Neurally Adjusted Ventilatory Assist Is Associated with Greater Initial Extubation Success in Postoperative Congenital Heart Disease Patients when Compared to Conventional Mechanical Ventilation

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J Pediatr Intensive Care 2018;7:147–158.

Abstract

Extubation failure is associated with considerable morbidity and mortality in postoperative patients with congenital heart disease (CHD). The study purpose was to investigate initial extubation success utilizing neurally adjusted ventilatory assist (NAVA) compared with pressure-regulated volume controlled, synchronized intermittent mandatory ventilation with pressure support (SIMV-PRVC + PS) for ventilatory weaning in patients who required prolonged mechanical ventilation (MV). Also, total days on MV, inotropes, sedation, analgesia, and pediatric intensive care unit (PICU) length of stay (LOS) between both groups were compared. This was a non-randomized pilot study utilizing historical controls (SIMV-PRVC + PS; $n = 40$) compared with a prospective study population (NAVA; $n = 35$) in a Level I PICU and was implemented to help future trial designs. All patients ($n = 75$) required prolonged MV ≥ 96 hours due to their complex postoperative course. Ventilator weaning initiation and management was standardized between both groups. Ninety-seven percent of the NAVA group was successfully extubated on the initial attempt, while 80% were in the SIMV-PRVC + PS group ($p = 0.0317$). Patients placed on NAVA were eight times more likely to have successful initial extubation (odds ratio [OR]: 8.50, 95% confidence interval [CI]: 1.01, 71.82). The NAVA group demonstrated a shorter median duration on MV (9.0 vs. 11.0 days, $p = 0.032$), PICU LOS (9.0 vs. 13.5 days, $p < 0.0001$), and shorter median duration of days on dopamine (8.0 vs. 11.0 days, $p = 0.0022$), milrinone (9.0 vs. 12.0 days, $p = 0.0002$), midazolam (8.0 vs. 12.0 days, $p < 0.0001$), and fentanyl (9.0 vs. 12.5 days, $p < 0.0001$) compared with the SIMV-PRVC + PS group. NAVA compared with SIMV-PRVC + PS was associated with a greater initial extubation success rate. NAVA should be considered as a mechanical ventilator weaning strategy in postoperative congenital heart disease (CHD) patients and warrants further investigation.

Keywords

- ▶ neurally adjusted ventilatory assist
- ▶ mechanical ventilation
- ▶ NAVA
- ▶ extubation
- ▶ congenital heart disease

received
November 8, 2017
accepted after revision
January 8, 2017
published online
February 5, 2018

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Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0038-1627099>
ISSN 2146-4618.

Introduction

Failed extubation attempts have been associated with longer intensive care stays, considerable postoperative morbidity, and a fivefold increased risk of death in patients with congenital heart disease (CHD) after cardiac surgery.^{1–4} Risk factors such as complex CHD, younger age, greater severity of illness at postoperative admission, and prolonged cardiopulmonary bypass time often necessitate the clinician to forego early extubation or rapid mechanical ventilator weaning attempts.^{5,6} For those who cannot be extubated early or weaned from mechanical ventilation (MV) in the early postoperative course, optimal timing of MV weaning and extubation in infants and children after cardiac surgery is based upon the patient's ability to sustain the workload of spontaneous breathing without cardiac or respiratory insufficiency.

Patients who require prolonged MV after surgery for CHD are more likely to suffer from clinically significant cardiovascular dysfunction.⁷ Premature removal from MV may worsen an ongoing compensated low cardiac output state and precipitate sudden cardiopulmonary collapse.² Paradoxically, prolonged MV also significantly increases the likelihood of failed initial extubation in pediatric patients with CHD after surgery.^{6–10} Due to numerous complications with prolonged MV, including ventilator-associated pneumonias, increased requirements for sedatives, and barotrauma secondary to positive pressure ventilation, it is widely recognized as advantageous to remove the patient from MV as early in the postoperative clinical course as possible.^{1–5,7,8}

Neurally adjusted ventilatory assist (NAVA) is a mode of MV that delivers inspiratory airway pressure proportional to the integral of the electrical activity of the diaphragm (Edi).^{11–14} By improving synchronous inspiratory diaphragmatic muscle activity, increased ventilatory variability, and feedback-controlled limitation of lung volumes, NAVA has been demonstrated to protect against excess airway pressures, improve oxygenation, and optimize patient-ventilator interaction when compared with other conventional ventilatory modes.^{11–14} Postoperative CHD patients are at risk of compromised cardiac performance, especially under periods of increased oxygen consumption, weaning of mechanical ventilatory support, and the stress of extubation. By NAVA minimizing patient-ventilator asynchrony, dynamic hyperinflation, auto-positive end expiratory pressure (PEEP) and oxygen consumption of respiratory muscles, while maximizing diaphragmatic muscle conditioning, we hypothesize that NAVA's physiological advantages will lead to earlier successful initial extubation attempts by facilitating improved myocardial and diaphragmatic function.^{11–15}

The goal of this study was to investigate the effects of NAVA compared with pressure-regulated volume-controlled synchronized intermittent mandatory ventilation with pressure support (SIMV-PRVC + PS) during the MV weaning phase on initial extubation success in a homogenous group of postoperative cardiac patients who required prolonged MV. Secondary aims of the study were to compare total days on MV, inotropes, sedation and analgesia, as well as pediatric intensive care unit (PICU) length of stay (LOS) and mean airway pressures

($\bar{P}_{aw}$) while assessing patient-ventilator asynchrony between both groups.

Materials and Methods

This was a non-randomized pilot study occurring between August 2010 and May 2014 utilizing a historical control group (SIMV-PRVC + PS) and a prospective study group (NAVA) conducted in the PICU by the Department of Pediatric Critical Care at the Children's Hospital at Saint Francis with approval by the hospital's Institutional Research Ethics Board. The study population included postoperative CHD patients who required cardiopulmonary bypass and conventional MV (SIMV-PRVC + PS) for a minimum of 96 hours postoperatively without the ability to be weaned clinically or by blood gas analysis. Of the 442 patients who required surgery with cardiopulmonary bypass during that period, 75 patients met our study criteria.

