Reducing Reintubation Risk in High-Risk Cardiac Surgery Patients with High-Flow Nasal Cannula

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1.0 Background

The iCAN trial is a pragmatic randomized controlled trial that aims to test the hypothesis that HFNC versus usual care oxygenation strategies applied immediately after initial extubation after cardiac surgery decreases the all-cause 48-hour reintubation rate (extubation failure within 48 hours of initial extubation).

2.0 Rationale and Specific Aims

HFNC may be employed as a strategy to facilitate early extubation and prevent reintubation of patients following cardiac surgery. HFNC is routinely employed by providers in the cardiovascular intensive care unit and is selectively employed in patients who are judged by the provider to be high-risk, along with other therapies: bi-level positive airway pressure, non-rebreather masks, among others.

To guide a future, larger, multicenter randomized controlled pragmatic clinical trial, we will perform a study in a single, high-volume cardiovascular intensive care unit. We will perform a prospective, randomized, pragmatic clinical trial of HFNC compared to provider choice of usual care in these patients to test the hypothesis that HFNC versus usual care oxygenation strategies applied immediately after initial extubation after cardiac surgery decreases the all-cause 48-hour reintubation rate (extubation failure within 48 hours of initial extubation).

We will then plan to use data from this study to conduct secondary analyses to better understand features of HFNC responders, including within predicted risk strata, compared to non-responders, and work to better understand optimal time of extubation retrospectively, with the hopes of generating data that could be used by providers to facilitate early extubation.

3.0 Animal Studies and Previous Human Studies

HFNC has been shown to be non-inferior to bi-level positive airway pressure in preventing reintubation following cardiac surgery. It may be effective at preventing reintubation in high-risk patients but, to date, this has not been specifically studied.

4.0 Inclusion/Exclusion Criteria

Study Population
The trial will enroll adult patients undergoing cardiac surgery, defined as surgery on the heart or thoracic aorta, excluding percutaneous procedures, at VUMC who fulfill the following inclusion and exclusion criteria:

Inclusion Criteria

- Age ≥18 years

- Undergoing cardiac surgery, defined as a documented surgical service of "cardiac surgery" in the EHR, performed in the main operating rooms at Vanderbilt University Medical Center
- Admitted to the cardiovascular intensive care unit postoperatively with an endotracheal tube in place and mechanically ventilated
- Surgery duration (documented time between "Anesthesia start" and "Anesthesia stop" in the EHR) of at least 180 minutes
- Received an order to be extubated by a treating provider
    - Patients who meet all other criteria but do not receive an order to extubate will be randomized but not enrolled

Exclusion Criteria

- None

5.0 Enrollment/Randomization

HFNC is widely used by providers to treat high-risk patients following cardiac surgery and is an accepted treatment to prevent reintubation. This study uses therapies that are accepted treatments routinely used by providers; therefore, we are requesting a waiver of the requirement for informed consent.

Screening, enrollment, and randomization will be performed using tools embedded within the EHR. Among patients that meet inclusion criteria, randomization will be performed at the documentation of "anesthesia stop" (at the conclusion of the surgical procedure), using a random number that will be generated and associated with the patient's hospital admission medical record. Randomization will not be visible to clinicians or investigators and will not be stratified.

Enrollment is performed using an order set in the EHR. At the time an order is placed to extubate the patient after surgery, an order set will be automatically placed based on the previously generated random number. According to hospital policy, patients may not be extubated without an extubation order. The order will assign treatment (usual care or HFNC following extubation), based on the randomization allocation.

6.0 Study Procedures

- This study is a prospective, pragmatic, randomized controlled trial. Blinding to treatment assignment will be maintained throughout surgery and the early postoperative period until an order is placed to extubate the patient in the EHR.
- Patients will be randomized 1:1 at the time of extubation to either 1] usual care (treatment at the discretion of the treating provider) or 2] HFNC, per the existing intensive care unit protocol. Respiratory therapists will be instructed to target 24 hours of HFNC, if clinically appropriate in the judgement of the patient care team,

with an absolute minimum of 1 hour of therapy. Respiratory therapists may use any HFNC device, at their discretion, with initial settings and titration at the discretion of the clinical team. Escalation of care beyond HFNC and transition to alternative means of oxygenation will be at the discretion of the patient care team. Similarly, usual care is at the discretion of the patient care team and may include HFNC. Typical treatment modalities in usual care include, but are not limited to, nasal cannula, face mask, HFNC, and bilevel positive airway pressure. All concomitant care and interventions will be permitted to continue to ensure pragmatism. The decision to reintubate a patient will be at the sole discretion of the patient care team; there are no protocolized criteria for reintubation.

