High flow nasal oxygen during procedural sedation for cardiac implantable electronic device procedures

A randomised controlled trial

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BACKGROUND High flow nasal oxygen may better support the vulnerable respiratory 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 face-mask oxygen on ventilation during cardiac implantable electronic device procedures performed with procedural sedation.

DESIGN A randomised controlled trial.

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

PARTICIPANTS Adults undergoing elective cardiac implantable electronic device procedures with sedation administered by an anaesthesia assistant, supervised by an anaesthesiologist from August 2019 to March 2020.

INTERVENTIONS Participants were randomised 1:1 to facemask (≥8 l min⁻¹) or high flow nasal oxygen (50 l min⁻¹ and a 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 randomised and received sedation were included. The difference in peak transcutaneous carbon dioxide was 0.0 kPa (95% CI -0.17 to 0.18). 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 from a clinically important amount between high flow nasal oxygen at 50 l min⁻¹ or facemask oxygen at 8 l min⁻¹. 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.

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Introduction
Cardiac implantable electronic device (CIED) procedures are commonly performed with procedural sedation. Oxygen is administered to reduce hypoxaemia from sedation-induced hypoventilation. High flow nasal oxygen (HFNO) is a promising device for oxygen supplementation. HFNO allows for heated, humidified gas with a titratable oxygen:air ratio to be administered via nasal prongs at flows up to 70 l min⁻¹. Delivering oxygen at such high flow-rates has physiological effects that may support the vulnerable respiratory 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 apnoea due to turbulent supraglottic flow vortices. 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 Anesthesiologists have stated that there is insufficient evidence regarding which supplementary oxygen device (nasal cannula, face mask or specialised devices such as HFNO) is most effective. 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.

Materials and methods

Design

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

Participants

(1) Adults undergoing an elective CIED procedure with sedation administered by an anaesthesia assistant at one large academic hospital in Canada were randomised 1:1 to
(2) Facemask oxygen; or
(3) High flow nasal oxygen.

Exclusion criteria are listed as follows:

(1) <16 years.
(2) Underlying condition requiring chronic oxygen supplementation.
(3) Diagnosed respiratory condition with current hypercapnia defined as PaCO₂ during admission over 6.0 kPa (45 mmHg).
(4) Pre-existing untreated pneumothorax.
(5) Planned transoesophageal echocardiography.
(6) Active nasal bleeding.
(7) Complete nasal obstruction.
(8) Recent upper airway surgery or base of skull fracture.
(9) Previous participation.

The model of sedation at the site where this trial was conducted follows recommendations from the Canadian Anesthesiologists’ Society. Sedation was provided by a team that included a sedation supervisor (anesthesiologist) and an approved and credentialled sedation assistant (anaesthesia assistant) who was delegated to provide sedation and monitor the patient. The anaesthesia assistant remained in constant attendance with the patient, providing continuous monitoring and immediately informing the sedation supervisor of any concerns. The sedation supervisor retained 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 anaesthesia 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

Supplementary oxygen was delivered using a standard facemask with an integrated exhaled CO₂ sampling line. The flow-rate chosen by the anaesthesia assistant was according to their standard practice, which was mostly at least 81 min⁻¹.

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 (range 30°C to 32°C). The gas flow-rate was commenced at 301 min⁻¹ prior to sedation administration and titrated up to 501 min⁻¹ as tolerated by the patient after sedative medication was administered. The fraction of oxygen in the gas began at 0.5 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 anaesthesia assistants with set-up, application and trouble-shooting if required.

Concomitant care

There were no restrictions on concomitant care. Anaesthesia assistants were permitted to use standard physiological monitoring devices, as dictated by the Canadian Anesthesiologists’ Society (CAS), and to titrate sedation according to their usual practice. Concomitant care most relevant to this trial was the use of capnography. Anaesthesia assistants elected to use capnography regardless of whether supplementary oxygen was delivered via HFNO or facemask, as this is a requirement from the Canadian Anesthesiologists’ Society anytime that procedural sedation is being administered. The facemask had an integrated CO₂ sampling tube. For participants randomised to HFNO, anaesthesia assistants used the CO₂ sampling adaptor 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, anaesthesia assistants placed a facemask with an integrated CO₂ sampling tube over the HFNO nasal cannula. Oxygen supplementation was delivered through the
HFNO nasal cannula and CO₂ was sampled from the sampling tube integrated into the facemask.

