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Assessing Initial Response to High-Frequency Jet Ventilation in Premature Infants With Hypercapnic Respiratory Failure

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BACKGROUND: High-frequency jet ventilation (HFJV) has been used in conjunction with conventional ventilation for infants with respiratory failure. We sought to identify parameters that were associated with successful application of HFJV in patients with hypercapnic respiratory failure. METHODS: A single-center, retrospective review of infants who received HFJV was conducted. Subjects were enrolled if birthweight was ≤2,000 g and capillary P_{CO_2} was ≥55 mm Hg. Ventilator parameters and physiologic data were recorded at 1 h before HFJV initiation and at hours 1, 4, and 6 following conversion. Subjects were classified as responders if capillary P_{CO_2} was reduced by ≥10% after 1 h of HFJV. Data included peak inspiratory pressure, PEEP, capillary P_{CO_2}, and oxygen saturation index (equal to mean airway pressure × F_{IO_2} × 100/S_{pO_2}). Because the data were not normally distributed, they are reported as median (interquartile range), and the Mann-Whitney test was used to assess differences in continuous data between groups. Categorical data were analyzed using a chi-square and Fisher exact test. RESULTS: Thirty-four premature infants (n = 24 male) were studied. Twenty-five subjects were classified as responders and demonstrated a significant reduction of capillary P_{CO_2} and F_{IO_2} and increased pH within the first hour. The non-responders demonstrated a higher conventional ventilation peak inspiratory pressure (25 cm H_2O vs 19 cm H_2O, P = .005) and had a greater postmenstrual age (30 weeks vs 26.5 weeks, P = .01). This group had a higher oxygen saturation index (7.25 vs 3.36, P = .03) and F_{IO_2} requirements (0.6 vs 0.35, P = .038) at 4 h. CONCLUSIONS: We identified that lower postmenstrual age, improvements in capillary P_{CO_2} and pH at 1 h, and a reduction of F_{IO_2} were associated with good response to HFJV. These data may help to identify patients who are likely to benefit from HFJV in the neonatal intensive care unit. *Key words: respiratory distress syndrome; prematurity; mechanical ventilation; high-frequency jet ventilation; high-frequency oscillatory ventilation; chronic lung disease*. [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Respiratory distress syndrome (RDS) is the most common etiology of respiratory failure in preterm infants, resulting from surfactant deficiency and associated with lower gestational age.[1] Whereas the specific etiologies of respiratory failure in premature infants may be multifactorial, it remains a principle indication for mechanical ventilation. Although mechanical ventilation is a lifesaving modality,

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chronic lung injury and subsequent bronchopulmonary dysplasia are associated complications, and therefore, strategies to mitigate these effects are desirable.[2]

High-frequency ventilation is a form of mechanical ventilation that utilizes rapid breathing frequencies (240–900 breaths/min), and delivers small tidal volumes (V_T) that can be smaller than anatomic dead space.[3] The most commonly used modes of high-frequency ventilation in the United States include high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). Both modes have been used clinically for >30 years and are considered standard alternatives for infants with refractory respiratory failure while receiving conventional mechanical ventilation. Although systematic reviews have reported no improved benefit in outcomes data for the elective use of either HFOV or HFJV in infants with RDS when compared with conventional ventilation, many clinicians reserve these modalities for rescue use.[4-7] Several of the trials included within these reviews and other studies looking at rescue use were conducted decades ago, before the availability of surfactant replacement therapy and routine use of antenatal steroids.[8-10] Furthermore, there are no large studies comparing HFOV directly with HFJV, and HFJV research is far less robust; therefore, the decision to use one mode over another is often left to clinical judgment. There are also limited data on treatment guiding the clinician to decide whether a patient has positively or negatively responded to HFJV. Therefore, we sought to identify parameters that are associated with successful application of HFJV in subjects with hypercapnic respiratory failure refractory to conventional ventilation or HFOV. We hypothesized that differences in measurable physiologic parameters would be observed between subjects who initially "responded," when compared with those subjects who did not.

