. High flow nasal oxygen.

Informed consent was obtained. The study protocol conforms to the 1975 Declaration of Helsinki and received approval by the hospital research ethics board (18-6343). 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

a. <16 years.

b. Underlying condition requiring chronic oxygen supplementation.

c. Diagnosed respiratory condition with current hypercapnia defined as $PaCO_2$ during admission over 45mmHg.

d. Pre-existing untreated pneumothorax.

e. Planned transesophageal echocardiography.

f. Active nasal-bleeding.

g. Complete nasal obstruction.

h. Recent upper-airway surgery or base of skull fracture.

i. 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 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 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). 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).[8,9] The primary outcome was peak transcutaneous carbon dioxide ($TcCO_2$) concentration. Secondary outcomes were:

a. Mean $TcCO_2$.

b. Trajectory of $TcCO_2$ as a function of time.

c. 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.

d. Adverse sedation events, measured using the Tracking and reporting outcomes of procedural sedation (TROOPS) tool.

e. Patient satisfaction with sedation.

f. Comfort of the oxygen delivery device.

g. Anesthesia Assistant rating of difficulty maintaining oxygenation status.

h. 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 $PaCO_2$.[10] $TcCO_2$ 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).[11] 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.[12] Satisfaction with sedation was measured using the Iowa Satisfaction with Anesthesia Scale (ISAS).[13,14] 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.[15,16] Differences in CO_2 level of a similar magnitude have been detected in previous trials evaluating the efficacy of interventions to improve sedation safety.[17–21]

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 using the redcapAPI package in R.[22] 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. 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.[23] 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.[24] 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[25]. 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[26], 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[27] 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. 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 $TcCO_2$ 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.

Comparisons between groups

Primary outcome

Results are presented in Table 2. 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 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 easier 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 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. 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 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 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 $TcCO_2$ 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 $PaCO_2$ 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).[28] Likewise, in a larger trial of pre-oxygenation with 80 patients, the end-tidal CO_2 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).[29] Importantly, in contrast to these trials where ventilation status was assessed at one specific point in time with either $PaCO_2$ or $ETCO_2$ samples, we used continuous $TcCO_2$ 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 AUC_{DESAT} outcome. The probability that AUC_{DESAT} 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 >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. As a consequence, clinicians may not have been 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.[30–32] 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.[33] 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 $TcCO_2$ 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.

The evidence base for the effects of HFNO therapy for procedural sedation in other clinical contexts is limited. One large[34] and three small randomized controlled trials of HFNO during procedural sedation have been published in 2019, with several more on-going trials registered.[35] The primary outcomes for all the trials to date have focused on investigating the impact 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 oxygen at 10-15L/min through a facemask.[36] 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.[37] 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.[38]

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).[34] 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 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 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. This approach is sensitive to how the baseline and peak measurements were chosen. We chose the $TcCO_2$ concentration at the time sedation was first administered as the baseline measurement and the maximum $TcCO_2$ 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 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.[39] 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 cannot be directly generalized 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 FiO_2 approximately equivalent to that achieved from standard practice with facemask oxygen. Ventilation, as measured by $TcCO_2$, 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.

References

1. Conway A, Rolley J, Page K, Fulbrook P. Trends in nurse-administered procedural sedation and analgesia across cardiac catheterisation laboratories in australia and new zealand: Results of an electronic survey. Australian Critical Care 2014;27:4–10.

2. Conway A, Collins P, Chang K, Mafeld S, Sutherland J, Fingleton J. Sequence analysis of capnography waveform abnormalities during nurse-administered procedural sedation and analgesia in the cardiac catheterization laboratory. Scientific Reports 2019;9. Available at: https://doi.org/10.1038/s41598-019-46751-2.

3. Conway A, Page K, Rolley J, Fulbrook P. Risk factors for impaired respiratory function during nurse-administered procedural sedation and analgesia in the cardiac catheterisation laboratory: A matched case–control study. European Journal of Cardiovascular Nursing 2013;12:393–9.