- Blinding to the treatment assignment will be maintained throughout surgery and the early postoperative period, until an order is placed to extubate the patient in the EHR. The clinical care team will not be blinded to treatment arm following enrollment, as blinding cannot be practically performed once patients are extubated. Some patients may be randomized but not enrolled if they do not receive an extubation order. Most commonly this is due to self-extubation or patient death prior to planned extubation

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7.0 Risks

Reintubation and respiratory failure are risks in the post cardiac surgery population. It is not known if this risk will be lower in one group or the other. HFNC is widely employed in the study population, in addition to other adjunct therapies, such as bilevel positive airway pressure, but its use is not standardized. It is an accepted treatment, routinely used by providers, particularly in high-risk patients. Previous studies have demonstrated that HFNC is non-inferior to bilevel positive airway pressure therapy in cardiac surgery patients.

Currently, no high-quality clinical data exist to demonstrate that HFNC may decrease the risk of reintubation in this critically ill adult population. The trial is felt to pose minimal risk as 1) exposure to the intervention occurs only in patients deemed ready for extubation by the treating clinician 2) the intervention is already commonly employed in routine practice in the study environment 3) no definitive prior data exist to show clinical outcomes are better with HFNC; the largest study to date did, however, demonstrate non-inferiority to bilevel positive airway pressure 4) We will perform an intention to treat analysis and, ultimately, the choice of therapy will be left to the treating clinician 5) Providers will be blinded to the predicted risk of reintubation and will rely exclusively on their clinical judgement, which is considered usual care in routine clinical practice.

Given this minimal risk, the focus of the study on adjunct post-extubation therapy in the ICU, and the impracticability of consenting each patient undergoing cardiac surgery, a waiver of documentation and alteration of informed consent process are requested.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Any unanticipated, serious, study related adverse events will be reported per IRB policies and procedures.

9.0 Statistical Considerations

Sample size calculations were based on data from a prior study of reintubation after cardiac surgery performed at VUMC (PI: Freundlich, Ann Thorac Surg 2022, PMID 34329600). Assuming a 3.2% reintubation rate among the control arm and a 1:1 ratio of intervention patients to control patients, with at least 1435 patients in each group, a two-sample test of binomial proportions achieves 80% power to detect a relative decrease of 50% in the 48-hour reintubation rate among the HFNC arm (i.e. from 3.2% to 1.6%) at a type 1 error rate of 5%. Accounting for at least 15% crossover between groups, we will require at least 1688 patients in each arm of the study using the N/(1-R) crossover methodology. The intervention and primary outcome are in hospital; as such, we do not anticipate any drop out. Total enrollment will be about 3800.

The primary endpoint is all-cause unadjusted reintubation at 48 hours after initial extubation following cardiac surgery (that is, extubation failure within 48 hours). We will not attempt to determine causality of the reintubation as this is frequently multifactorial and would introduce subjective bias into the analysis.

Analysis of the primary endpoint will compare rates of reintubation within 48 hours of initial extubation after cardiac surgery between the HRNC intervention and control arms, based on intention to treat, in which patients are included in the group to which they were randomized regardless of the treatment received.

Data generated in the study will be used for secondary analyses to better understand treatment response and failure in patients treated with HFNC across strata defined by predicted reintubation risk, as well as to better understand optimal time of extubation.

Prespecified secondary endpoints are listed below

- Reintubation within 72 hours of extubation
- Reintubation at any time after extubation
- All-cause 30-day mortality
- Hospital length of stay
- Intensive care unit length of stay
- Ventilator-free days
- In-hospital mortality
- Adjusted reintubation rate, if needed based on clinically relevant imbalance in baseline characteristics between groups

All data analyzed, including demographic and outcome data, will be limited to data generated by clinicians in routine clinical care and captured via query of existing databases available within the EHR. In previous work, we have demonstrated that we are

able to obtain these data without any missingness, based on our extensive experience querying the EHR, as well as by limiting our analysis to those data elements that are readily available (PI: Freundlich, Ann Thorac Surg 2022, PMID 34329600). We have shown that this may be generalizable (PI: Freundlich, J Clin Anesth 2024, PMID 37883900). We will analyze data on a modified intention-to-treat basis that includes all randomized and enrolled participants grouped according to the treatment assigned at randomization as described below.