QUICK LOOK

Current knowledge

The use of rescue high-frequency jet ventilation (HFJV) in premature infants with respiratory failure is an accepted standard of care in most neonatal ICUs. There are no established guidelines for the use HFJV as a rescue strategy, and the body of literature on this topic is inconclusive.

What this paper contributes to our knowledge

In a retrospective review of premature subjects with respiratory failure, HFJV was used as a rescue mode of ventilation. Responders to HFJV were most likely to demonstrate improved CO_2 clearance and lower oxygen saturation index within 4 h following the initiation of HFJV. Subjects who did not initially respond were transitioned from higher conventional ventilation PIP, administered HFJV later, and exhibited higher oxygen saturation index 4 h following transition.

Methods

Subjects

All subjects were outborn and were transferred to the Boston Children's Hospital neonatal ICU for further medical or surgical management. An institutional review board approved (P00021911) retrospective analysis of subjects admitted to the neonatal ICU who underwent HFJV between January 2012 and January 2016. Subjects were included in the study if birthweight was ≤2,000 g and capillary partial pressure of carbon dioxide (capillary P_{CO_2}) was ≥55 mm Hg. The timing of transition to HFJV was left to the discretion of the medical team. Patients were excluded if they had unrepaired complex congenital heart disease, weighed >2,000 g, or were placed on HFJV at the time of admission. The primary aims of this study were to elucidate which physiologic parameters could be used to identify a successful response in premature infants who received HFJV as a rescue therapy.

All subjects were ventilated with a Servo-i (Maquet, Camden, New Jersey) in pressure control-intermittent mandatory ventilation mode or HFOV (3100A, BD, Franklin Lakes, New Jersey) before conversion to HFJV (Life Pulse, Bunnell, Salt Lake City, Utah). Equipment was calibrated according to manufacturer specifications before application. All endotracheal tube adapters were exchanged with an adapter (LifePort, Bunnell, Salt Lake City, Utah) of appropriate size to allow for HFJV monitoring and regulation of proximal airway pressures according to manufacturer recommendations. The conventional ventilator was used in tandem with HFJV to provide PEEP, sigh-breaths, bias flow, and an exhalation valve, as specified by manufacturer recommendations.

Subjects were converted to HFJV in accordance with institutional guidelines using a peak inspiratory pressure (HFJV PIP) of 3–5 cm H_2O above the set PIP while receiving conventional ventilation, frequency of 420 (7 Hz), and a jet valve on-time of 20 ms. PEEP was increased by 1–2 cm H_2O, to maintain the same mean airway pressure ($\bar{P}_{aw}$) preceding the transition to HFJV. In subjects transitioned from HFOV, PEEP was initially titrated to attain a similar $\bar{P}_{aw}$ as HFOV. HFJV PIP was primarily adjusted to maintain a pH of ≥7.25 and capillary P_{CO_2} between 50 and 60 mm Hg. F_{IO_2} was titrated to maintain S_{pO_2} between 88 and 96%. If F_{IO_2} could not be weaned below 0.6, PEEP was increased in 1–2 cm H_2O increments until this target had been met.

Demographic information, along with ventilator, physiologic, and laboratory data were collected. Data included PIP, PEEP, $\bar{P}_{aw}$, capillary P_{CO_2}, and oxygen saturation in-

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Table 1. Subject Demographics