4. Drake MG. High-flow nasal cannula oxygen in adults: An evidence-based assessment. Annals of the American Thoracic Society 2018;15:145–55.

5. Hermez LA, Spence CJ, Payton MJ, Nouraei SAR, Patel A, Barnes TH. A physiological study to determine the mechanism of carbon dioxide clearance during apnoea when using transnasal humidified rapid insufflation ventilatory exchange (thrive). Anaesthesia 2019;74:441–9. Available at: https://doi.org/10.1111/anae.14541.

6. Apfelbaum J, Gross J, Connis R, Agarkar M, Arnold D, Coté C, Tung A. Practice guidelines for moderate procedural sedation and analgesia 2018: A report by the american society of anesthesiologists task force on moderate procedural sedation and

analgesia, the american association of oral and maxillofacial surgeons, american college of radiology, american dental association, american society of dentist anesthesiologists, and society of interventional radiology. Anesthesiology 2018;128:437–79.

7. Dobson G, Chong MA, Chow L, Flexman A, Hurdle H, Kurrek M, Laflamme C, Perrault M-A, Sparrow K, Stacey S, Swart PA, Wong M. Procedural sedation: A position paper of the canadian anesthesiologists' society. Canadian Journal of Anesthesia 2018;65:1372–84. Available at: https://doi.org/10.1007/s12630-018-1230-z.

8. Williams MR, Ward DS, Carlson D, Cravero J, Dexter F, Lightdale JR, Mason KP, Miner J, Vargo JJ, Berkenbosch JW, Clark RM, Constant I, Dionne R, Dworkin RH, Gozal D, Grayzel D, Irwin MG, Lerman J, O'Connor RE, Pandharipande P, Rappaport BA, Riker RR, Tobin JR, Turk DC, Twersky RS, Sessler DI. Evaluating patient-centered outcomes in clinical trials of procedural sedation, part 1 efficacy: Sedation consortium on endpoints and procedures for treatment, education, and research recommendations. Anesthesia & Analgesia 2017;124:821–30. Available at: https://doi.org/10.1213/ane.0000000000001566.

9. Ward DS, Williams MR, Berkenbosch JW, Bhatt M, Carlson D, Chappell P, Clark RM, Constant I, Conway A, Cravero J, Dahan A, Dexter F, Dionne R, Dworkin RH, Gan TJ, Gozal D, Green S, Irwin MG, Karan S, Kochman M, Lerman J, Lightdale JR, Litman RS, Mason KP, Miner J, O'Connor RE, Pandharipande P, Riker RR, Roback MG, Sessler DI, et al. Evaluating patient-centered outcomes in clinical trials of procedural sedation, part 2 safety: Sedation consortium on endpoints and procedures for treatment,

education, and research recommendations. Anesthesia & Analgesia 2018;127:1146–54. Available at: https://doi.org/10.1213/ane.0000000000003409.

10. Conway A, Tipton E, Liu W-H, Conway Z, Soalheira K, Sutherland J, Fingleton J. Accuracy and precision of transcutaneous carbon dioxide monitoring: A systematic review and meta-analysis. Thorax 2019;74:157–63.

11. Fingleton J, Mckinstry S, Pilcher J, Weatherall M, Beasley R, Bardsley G. Accuracy of transcutaneous carbon dioxide measurement for change over time. 2017;22:98.

12. Roback MG, Green SM, Andolfatto G, Leroy PL, Mason KP. Tracking and reporting outcomes of procedural sedation (troops): Standardized quality improvement and research tools from the international committee for the advancement of procedural sedation. British Journal of Anaesthesia 2018;120:164–72.

13. Dexter F, Aker J, Wright WA. Development of a measure of patient satisfaction with monitored anesthesia care the iowa satisfaction with anesthesia scale. Anesthesiology 1997;87:865–73.

14. Dexter F, Candiotti KA. Multicenter assessment of the iowa satisfaction with anesthesia scale, an instrument that measures patient satisfaction with monitored anesthesia care. Anesthesia & Analgesia 2011;113:364–8.

15. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, Baker T, Weatherall M, Beasley R. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax 2011;66:937–41.

16. Wijesinghe M, Perrin K, Healy B, Weatherall M, Beasley R. Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia. Journal of the Royal Society of Medicine 2012;105:208–16.

17. Baulig W, Keselj M, Baulig B, Guzzella S, Borgeat A, Aguirre J. Transcutaneous continuous carbon dioxide tension monitoring reduced incidence, degree and duration of hypercapnia during combined regional anaesthesia and monitored anaesthesia care in shoulder surgery patients. Journal of Clinical Monitoring and Computing 2015;29:499–507.

18. Carmi U, Kramer MR, Zemtzov D, Rosengarten D, Fruchter O. Propofol safety in bronchoscopy: Prospective randomized trial using transcutaneous carbon dioxide tension monitoring. Respiration 2011;82:515–21.

19. De Oliveira Jr GS, Ahmad S, Fitzgerald PC, McCarthy RJ. Detection of hypoventilation during deep sedation in patients undergoing ambulatory gynaecological hysteroscopy: A comparison between transcutaneous and nasal end-tidal carbon dioxide measurements. British Journal of Anaesthesia 2010;104:774–8.

20. De Oliveira Jr GS, Fitzgerald PC, Hansen N, Ahmad S, McCarthy RJ. The effect of ketamine on hypoventilation during deep sedation with midazolam and propofol: A randomised, double-blind, placebo-controlled trial. European Journal of Anaesthesiology 2014;31:654–62.

21. Smith SB, Carr S, Psikula S, Das A, Grichnik K. A pilot study on the effect of nasal continuous positive airway pressure on arterial partial pressure of carbon dioxide during

spinal anesthesia with intravenous sedation for total knee arthroplasty. Anesthesia & Analgesia 2015;120:479–83.

22. Nutter B, Lane S. redcapAPI: Accessing data from redcap projects using the api., 2020. Available at: https://github.com/nutterb/redcapAPI/wiki.

23. Gelman A, Jakulin A, Pittau MG, Su Y-S, others. A weakly informative default prior distribution for logistic and other regression models. The annals of applied statistics 2008;2:1360–83.

24. Egbewale BE, Lewis M, Sim J. Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: A simulation study. BMC Medical Research Methodology 2014;14:49.

25. Yue Y (Ryan), Bolin D, Rue H, Wang X-F. Bayesian generalized two-way anova for functional data using inla. Statistica Sinica 2019;29:741–67.

26. Bürkner P-C. Brms: An r package for bayesian multilevel models using stan. Journal of Statistical Software 2017;80:1–28.

27. Rue H, Martino S, Chopin N. Approximate bayesian inference for latent gaussian models by using integrated nested laplace approximations. Journal of the Royal Statistical Society 2009;71:319–92. Available at: http://myaccess.library.utoronto.ca/login?url=https://search-proquest-com.myaccess.library.utoronto.ca/docview/37127083?accountid=14771.

28. Mir F, Patel A, Iqbal R, Cecconi M, Nouraei S. A randomised controlled trial comparing transnasal humidified rapid insufflation ventilatory exchange (thrive) pre-

oxygenation with facemask pre-oxygenation in patients undergoing rapid sequence induction of anaesthesia. Anaesthesia 2017;72:439–43.

29. Lodenius Å, Piehl J, Östlund A, Ullman J, Jonsson Fagerlund M. Transnasal humidified rapid-insufflation ventilatory exchange (thrive) vs. Facemask breathing pre-oxygenation for rapid sequence induction in adults: A prospective randomised non-blinded clinical trial. Anaesthesia 2018;73:564–71.

30. Conway A, Douglas C, Sutherland J. A systematic review of capnography for sedation. Anaesthesia 2016;71:450–4.

31. Conway A, Collins P, Chang K, Mafeld S, Sutherland J, Fingleton J, Parotto M. Pre-apneic capnography waveform abnormalities during procedural sedation and analgesia. Journal of Clinical Monitoring and Computing 2019:1–8.