- Some patients may be randomized but not enrolled if they do not receive an extubation order. Most commonly this is due to self-extubation or patient death prior to planned extubation. We will report demographic and outcome data on patients who were randomized but not enrolled in a separate analysis to help ensure that post-randomization exclusions do not introduce significant bias.
- A proportion of lung transplants are scheduled as being performed by "cardiac surgery" and will be enrolled. Upon the recommendation of the DSMB, these patients will be analyzed in the primary intention-to-treat analysis, but we will perform a prespecified subgroup analysis excluding these patients.

10.0 Privacy/Confidentiality Issues

Participant records will be assigned a code and the key to the code will be accessible only by Key Study Personnel (KSP). Data will be stored on password protected servers accessible only by KSP.

11.0 Follow-up and Record Retention

Data will be stored on password protected VUMC servers indefinitely.

References

1. Khandelwal N, Dale CR, Benkeser DC, et al. Variation in tracheal reintubations among patients undergoing cardiac surgery across Washington state hospitals. J Cardiothorac Vasc Anesth 2015;29(3):551-9. doi: 10.1053/j.jvca.2014.11.009 [published Online First: 2015/03/25]
2. Freundlich RE, Maile MD, Hajjar MM, et al. Years of Life Lost After Complications of Coronary Artery Bypass Operations. Ann Thorac Surg 2017;103(6):1893-99. doi: 10.1016/j.athoracsur.2016.09.048 [published Online First: 2016/12/13]
3. Dorsa AG, Rossi AI, Thierer J, et al. Immediate extubation after off-pump coronary artery bypass graft surgery in 1,196 consecutive patients: feasibility, safety and predictors of when not to attempt it. J Cardiothorac Vasc Anesth 2011;25(3):431-6. doi: 10.1053/j.jvca.2010.08.013 [published Online First: 2010/11/03]
4. Chan JL, Miller JG, Murphy M, et al. A Multidisciplinary Protocol-Driven Approach to Improve Extubation Times Following Cardiac Surgery. Ann Thorac Surg 2018 doi: 10.1016/j.athoracsur.2018.02.008 [published Online First: 2018/03/14]
5. Roca O, Hernandez G, Diaz-Lobato S, et al. Current evidence for the effectiveness of heated and humidified high flow nasal cannula supportive therapy in adult patients with respiratory failure. Crit Care 2016;20(1):109. doi: 10.1186/s13054-016-1263-z [published Online First: 2016/04/29]
6. Markovitz GH, Colthurst J, Storer TW, et al. Effective inspired oxygen concentration measured via transtracheal and oral gas analysis. Respir Care 2010;55(4):453-9. [published Online First: 2010/04/22]
7. Bazuaye EA, Stone TN, Corris PA, et al. Variability of inspired oxygen concentration with nasal cannulas. Thorax 1992;47(8):609-11. [published Online First: 1992/08/01]
8. Stephan F, Barrucand B, Petit P, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A Randomized Clinical Trial. Jama 2015;313(23):2331-9. doi: 10.1001/jama.2015.5213 [published Online First: 2015/05/20]
9. Masip J, Peacock WF, Price S, et al. Indications and practical approach to non-invasive ventilation in acute heart failure. Eur Heart J 2018;39(1):17-25. doi: 10.1093/eurheartj/ehx580 [published Online First: 2017/12/01]
10. Corley A, Caruana LR, Barnett AG, et al. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 2011;107(6):998-1004. doi: 10.1093/bja/aer265 [published Online First: 2011/09/13]
11. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. Br J Anaesth 2009;103(6):886-90. doi: 10.1093/bja/aep280 [published Online First: 2009/10/23]
12. Zhu Y, Yin H, Zhang R, et al. High-flow nasal cannula oxygen therapy vs conventional oxygen therapy in cardiac surgical patients: A meta-analysis. J Crit Care 2017;38:123-28. doi: 10.1016/j.jcrc.2016.10.027 [published Online First: 2016/11/26]