Characteristics	Responders (n = 25)	Non-Responders (n = 9)	P
Male/female sex, n	16/9	8/1	.23
PMA, median (IQR) weeks	26.5 (25–28)	30 (26.6–31.9)	.01
Gestational age, median (IQR) weeks	24.7 (23–25.9)	27 (25.5–29.5)	.02
Weight, median (IQR) g	700 (600–670)	1,000 (670–1650)	.058
Ventilator duration before HFJV, median (IQR) h	23 (10–59)	18 (3–219)	.68
Duration of HFJV, median (IQR) h	78 (46–196)	71 (10–145)	.29
Received antenatal steroids, n (%)	13 (52)	7 (78)	.25
Surfactant administered, n (%)	21 (84)	9 (100)	.40
Reason for admission, n (%)			
RDS	21 (84)	9 (100)	.55
Respiratory failure	4 (16)	0	.55
Secondary diagnosis, n (%)			
Necrotizing entercolitis	5 (20)	2 (22)	>.99
PDA	5 (20)	2 (22)	>.99
Ventilator mode before HFJV, n (%)			
PC-SIMV	18 (72)	7 (78)	>.99
HFOV	7 (28)	2 (22)	>.99
Outcome, n (%)			
Survived to discharge	18 (72)	8 (88)	.40

PMA = postmenstrual age
IQR = interquartile range
HFJV = high-frequency jet ventilation
RDS = respiratory distress syndrome
PDA = patient ductus arteriosus
PC-SIMV = pressure control-synchronized intermittent mandatory ventilation
HFOV = high-frequency oscillatory ventilation

dex (OSI = mean airway pressure × F_{IO_2} × 100/S_{pO_2}). Ventilator parameters and physiologic data were extracted from the electronic medical record and analyzed at 1 h before HFJV and at hours 1, 4, and 6 following conversion. Capillary P_{CO_2} and pH were included for analysis. provided that values were collected 45 min before or after each time interval. Laboratory data that were missing or did not correspond with these intervals or were omitted.

Subjects were classified as responders if capillary P_{CO_2} was reduced by ≥10% at 1 h of HFJV. This threshold was decided a priori and was comparable with statistically significant reductions in P_{aCO_2} observed during a randomized trial of HFJV versus conventional ventilation.[11] The cohort was then divided into responder and non-responder categories, respectively, and transcribed into Excel 15.24 (Microsoft Corp, Redmond, Washington) spreadsheets. Prism 6.0 (GraphPad Software, La Jolla, California) was used to analyze all data. Since the data were not normally distributed, they are reported as median (interquartile range). Mann-Whitney unpaired t test was used to assess differences in continuous variables, and the chi-square and Fisher exact test were used for categorical variables between the groups. Friedman tests were used to detect whether there were significant changes in OSI within groups using the baseline values as a referent. Post hoc analysis was conducted using the Dunn test. All tests were 2-sided, and differences of <.05 were considered significant. Plavka et al[12] have previously reported mean ± SD CO_2 values of 61.5 ± 10.3 mm Hg in premature infants preceding HFJV. A power analysis indicated that a total sample of 16 subjects would be required to detect a 10% change in CO_2 with 80% power ($1 - \beta$), using a t test with an α of .05.

Results

Thirty-four premature subjects (n = 24 male) were studied. Before conversion to HFJV, the median V_T was 7 mL/kg (6–7.7 mL/kg) and a set frequency of 40 breaths/min (38–45 breaths/min) receiving conventional ventilation. Thirty subjects were categorized as RDS based upon age, history of at least one dose of exogenous surfactant, and radiographic documentation of surfactant deficiency. Four subjects were admitted with other diagnoses (congenital pulmonary airway malformation, omphalocele, and two with complete heart block) and were classified as respiratory failure. The median postmenstrual age was 26.6 weeks (25–28 weeks) in the responder group and 30 weeks (26.6–31 weeks) in non-responders (P = .01) at the time HFJV was initiated. Overall survival to discharge was 76% with no statistical difference observed between groups. Demographic data and subject characteristics are displayed in Table 1. In total, 9 subjects (26%) were transitioned