Data were collected prospectively from consecutive patients who utilized NAVA during the ventilator weaning period of MV to an endpoint of extubation. A 100% accrual rate for informed consent was obtained in the prospective NAVA group. For this pilot project, we utilized control group data that were obtained retrospectively. The historical controls utilized SIMV-PRVC + PS as a sole strategy to an endpoint of extubation. Our primary outcome variable was first-time airway extubation success rate, defined as remaining extubated for ≥ 24 hours. Our secondary outcome variables included total days on MV, inotropes, continuous infusions of sedation and analgesia, measurement of $\bar{P}_{aw}$ upon initiation of ventilator weaning, and PICU LOS.

Inclusion criteria for this study included (a) patients with CHD who underwent palliative or corrective surgery requiring cardiopulmonary bypass; (b) mechanically ventilated via an endotracheal tube with inability for ventilator weaning for ≥ 96 hours; and (c) no known or suspected impairment of neuromuscular function or diaphragmatic paralysis/palsy. Exclusion criteria for the study included (a) no postoperative MV needed or duration of postoperative MV < 96 hours; (b) suspected impairment of neuromuscular function or diaphragmatic paralysis/palsy; (c) cardiopulmonary bypass was not required; and (d) parental non-consent.

Other study variables included patient age, diagnosis, risk adjusted for CHD surgery (RACHS-1) score, and types and duration of continuous infusions of analgesia, sedation, and inotropic support. Hemodynamic indices included arterial blood pressures from an arterial catheter and central venous pressures from a central venous catheter. MV settings were recorded every 6 hours. Edi peak and minimum signals from the Edi catheter were recorded continuously with a specifically designed software program within the ventilator.

Initially, for both NAVA and SIMV-PRVC + PS groups, a Servo-I Ventilator (Maquet Critical Care, Solna, Sweden) with SIMV-PRVC + PS mode was utilized. When patients required no escalation of inotropic support or fluid boluses for eight consecutive hours and had spontaneous respirations greater than the set MV rate for greater than four consecutive hours, mechanical ventilator weaning was initiated. Both NAVA and

SIMV-PRVC + PS groups were weaned identically utilizing parameters including arterial blood gases (ABGs), lactic acid levels, inspired oxygen requirements, and native respiratory rate (RR) assessments (►Fig. 1). No other MV parameters including triggering sensitivity and inspiratory time were adjusted in either group. Apnea times for both groups were set at 10 seconds throughout the mechanical ventilatory course. ABGs were monitored every 6 hours, and all patients had continuous end tidal CO₂ and continuous pulse oximetry monitoring.

The SIMV-PRVC + PS group had mechanical ventilator rates weaned via a PICU standardized protocol by two breaths per minute every 6 hours maintaining a PaCO₂ ≤ 50 mm Hg and a pH ≥ 7.30 to a lower limit of eight breaths per minute.

Lactic acid levels were required to be <2.0 mmol/L and were assessed every 6 hours. Once the patient's MV rate was eight breaths per minute with no escalation of oxygen or inotropic support, a PS trial was initiated. The 2-hour extubation readiness PS trial included setting a PEEP of 5 cm H₂O with PS of 6 cm H₂O above PEEP. Immediately after the trial, patients were extubated if their RR was ≤1.5 times the standard deviation normal mean RR of age, PaCO₂ ≤ 50 mm Hg with pH ≥ 7.30, and lactic acid < 2.0 mmol/L with no escalation of oxygen required.

In the NAVA group, patients were placed into NAVA from SIMV-PRVC + PS when spontaneous breathing occurred over the mechanical ventilator rate for ≥4 hours and met ABG parameters with no fluid bolus requirements and no escalation

Fig. 1 Ventilator weaning to extubation flow diagram. NAVA, neurally adjusted ventilatory assist; PRVC, pressure-regulated volume controlled; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

of inotropes over eight consecutive hours. Edi was obtained through a nasogastric tube with multiple arrays of electrodes at its distal end. The initial placement was directed after estimation of the proper catheter position, using the measured distance from the nostril, tragus of the ear, and xiphoid process of the sternum. Confirmation of appropriate placement was verified from electronic signals from the catheter.

The initial NAVA level ranged between 1.0 and 2.5 cm H₂O/ μ V designed to deliver a tidal volume (V_t) of 4 to 6cc/kg. This support had been left unchanged for 6 hours and then weaned by 0.2 cm H₂O/ μ V tolerating a PaCO₂ $\leq$ 50 mm Hg with pH $\geq$ 7.30, lactic acid $<$ 2.0 mmol/L, and a desired Edi range of 5 to 15 μ V to a lower limit NAVA setting of 0.4 cm H₂O/ μ V. No escalation of inspired oxygen or inotropic support or fluid boluses occurred during the weaning process. Backup mode ventilator settings were chosen to match pre-NAVA ventilator settings. Prior to extubation, patients in the NAVA group were maintained on a NAVA support of 0.4 cm H₂O/ μ V for 2 hours to assess extubation readiness. Immediately after this 2-hour period, if the patient had a RR $\leq$ 1.5 times the mean normal RR for age, PaCO₂ $\leq$ 50 mm Hg with pH $\geq$ 7.30, lactic acid $<$ 2.0 mmol/L, Edi $\leq$ 15 μ V, and no escalation of oxygen requirement, extubation was initiated.

All patients in both groups were extubated to high flow nasal cannula at 5 L per minute. Dexamethasone was administered intravenously at 0.15 mg/kg per dose every 6 hours for four doses, 24 hours prior to extubation for every patient in each group for stridor prevention. Both groups had identical reintubation criteria for extubation failure which included a PaCO₂ $>$ 55 mm Hg with a pH $<$ 7.25 or a lactic acid level of $>$ 2.0 mmol/L.

