**Remifentanil versus Dexmedetomidine in Cardiac Surgery Patients with Noninvasive Ventilation Intolerance: Protocol for the REDNIVI Trial**

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1. Introduction

Respiratory failure is one of the most common complications after cardiac surgery [1–3]. Most patients recover in a short period due to sufficient cardiopulmonary reserve. However, high-risk patients with existing respiratory diseases or who underwent prolonged cardiopulmonary bypass may experience a postoperative decline in respiratory function. As a result, these patients may eventually suffer ex-tubation failure, resulting in a prolonged intensive care unit (ICU) stay or an increased risk of mortality [3–5].

Noninvasive ventilation (NIV) avoids re-intubation and mechanical ventilation (MV). It has been shown to increase tidal volume, reduce the work of breathing, reduce preload and afterload in the left ventricle [6,7], avoid the adverse effects of prolonged MV, decreases the risk of pneumonia and sinusitis, and reduce death risk [8–11] NIV is increasingly prevalent in patients with hypoxia and atelectasis following cardiac surgery. However, intolerance to noninvasive masks has been reported [5,8] at a rate of 15% [12]. Getting rid of the mask as a result of the discomfort may lead to NIV failure [13–15]. These patients have a high intubation rate of 44% and a mortality rate of 34% [13].

Various methods have been adopted to prevent and treat NIV intolerance, including sedation, thus preventing endotracheal intubation [16,17]. Our preliminary research concerning the treatment of cardiac surgery (CS) patients with moderate to severe NIV intolerance has shown that after sedation, endotracheal intubation was avoided in about 80% of the intolerant patients [18]. Dexmedetomidine (DEX) is a selective \(\alpha-2\) agonist that downregulates the release of norepinephrine in the central nervous system without suppressing breathing [19]. It is being widely used with good safety in CS patients [20,21]. And it is the standard sedation protocol adopted at Zhongshan Hospital, Fudan University. However, DEX use following cardiac surgery is limited by common side effects, such as bradycardia and hypotension [19,22]. Remifentanil (REM) is a potent opioid analgesic drug used for sedation. It is advantageous compared to DEX due to Rapid onset, Hemodynamic stability, Good analgesic effects, especially for postoperative se-
Inclusion and Mitigation of cardiogenic factors that necessitate patients to use NIV [19,23]. CS patients commonly present with an increase in respiratory rate. REM can effectively reduce sympathetic activation and decrease breathing work. Also, one meta-analysis has shown that REM reduces cardiac troponin release, time of MV and length of hospital stay in patients undergoing cardiac surgery [24]. Based on the above reasons, we set to comparatively evaluate REM and DEX in sedating CS patients intolerant to NIV.

2. Methods and Analysis

2.1 Design

This study is a multicenter, prospective, single-blind, randomized controlled trial. Personnel performing evaluations, such as the noninvasive score (NIS), listed in this protocol, will be blinded, as well as the patients. However, drug information will be disclosed to intensivists. The study is designed to evaluate the sedative effect of REM and DEX in postoperative CS patients who are unable to tolerate NIV and explore optimal sedation in these patients. Data will be collected from six hospitals in mainland China.

Postoperative CS patients receiving NIV will be evaluated regularly for enrollment by noninvasive ventilation intolerance score (see definition later). Patients with moderate or severe NIV intolerance will be randomly assigned to two groups (Group 1: remifentanil; Group 2: dexmedetomidine) in a 1:1 ratio (Fig. 1). The remission and mortality rate, duration of ICU stay, duration of MV, the need for intubation or tracheotomy, delirium, and hemodynamic changes will be evaluated between two groups.

2.2 Study Population

Inclusion and exclusion criteria are defined for enrolled patients.

2.2.1 Inclusion Criteria

Patients meeting all of the following criteria:
(1) Voluntarily sign the informed consent and comply with protocol requirements;
(2) Aged 18 years old or over regardless of gender;
(3) Intolerant to NIV following cardiac surgery.

