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Hemodynamic Effects of a High-Frequency Oscillatory Ventilation Open-Lung Strategy in Critically Ill Children With Acquired or Congenital Cardiac Disease

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OBJECTIVES: To study the hemodynamic consequences of an open-lung high-frequency oscillatory ventilation (HFOV) strategy in patients with an underlying cardiac anomaly with or without intracardiac shunt or primary pulmonary hypertension with severe lung injury.

DESIGN: Secondary analysis of prospectively collected data.

SETTING: Medical-surgical PICU.

PATIENTS: Children less than 18 years old with cardiac anomalies (± intracardiac shunt) or primary pulmonary hypertension.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Data from 52 subjects were analyzed, of whom 39 of 52 with cardiac anomaly (23/39 with intracardiac shunt) and 13 of 52 with primary pulmonary hypertension. Fourteen patients were admitted postoperatively, and 26 patients were admitted with acute respiratory failure. Five subjects (9.6%) were canulated for ECMO (of whom four for worsening respiratory status). Ten patients (19.2%) died during PICU stay. Median conventional mechanical ventilation settings prior to HFOV were peak inspiratory pressure 30 cm H_2O (27–33 cm H_2O), positive end-expiratory pressure 8 cm H_2O (6–10 cm H_2O), and F_{IO_2} 0.72 (0.56–0.94). After transitioning to HFOV, there was no negative effect on mean arterial blood pressure, central venous pressure, or arterial lactate. Heart rate decreased significantly over time ($p < 0.0001$), without group differences. The percentage of subjects receiving a fluid bolus decreased over time ($p = 0.003$), especially in those with primary pulmonary hypertension ($p = 0.0155$) and without intracardiac shunt ($p = 0.0328$). There were no significant differences in the cumulative number of daily boluses over time. Vasoactive Infusion Score did not increase over time. P_{aCO_2} decreased ($p < 0.0002$) and arterial pH significantly improved ($p < 0.0001$) over time in the whole cohort. Neuromuscular blocking agents were used in all subjects switched to HFOV. Daily cumulative sedative doses were unchanged, and no clinically apparent barotrauma was found.

CONCLUSIONS: No negative hemodynamic consequences occurred with an individualized, physiology-based open-lung HFOV approach in patients with cardiac anomalies or primary pulmonary hypertension suffering from severe lung injury.

KEY WORDS: acute lung injury; cardiac pediatric patients; congenital heart disease; high-frequency oscillatory ventilation; oxygenation; primary pulmonary hypertension

Respiratory complications due to heart failure, infection, atelectasis, and intrapulmonary fluid are not uncommon in mechanically ventilated patients with cardiac anomalies or pulmonary hypertension

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RESEARCH IN CONTEXT

- To avoid harmful ventilator settings in children, high-frequency oscillatory ventilation (HFOV) can be used in children.
- HFOV is often considered to be relatively contraindicated in children with cardiac anomalies or primary pulmonary hypertension as it is presumed that the high intrathoracic pressures associated with HFOV may aggravate right ventricular dysfunction through an increased afterload and decrease cardiac output.
- In our cohort, there were no negative hemodynamic consequences of an individualized, physiology-based open-lung HFOV approach in pediatric patients with a congenital or acquired cardiac anomaly or pulmonary hypertension with severe lung injury.

(1, 2). This may lead to significant decreases in lung compliance and end-expiratory lung volume (EELV), causing impairments in gas exchange. Alveolar collapse increases pulmonary vascular resistance (PVR), negatively affecting right ventricular (RV) function. These changes may necessitate the use of higher levels of inspiratory and positive end-expiratory pressures (PEEPs). However, higher inspiratory pressures and larger tidal volumes (Vts) may contribute to ventilator-induced lung injury (VILI) and should, therefore, be avoided. In addition, high levels of PEEP may impede venous return, thereby further compromising cardiac function.

One potential benefit of using high-frequency oscillatory ventilation (HFOV) in children with cardiac anomalies and pulmonary hypertension is that HFOV delivers a small Vt (1–2 mL/kg) and maintains EELV through the delivery of a continuous distending pressure (CDP). This combination targets two major components of VILI, specifically atelectrauma and volutrauma (3–6). However, HFOV is often seen as relatively contraindicated in this patient group because higher intrathoracic pressures are generally delivered when compared with conventional mechanical ventilation (CMV). Theoretically, these higher intrathoracic pressures may increase RV afterload and, thus, generate a more negative effect on RV function. It can also be argued that HFOV is less challenging to ventilate at the level of EELV where the PVR is the lowest, but this does require a lung volume optimization maneuver (LVOM) after transitioning to HFOV.

Previously, in noncardiac patients, we demonstrated the safety and feasibility of an open-lung HFOV strategy through an initial incremental-decremental CDP titration maneuver, a high frequency (8–15 Hz), and high set power to initially target a proximal pressure amplitude ($\Delta P_{proximal}$) of 70–90 cm H_2O, irrespective of age or weight (7, 8). Some pediatric data suggest that HFOV may also be safe and feasible in cardiac patients, but the HFOV strategy reported did not use an open-lung approach (9, 10). We, therefore, sought to explore the hemodynamic consequences of this open-lung approach in cardiac patients with and without intracardiac shunt and in patients with primary pulmonary hypertension by studying the level and time course hemodynamics variables and the use of inhaled nitric oxide, vasoactive medications, sedative-analgesic, and neuromuscular blocking agents (NMBAs) in 24 hours before and during the first 3 days of HFOV.