32. Conway A, Rolley J, Page K, Fulbrook P. Clinical practice guidelines for nurse-administered procedural sedation and analgesia in the cardiac catheterization laboratory: A modified delphi study. Journal of advanced nursing 2014;70:1040–53.

33. Horiuchi A, Graham DY. High-flow nasal cannula oxygen therapy obscures severe respiration depression, providing an illusion of safety. Gastrointestinal Endoscopy 2020;91:720–1.

34. Lin Y, Zhang X, Li L, Wei M, Zhao B, Wang X, Pan Z, Tian J, Yu W, Su D. High-flow nasal cannula oxygen therapy and hypoxia during gastroscopy with propofol sedation: A randomized multicenter clinical trial. Gastrointestinal endoscopy 2019;90:591–601.

35. Eugene A, Fromont L, Auvet A, Baert O, Mfam W-S, Remerand F, Boulain T, Nay M-A. High-flow nasal oxygenation versus standard oxygenation for gastrointestinal endoscopy with sedation. The prospective multicentre randomised controlled odephi study protocol. BMJ open 2020;10.

36. Douglas N, Ng I, Nazeem F, Lee K, Mezzavia P, Krieser R, Steinfort D, Irving L, Segal R. A randomised controlled trial comparing high-flow nasal oxygen with standard management for conscious sedation during bronchoscopy. Anaesthesia 2018;73:169–76.

37. Riccio CA, Sarmiento S, Minhajuddin A, Nasir D, Fox AA. High-flow versus standard nasal cannula in morbidly obese patients during colonoscopy: A prospective, randomized clinical trial. Journal of Clinical Anesthesia 2019;54:19–24.

38. Sago T, Harano N, Chogyoji Y, Nunomaki M, Shiiba S, Watanabe S. A nasal high-flow system prevents hypoxia in dental patients under intravenous sedation. Journal of Oral and Maxillofacial Surgery 2015;73:1058–64.

39. Furniss SS, Sneyd JR. Safe sedation in modern cardiological practice. Heart 2015;101:1526–30.

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%)
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)

Characteristic	High Flow nasal oxygen, N = 64[1]	Face mask oxygen, N = 65[1]
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)

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

Table 2. Results

Outcome	Summary value	Randomization: Face mask oxygen	Randomization: High flow nasal oxygen	Effect type	Estimated treatment effect (95% CI)*
Peak $TcCO_2$	N	65	61		
	Mean (sd)	49.0 mmHg (6.9)	47.8 mmHg (9.7)	Absolute difference	0.0 mmHg (-1.3, 1.37)
Mean $TcCO_2$	N	65	61		
	Mean (sd)	44.3 mmHg (5.9)	42.7 mmHg (7.2)	Absolute difference	-0.1 mmHg (-1.31, 1.14)
SpO_2	N	65	64		
	SpO_2 <90% event	7 (11%)	8 (12%)	Odds ratio	1.2 (0.37, 3.75)
	Median (IQR) Area under SpO_2 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		

Outcome	Summary value	Randomization: Face mask oxygen	Randomization: High flow nasal oxygen	Effect type	Estimated treatment effect (95% CI)*
	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
$TcCO_2$ = 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