2.2.2 Exclusion Criteria

(1) Patients with a history of an allergic reaction to any components of the study drug;
(2) Visual Analogue Scale (VAS) ≥4;
(3) Patients who have used DEX within 8 hours of the study;
(4) Patients who have used REM within 2 hours of the study;
(5) Patients experiencing difficulty in expectoration;
(6) Pregnant or lactating patients;
(7) Patients with coma or uncontrollable convulsions;
(8) Patients with a history of mental disorders or cognitive impairment;
(9) Patients who developed delirium before the start of the study;
(10) Severe liver function impairment (Child-Turcotte-Pugh (CTP) Level C);
(11) Patients with renal insufficiency (patients receiving renal replacement therapy);
(12) Pre-operative left ventricle ejection fraction (LVEF) <30%;
(13) History of alcohol or drug abuse;
(14) Other conditions deemed inappropriate for participation in the clinical trial by the investigator.
2.2.3 Criteria for Withdrawing From The Study

(1) Severe adverse events;
(2) Complications which develop after inclusion that hinder treatment continuation;
(3) Withdrawal of the informed consent;
(4) Poor compliance;
(5) Other conditions deemed inappropriate for further participation in the clinical trial by the investigator. These conditions would be disclosed fully in the final paper.

2.3 Management of NIV

2.3.1 Initiation of NIV

Patients meeting any of the following criteria [25,26]:
(a) Early extubation with sequential NIV in patients with failure of spontaneous breathing trial (SBT) will be carried out using pressure support (PS) at 5 cm H₂O and PEEP at 5 cm H₂O and will be continued for 30–60 minutes. Criteria for SBT failure include respiratory rate >30 breaths/min or rapid shallow breathing index (respiratory rate/tidal volume) >105 breaths/min/L, PaO₂/FiO₂ <200 mmHg, SpO₂ <90%, 20% increase or decrease from the baseline heart rate or blood pressure, use of accessory muscles, paradoxical abdominal movement, and substantial agitation, anxiety, or diaphoresis.

(b) Successful SBT in high-risk patients for post-extubation acute respiratory failure (ARF): body mass index (BMI) >30, left ventricular ejection fraction (LVEF) <40%, and failure of previous extubation.

(c) Successful SBT followed post-extubation ARF, defined as meeting at least one of the following: PaO₂/FiO₂ ratio <200 mmHg, respiratory rate >25/min for at least 2 hours, and use of accessory respiratory muscles or paradoxical respiration.

2.3.2 Settings for NIV

All patients will use a face mask (ZS-MZ-A Face Mask; Shanghai Zhongshan Medical Technology, Shanghai, China) during NIV using an ICU ventilator with a heated humidifier. All other devices for NIV, such as Helmet CPAP, will not be used.

Initial NIV settings: pressure support ventilation; PSV level: 5–15 cm H₂O; PEEP: 4–5 cm H₂O, up to 8–10 cm H₂O; Inspiratory trigger sensitivity as high as possible while avoiding auto triggering; expiratory trigger: 25–30%; F_iO₂: the lowest to reach the SpO₂ target.

NIV Targets: tidal volume: 6–8 mL/kg predicted body weight; respiratory rate ≤25 breaths/min; PaO₂/FiO₂ ≥200 mmHg; SpO₂: 95–98%. In both groups, nurses routinely used VAS to assess pain. Analgesic drugs will be used in necessary cases to achieve a target pain control level of 0–2. All patients will be monitored closely by intensivists and respiratory therapists for intermittent or continuous NIV need.

2.3.3 Withdrawal of NIV

NIV will be continued if the patient does not tolerate 48 hours of unsupported spontaneous breathing or is reintubated.

NIV withdrawal criteria: NIV will be discontinued if the patient receives less than 4 hours per day of NIV or receives nasal oxygen therapy. SaO₂ is over 95%, or a PaO₂/FiO₂ ratio is over 200 mmHg. NIV was restarted within 24 hours of discontinuation if necessitated by the patient’s clinical status. Success will be defined as an absence of ventilatory support for 48 hours.