MATERIALS AND METHODS

Study Design and Setting

This study was designed as a secondary analysis of prospectively collected data between January 2013 and July 2020 in our mixed medical-surgical tertiary PICU. The Institutional Review Board (IRB) of the hospital (Medisch Ethische Toetsing Commissie [METC], Universitair Medisch Centrum Groningen [UMCG]) approved the study and waived the need for informed consent in agreement with Dutch legislation (METC, UMCG, 10-6-2016, IRB number: 2016/235). Procedures were followed with the ethical standards of the responsible committee and the Helsinki declaration.

Patients

Subjects younger than 18 years old with underlying congenital or acquired cardiac anomalies or cardiac dysfunction and/or primary pulmonary hypertension not related to cardiac anomalies, who were managed with HFOV during their PICU admission were included. The decision to use HFOV was at the discretion

of the attending physician, although our unit has a clinical algorithm guiding the initiation and titration of HFOV (8). Briefly, HFOV is initiated in patients when peak inspiratory pressure (PIP) greater than or equal to 28–32 cm H_2O, PEEP greater than or equal to 8 cm H_2O, FIO_2 greater than or equal to 0.60, and worsening oxygenation index (OI) on three consecutive measurements (each ~ 1 hr apart). Children with a gestational age less than 40 weeks were excluded.

Data Collection

Demographic, physiologic, laboratory data, and use of medication and fluids were manually extracted from each subject's medical record. Disease severity was assessed by the Pediatric Risk of Mortality III 24-hour score. Transcutaneous measured oxygen saturation (SpO_2), heart rate, invasively measured arterial systolic, diastolic, and mean pressure (mABP), and, if a central catheter was in situ, central venous pressure (CVP) were continuously monitored using a Phillips MP70 Intellivue monitor (Philips Medical Systems, Best, the Netherlands) and documented hourly by the bedside nurse. Arterial blood samples were taken to measure arterial pH (pHa), PaO_2, $PaCO_2$, and lactate at least every 6 hours in the early phase after transition to HFOV at the discretion of the attending physician (Radiometer, Brønshøj, Denmark). Ventilator variables were documented hourly. CMV variables included PIP, mean airway pressure (mPaw), positive PEEP, expiratory Vt (Vte), and FIO_2. Vte was measured near the Y-piece of the endotracheal tube in patients less than 10 kg (VarFlex, Vyaire, Yorba Linda, CA). For HFOV, these included mPaw, frequency (F), $\Delta P_{proximal}$, and FIO_2. Using concurrent blood gas and ventilator data, the PaO_2/FIO_2 ratio and OI (mPaw × FIO_2 × 100)/ PaO_2) were calculated. We quantified the number of daily fluid boluses. To describe the need for vasoactive support, the daily Vasoactive Inotrope Score (VIS) was calculated (11). The use of NMBAs and cumulative dosages of sedatives and analgesic medications were documented daily. For comparison, all sedatives were expressed as equipotential opioid or benzodiazepine dosages, respectively methadone and lorazepam (12, 13).

CMV Protocol

Patients with acute lung injury were managed with a unit-based protocol, prescribing a time-cycled, pressure limited ventilation mode (pressure control [PC]/assist control in infants < 12 mo or PC/synchronized intermittent mandatory ventilation [SIMV] in older children) (8). Briefly, we target PIP less than 30 cm H_2O (< 32 cm H_2O in patients with clinically suspected decreased chest wall compliance) and Vte between 5 and 8 mL/kg actual bodyweight. Initial PEEP was at the discretion of the attending physician. Our protocol does not include the Acute Respiratory Distress Syndrome Network PEEP/FIO_2 grid or LVOMs, such as staircase PEEP titration or sustained inflation during CMV (14). Mandatory breath rate is dictated by underlying respiratory mechanics and age to maintain pHa within target range; the flow-time scalar is carefully observed to prevent auto-PEEP. The maximum inspiration:expiration ratio is 1:1. The amount of pressure support in the PC/SIMV mode is calculated by PIP minus PEEP. We use passive humidification by means of a heat-moisture exchanger in all patients on CMV (Gibeck; Teleflex Medical, Vianen, the Netherlands) and active humidification during HFOV.

HFOV Strategy

Patients are oscillated per a unit-based protocol which defines HFOV criteria, the LVOM, and titration of HFOV settings according to the evolving physiologic needs of the patient as described previously (8). Initial oscillator settings irrespective of age or bodyweight included frequency 10–12 Hz, mPaw 3–5 cm H_2O above mPaw on CMV, power setting targeted at $\Delta P_{proximal}$ 70–90 cm H_2O, inspiratory time 33%, and bias flow 20–40 L/min. The LVOM is an individualized staircase, incremental-decremental titration and is performed immediately after transitioning to HFOV using the SensorMedics 3100A/B oscillator (SensorMedics, Yorba Linda, CA). The mPaw is increased by 2 cm H_2O every 3–5 minutes until the onset of lung recruitment is identified by increasing SpO_2 ($mPaw_{recruitment}$). This stepwise increase of the mPaw is continued until no further improvement in oxygenation and/or sudden decrease in mean arterial blood pressure (mABP) occurs during two consecutive increments identifying the onset of overdistention of the lung ($mPaw_{hyperinflation}$). Subsequently, mPaw was stepwise decreased every 3–5 minutes by 2 cm H_2O until the SpO_2 decreased again during two consecutive increments indicating lung derecruitment ($mPaw_{derecruitment}$) or when other clinical situations gave rise to stop decreasing the mPaw. The