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from HFOV to HFJV. These subjects were all on an HFOV frequency of 15 Hz, $\bar{P}_{aw}$ of 11 cm H_2O (9–12.5 cm H_2O), and median pressure amplitude of 28 cm H_2O (23–40 cm H_2O). Twenty-five subjects were classified as responders and demonstrated a reduction of capillary P_{CO_2}, F_{IO_2} and increased pH within the first hour, and 9 subjects were classified as non-responders. The non-responder group was transitioned to HFJV from a higher conventional ventilation PIP (25 cm H_2O vs 19 cm H_2O, $P = .005$) and a later postmenstrual age (30 weeks vs 26.5 weeks, $P = .01$) than their counterparts. The non-responders also demonstrated significantly higher OSI (7.25 vs 3.36, $P = .03$) values and F_{IO_2} requirements (0.6 vs 0.35, $P = .038$) at 4 h. Capillary P_{CO_2} and pH preceding and 1 h following transition to HFJV were complete ($n = 34$). However, fewer blood gases were drawn at the 4-h ($n = 29$) and 6-h ($n = 24$) time frames. Ventilator parameters and physiologic data are displayed in Table 2. The Friedman test detected a statistically significant difference in OSI progression within the responder group, which was not present in the non-responder group ($P = .037$ and $P = .94$, respectively). Dunn's multiple comparisons post-test identified lower OSI values existing at both hours 4 and 6 in the responder group ($P < .05$), when compared with referent (baseline).

Table 2. Ventilator and Physiologic Data

Parameter	Responders	Non-Responders	*P*
Pre-HFJV			
Conventional mechanical ventilation PIP, cm H_2O	19 (17.5–21)	25 (23–25)	.005
PEEP, cm H_2O	5 (5–6)	6 (5–7)	.15
$\bar{P}_{aw}$, cm H_2O	10 (9–11)	10 (8–11.5)	.47
Capillary P_{CO_2}, mm Hg	72 (63–90)	71 (61–93)	.80
OSI	5.08 (3.45–7.22)	6.98 (5.18–8)	.13
F_{IO_2}	0.5 (0.35–0.7)	0.6 (0.52–0.88)	.16
pH	7.10 (6.98–7.16)	7.14 (7.06–7.24)	.22
HFJV hour 1			
HFJV PIP, cm H_2O	25 (22.5–31)	26 (19.5–33)	.95
PEEP, cm H_2O	7 (6–8)	7 (6–9)	.77
$\bar{P}_{aw}$, cm H_2O	10 (8.5–9.5)	11 (9.5–13.5)	.25
Capillary P_{CO_2}, mm Hg	49 (42–57.5)	87 (66.5–100)	<.001
OSI	4 (2.49–9.51)	6.9 (5.43–8.93)	.22
F_{IO_2}	0.4 (0.3–0.52)	0.6 (0.45–0.8)	.02
pH	7.24 (7.18–7.31)	7.11 (7.05–7.26)	.031
HFJV hour 4			
HFJV PIP, cm H_2O	25.5 (23–31.5)	31 (23.5–38)	.29
PEEP, cm H_2O	8 (6–9)	8 (6–9.5)	.74
$\bar{P}_{aw}$, cm H_2O	10 (8.3–11)	12 (9–14)	.11
Capillary P_{CO_2}, mm Hg	47 (43.5–57.5)	52 (37–109)	.73
OSI	3.36 (2.62–5.95)	7.25 (4.09–9.72)	.03
F_{IO_2}	0.35 (0.29–0.5)	0.6 (0.42–0.8)	.038
pH	7.25 (7.18–7.28)	7.23 (7.10–7.32)	.82
HFJV hour 6			
HFJV PIP, cm H_2O	26 (22.3–30)	28 (20–32)	.74
PEEP, cm H_2O	8 (6–8.8)	7 (6–9)	.86
$\bar{P}_{aw}$, cm H_2O	10 (8–11)	11.5 (8.5–13.5)	.23
Capillary P_{CO_2}, mm Hg	46 (38–58)	61 (36–67.5)	.38
OSI	3.62 (2.58–6.28)	5.55 (4.34–10.26)	.12
F_{IO_2}	0.37 (0.26–0.5)	0.5 (0.35–0.65)	.22
pH	7.26 (7.2–7.32)	7.24 (7.19–7.29)	.65