Criteria for re-intubation: (1) tachypnea with a RR >35 bpm and use of accessory muscle; (2) refractory hypoxemia: PaO₂ <50 mmHg or PaO₂/FiO₂ <100 mmHg; (3) respiratory acidosis, with pH <7.30 and PaCO₂ >50 mmHg; (4) altered mental status; (5) hemodynamic instability; (6) loss of ability to protect the airway.

2.4 Randomization and Blinding

Block randomization will be conducted using a computer-generated random sequence without center-based stratification. The random coding scheme will be distributed in envelopes and sent to each center. An individual will be responsible for the custody of the envelopes. The custodian will not participate in the inclusion, grouping, and treatment of the patients. According to the estimated sample size of 178 cases, to ensure that each center has surplus envelopes, 420 envelopes will be set up and distributed to each center according to the expected number of participants in each center. For balanced grouping, the sample size of each center should be n times the number of subjects in a block (n ≥1, the block length is 4, the sample size is at least a multiple of 4). The clinician will notify the custodian if a patient meets the inclusion criteria and request for number allocation.

2.5 Definition

Intolerance to NIV is defined by the noninvasive score (NIS) ≥3. NIS 1: The patient tolerates NIV. The subject feels comfortable and relaxed. NIS 2: The patient experiences mild intolerance. The subject feels some discomfort and uses the mask most of the time. NIS 3: The patient experiences moderate intolerance. The subject feels uncomfortable most of the time and tries to get rid of the mask frequently. NIS 4: The patient shows severe intolerance. The subject is agitated and does not place the mask correctly [14].

2.6 Data to Be Collected

Baseline and demographic variables will be collected when patients present with NIV intolerance in each participating centre. These variables include age, height, weight, gender, ethnicity, date of birth, past medical history (hypertension, coronary heart disease, diabetes, allergy, and surgery), history of smoking, and alcohol abuse. Present
medical history including the cardiac surgery operation details, pre-operative echocardiography features (LVEF, pulmonary arterial pressure [PAP] and tricuspid annular plane systolic excursion [TAPSE]), New York Heart Association Functional Classification (NYHA), Acute Physiology and Chronic Health Evaluation II (APACHE II), and The European System for Cardiac Operative Risk Evaluation II (EUROScore II) will be recorded. Use of other analgesics will also be recorded (Table 1).

The following data will be collected at 15 minutes, 1, 3, 6, 12, 24, 36, 48, 60, 72 hours after initiation of treatment or until NIV withdrawal:

**Vital signs**: Temperature, respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, central venous pressure, pH, partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂), oxygen saturation (SpO₂).

**Ventilation Status**: Tidal volume, pressure support, a fraction of inspired oxygen (F\textsubscript{IO₂}).

**NIV status**: Different levels of intolerance, NIS.

**Drug information**: Dosage of REM or DEX, use of other analgesics, use of inotropes and vasoactive drugs.

The following data will be collected on day 1, 2 and 3 after initiation of treatment or until withdrawal:

**Full blood count**: White blood cell, hemoglobin, and platelet count.

**Liver and kidney function**: Alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), creatine (Cr), creatine clearance.

**24 h fluid intake and output**

**Delirium**

### 2.7 Interventions

REM and DEX will be administered at an initial dosage of 0.05 µg/kg/min and 0.5 µg/kg/h, respectively, and adjusted to the patient’s status (Target of treatment: NIS ≤2). The maximum dosage for REM and DEX will be 0.12 µg/kg/min and 1.0 µg/kg/h, respectively. Midazolam will be administrated if the drugs fail to achieve the treatment target at maximal doses.