LVOM was repeated to $mPaw_{hyperinflation}$ with setting the "optimal" mPaw 2 cm H_2O above the $mPaw_{derecruitment}$. During the LVOM, power remained constant, and frequency was only decreased in patients with severe increasing hypercapnia resulting in acidosis (pH < 7.25), so that $\Delta P_{proximal}$ could reflect changes in compliance. During the HFOV course, the mPaw is actively decreased if FIO_2 less than 0.40–0.50; frequency is decreased when pH is below target range and increased when above. Failure of HFOV is defined by a worsening of OI despite "maximum" HFOV settings or the inability to wean either the mPaw or the FIO_2 over the first 24 hours following the start of HFOV. Subsequent cannulation for extracorporeal life support for pulmonary support is considered in case of HFOV failure.

After stabilization of the patient, we use a daily CDP titration to determine the level of CDP that is necessary to maintain adequate oxygenation. This titration is similar to the LVOM described above, but it starts with the decremental phase instead of the incremental phase.

Supportive Care and Targets

FIO_2 is adjusted to maintain SpO_2 in range depending on the presence of absence of an intracardiac shunt. In general, SpO_2 is maintained 88–92% in patients without an intracardiac shunt, for patients with intracardiac shunt 65–80%, and for patients with pulmonary hypertension 92–97%. Permissive hypercapnia is allowed targeting pH greater than 7.20 irrespective of PCO_2; in pulmonary hypertension patients, pH greater than 7.40 is targeted. Patients are ventilated in supine position. In all patients, continuous IV infusion of analgesic-sedative drugs, including fentanyl, morphine, and midazolam, is titrated by the bedside nurse (based on bispectral index value, heart rate and pupils for patients on NMBA, and Comfort B Score for nonparalyzed patients) (15). Hemodynamic management of patients included targeting negative fluid balance via fluid restriction (±75% of normal fluid intake) and, if necessary, diuretic therapy (continuous IV administration of furosemide).

Study Endpoints

The primary endpoints of this study were the level and trajectory of hemodynamic variables, number of fluid boluses, and Vasoactive Infusion Score. Secondary endpoints included daily cumulative dosage of sedative-analgesics, use of NMBA, and metrics for oxygenation and ventilation.

Statistical Analysis

To describe the study population, we stratified the cohort into patients admitted postoperative after cardiac surgery, nonpostoperative admissions, and those with primary pulmonary hypertension. For analytical purposes, we stratified to cohort based on their cardiac pathology: cardiac anomaly with intracardiac shunt, cardiac anomaly without intracardiac shunt, and primary pulmonary hypertension (PPH). The reason for doing this was the differences in oxygenation variables between patients with and without intracardiac shunt as the oxygenation response is traditionally being used when titrating HFOV and baseline oxygenation values are different between patients with and without intracardiac shunt. Absolute numbers are presented as a percentage of total, and continuous data as median and 25–75% interquartile range when assumptions of normality are not satisfied. Comparisons between patients with cardiac anomaly with intracardiac shunt, cardiac anomaly without intracardiac shunt, and PPH were made using the Kruskal-Wallis test (for continuous data) and the chi-square test (for categorical data) using GraphPad Version 9 (GraphPad Software, San Diego, CA). To analyze the interaction between time and group stratum, mixed effects analyses were performed using GraphPad Version 9 (GraphPad Software, San Diego, CA). *p* values less than 0.05 were accepted as statistically significant.

RESULTS

Patient Characteristics

Fifty-two subjects were included in this study, of whom 23 of 52 had a cardiac anomaly with an intracardiac shunt, 16/52 a cardiac anomaly without an intracardiac shunt, and 13 of 52 had PPH. Fourteen patients were admitted postoperatively after cardiac surgery, and 26 patients were admitted with acute respiratory failure from a pulmonary infection. There were no statistically significant differences in baseline characteristics between the three groups (**Table 1**; and **eTable 1**, http://links.lww.com/PCC/C338).

Median CMV settings prior to HFOV were PIP 30 cm H_2O (27–33 cm H_2O), PEEP 8 cm H_2O (6–10 cm H2O), and FIO_2 0.72 (0.560–0.94). No significant differences were found in CMV settings prior to HFOV between the three groups or the time on CMV before HFOV. Children diagnosed with PPH had a significant longer time on HFOV compared with subjects without an intracardiac shunt (p = 0.0200). Five patients (9.6%) were canulated for ECMO: one had PPH, one without intracardiac shunt, and three with an intracardiac shunt. In four of them, ECMO was initiated because of worsening respiratory status. One patient was cannulated as bridge to operative correction. Total ventilation time and length of PICU stay were comparable among the three groups. Ten patients (19.2%) died during their PICU stay. In nine of them, treatment was redirected based on underlying disorder (e.g., refractory PPH [n = 5] or cardiac failure with multiple organ failure [n = 4]). In one patient, treatment was withdrawn because futility.

Effect on Hemodynamics

For the whole cohort, we did not observe a negative effect over time on mABP, CVP, or arterial lactate among patients with cardiac anomaly with intracardiac shunt, cardiac anomaly without intracardiac shunt, and PPH (**Fig. 1**).