MV setting assessments were performed every 4 hours by assigned respiratory therapists. Data collected included ventilator-set RR, native patient RR, V_t , peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), PS, $\bar{P}_{aw}$, and fraction of inspired oxygen (FiO₂). Patient-ventilator asynchrony assessments were also monitored every 4 hours. Parameters including ineffective efforts, double triggering, and auto-PEEP were assessed and recorded as present or non-present by observation of flow waveforms, while auto-triggering was determined by direct patient-ventilator assessment. In particular, auto-PEEP was determined present by the lack of return to baseline during the expiration phase of the flow-time waveform. A percentage of each parameter, present or non-present, was then developed during the duration of MV for either NAVA or SIMV-PRVC + PS modes.

Inotropic support included any combination of epinephrine, dopamine, and milrinone. Inotropes were weaned identically in both groups. No more than one inotrope was weaned at a time. Initially epinephrine was weaned by 0.01 μ g/kg/min every 2 hours tolerating a mean arterial pressure (MAP) $\geq$ fifth percentile of normal range per age of patient. After discontinuation of epinephrine, dopamine was weaned by 1 μ g/kg/min every 2 hours tolerating MAP $\geq$ fifth percentile of normal range per age of patient. All patients were extubated receiving milrinone. Milrinone was weaned 24 hours after extubation by decreasing the infusion by 50% and in 12 to 24 hours disconti-

nuing milrinone ensuring MAP $\geq$ the fifth percentile of normal range per age of patient.

For sedation and analgesia, a combination of midazolam and fentanyl as continuous infusions was administered. If a patient in either group had been on sedation or analgesia for $\geq$ 5 days, weaning by 10% of the current infusion doses occurred and if for $<$ 5 days, weaning by 20% of the current infusion doses was initiated. Weaning intervals occurred every 6 hours, alternating between each medication. Weaning continued if the patient tolerated a COMFORT scale score $<$ 17. Methadone and Ativan were added for a Withdrawal Assessment Tool – Version 1 (WAT-1) score $>$ 3.

Exploratory analysis of all study variables was performed to obtain descriptive statistics. Association between extubation success rate and mechanical ventilator modes was evaluated by Fisher's exact test, whereas, Chi-square test of independence was used for other categorical variables. Tests for normality indicated that data for continuous variables including age, weight, and secondary outcome variables were not normally distributed; therefore, Wilcoxon-Mann-Whitney test was used to examine differences between the intervention groups for the baseline characteristics and secondary outcome variables. Differences in $\bar{P}_{aw}$ pre- and post-weaning was assessed by the Student's *t*-test. Association between mode of MV and extubation success were examined by logistic regression analysis; odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Life table analysis was performed to obtain Kaplan-Meier (K-M) plots and to evaluate successful extubation rates at different time points (number of mechanical ventilator days). K-M plots were also used to evaluate median extubation rates at different time points according to the interventions (NAVA versus SIMV-PRVC). Hazard ratio (HR) and 95% CI were obtained from Cox proportional hazard models to evaluate associations between extubation rates and intervention for the duration of mechanical ventilator days and PICU days. All the analyses were conducted using SAS v9.4 and an α level of 0.05 was used for statistical significance.

Results

A total of 75 continuous mechanically ventilated patients were included in the study. Thirty-five patients were transitioned from SIMV-PRVC + PS to NAVA (prospective group), and 40 patients remained exclusively in the SIMV-PRVC + PS group (retrospective group) (**► Table 1**). Median age of study participants was 2 months (interquartile range [IQR] = 3.70), and 55% ($n = 41$) of patients were male. There was no significant difference in the age, weight, or gender between the study groups (**► Table 2**).

The NAVA group had median RACHS-1 score of 4 (IQR = 1.00), and the historical SIMV-PRVC + PS group had median (min, max) RACHS-1 score of 3 (IQR = 2). No statistically significant difference was observed in the RACHS-1 scores between both groups ($p = 0.06$), but a trend of higher RACHS-1 scores was found in the NAVA group. There was no significant difference between the NAVA and SIMV-PRVC + PS group for having a syndrome ($p = 0.93$). 14% ($n = 5$) of

Table 1 Congenital heart disease diagnosis in each intervention group

Congenital heart disease diagnosis	NAVA	SIMV-PRVC + PS
ALCAPA	2	1
Aortic arch hypoplasia	4	4
Aortic stenosis	1	0
AVC	8	10
DORV	1	2
Ebstein anomaly	1	0
HLHS	2	4
Pulmonary atresia	0	3
Shone's complex	1	0
TAPVR	4	3
TGV	6	5
TOF	3	8
Truncus arteriosus	2	0
Total patients	35	40
Patients who required ECMO	1	1

Abbreviations: ALCAPA, anomalous left coronary artery from the pulmonary artery; AVC, atrioventricular canal; DORV, double outlet right ventricle; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; NAVA, neurally adjusted ventilatory assist; PRVC, pressure-regulated volume controlled; PS, pressure support; RACHS-1, risk adjustment for congenital heart surgery; SIMV, synchronized intermittent mandatory ventilation; TAPVR, total anomalous pulmonary venous return; TGV, transposition of the great vessels; TOF, tetralogy of Fallot.

the NAVA group, and 15% ($n = 6$) of the patients in the SIMV-PRVC + PS group had either Trisomy 21 or Di George syndrome.

Analysis of the primary endpoint, extubation success rate, showed that 97.1% of patients in the NAVA group were successfully extubated on the initial attempt, whereas

among the SIMV-PRVC + PS group initial extubation success rate was 80.0% ($p = 0.03$) (►Table 3). Results of logistic regression analysis indicated that patients treated with NAVA were eight times more likely to have successful extubation on the first attempt (OR: 8.5, 95% CI: 1.01, 71.8).