Results are median (interquartile range).
HFJV = high-frequency jet ventilation
PIP = peak inspiratory pressure
$\bar{P}_{aw}$ = mean airway pressure
Capillary P_{CO_2} = capillary partial pressure of carbon dioxide
OSI = oxygen saturation index

Discussion

Subjects who demonstrated a positive response to HFJV were characterized by improved pH, lower capillary P_{CO_2}, and stabilization of ventilator parameters after 1 h. Non-responders exhibited worsening oxygenation deficits at 4 h and may have potentially benefited from further increases in PEEP.

HFJV has been associated with improvements in CO_2 elimination and subsequently increased arterial pH following rescue use in premature and term infants.[13-15] In the current study, capillary P_{CO_2} and pH were studied considering that the majority of subjects ($n = 29$, 85%) did not have arterial access when HFJV was initiated. A significant reduction in capillary P_{CO_2} and elevation of pH were observed in the responder group following 1 h of HFJV. These subjects were also noted to have significantly lower conventional ventilation peak inspiratory pressures before HFJV conversion. In the responder group, capillary P_{CO_2} and pH remained within targeted clinical range without significant escalation in ventilator support at hours 4 and 6. Two subjects in the non-responder group had persistent hypercapnia and hypoxia despite nearly maximal settings and were transitioned back to conventional ventilation and HFOV at 5 and 6 h, respectively.

OSI was a secondary outcome observed between cohorts to assess the severity of hypoxic respiratory failure as described by Rawat et al.[16] OSI was similar between groups before and 1 h after conversion to HFJV and was significantly higher in non-responders at hour 4. Additionally, F_{IO_2} was significantly higher for non-responders during this time, at similar ventilating pressures, which may suggest that these subjects may have benefited from increased PEEP. Furthermore, these findings may suggest that subjects failing HFJV had a more significant oxygenation derangement and are in accordance with those of Stewart et al.[15] These authors found that responders to HFJV were characterized by a decrease in oxygenation index at hour 4 (10.7 ± 5.2) compared with (17.6 ± 13.4) in non-responders, without an increase in $\bar{P}_{aw}$. Similarly, Baumgart et al[13] reviewed 73 extracorporeal membrane oxygenation-eligible infants of >34 weeks gestational age who received HFJV secondary to intractable respiratory failure. These authors found that infants who survived with HFJV alone had significantly lower oxygenation index at 1 and 6 h and identified subjects with RDS as

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having the most favorable response to HFJV. Although the subjects in the current study were not extracorporeal membrane oxygenation candidates due to size limitation, and neither oxygenation index nor OSI were used for inclusion criteria, our findings suggest that OSI is a useful metric for non-invasively assessing oxygenation status during HFJV. Moreover, failure to improve from an oxygenation or ventilation standpoint by 6 h of HFJV may prompt clinicians to optimize recruitment or consider alternative treatment strategies.