HR decreased significantly over time ($p < 0.0001$), without group differences. The percentage of subjects receiving a fluid bolus also decreased over time (p = 0.0208), especially in those with PPH (p = 0.0155) and without intracardiac shunt (p = 0.0328). There were no significant differences in the cumulative number of daily boluses over time. The percentage of subjects who required vasoactive support was stable over time, except for the PPH group (p = 0.0366) (**Fig. 2**). No significant increase in VIS was found over time in subjects who required vasoactive support (Fig. 2).

Effect on Metrics for Oxygenation and Ventilation

Oscillator settings over time stratified by diagnosis are graphically depicted in **eFigure 1** (http://links.lww.com/PCC/C338). FIO_2 decreased over time ($p < 0.0001$) without a significant difference between the three groups (**eFig. 2**, http://links.lww.com/PCC/C338). There were no significant differences over time in the PaO_2/FIO_2 ratio and OI over the first 3 days. $PaCO_2$ also decreased ($p < 0.0002$), and pH significantly improved ($p < 0.0001$) over time during the first 3 days on HFOV (**eFig. 3**, http://links.lww.com/PCC/C338).

Use of Sedative-Analgesics and NMBA

All subjects were on NMBA before switching to HFOV, and this percentage decreased significantly over time ($p < 0.0001$). Equipotent dosage of lorazepam and methadone dosage remained stable over time (**Fig. 3**).

AT THE BEDSIDE

- An open-lung HFOV strategy does not lead to hemodynamic compromise.
- Use of high, age-independent frequencies allows for adequate ventilation.
- HFOV can be considered in cardiac patients with oxygenation, and ventilation targets cannot be maintained with safe conventional mechanical ventilation.

DISCUSSION

To the best of our knowledge, this is the first study reporting an individualized, physiology-based open-lung approach of HFOV in pediatric cardiac and PPH patients. We showed that such an approach, together with a high F and high initial $\Delta P_{proximal}$ to deliver the smallest stroke volume, did not negatively affect hemodynamic variables in critically ill children with cardiac disorders with or without intracardiac shunt or those with PPH. These findings are in line with our previous observations noncardiac patients (8).

HFOV is often considered to be contraindicated in children with RV impairment or PH as it is feared that the high intrathoracic pressures associated with HFOV may aggravate RV dysfunction through an increased RV afterload. Although higher intrathoracic pressures undoubtfully may increase RV afterload, PVR is the main determinant of RV afterload and is directly affected by changes in lung volume (16). PVR raises at both extremes of lung volume. The lowest PVR at the

TABLE 1.

Study Population Characteristics and Last Ventilator Settings Prior to High-Frequency Oscillatory Ventilation

Variable	Intracardiac Shunt ($n = 23$)	No Intracardiac Shunt ($n = 16$)	Primary Pulmonary Hypertension ($n = 13$)	p
Age (mo)	5.0 (3.0–8.0)	7.5 (1.8–32.8)	9.0 (3.5–12.5)	0.3338
0–6 (%)	56.5	37.5	46.2	
7–12 (%)	34.8	25.0	30.8	
≥ 13 (%)	8.7	37.5	23.1	
Male (%)	69.6	56.3	38.5	0.6530
Weight (kg)	5.7 (5.2–7.0)	8.2 (4.8–12.4)	6.9 (4.4–8.3)	0.1218
Pediatric Risk of Mortality-III 24 hr	4.0 (3.0–6.0)	2.5 (1.0–4.8)	5 (0.5–6.5)	0.2493
Admission diagnosis (%)				
Pulmonary infection	60.9	31.3	69.2	
Postoperative	21.7	43.8	0	
Circulatory failure caused by cardiac diagnosis	8.7	6.3	0	
Pulmonary hypertension	0	0	30.8	
Cardiomyopathy	0	6.3	0	
Myocarditis	0	6.3	0	
Sepsis	4.3	6.3	0	
Pulmonary hemorrhage	4.3	0	0	
Inhaled nitric oxide (%)	60.9	31.3	100	0.0006*
PICU stay (d)	27 (13–44)	17 (10–32)	24 (16–46)	0.5080
Time on conventional mechanical ventilation before start HFOV (hr)	28 (9–48)	50 (15–165)	4 (3–35)	0.0956
Total length of HFOV (hr)	97 (64–169)	101 (44–144)	192 (91–302)	0.0200[a]
Total length of ventilation (hr)	450 (255–893)	265 (194–571)	376 (221–525)	0.3673
Switch to extracorporeal life support from HFOV (%)	13.0	6.3	7.7	0.8288
PICU mortality (%)	21.7	12.5	23.1	0.7105
Last ventilator settings and ventilation variables on conventional mechanical ventilation before switch to HFOV				
Peak inspiratory pressure (cm H_2O)	29 (27–32)	31 (28–35)	31 (26–37)	0.2813
Mean airway pressure (cm H_2O)	17 (15–20)	17 (17–20)	17 (14–21)	0.7857
Positive end-expiratory pressure (cm H_2O)	8 (6–10)	9 (8–12)	8 (6–10)	0.0792
Expiratory tidal volume (mL/kg)	7.1(5.8–10.1)	6.3 (4.9–6.9)	7.4 (6.2–8.4)	0.0743
F_{IO_2} (fraction)	0.85 (0.50–0.96)	0.60 (0.4–0.91)	0.72 (0.61–0.82)	0.5882
C_{O_2} (mmHg)	53 (40–67)	54 (44–66)	53 (44–72)	0.9474
pH	7.28 (7.21–7.42)	7.38 (7.24–7.42)	7.39 (7.21–7.44)	0.8075

HFOV = high-frequency oscillatory ventilation.