Baseline ventilator settings between the two groups prior to conversion of one group into the NAVA mode for weaning or continuation in SIMV-PRVC + PS mode for weaning showed no significant difference in ventilator-set RR, V_t , PEEP, PS, or FiO_2 (►Table 4). At baseline, the group prior to being placed in NAVA mode had a significant higher $\bar{P}aw$ and PIP than the group that would remain in SIMV-PRVC + PS mode (►Table 4). Within an hour of initiation of weaning, the NAVA group had a significant reduction in PIP and $\bar{P}aw$ with constant delivered V_t when compared with the SIMV-PRVC + PS group. Immediately prior to the initial extubation attempts, both $\bar{P}aw$ and PIP were significantly lower despite similar delivered V_t 's in the NAVA group compared with SIMV-PRVC + PS group.

The onset of weaning in both groups showed no statistically significant difference; however, the NAVA group had a longer duration of MV support prior to weaning compared with the SIMV-PRVC + PS group (►Table 2). Despite this, patients in the NAVA group had significantly shorter median duration of total days on MV compared with the SIMV-PRVC + PS group (9.0 days versus 11.0 days; log-rank test $p = 0.0128$) (►Table 3). The K-M plot indicated that at 12 days, 77% of NAVA group patients were successfully extubated, versus 55% in the SIMV-PRVC + PS group (►Fig. 2). Similarly, 97% of patients in the NAVA group and 85% of the SIMV-PRVC + PS group had extubation by day 24 on MV.

Hazard ratio for the duration of ventilator days was significantly higher for NAVA group compared with the SIMV-PRVC + PS group (HR: 1.77, 95% CI: 1.09, 2.9), indicating significantly shorter duration of stay on mechanical ventilator for patients utilizing NAVA. Similarly, the median number of days in PICU among the NAVA group (9.0) was significantly less than those for the SIMV-PRVC + PS group (13.5) ($p < 0.0001$) (►Table 3). Results of the Cox proportional hazard model indicated that

Table 2 Baseline characteristics of the study participants ($n = 75$)

Characteristics	Overall median (IQR)	Intervention Median (IQR)		p -Value ^a
		NAVA $n = 35$	SIMV-PRVC + PS $n = 40$	
Age (mo)	2.0 (3.7)	1.0 (3.7)	2.0 (3.7)	0.96
Gender n (%)				
Female	34 (45.3)	16 (45.7)	18 (45.0)	0.95
Male	41 (54.7)	19 (54.3)	22 (55.0)	
Weight (kg)	4.3 (1.7)	4.3 (1.9)	4.3 (1.6)	0.82
RACHS-1	3.0 (1.0)	4.0 (1.0)	3.0 (2.0)	0.06
Days before weaning	5.0 (4.0)	6.0 (4.0)	4.5 (3.5)	0.11

Abbreviations: IQR, interquartile range; NAVA, neurally adjusted ventilatory assist; PRVC, pressure-regulated volume controlled; PS, pressure support; RACHS-1, risk adjustment for congenital heart surgery; SIMV, synchronized intermittent mandatory ventilation.

^aChi-square test of independence was used for gender. For all other variables, Wilcoxon-Mann-Whitney test was used.

Table 3 Study parameters by intervention groups ($n = 75$)

Characteristics	Overall median (IQR)	Intervention Median (IQR)		p-Value ^a
		NAVA $n = 35$	SIMV-PRVC + PS $n = 40$	
Days weaning	4.0 (4.0)	3.0 (1.0)	6.5 (4.0)	<0.0001
Days on dopamine	9.0 (7.0)	8.0 (4.0)	11.0 (8.0)	0.002
Days on epinephrine ^b	2.0 (3.0)	2.0 (2.0)	2.0 (3.0)	0.69
Days on milrinone	10.0 (7.0)	9.0 (5.0)	12.0 (8.0)	0.0002
Days on fentanyl	12.0 (8.0)	9.0 (5.0)	12.5 (7.0)	<0.0001
Days on midazolam	10.0 (6.0)	8.0 (4.0)	12.0 (7.0)	<0.0001
Total days of ventilation	10.0 (7.0)	9.0 (4.0)	11.0 (7.5)	0.032
PICU length of stay	12.0 (8.0)	9.0 (4.0)	13.5 (7.5)	<0.0001
Extubation success n (%)				
Yes	66	34 (97.1)	32 (80.0)	0.032
No	9	1 (2.9)	8 (20.0)	

Abbreviations: IQR, interquartile range; NAVA, neurally adjusted ventilatory assist; PICU, pediatric intensive care unit; PRVC, pressure-regulated volume controlled; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

^aFisher's exact test was used for association between extubation success and intervention, whereas for all other variables, Wilcoxon–Mann–Whitney test was used.

^bEpinephrine was received by 36 patients (19 in NAVA group and 17 in control group).

Table 4 Ventilation settings at different steps by intervention groups ($n = 75$)

Ventilation settings	Overall median (IQR)	Intervention Median (IQR)		p-Value ^a
		NAVA n = 35	SIMV-PRVC + PS n = 40	
Baseline				
RR (vent)	24.0 (4.0)	24.0 (5.0)	24.0 (2.0)	0.99
V _t (cc/kg)	6.2 (0.6)	6.4 (0.6)	6.0 (0.7)	0.15
PIP (cmH ₂ O)	26.0 (3.0)	26.0 (3.0)	24.5 (2.0)	0.006
PEEP (cmH ₂ O)	5.0 (1.0)	5.0 (1.0)	5.0 (1.0)	0.43
PS (cmH ₂ O)	10.0 (0.0)	10.0 (0.0)	10.0 (0.0)	0.17
P _{aw} (cmH ₂ O)	11.0 (3.0)	12.0 (2.0)	11.0 (3.0)	<0.0001
FiO ₂ (%)	40.0 (10.0)	40.0 (7.0)	40.0 (10.0)	0.23
Beginning of weaning				
V _t (cc/kg)	6.0 (0.5)	5.8 (0.7)	6.0 (0.7)	0.001
PIP (cmH ₂ O)	22.0 (6.0)	19.0 (2.0)	24.5 (2.0)	<0.0001
PEEP (cmH ₂ O)	5.0 (1.0)	5.0 (1.0)	5.0 (1.0)	0.43
P _{aw} (cmH ₂ O)	10.0 (2.0)	10.0 (2.0)	11.0 (3.0)	0.043
FiO ₂ (%)	40.0 (10.0)	40.0(7.0)	40.0 (10.0)	0.23
Before extubation				
V _t (cc/kg)	5.3 (0.6)	5.2 (0.5)	5.4 (0.5)	0.02
PIP (cmH ₂ O)	16.0 (4.0)	14.0 (3.0)	18.0 (2.0)	<0.0001
PEEP (cmH ₂ O)	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)	1.0
P _{aw} (cmH ₂ O)	9.0 (2.0)	9.0 (1.0)	10.0 (1.5)	0.0003
FiO ₂ (%)	25.0 (5.0)	25.0 (5.0)	25.0 (5.0)	0.84

Abbreviations: FiO₂, fraction of inspired oxygen; IQR, interquartile range; $\bar{P}_{aw}$, mean airway pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PS, pressure support; RR, respiratory rate; V_t , tidal volume.