**Outcomes**

Outcome selection was informed by recommendations from the Sedation Consortium on Endpoints and Procedures for Treatment, Education and Research (SCEP-TER). The primary outcome was peak transcutaneous carbon dioxide (TcCO₂) concentration. Secondary outcomes were as follows:

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

**Data collection**

**Instruments**

TcCO₂ was measured continuously using the Sentec Digital Monitoring system with VSign 2 sensor (Sentec-AG, Thewil, Switzerland). TcCO₂ monitoring which provides continuous, accurate and precise estimates of PaCO₂. TcCO₂ monitoring may provide even more precise estimates of changes in PaCO₂ (mean bias 0.004 kPa, 95% limits of agreement -0.059 to 0.051 kPa). The Sentec VSign 2 sensor was attached to the forehead. Once the TcCO₂ stabilised, the monitor was covered with a drape so that it was not visible to research staff or clinicians. It was not used by the clinicians to guide treatment. TcCO₂ was sampled at a frequency of one measurement per minute. The recorded SpO₂ was extracted from the Drug Reconciliation and Electronic Monitoring System at a frequency of one measurement per second. The recorded SpO₂ was observed to fall below the 90% threshold for the duration of the intervention period. A difference in TcCO₂ levels of 4 mmHg (0.5 kPa) was selected for this sample size calculation because it was considered to be clinically relevant and was used to power previous trials. Differences in CO₂ level of a similar magnitude have been detected in previous trials evaluating the efficacy of interventions to improve sedation safety.

**Sample size calculation**

Our estimate was based on earlier work that found the mean ± SD peak TcCO₂ level in the control group to be 6.3 ± 0.9 kPa. Assuming a type I error rate of 5%, a sample of 130 participants would achieve 90% power to detect a reduction in mean TcCO₂ levels of 0.5 kPa in the intervention period. A difference in TcCO₂ levels of 4 mmHg was selected for this sample size calculation because it was considered to be clinically relevant and was used to power previous trials.

**Random sequence generation and concealment**

A block randomised sequence stratified by diagnosis of obstructive sleep apnoea and type of procedure and cardiac resynchronisation therapy device implant was generated and concealed using the web-based randomisation feature in REDCap. The research assistant 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 (https://hfnosedrct.netlify.app/flexdashboard) and archived (https://doi.org/10.5281/zenodo.3908492). 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 variables. Covariate adjustments were made for the stratification variable obstructive sleep apnoea status and whether or not the procedure was a cardiac resynchronisation therapy device implant, in addition to baseline TcCO₂ concentration, which was modelled using splines. Continuous outcomes were analysed using robust regression models. A functional analysis of variance (ANOVA) model was used to investigate how mean TcCO₂ concentration levels differ between groups as a function of procedure time. Logistic regression was used for dichotomous outcomes. Proportional-odds models were used for ordinal outcomes. Analysis was performed only on those participants whose SpO₂ was observed to fall below the 90% threshold for the AUC_{DESAT} outcome.

Posterior inference for all models except the functional ANOVA model was performed using Hamiltonian Monte Carlo through the brms package, version 2.12.0. For this set of models, 2000 posterior samples were obtained from four independent chains of 2000 samples, of which the first 1000 warm-up samples were discarded. Posterior inference for the functional ANOVA model was performed using the Integrated Nested Laplacian Approximation through the INLA package, version 20.5.12. The marginal posterior distribution of variables was

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summarised 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\textsubscript{2} concentration was evaluated by computing the posterior probability that an effect exceeds 0.5 kPa 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 (Fig. 1). A total of 130 participants were randomised. Two were excluded, one because the procedure was cancelled, and another, who was randomised to the HFNO group, had their procedure rescheduled to a time when the Research Assistant was unavailable. This participant received oxygen via a standard face mask and TcCO\textsubscript{2} data were not collected. For two participants, the TcCO\textsubscript{2} sensor failed to calibrate prior to commencement of the procedure. Most anaesthesia assistants (n = 29, 45%) reported having used HFNO between two and five times.

Participant characteristics are presented in Table 1. The sample was mostly elderly and male. Anaesthesia assistants rated the ASA Physical Classification Status as either III or IV. Obstructive sleep apnoea 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 TcCO₂ was estimated to be 0.0 kPa (95% CI -0.17 to 0.18). The probability that it exceeds the 0.5 kPa clinical significance threshold in either direction is 0.

Secondary outcomes

The effect of HFNO on the mean TcCO₂ concentration was estimated to be -0.013 kPa (95% CI -1.31 to 1.14). The probability that it exceeds the 0.5 kPa clinical significance threshold in either direction is 0. There is no discernible 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 with the facemask is 70%.

The odds ratio for anaesthesia 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 anaesthesia assistants’ ratings of difficulty using the oxygen device and difficulty maintaining oxygenation were missing 45 and 46 responses, respectively, probably because the survey was voluntary. It is unlikely that omission of
ratings occurred completely at random, so a best-case 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-case 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 0.05 to 0.31).

A visualisation of the SpO\textsubscript{2} trajectories for patients whose SpO\textsubscript{2} was below 90% is available (https://hfnosedrct.netlify.app/flexdashboard).