[a]$p < 0.05$.

Data depicted as median (25–75 interquartile range) or percentage (% of total).

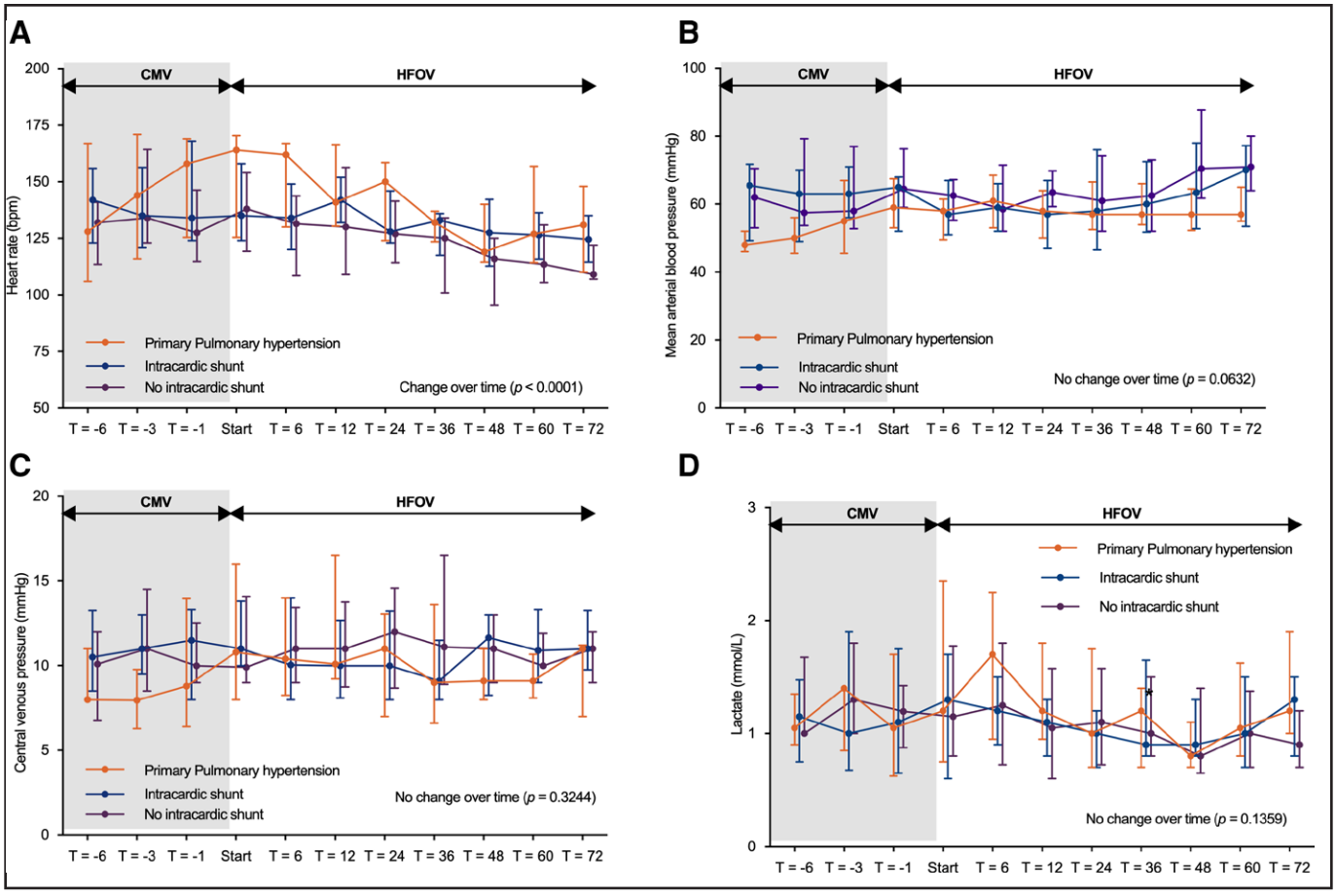

Figure 1. Level and time course of hemodynamic variables including heart rate (**A**), mean arterial blood pressure (**B**), central venous pressure (**C**), and blood lactate (**D**) during the last 6 hr of conventional mechanical ventilation and the subsequent first 72 hr of high-frequency oscillatory ventilation, stratified by underlying diagnosis (with intracardiac shunt [$n = 23$], without intracardiac shunt [$n = 16$], and with primary pulmonary hypertension [$n = 13$]). "Start" is the first measurement immediately after the recruitment maneuver. Data are depicted as median (25–75 interquartile range). *$p < 0.05$. CMV = conventional mechanical ventilation, HFOV = high-frequency oscillatory ventilation.