^aWilcoxon–Mann–Whitney test was used to evaluate differences in ventilation settings between intervention groups.

Fig. 2 Kaplan-Meier plot for extubation rates and number of days on mechanical ventilator. NAVA, neurally adjusted ventilatory assist; SIMV, synchronized intermittent mandatory ventilation.

patients in the NAVA group were twice more likely to have less number of days in PICU as compared with patients in the SIMV-PRVC + PS group (HR: 2.49, 95% CI: 1.5, 4.07).

In our asynchrony assessment, 100% of patients in the NAVA group had $\leq 5\%$ ineffective efforts, while in the SIMV-PRVC + PS group 35% had $>5\%$ ineffective efforts. In the NAVA group, 100% of the patients had no documented double triggering or auto-triggering, while in the SIMV-PRVC + PS group double triggering and auto-triggering occurred 65% and 70% of the times assessed, respectively. In the NAVA group, 85.7% of patients had no documented occurrences of auto-PEEP. In contrast, 52.5% of SIMV-PRVC + PS group had documented occurrences of auto-PEEP episodes in greater than 10% of the assessments (**► Table 5**).

At baseline, there was no statistically significant difference in auto-PEEP incidence between patients to be weaned in the NAVA mode (31.4%) compared with those patients to be weaned in the SIMV-PRVC + PS group (30.0%). When patients were placed in the NAVA mode, and weaning was initiated, after 1-hour auto-PEEP incidence dropped to 5.7% measured in our assessments. In comparison, those weaned in SIMV-PRVC + PS had a 42.5% incidence in auto-PEEP occurrence measured 1 hour after initial weaning. Immediately prior to initial extubation attempts, the NAVA group had no patients demonstrating auto-PEEP, while 45% of the assessments in the SIMV-PRVC + PS group elicited evidence of auto-PEEP occurrence (**► Table 6**).

Baseline ABG analysis between the two groups prior to the placement in NAVA or continuation in SIMV-PRVC + PS

Table 5 Patient-ventilator asynchrony parameters by intervention groups ($n = 75$)

% of Times	Overall <i>n</i> (%)	Intervention <i>n</i> (%)		<i>p</i> -Value ^a
		NAVA <i>n</i> = 35	SIMV-PRVC + PS <i>n</i> = 40	
Ineffective efforts%				
0	37 (49.3)	31 (88.6)	6 (15.0)	<0.0001
1–5	24 (32.0)	4 (11.4)	20 (50.0)	
6–10	11 (14.7)	0	11 (27.5)	
11–15	3 (4.0)	0	3 (7.5)	
Auto-PEEP%				
0	33 (44.4)	30 (85.7)	3 (7.5)	<0.0001
1–5	8 (10.7)	4 (11.4)	4 (10.0)	
6–10	13 (17.3)	1 (2.9)	12 (30.0)	
11–15	14 (18.7)	0	14 (35.0)	
16–20	7 (9.3)	0	7 (17.5)	
Double triggering%				
0	49 (65.3)	35 (100.0)	14 (35.0)	<0.0001
1–5	23 (30.7)	0	23 (57.5)	
6–10	3 (4.0)	0	3 (7.5)	
Auto triggering%				
0	47 (62.7)	35 (100.0)	12 (30.0)	<0.0001
1–5	25 (33.3)	0	25 (62.5)	
6–10	3 (4.0)	0	3 (7.5)	

Abbreviations: NAVA, neurally adjusted ventilatory assist; PEEP, positive end expiratory pressure; PRVC, pressure-regulated volume controlled; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

^aFisher's exact test was used for association between asynchrony and intervention.

Table 6 Auto-PEEP at different steps by intervention groups ($n = 75$)

Auto-PEEP	Overall <i>n</i> (%)	Intervention <i>n</i> (%)		<i>p</i> -Value ^a
		NAVA <i>n</i> = 35	SIMV-PRVC + PS <i>n</i> = 40	
Baseline				
Yes	23 (30.7)	11 (31.4)	12 (30.0)	1.000
No	52 (69.3)	24 (68.6)	28 (70.0)	
First after weaning				
Yes	19 (25.5)	2 (5.7)	17 (42.5)	0.0003
No	56 (74.7)	33 (94.3)	23 (57.5)	
Before extubation				
Yes	18 (24.0)	0 (0.0)	18 (45.0)	<0.0001
No	57 (76.0)	35 (100.0)	22 (55.0)	

Abbreviations: NAVA, neurally adjusted ventilatory assist; PEEP, positive end expiratory pressure; PRVC, pressure-regulated volume controlled; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

^aFisher's exact test was used for association between asynchrony and intervention.

revealed no statistically significant difference in PaO_2 . At baseline, the group prior to being placed in NAVA mode demonstrated a significantly lower pH, a higher PaCO_2 , and higher arterial lactate level than the group that would remain in SIMV-PRVC + PS mode. One hour after the initiation of ventilator weaning, a significant increase in pH and PaO_2 and decrease in PaCO_2 in the NAVA group was observed compared with the SIMV-PRVC + PS group. Immediately prior to the initial extubation attempts, there were no significant difference between NAVA and SIMV-PRVC + PS groups in regards to pH, PaO_2 , PaCO_2 , and lactate levels; however, when ABGs were analyzed 1 hour after extubation, the NAVA group had significant increases in pH, PaO_2 , and a significant decrease in PaCO_2 and arterial lactate levels compared with the SIMV-PRVC + PS group (►Table 7).

