Aaron Conway
BN(Hons), PhD

aaronconway.info
aaron.conway@utoronto.ca
+1 (416) 946-7112

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,

Aaron Conway
BN(Hons), PhD

RBC Chair in Cardiovascular Nursing Research
Peter Munk Cardiac Centre
Univeristy Health Network

Assistant Professor
Lawrence S. Bloomberg Faculty of Nursing
University of Toronto

aaronconway.info
aaron.conway@utoronto.ca
+1 (416) 946-7112

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.