U-shaped curve coincides with normal functional residual capacity (17). This would favor the use of modes that facilitate ventilation at this level. This may also hold true for patients with PPH, in whom it is even more imperative to maintain adequate lung volume to keep PVR low and to achieve a normal pHa. Despite this, experiences with HFOV in cardiac patients are limited and mainly stem from retrospective observational studies. One group of investigators reported a shorter length of mechanical ventilation among neonates and infants with respiratory distress following congenital cardiac surgery when they were managed with HFOV (9). Others found that high-frequency jet ventilation reduced PVR in children after Fontan procedure, although no outcome data were reported (10). Despite the higher intrathoracic pressures associated with HFOV, our data did not demonstrate hemodynamic deterioration over time in all groups of patients. In fact, the use of vasoactive inotropic agents and the VIS score remained constant during the first 3 days of HFOV. The increased use of vasoactive drugs in subjects with PPH does not necessarily mean that HFOV was detrimental since the VIS remained constant. We propose that the increase could easily be explained by the routine use of milrinone in these subjects.

LVOMs are often guided by changes in oxygenation. In our study, changes in Spo_2 were measured during the incremental-decremental CDP titration, assuming that there we no increase in lung volume if the Spo_2 no longer increased. However, especially in patients with an intracardiac shunt, it cannot be ruled out that there was still potential for recruitment despite the absence of increase in Spo_2 as many other variables, such as shunt itself, influence the Spo_2 (18). Increases in intrathoracic pressure or PVR may cause the direction of the shunt to change, leading to increased mixing of oxygenated

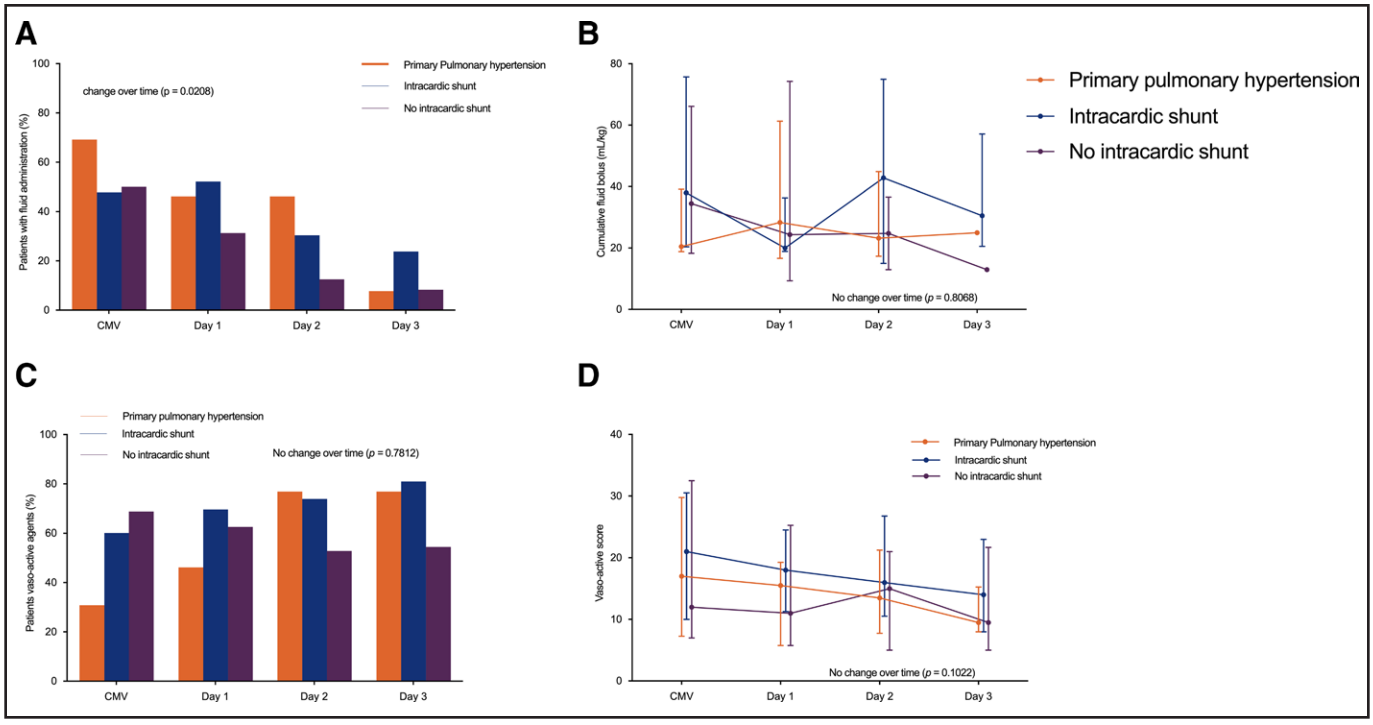

Figure 2. Level and time course of the percentage of patients who received fluid boluses per day (**A**) and the cumulative amount of fluid boluses in mL/kg (**B**), patients on vasoactive support per day (**C**) and vasoactive score (**D**) stratified by underlying diagnosis (with intracardiac shunt [$n = 23$], without intracardiac shunt [$n = 16$], and with primary pulmonary hypertension [$n = 13$]). Continuous data are depicted as median (25–75 interquartile range), and categorical data as percent of total. CMV = conventional mechanical ventilation. $^{*}p < 0.05$.

with deoxygenated blood. The lack of EELV monitoring tools other than surrogate clinical variables, such the Spo_2, OI, and Pao_2/Fio_2, is a major limitation when transitioning to HFOV (19, 20). Despite that the fact in our study we did not quantify the intracardiac shunt, our data showed that there was no worsening of oxygenation during HFOV compatible with right-to-left changes in shunt. We did not use chest radiography to assess lung volume as there are no data on the validity of this type of imaging to identify optimal lung volume nor how to appropriately identify lung overdistension. Obviously, novel bedside tools measuring lung volume could improve the LVOM in all patients and particularly in cardiac patients with intracardiac shunt.