Extremely premature infants with evolving chronic lung injury are characterized by the development of heterogeneous aeration, structural immaturity of the lung, high airway resistance, and gas trapping, particularly during exhalation.[12] In the current review, 9 subjects were transitioned to HFJV from HFOV in the setting of persistent respiratory failure. Of these subjects, 7 responded to HFJV with a median 29% reduction of capillary P_{CO_2} and 32% reduction in OSI; 2 subjects with air leak did not respond at hour 1 and then improved by 6 h of HFJV. It is possible that the longer passive expiratory phase receiving HFJV at 7 Hz (123 ms) compared with HFOV at 15 Hz (44 ms), may have contributed to improved gas exchange in this subset of subjects. The optimal range of frequencies of either device is dependent on patient size, the underlying disease process, and associated pulmonary time constants.[17,18] The majority of randomized control trials reported using HFOV frequencies between 10 and 15 Hz in premature infants with respiratory failure.[4] Squires et al[19] describe the utilization of lower HFOV frequencies (5–6 Hz) to afford a longer expiratory phase in infants with pulmonary interstitial emphysema and concluded that this strategy may provide some benefit in gas exchange. Reducing HFOV frequency concomitantly increases the inspiratory time, results in larger V_T, and could potentially exacerbate lung injury in infants with low lung compliance. The ability to maintain a short inspiratory time during HFJV while extending expiratory time may be advantageous in premature infants. Similar findings have been reported in a retrospective review of 10 premature infants with chronic lung injury, hyperinflation, and hypoxic respiratory failure refractory to low frequency HFOV. Friedlich et al[20] described a reduction in oxygenation index, $\bar{P}_{aw}$, and F_{IO_2} within 3 h of HFJV initiation. These authors speculated that HFOV may have contributed to gas trapping by a mechanism of dynamic airway collapse resulting from the active exhalation and fixed 1:2 inspiratory-expiratory ratio. They concluded that passive exhalation, longer expiratory times during HFJV (eg, 1:3.5–1:11.5), and mechanical differences between devices were potentially responsible for improvements in gas exchange.[20]

It is important to mention the limitations of our current study. First, this study was retrospective and therefore reliant on the accuracy of the medical record. This design introduces the potential for selection bias and is uncontrolled. We attempted to limit selection bias with the aforementioned inclusion and exclusion criteria. Second, our results are reflective of intuition guidelines and suggest that HFJV was a viable strategy in subjects with RDS and persistent hypercapnia refractory to conventional ventilation or HFOV. However, we cannot determine with absolute certainty that subjects improved as a direct result of HFJV, since we did not have a control group of subjects for comparison who continued to receive conventional ventilation or HFOV. Third, capillary pH and capillary P_{CO_2} are acceptable alternatives to arterial blood gas samples; capillary oxygenation is not a reliable surrogate for P_{aO_2} value. Therefore, the present investigation utilized S_{pO_2} and OSI to quantify oxygenation and may not be as accurate as arterial blood gas analysis. However, these metrics have been validated in children.[16,21] Fourth, long-term follow up was limited due to the nature of the study; therefore, important long-term pulmonary, neurologic, and developmental outcomes were not assessed. Last, we did not utilize severity scoring because many of these systems (eg, newborn respiratory distress scoring system, clinical risk index for babies, and score for neonatal acute physiology) were developed to evaluate the initial risk at time of admission and are limited to the first hours and days of life.[22,23] Since all patients in our neonatal ICU are postnatally transferred (sometimes days or weeks following birth), we do not utilize these scoring systems. For these reasons, we chose not to include them in our paper.

High-frequency ventilation has been used extensively in addition to other conventional modes of neonatal ventilation. Evidence remains inconclusive; therefore, clinical judgment, institutional preference, and experience generally dictate which mode is used and when. Further research is needed to delineate the optimal modes of ventilation in a context specific to the underlying physiology and disease state. Moreover, prospective randomized control trials are needed to rigorously evaluate differences between high-frequency devices. The current study suggests that HFJV may be more efficacious when initiated earlier and further elaborates on the initial physiologic parameters that may suggest a positive response to HFJV.

Conclusions

We identified that lower postmenstrual age, reduced PIP while receiving conventional ventilation, reduced F_{IO_2}, reduced capillary P_{CO_2}, and improved pH during HFJV at 1 h were associated with a good response to HFJV, without escalation in ventilator settings. The non-responder group demonstrated a concomitant increase in both OSI and F_{IO_2} with no significant change in ventilator pressures at hour 4, which may suggest the need to increase PEEP/$\bar{P}_{aw}$. These data may lead to early identification of infants who are

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most likely to benefit from HFJV in the neonatal ICU and may prevent extended application of HFJV in patients who do not demonstrate a benefit within 6 hours.

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