Compared with the SIMV-PRVC + PS group, the NAVA group had a statistically significant shorter median duration of days on dopamine (8.0 vs. 11.0; $p = 0.002$) and milrinone (9.0 vs. 12.0; $p = 0.0002$). There was no significant difference in the median days on epinephrine between both groups ($p = 0.69$). The NAVA group demonstrated statistically significantly less median sedation days compared with the SIMV-PRVC + PS group for midazolam (8.0 versus 12.0; $p < 0.0001$) and for fentanyl (9.0 versus 12.5; $p < 0.0001$; ►Table 3).

Discussion

In this study, weaning MV with NAVA in postoperative CHD patients who required cardiopulmonary bypass and prolonged MV ≥ 96 hours was associated with earlier and greater initial extubation success when compared with weaning MV with SIMV-PRVC + PS. Patients weaned on NAVA also demonstrated less total days on MV, dopamine, milrinone, midazolam, and fentanyl; a significant reduction in $\bar{P}_{\text{aw}}$; and an overall shorter PICU LOS when compared with SIMV-PRVC + PS. To our knowledge, this is the first published comparison of NAVA versus SIMV-PRVC + PS describing extubation success rates in postoperative CHD patients.

Patients' reintubation rates utilizing MV after pediatric cardiac surgery range from 6 to 27% in existing literature.² Our institution demonstrated a 20% initial extubation failure rate in postoperative cardiac patients who required MV ≥ 96 hours. After implementation of NAVA for MV weaning, our extubation failure rate decreased to 2.9%. We postulate that improved patient-ventilator synchrony, breath to breath variability, diaphragmatic muscle conditioning, and lower $\bar{P}_{\text{aw}}$ in NAVA compared with SIMV-PRVC + PS benefits cardiac performance by minimizing respiratory muscle oxygen demands and cardiac workload, which attributed directly to our statistically significant improvement in initial extubation success rate.

NAVA minimizes patient-ventilator asynchrony: NAVA is different from other modes of MV as it utilizes Edi to control the timing and level of assist delivered to the patient independent of pneumatic means.^{11–14} Edi correlates with phrenic nerve impulses translated into diaphragmatic muscle action potentials which establishes shorter trigger delays and reduces response times of the ventilator.^{11–16} As 10 to 30% of a patient's total breathing work is used during the inspiratory effort to trigger the ventilator, reducing trigger delay directly correlates with decreased respiratory effort.^{14–16} By utilizing Edi, NAVA allows for immediate identification of triggering asynchrony which improves patient-ventilator synchrony by reducing triggering and cycling off delays.^{14–16} As improvement in patient-ventilator synchrony is associated with shorter weaning and duration of MV in infants and children, NAVA is directly beneficial to successful weaning in this patient population.^{17–19} In our study, NAVA was associated with a statistical and clinically significant decrease in the incidence of ineffective efforts, double triggering, auto-triggering, and auto-PEEP when compared with the SIMV-PRVC + PS group ($p < 0.0001$).

NAVA maximizes diaphragmatic muscle conditioning: MV > 72 hours leads to oxidative stress-induced proteolysis, which increases diaphragmatic atrophy and weakness precipitating difficulties in weaning patients from MV.^{20–22} NAVA's potential to improve diaphragmatic efficiency is

Table 7 Arterial blood gas analysis at different steps by intervention groups ($n = 75$)

Arterial blood gas	Overall median (IQR)	Intervention Median (IQR)		p-Value ^a
		NAVA <i>n</i> = 35	SIMV-PRVC + PS <i>n</i> = 40	
Baseline				
pH	7.4 (0.04)	7.4 (0.06)	7.4 (0.03)	0.047
PaO ₂ (mm Hg)	68.0 (13.0)	67.0 (8.0)	69.0 (14.0)	0.48
PaCO ₂ (mm Hg)	41.0 (5.0)	42.0 (4.0)	40.0 (4.0)	0.02
Lactate (mmol/L)	1.1 (0.5)	1.3 (0.6)	1.0 (0.3)	0.0003
Initial after weaning				
pH	7.4 (0.05)	7.4 (0.05)	7.4 (0.02)	<0.0001
PaO ₂ (mm Hg)	70.0 (12.0)	74.0 (8.0)	66.0 (12.0)	0.0008
PaCO ₂ (mm Hg)	41.0 (5.0)	40.0 (3.0)	43.5 (4.0)	<0.0001
Lactate (mmol/L)	1.2 (0.5)	1.2 (0.6)	1.1 (0.4)	0.97
Before extubation				
pH	7.39 (0.03)	7.4 (0.03)	7.4 (0.04)	0.97
PaO ₂ (mm Hg)	76.00 (12.00)	76.0 (10.0)	73.0 (12.0)	0.11
PaCO ₂ (mm Hg)	41.00 (3.00)	40.0 (3.0)	41.5 (2.5)	0.20
Lactate (mmol/L)	1.00 (0.20)	0.9 (0.2)	1.0 (0.25)	0.84
After extubation				
pH	7.4 (0.05)	7.4 (0.04)	7.4 (0.05)	<0.0001
PaO ₂ (mm Hg)	70.5 (10.0)	77.0 (10.0)	68.0 (9.0)	<0.0001
PaCO ₂ (mm Hg)	45.0 (5.0)	44.0 (3.0)	46.0 (3.0)	<0.0001
Lactate (mmol/L)	1.0 (0.3)	1.0 (0.2)	1.2 (0.4)	<0.0001

Abbreviations: ABG, arterial blood gas; IQR, interquartile range; NAVA, neurally adjusted ventilatory assist; PRVC, pressure-regulated volume controlled; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

^aWilcoxon–Mann–Whitney test was used to evaluate ABG differences between intervention groups.

based on the continuous coupling between the patient's neural output and ventilator assistance, which leads to breathing pattern variability.^{22,23} In NAVA, this variability is achieved as the magnitude of delivered pressure is the product of the Edi amplitude and the user-controlled NAVA level.¹¹ As breathing pattern variability indicates an adequate balance between respiratory muscle load and ventilatory assistance, NAVA prevents much of the diaphragmatic atrophy observed in conventional MV.^{24–26} We believe that improved diaphragmatic muscle conditioning resulting from the utilization of NAVA facilitated weaning and contributed toward earlier extubation from prolonged MV in our study.