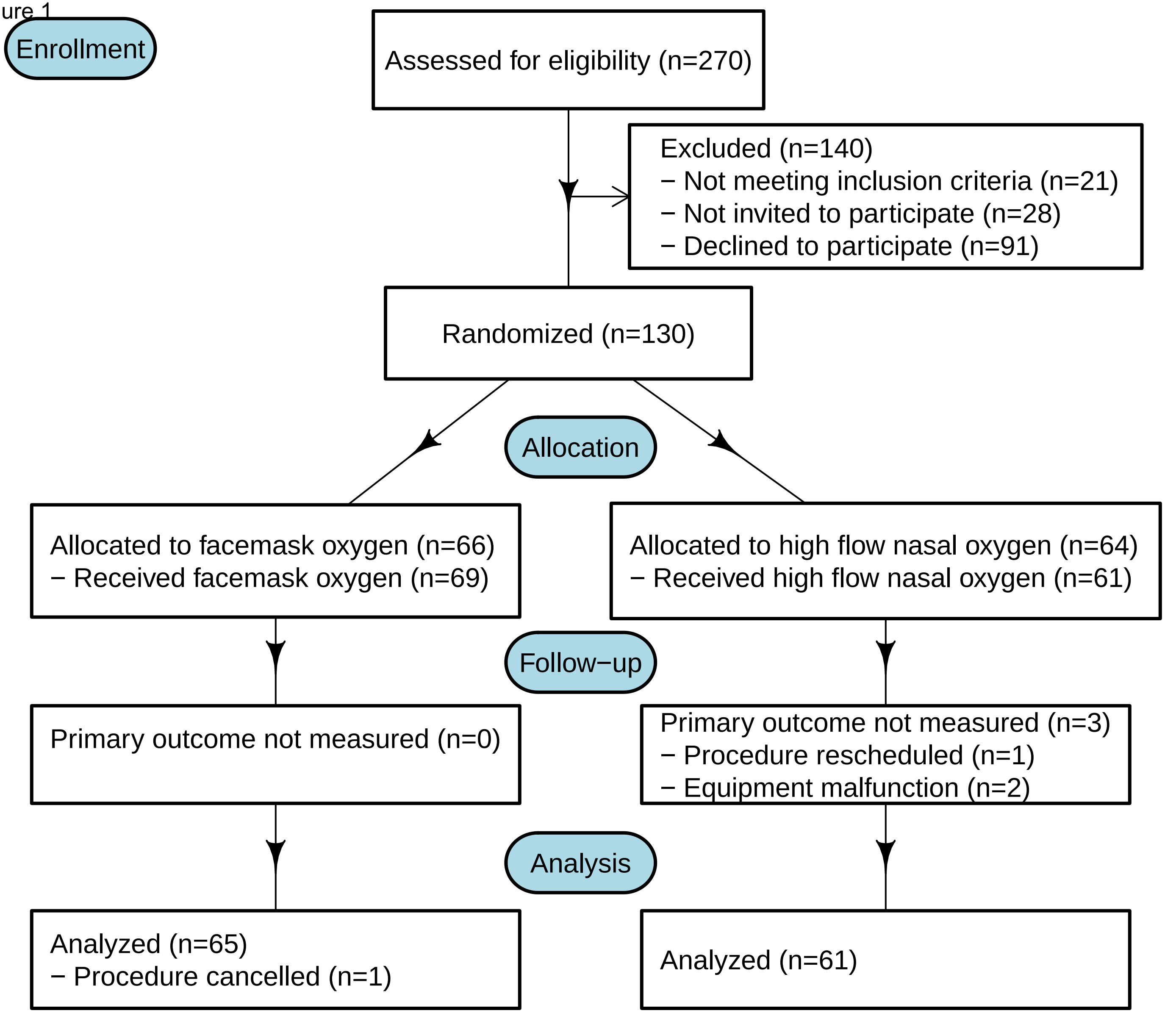
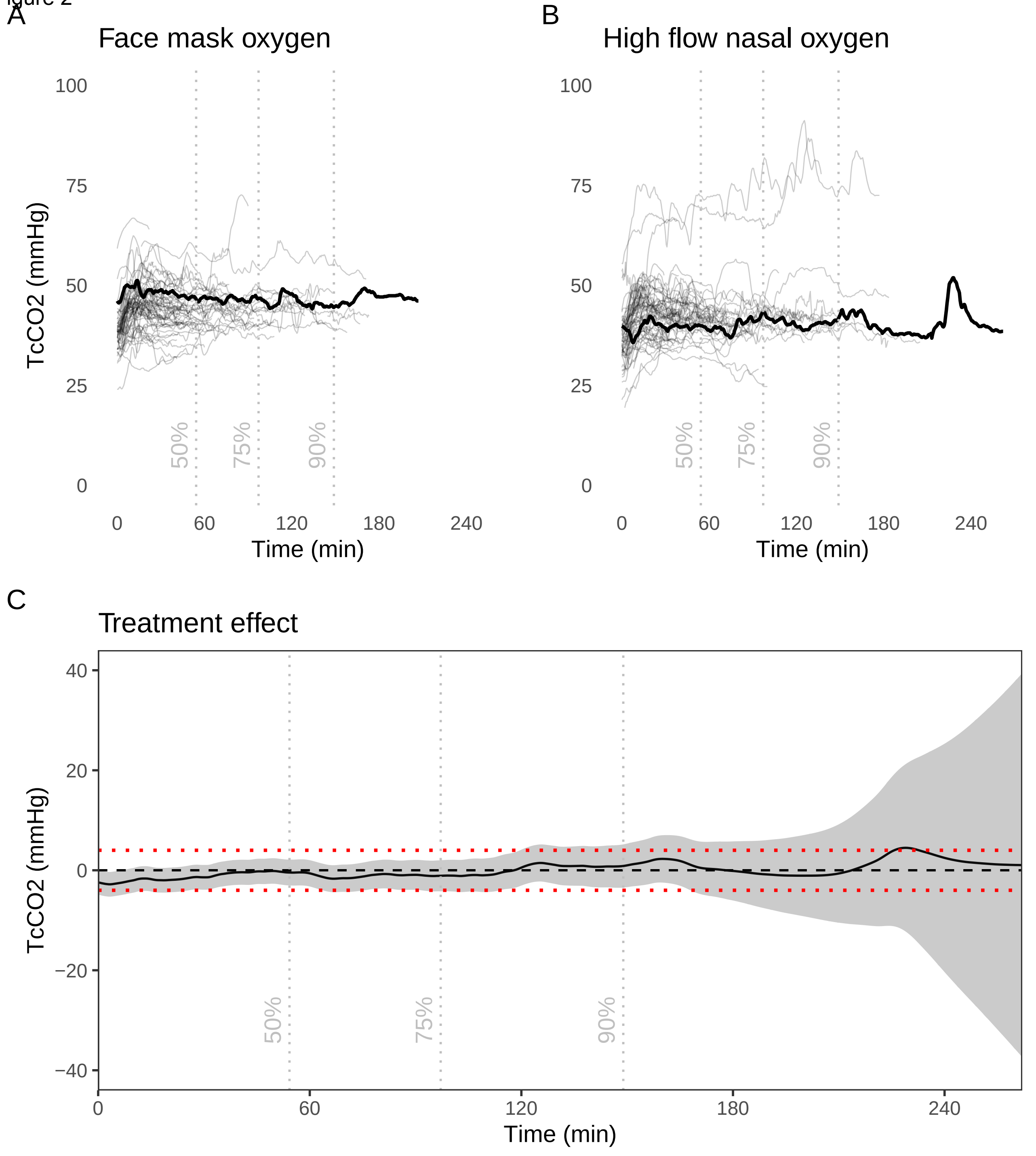
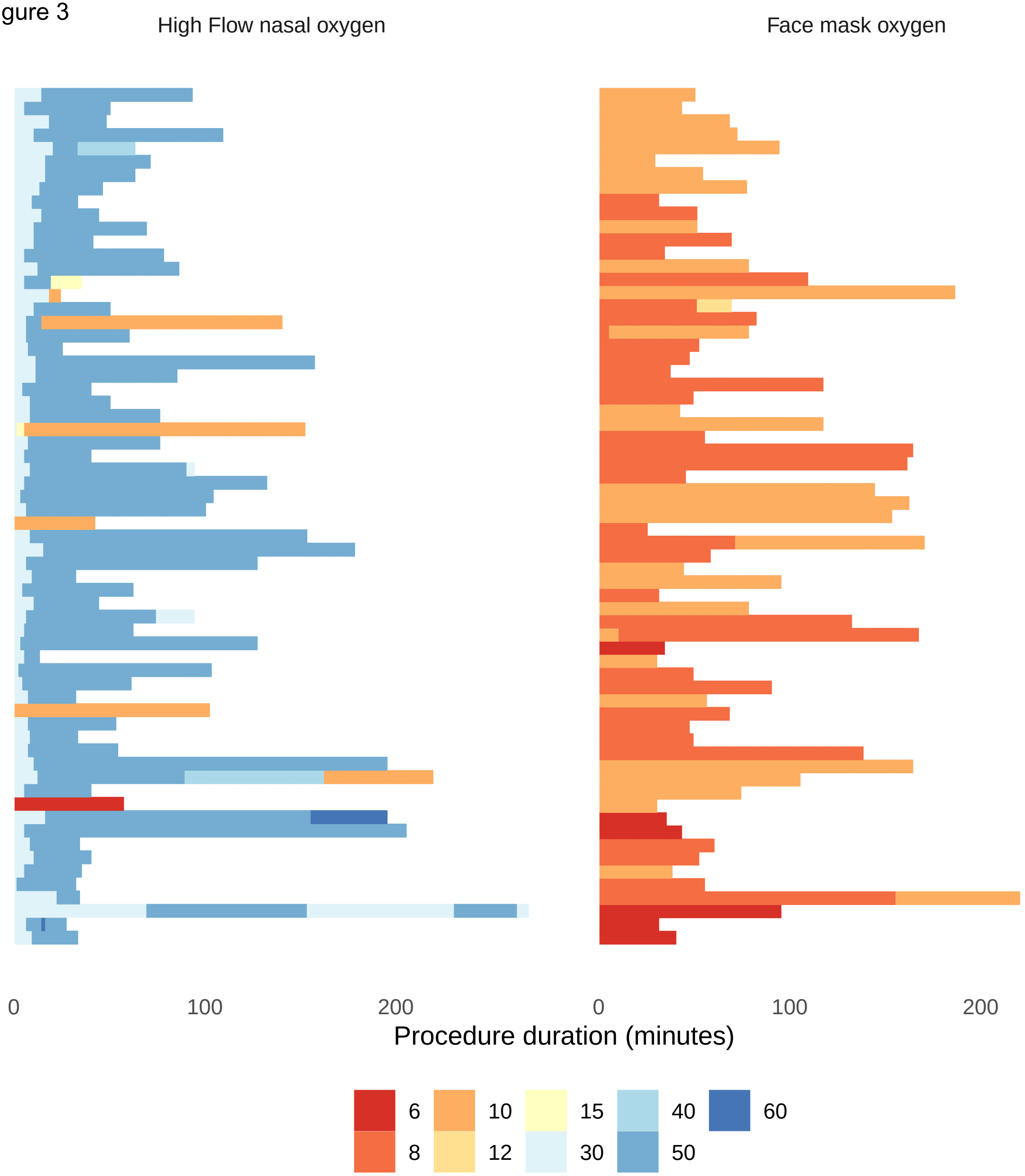

Enrollment
Assessed for eligibility (n=270)
Excluded (n=140)
− Not meeting inclusion criteria (n=21)
− Not invited to participate (n=28)
− Declined to participate (n=91)
Randomized (n=130)
Allocation
Allocated to facemask oxygen (n=66)
− Received facemask oxygen (n=69)
Allocated to high flow nasal oxygen (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

CRediT author statement

High flow nasal oxygen during sedation for cardiac implantable electronic device procedures: A randomized controlled trial

Aaron Conway: Conceptualization, Project administration, Investigation, Visualization, Formal analysis, Writing - Original Draft, Supervision, Funding acquisition

Peter Collins: Methodology, Visualization, Formal analysis, Writing - Review & Editing

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Ana Lopez-Filici: Methodology, Resources, Writing - Review & Editing

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