### Oxygen flow-rates
Most participants randomised to the HFNO group had the flow-rate set at 50 l min\textsuperscript{-1} (Fig. 3). Most participants randomised to the facemask group received oxygen at least 8 l min\textsuperscript{-1}. Two participants who were randomised to HFNO did not receive this intervention at all and four who were randomised to HFNO stopped receiving this intervention at a certain timepoint during procedures at the discretion of the anaesthesia 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 501min\textsuperscript{-1} for patients undergoing elective CIED procedures with sedation is highly unlikely to decrease or increase peak TcCO\textsubscript{2} concentration by a clinically important amount in comparison with standard facemask oxygen at least 81 min\textsuperscript{-1}. An earlier
physiological modelling study of apnoeic oxygenation identified a mechanism by which HFNO promotes carbon dioxide clearance.\textsuperscript{5} We did not observe a significant reduction in peak TcCO$_2$ concentration. This result is consistent with existing clinical research in the nonsedation context. The difference in PaCO$_2$ observed between HFNO (5.81 ± 1.1 kPa) and facemask oxygen (5.6 ± 1.0 kPa) from a randomised trial of 20 patients who were receiving pre-oxygenation for induction of anaesthesia prior to emergency surgery was not significant ($P = 0.631$).\textsuperscript{21} 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 ± 0.8 kPa) and standard facemask (5.3 ± 1.0 kPa; $P = 0.18$).\textsuperscript{22} Importantly, in contrast to these trials wherein 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.

Another commonly proposed physiological effect of HFNO, which has been observed in a study of healthy volunteers, is increased pressure in the upper airways.\textsuperscript{23}
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 80 l/min. We neither directly measured airway pressure nor 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 cause noted for these events by the anaesthesia 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 at least 81 min⁻¹ of 100% O₂. Further research with a larger sample size would be useful to determine the optimal oxygen:air ratio for HFNO during sedation for CIED procedures, with an emphasis on adverse sedation events or hypoxaemia as the primary outcome.

Another plausible mechanism is that the ability to monitor capnography waveforms was diminished with HFNO. Capnography is widely considered as an essential aspect of physiological monitoring during sedation. 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. 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 CO$_2$ sampling tube was used for the majority of patients. According to the manufacturer’s instructions, the CO$_2$ sampling tube in these cannulae should be positioned at the entrance of a nostril or the mouth. There have been no studies reporting a comparison in the quality of the capnography waveform produced from this new cannula or alternative ways to monitor capnography during HFNO therapy. Capnography monitoring for the subset of patients enrolled in the first 2 months of our trial, who were randomised to HFNO, was achieved by placing a facemask with an integrated CO$_2$ sampling tube (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 probably because both methods involve CO$_2$ 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 EtCO$_2$ sampling may be a potential solution. 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 affected 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 and three small randomised controlled trials were published in 2019, with several more ongoing trials registered. The primary outcomes for all the trials to date have investigated the impact of HFNO on oxygenation with inconsistent results. One of the small trials randomised 60 participants undergoing bronchoscopy to receive HFNO at 501 min$^{-1}$ with 100% oxygen or oxygen at 10 to 15 l min$^{-1}$ through a facemask. No significant difference was 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 randomised 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 60 l min$^{-1}$ or via nasal cannula at 41·min$^{-1}$. Again, there was no significant difference in the primary outcome of oxygen desaturation (SpO$_2$ <90%). The third study randomised 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 501 min$^{-1}$, via HFNO at a flow-rate of 301 min$^{-1}$ or via nasal cannula at 51 min$^{-1}$. Participants randomised 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 hypoxaemia, 8.4% in the control group and 0% in the HFNO group. The probable explanation for this is the large difference in FiO$_2$ between the two groups. In the HFNO group, participants received 601 min$^{-1}$ of 100% oxygen and in the control group patients received just 21 min$^{-1}$ of oxygen.

Satisfaction with sedation is most probably going 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 anaesthesia assistants to use compared with the standard facemask. None of the anaesthesia assistants rated the HFNO device as difficult to use and most had very limited experience using the device. Also, most anaesthesia assistants participating reported they had used HFNO between two and five 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. Severe oxygen desaturation is not a common event when oxygen is delivered at flow-rates between 6 and 101 min$^{-1}$ through a face mask during procedures performed with sedation. Results from our trial cannot be directly generalised to other clinical settings wherein desaturation is more severe and occurs more often. Considering anaesthesia assistants had had limited experience 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, they did 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 a FiO2 approximately similar to that achieved with standard practice in the facemask group, typically in the region of 81 min⁻¹. 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 501 · min⁻¹ and a 50:50 oxygen to air ratio for the majority of time during sedation compared with facemask oxygen at least 81 · min⁻¹. The main finding from our primary outcome is that ventilation, as measured by TeC02, 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 desaturation is probably worse with HFNO at 50-1·min⁻¹ and a 50:50 oxygen to air ratio compared with facemask oxygen at least 81 · min⁻¹, but 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 at least 81 min⁻¹ in the cohort 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 expected to be similar.

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