NAVA minimizes oxygen consumption requirements of respiratory muscles: Mechanical ventilator weaning and successfully extubating a postoperative CHD patient after prolonged MV requires the clinician to ensure the patient's cardiac performance is capable of delivering oxygen to meet tissue metabolic needs of the diaphragm, respiratory muscles, and end organs. At rest, oxygen consumption of respiratory muscles is 1 to 2% of basal total body oxygen consumption and as work of breathing increases, oxygen consumption of respiratory muscles increases hyperbolically.²⁷ In a study of patients being weaned from MV, 24% of the total body oxygen delivery was consumed by respiratory muscles and was >50% in some patients.^{27,28} Based on

these data, a patient with increased work of breathing and patient–ventilator asynchrony occurring during MV weaning with a deconditioned heart can lead to cardiogenic shock and ultimately extubation failure. In fact, poor cardiac function has been demonstrated to be the most common cause of failed extubation in postoperative patients who underwent CHD surgery.¹ Ventilation with NAVA enhances myocardial function by improving patient–ventilator synchrony leading to decreased diaphragmatic work and minimizing patient stress thereby reducing oxygen delivery demands on the myocardium.²⁹

NAVA minimizes dynamic hyperinflation and decreases $\bar{P}_{aw}$: As native respiratory rates increase during mechanical ventilatory weaning in infants and children, dynamic hyperinflation risks increase. By means of coupling Edi to the clinician-determined NAVA level, NAVA decreases the risk of dynamic hyperinflation by preventing the continued delivery of assist breaths in the neural expiratory phase seen in conventional MV.¹⁰ Dynamic hyperinflation promotes an unnecessary increase in $\bar{P}_{aw}$, which may lead to increased right atrial pressure, decreased right atrial filling, increased transpulmonary pressures, and increased right ventricular afterload.

In our study, there was a significant 20.12% reduction in $\bar{P}_{aw}$ in the NAVA group from immediate pre- to post-weaning

(12.37 to 9.89 cmH₂O; $p < 0.0001$). Among the SIMV-PRVC + PS group, no difference was observed in $\bar{P}_{aw}$ before and after weaning initiation (–Table 4). Although there was a statistically significant decrease in delivered V_t while comparing NAVA to SIMV-PRVC + PS (–Table 4), this was not clinically significant; however, there was a statistically and clinically significant reduction in PIP in the NAVA group which led to a lower $\bar{P}_{aw}$ when compared with the SIMV-PRVC + PS group. NAVA's synchronized ventilation allows for a more patient-determined inspiratory time and minimizes auto-PEEP and asynchrony, which likely improves functional residual capacity and dynamic compliance of the lungs resulting in lower PIP with decreased $\bar{P}_{aw}$. These effects would seem to promote decreased oxygen consumption by respiratory muscles during MV weaning while enhancing preload and myocardial function and decreasing pulmonary vascular resistance.

Given the morbidity of prolonged MV and the consequences and increased mortality risks of failed extubation, the benefits of NAVA in improving patient-ventilator synchrony, diaphragmatic efficiency, and lower $\bar{P}_{aw}$ exposure improve cardiac performance, which makes it the ideal mode of ventilation for ventilator weaning in this patient population.

Pediatric patients who failed extubation after cardiac surgery have a 65% increased mortality compared with successfully extubated patients.³ Patients with high inotropic support requirements, low PaO₂, and prolonged sedation exposure prior to extubation are especially at risk for extubation failure.¹ Our study patients had an increased risk of extubation failure due to prolonged MV, inotropic support, and sedation. Omitting respiratory failure due to stridor, all patients in the SIMV-PRVC + PS group who failed extubation had a suspected etiology due to cardiac dysfunction manifested as tachycardia, decreased urine output, and lactic acidosis with only minimal or no increase in PaCO₂ levels. The mean lactic acid level taken within 1 hour after these failed extubation attempts was 3.6 mmol/L (median 3.7 mmol/L). Interestingly, the one patient who failed extubation in the NAVA group elicited signs of lactic acidosis repeatedly during weaning, which prohibited extubation attempts and went for elective tracheostomy.

Our study demonstrated a significant reduction in days on sedation and analgesics in the NAVA group compared with SIMV-PRVC + PS group. NAVA's ability to reduce patient-ventilator asynchrony and increase breath-to-breath variability decreases patient distress and results in a notable reduction in sedatives and analgesics.^{30,31} Reducing the dose of sedatives and analgesics has been demonstrated to decrease the duration of MV.³²

We postulated that NAVA facilitates improved cardiac performance and lessens myocardial oxygen demands. NAVA's lower $\bar{P}_{aw}$ enhances right atrial filling and decreases ventricular afterload. These effects likely facilitated dopamine and milrinone infusions being weaned more rapidly in the NAVA group compared with the SIMV-PRVC + PS group. The weaning of epinephrine showed no statistically significant difference between the two groups. This result may be due to only 54.3% of NAVA patients and 42.5% of SIMV-PRVC + PS patients required epinephrine and also due to our standardized PICU inotropic weaning protocol, which recommends initial wean-

ing and discontinuation epinephrine before beginning dopamine and milrinone weaning.