### 2.8 Outcome Measures

Primary outcomes are intolerance remission rate at different timings (15 minutes, 1, 3, 6, 12, 24, 36, 48, 60, 72 hours after initiation of treatment) and 72 h average remission rate. Secondary outcomes include mortality, duration of ICU stay or MV, the need for endotracheal intubation or tracheostomy, hemodynamic changes, and delirium. Intolerance remission rate will be measured 15 minutes, 1, 3, 6, 12, 24, 36, 48, 60, 72 hours after initiation of treatment or until withdrawal. Four levels of intolerance will be given to evaluate remission: NIV failure, NIV intolerance (NIS ≥3), NIV tolerance (NIS ≤2), and NIV withdrawal. Remission is defined by NIS ≤2 or NIV withdrawal.

### 2.9 Safety

Adverse events, including but are not limited to bradycardia, hypotension, nausea, vomiting, chest wall rigidity, and respiratory arrest, will be recorded during treatment. Efforts will be made to determine if the events are related to the studied drug and whether necessary measures, such as dosage adjustment, will be needed. All treatments to reverse any adverse events will also be recorded during the study.

### 2.10 Sample Size

The primary objective of this study is to compare the remission rate of REM and DEX in patients with NIV intolerance after cardiac surgery. A previous study comparing the average remission rate within 3 hours after initiation of treatment showed the average remission rate was 88% for the REM group and 70% for the DEX group [18]. Thus the sample size was calculated as 80 subjects in each group. This sample size was calculated based on the assumption that the remission rate of REM and DEX will be 70% and 88% respectively, with the power of 85% and two-sided significance of 0.05 re-calculation of the sample size considering a drop-out rate of 10% resulted in 89 subjects in each group.

### 2.11 Statistical Analysis

Data from the six centers included in this study will. Demographics and baseline characteristics will be summarized using descriptive statistics. Continuous variables will be summarized using mean, standard deviation, minimum, maximum, and median values. Differences between groups will be compared using the Student’s t-test or the Mann–Whitney U test based on whether the data meets the normal distribution. Categorical variables will be descriptively summarized based on the number of subjects in each category and their corresponding percentages, and the Chi-Square test will be used. If necessary, Fisher’s exact test will be used to analyze the differences between groups.

A percentage stacked area chart will be used to describe changes in the patient’s status with the drug use. The generalized estimating equation will analyze changes in remission rate between the two groups over time. To explore factors related to delirium remission, single-factor logistic regression will be performed to screen variables with p < 0.05 into the multivariate regression model and stepwise regression. α = 0.05 (two-sided test), p < 0.05 is defined as statistically significant. All analyses will be performed using SAS Software Version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

### 2.12 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.
| Timepoints | Day of admission (D0) | Treatment |
|------------|----------------------|-----------|
| Enrollment | 15 min 1 h 3 h 6 h 12 h 24 h 36 h 48 h 60 h 72 h |
| Informed consent | × |
| Inclusion and exclusion criteria | × |
| Demographics[a] | × |
| Past medical history[b] | × |
| Operative information | × |
| Assessment | × |
| Temperature | × × × × × × × × × × |
| Respiratory rate | × × × × × × × × × × |
| Heart rate | × × × × × × × × × × |
| Systolic blood pressure | × × × × × × × × × × |
| Diastolic blood pressure | × × × × × × × × × × |
| Mean arterial pressure | × × × × × × × × × × |
| Central venous pressure | × × × × × × × × × × |
| Arterial blood gas | × × × × × × × × × × |
| SpO₂ | × × × × × × × × × × |
| FBC[d] | × × × × |
| Liver function[e] | × × × × |
| Cr | × × × × |
| Cr clearance | × × × × |
| NT-ProBNP | × × × × |
| cTnT | × × × × |
| 24 h fluid intake and output | × × × × |
| Delirium | × × × × |
| Respiratory parameters[f] | × × × × × × × × × × |
| NIV status | × × × × × × × × × × |
| NIS | × × × × × × × × × × |
| Use of other analgesics | × × × × |
| Use of inotropes and vasoactive drugs | × × × × |
| Doses of studied drug | × × × × × × × × × × |

Note: [a] Age, height, weight, gender, ethnicity and date of birth; [b] History of smoking, alcohol, hypertension, coronary heart disease, diabetes, allergy, surgery. [c] NYHA, APACHE II, EUROScore, LVEF, PAP, TAPSE. [d] HGB, WBC, PLT. [e] ALT, AST, TBIL, DBIL. [f] VT, PS, F, O₂.