Our study was not designed to test the superiority of HFOV over CMV, and it cannot be ruled out that the improvements seen in for example the hemodynamic variables might also have occurred over time if HFOV was not used. To date, no pediatric or adult studies in noncardiac patients have reported improved outcomes from HFOV (21–23). However, we propose that how HFOV is used determines patient outcome (24, 25). Most studies do not report a LVOM to guarantee an optimal lung volume and oscillating at EELV in the individual patient (26). The importance of recruiting lung volume when transitioning to HFOV is emphasized in experimental work as not only oxygenation improves with more recruited lung volume but there is also a decreased risk for collapsed, atelectatic lung units to become exposed to larger, potentially more injurious pressure swings (27, 28). Our present study confirms that such an approach is safe and feasible in cardiac patients, making this patient population a target for inclusion in future randomized controlled trials. Such trials will ultimately answer the question if our approach leads to improved patient outcomes such as ventilator-free days and length of PICU stay.

There are limitations to our study. First, this is a retrospective single-center study, conducted in a high HFOV usage center. We apply liberal criteria for transitioning to HFOV in our pediatric population rather than using HFOV as rescue therapy. In the group of patients with a cardiac anomaly, we tend to be more restrictive than in patients without cardiac impairment. Nonetheless, in cases of severe pulmonary impairment, HFOV is used to avoid harmful conventional ventilator settings. Thus, the experiences in the study come from a center with extensive experience in

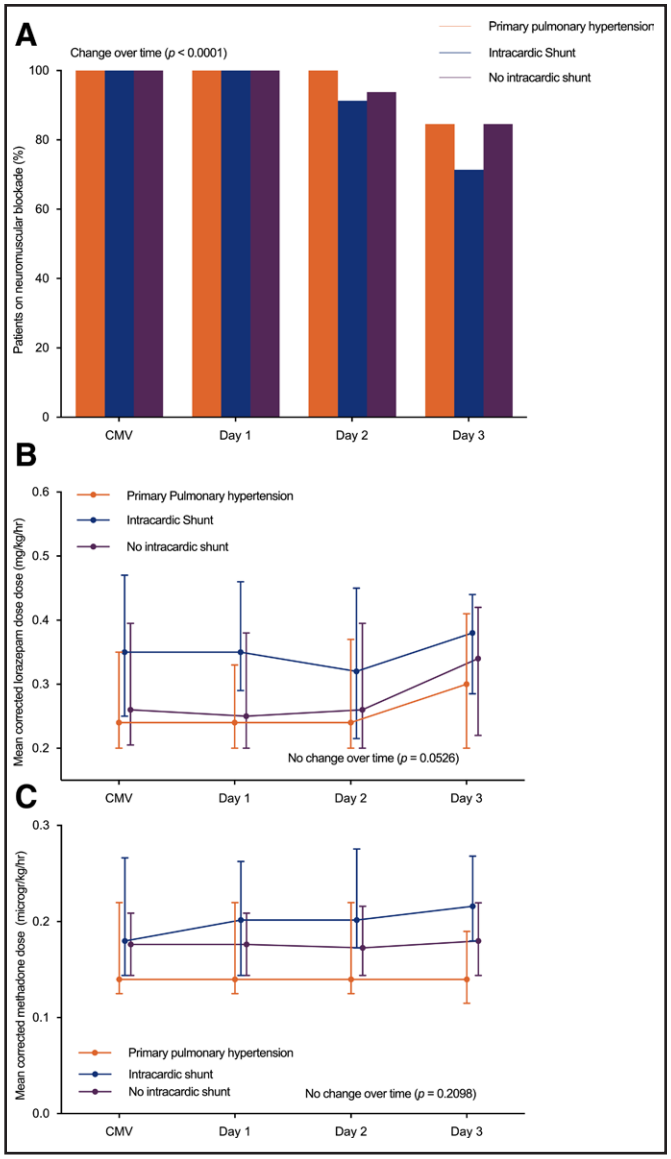

Figure 3. Percentage of patients who were on neuromuscular blocking agents (**A**), mean equipotent dosage of lorazepam (**B**), and mean equipotent dosage of methadone dosage (**C**) stratified by underlying diagnosis (with intracardiac shunt [$n = 23$], without intracardiac shunt [$n = 16$], and with primary pulmonary hypertension [$n = 13$]). Continuous data are depicted as median (25–75 interquartile range) and categorical data as percent of total. CMV = conventional mechanical ventilation. *$p < 0.05$.

HFOV, which is essential for children with right heart failure. In addition, practice variability in, for example, fluid and hemodynamic management cannot be ruled out due to our study design. Second, although an objective ventilation management protocol was used in our unit, a notable portion of the management is at the discretion of the attending physician, inherently leading to practice variability that cannot be accounted for. Nevertheless, our study was designed as a pragmatic observational study, examining the feasibility of an open-lung HFOV approach in subjects with cardiac anomalies. It was not designed to test superiority of HFOV over CMV; this obviously requires a randomized controlled trial. Third, the studied cohort reflects a heterogenous group of patients, and the number of patients is insufficient to perform subgroup analyses. A more granular description would allow for better identification of subjects in whom HFOV might have more effects on the cardiac output than other congenital anomalies, but we are concerned that the sample size does not allow this. Nonetheless, our study includes one of the largest cohorts of pediatric patients with cardiac impairment or PPH managed with HFOV.