Weaning is estimated to represent 40 to 50% of the duration of MV.³³ Our results showed implementing NAVA in weaning patients from MV decreased the total median ventilator days by 2 and median PICU LOS by 4.5 days compared with the SIMV-PRVC + PS group. NAVA proved to be a suitable mode for MV weaning and exhibited no technical problems with its utilization. Of 35 patients studied in NAVA, none had technical issues with placement of the Edi catheter or accurate Edi monitoring. We elected to omit patients who failed extubation due to stridor (NAVA: one patient, SIMV-PRVC + PS: two patients). Nonetheless, while including these patients in primary and secondary outcome variable analysis, the study results remained unchanged.

Although the NAVA group trended toward higher RACHS-1 scores than did the SIMV-PRVC + PS group, the SIMV-PRVC + PS group had longer days on milrinone, dopamine, fentanyl, and midazolam. This could potentially suggest that despite lower RACHS-1 scores, the SIMV-PRVC + PS group was more clinically ill than was the NAVA group. However, the duration of MV is usually directly correlated to the length of time on inotropic and sedative/analgesic support. Both NAVA and SIMV-PRVC + PS groups were weaned identically while the SIMV-PRVC + PS group began weaning by a median of 1.5 days earlier than the NAVA group, while the NAVA group still had statistically significant less total MV days. This would suggest that the SIMV-PRVC + PS group may have been less ill than was the NAVA group and the implementation of NAVA facilitated improved cardiopulmonary function and more efficient MV weaning.

This single-center pilot study initially utilized a prospective group of patients who received NAVA, and then retrospectively reviewed patients weaned in standard MV using SIMV-PRVC + PS. This study design had several limitations. The retrospective nature of studying the SIMV-PRVC + PS patients rendered it susceptible to study design flaws and bias. However, the time frame between both study groups was consecutive, and cohorts are matched well for the commonest possible confounding variables. Thus, potential biases have been reduced, although this does not ensure the study to be free from any selection bias. Based on these limitations, our results may be unique to our institution and our findings cannot be definite in the absence of a well-powered randomized, prospective trial. Nonetheless, both NAVA and SIMV-PRVC + PS groups had identical weaning parameters and intervals from a standardized PICU MV weaning protocol that utilized objective data including ABGs, lactic acid levels, inspired oxygen requirements, and native respiratory rate assessments. Additionally, our standardized PICU protocols for MV weaning, inotropic agent weaning, and weaning of analgesics and sedatives did not change over the study duration. Moreover, there was no significant difference between the NAVA and SIMV-PRVC + PS groups in regards to fentanyl or midazolam infusions at baseline prior to weaning and initially after weaning MV. The NAVA group had significantly decreased fentanyl and midazolam infusions compared with the SIMV-PRVC + PS group

Table 8 Analgesics and sedatives at different steps by intervention groups ($n = 75$)

Medication ^a	Overall median (IQR)	Intervention Median (IQR)		<i>p</i> -Value ^b
		NAVA <i>n</i> = 35	SIMV-PRVC + PS <i>n</i> = 40	
Baseline				
Fentanyl (µg/kg/h)	1.5 (0.5)	1.5 (0.5)	1.75 (0.5)	0.46
Midazolam (mg/kg/h)	0.1 (0.05)	0.1 (0.05)	0.125 (0.05)	0.62
First after weaning				
Fentanyl (µg/kg/h)	1.5 (0.25)	1.5 (0.0)	1.5 (0.25)	0.09
Midazolam (mg/kg/h)	0.1 (0.075)	0.1 (0.05)	0.1 (0.05)	0.47
Before extubation				
Fentanyl (µg/kg/h)	0.75 (0.5)	0.5 (0.5)	0.88 (0.5)	0.033
Midazolam (mg/kg/h)	0.025 (0.05)	0.0 (0.05)	0.05 (0.05)	0.082
After extubation				
Fentanyl (µg/kg/h)	0.75 (0.5)	0.5 (0.5)	0.88 (0.5)	0.033
Midazolam (mg/kg/h)	0.025 (0.05)	0.0 (0.5)	0.05 (0.05)	0.082

Abbreviations: IQR, interquartile range; NAVA, neurally adjusted ventilatory assist; PRVC, pressure-regulated volume controlled; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation.

^aDosage of fentanyl is in $\mu\text{g/kg/h}$ and midazolam in mg/kg/h .

^bWilcoxon–Mann–Whitney test was used to evaluate differences in ventilation settings between intervention groups.

immediately prior to extubation and 1 hour after extubation (► **Table 8**). These differences were not clinically relevant enough to lead to hypoventilation or apnea and promote extubation failure in the SIMV-PRVC + PS group. NAVA minimizing patient–ventilator asynchrony likely contributed to a quicker weaning of fentanyl and midazolam.

Measurements of patient–ventilator asynchrony (ineffective efforts, double triggering, auto-triggering, and auto-PEEP) were limited to respiratory therapist documentation of “present” or “not present,” which allowed only for calculations of a percentage of occurrences per assessments made and may not reflect the actual duration of patient–ventilator asynchrony during MV. Another limitation was that auto-PEEP was not directly measured by expiratory-hold maneuvers, which did not allow for numerical documentation of degree of auto-PEEP.

In our study, cardiac performance was not determined by serial echocardiograms or left atrial pressure measurements. We elected to utilize serum arterial lactate levels as an objective numerical measurement of end organ perfusion and a surrogate measurement of cardiac performance. As the most common cause of extubation failure in postoperative CHD patients is poor cardiac performance, future randomized trials should consider more direct measurements of cardiac function.

Conclusion

In postoperative CHD patients who required conventional MV for a minimum of 96 hours postoperatively, initiation of NAVA for MV weaning when compared with SIMV-PRVC + PS was associated with a greater initial extubation success rate, fewer days on MV, dopamine, milrinone, fentanyl, and midazolam, a decrease in $\bar{P}_{\text{aw}}$, and overall shorter PICU LOS.

These findings support consideration of initiating prospective, randomized controlled trials comparing NAVA and conventional MV modes in postoperative CHD patients. NAVA should be considered as a mechanical ventilator weaning strategy in postoperative CHD patients.

Conflict of Interest

None.

Acknowledgment

We would like to acknowledge Rohan Thukaram. We thank Rohan for his assistance in data collection and table development.

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