3. Discussion

Sedation has been widely accepted as a safe and effective way to manage patients with NIV intolerance [16, 27,28]. However, protocols vary greatly. A randomized controlled trial (RCT) conducted to compare the effects of DEX and midazolam in 40 uncooperative patients receiving NIV for acute respiratory failure, concluded that DEX required fewer dosing adjustments to maintain adequate sedation [29]. This suggests that different drugs could have various effects. There have been no RCTs comparing different sedatives in CS patients receiving NIV. A previous retrospective study by our research team showed that REM
was as effective as DEX in CS patients with moderate to severe NIV intolerance. REM had better effects than DEX over the first 3 h. However, the cumulative effects were similar. Since this was a single-center cohort study with a limited number of patients, more evidence is required [18].

REDNIVI is designed to evaluate the sedation effects of REM and DEX in postoperative CS patients intolerant to NIV and explore the best sedation protocol. Intolerance remission rate at different timings (15 minutes, 1, 3, 6, 12, 24, 36, 48, 60, 72 hours after initiation of treatment) and 72 h average remission rate will be determined. Mortality, duration of ICU stays or MV, the need for endotracheal intubation or tracheostomy, hemodynamic changes and delirium incidence will also be compared between the two groups.

The study has several strengths. It will be the first RCT to evaluate the sedative effect of REM and DEX in postoperative CS patients intolerant to NIV. The findings of this study may serve as a basis for developing a new sedation protocol for NIV, reducing NIV intolerance to improve patient outcomes.

Some of the study limitations include: First, this will be a single-blind study with the study intensivist aware of the drugs administered as different initial dosages will be used and adjusted to the patient’s clinical status. Second, baseline and demographic characteristics should be matched between the two groups, as various comorbidities such as chronic obstructive pulmonary disease and pre-operative conditions would affect the primary and secondary outcomes in this study.

4. Conclusions

REDNIVI will be a multicenter, prospective, single-blind, randomized controlled trial carried out in six clinical sites in China. It will provide evidence to determine the effects of remifentanil and dexmedetomidine in patients with NIV intolerance after cardiac surgery.

Author Contributions

MHL, GWH and KL were involved in the conceptualization and methodology of the study. GWT, MHL, GWH and KL designed the study. KY, YS, HW, and SJY provided help and advice on the study. JCL, WQP, YQW, YHW drafted figures and tables. MHL, GWH and KL wrote the manuscript. GWT and ZL provided administrative support. All authors contributed to editorial changes in the manuscript, read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study protocol (version 1.0; December 10, 2020) was approved by the ethics committee of Zhongshan Hospital, Shanghai, China (No. B2020-374R). In addition, all study protocols will adhere to the Declaration of Helsinki. Informed consent will be acquired from the patient or the patient’s legal representative.

Acknowledgment

Not applicable.

Funding

This research was supported by grants from Clinical Research Funds of Zhongshan Hospital (2020ZSLC38 and 2020ZSLC27), the construction program of key but weak disciplines of the Shanghai Health Commission (2019ZB0105), Natural Science Foundation of Shanghai (20ZR1411100), Program of Shanghai Academic/Technology Research Leader (20XD1421000), National Natural Science Foundation of China (82070085 and 82072131), Smart Medical Care of Zhongshan Hospital (2020ZH1Z01) and Science and Technology Commission of Shanghai Municipality (20DZ2261200).

Conflict of Interest

The authors declare no conflict of interest.

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