CONCLUSIONS

In our cohort, there were no negative hemodynamic consequences of an alternative, individualized, physiology-based open-lung HFOV approach that targets high frequency and high ΔPproximal in pediatric patients with a congenital or acquired cardiac anomaly or pulmonary hypertension with severe lung injury. Future investigations are needed to describe outcome benefits of this HFOV approach.

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REFERENCES

1. Healy F, Hanna BD, Zinman R: Pulmonary complications of congenital heart disease. *Paediatr Respir Rev* 2012; 13:10–15
2. Johnson BN, Fierro JL, Panitch HB: Pulmonary manifestations of congenital heart disease in children. *Pediatr Clin North Am* 2021; 68:25–40
3. Imai Y, Slutsky AS: High-frequency oscillatory ventilation and ventilator-induced lung injury. *Crit Care Med* 2005; 33:S129–S134
4. Imai Y, Nakagawa S, Ito Y, et al: Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation. *J Appl Physiol (1985)* 2001; 91:1836–1844
5. Carney D, DiRocco J, Nieman G: Dynamic alveolar mechanics and ventilator-induced lung injury. *Crit Care Med* 2005; 33:S122–S128
6. Slutsky AS, Ranieri VM: Ventilator-induced lung injury. *N Engl J Med* 2013; 369:2126–2136
7. Brazelton TB, 3rd, Watson KF, Murphy M, et al: Identification of optimal lung volume during high-frequency oscillatory ventilation using respiratory inductive plethysmography. *Crit Care Med* 2001; 29:2349–2359
8. de Jager P, Kamp T, Dijkstra SK, et al: Feasibility of an alternative, physiologic, individualized open-lung approach to high-frequency oscillatory ventilation in children. *Ann Intensive Care* 2019; 9:9
9. Bojan M, Gioanni S, Mauriat P, et al: High-frequency oscillatory ventilation and short-term outcome in neonates and infants undergoing cardiac surgery: A propensity score analysis. *Crit Care* 2011; 15:R259
10. Meliones JN, Bove EL, Dekeon MK, et al.: High-frequency jet ventilation improves cardiac function after the Fontan procedure. *Circulation* 1991; 84:III364–368
11. Gaies MG, Gurney JG, Yen AH, et al: Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010; 11:234–238
12. Tobias JD: Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med* 2000; 28:2122–2132
13. Siddappa R, Fletcher JE, Heard AM, et al: Methadone dosage for prevention of opioid withdrawal in children. *Paediatr Anaesth* 2003; 13:805–810
14. Keenan JC, Formenti P, Marini JJ: Lung recruitment in acute respiratory distress syndrome: What is the best strategy? *Curr Opin Crit Care* 2014; 20:63–68
15. Ista E, van Dijk M, Tibboel D, et al: Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. *Pediatr Crit Care Med* 2005; 6:58–63
16. Hakim TS, Michel RP, Chang HK: Effect of lung inflation on pulmonary vascular resistance by arterial and venous occlusion. *J Appl Physiol Respir Environ Exerc Physiol* 1982; 53:1110–1115
17. Elhoff JJ, Shekerdemian LS: The slow burn: Are we neglecting potential long-term cardiovascular sequelae of critical illness in children? *Lancet Child Adolesc Health* 2017; 1:254–256
18. Caironi P, Gattinoni L: How to monitor lung recruitment in patients with acute lung injury. *Curr Opin Crit Care* 2007; 13:338–343
19. Goffi A, Ferguson ND: High-frequency oscillatory ventilation for early acute respiratory distress syndrome in adults. *Curr Opin Crit Care* 2014; 20:77–85
20. Ng J, Ferguson ND: High-frequency oscillatory ventilation: Still a role? *Curr Opin Crit Care* 2017; 23:175–179
21. Arnold JH, Hanson JH, Toro-Figuero LO, et al: Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med* 1994; 22:1530–1539
22. Ferguson ND, Cook DJ, Guyatt GH, et al: High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; 368:795–805
23. Young D, Lamb SE, Shah S, et al: High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013; 368:806–813
24. Kneyber MC, Markhorst DG: Do we really know how to use high-frequency oscillatory ventilation in critically Ill children? *Am J Respir Crit Care Med* 2016; 193:1067–1068
25. Kneyber MC, Markhorst DG: Any trial can (almost) kill a good technique. *Intensive Care Med* 2016; 42:1092–1093
26. de Jager P, Burgerhof JGM, Koopman AA, et al: Physiologic responses to a staircase lung volume optimization maneuver in pediatric high-frequency oscillatory ventilation. *Ann Intensive Care* 2020; 10:153
27. Pillow JJ: High-frequency oscillatory ventilation: Mechanisms of gas exchange and lung mechanics. *Crit Care Med* 2005; 33:S135–S141
28. Suzuki H, Papazoglou K, Bryan AC: Relationship between PaO2 and lung volume during high frequency oscillatory ventilation. *Acta Paediatr Jpn* 1992; 34:494–500