Comparison of High-Frequency Oscillatory Ventilation and Conventional Mechanical Ventilation in Pediatric Respiratory Failure

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**Importance** Outcomes associated with use of high-frequency oscillatory ventilation (HFOV) in children with acute respiratory failure have not been established.

**Objective** To compare the outcomes of HFOV with those of conventional mechanical ventilation (CMV) in children with acute respiratory failure.

**Design, Setting, and Participants** We performed a retrospective, observational study using deidentified data obtained from all consecutive patients receiving mechanical ventilation aged 1 month to 18 years in the Virtual PICU System database from January 1, 2009, through December 31, 2011. The study population was divided into 2 groups: HFOV and CMV. The HFOV group was further divided into early and late HFOV. Propensity score matching was performed as a 1-to-1 match of HFOV and CMV patients. A similar matching process was performed for early HFOV and CMV patients.

**Exposure** High-frequency oscillatory ventilation.

**Main Outcomes and Measures** Length of mechanical ventilation, intensive care unit (ICU) length of stay, ICU mortality, and standardized mortality ratio (SMR).

**Results** A total of 9177 patients from 98 hospitals qualified for inclusion. Of these, 902 (9.8%) received HFOV, whereas 8275 (90.2%) received CMV. A total of 1764 patients were matched to compare HFOV and CMV, whereas 942 patients were matched to compare early HFOV and CMV. Length of mechanical ventilation (CMV vs HFOV: 14.6 vs 20.3 days, \( P < .001 \); CMV vs early HFOV: 14.6 vs 15.9 days, \( P < .001 \), ICU length of stay (19.1 vs 24.9 days, \( P < .001 \); 19.3 vs 19.5 days, \( P = .03 \)), and mortality (8.4% vs 17.3%, \( P < .001 \); 8.3% vs 18.1%, \( P < .001 \)) were significantly higher in HFOV and early HFOV patients compared with CMV patients. The SMR in the HFOV group was 2.00 (95% CI, 1.71-2.35) compared with an SMR in the CMV group of 0.85 (95% CI, 0.68-1.07). The SMR in the early HFOV group was 1.62 (95% CI, 1.31-2.01) compared with an SMR in the CMV group of 0.76 (95% CI, 0.62-1.16).

**Conclusions and Relevance** Application of HFOV and early HFOV compared with CMV in children with acute respiratory failure is associated with worse outcomes. The results of our study are similar to recently published studies in adults comparing these 2 modalities of ventilation for acute respiratory distress syndrome.

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Respiratory failure due to acute lung injury and acute respiratory distress syndrome is a major cause of mortality in critically ill children. The use of conventional mechanical ventilation (CMV) has been associated with high airway pressures and pulmonary air leaks.1–3 It has been postulated that high-frequency oscillatory ventilation (HFOV) can be used to decrease induced injury as part of a lung-protective strategy.4–7 High-frequency oscillatory ventilation delivers small tidal volumes at high rates (3-15 breaths per second)8,9 and is used as both elective and rescue therapy for acute respiratory failure treatment in pediatric intensive care units (ICUs).

Limited pediatric literature suggests improvement in oxygenation in patients managed with HFOV compared with CMV.7 In 2 recently concluded randomized, controlled, multicenter trials in adults, use of HFOV was not associated with decreased mortality.10,11 With insufficient evidence demonstrating the efficacy of HFOV in children, we conducted a post hoc analysis of data contributed to the Virtual PICU System LLC (VPS) database. The primary objective of this study was to compare the outcomes of HFOV with those of CMV in children with acute respiratory failure. The outcomes evaluated included length of mechanical ventilation, ICU length of stay (LOS), ICU mortality, and standardized mortality ratio (SMR).

Methods

Population and Sample Selection

The study population was divided into 2 groups: HFOV and CMV. Propensity score matching was performed as a 1-to-1 match of HFOV and CMV patients with similar demographic and clinical characteristics. Propensity score matching was performed using the estimated probability of patients receiving HFOV based on logistic regression models.12–14 The HFOV group included patients receiving HFOV for 24 hours or longer, and the CMV group included patients receiving CMV for 96 hours or longer. The HFOV group was further divided into early and late HFOV; the early group received HFOV within 24 hours of intubation, whereas the late group received HFOV after 24 hours of intubation. For statistical purposes, the patients in one group were not allowed to cross over to the other group.

Deidentified data were obtained from all consecutive patients receiving mechanical ventilation aged 1 month to 18 years in the VPS database from January 1, 2009, through December 31, 2011. Patients with the primary or secondary diagnosis of acute respiratory failure (VPS star codes 518.5, 799.1, and 786) or sepsis (VPS star codes 785.52 and 038.8) were included in the study. The institutional review board at the University of Arkansas for Medical Sciences exempted the study for review because the data involved the analysis of deidentified patient information. Informed consent was waived.

The following patients were excluded from the study: (1) patients in cardiac ICUs, (2) patients receiving jet ventilation or liquid ventilation, (3) patients with congenital heart disease, (4) patients with active diagnosis of myocardopathy or myocarditis, (5) patients admitted to the ICU after surgery for congenital heart defects, (6) patients admitted to the ICU with repair of congenital diaphragmatic hernia, and (7) patients with altered code status. Data on demographics, patient diagnosis, mechanical ventilation, severity of illness, and outcomes were collected. Specific data collected for demographics and severity of illness included age, sex, primary diagnosis, reason for admission, ICU admission and discharge date and time, Pediatric Index of Mortality 2 (PIM-2) score, and Pediatric Risk of Mortality 3 (PRISM-3) score. Data were also collected on arterial catheter use, central venous access, dialysis catheter use, and use of extracorporeal membrane oxygenation (ECMO).

Statistical Analysis

Power calculations were performed using PASS statistical software, version 11 (NCSS LLC). We assumed a 2-sided test with a significance level of .05 for all the power calculations. With approximately 900 patients receiving HFOV and 8000 patients receiving CMV, we determined that we would have at least 80% power to detect an effect size of 0.1 for continuous variables and a change of 5% in an estimated rate of 50% for one of the groups for categorical variables. With approximately 400 patients in both the early and late HFOV groups, we would have at least 80% power to detect an effect size of 0.2 for continuous variables and a change of 10% for categorical variables. For a matched sample of approximately 800 patients, there would be at least 80% power to detect an effect size of 0.1 for continuous variables and a change of 7.2% in an estimated discordant rate of 50% for categorical variables. We calculated that a matched sample of approximately 450 patients would result in at least 80% power to detect an effect size of 0.14 for continuous variables and a change of 10% for categorical variables. For fitting a multiple logistic regression based on a sample of 900 HFOV and 8000 CMV patients, we would be able to include approximately 45 to 60 df for the risk factors included. All the data were analyzed using R statistical software, version 2.15.0 (R Core Team). Descriptive statistics were summarized as mean (SD) for continuous variables and number (percentage) for categorical variables. The SMR was calculated for patients in the matched samples using the method described by Breslow and Day.15 Expected deaths in the SMR were calculated using the PIM-2 score for patients in the matched samples.
Propensity Score Matching
We fitted the logistic regression model to estimate the probability of receiving HFOV. Clinically important variables with missing data of 8% or less in the VPS database were chosen for inclusion in propensity score modeling. The risk factors included in the model for propensity score matching were age, weight, sex, cardiopulmonary resuscitation (CPR) or defibrillator use, PIM-2 score, PRISM-3 score, ECMO, dialysis, arterial catheter, central access, high systolic blood pressure, low systolic blood pressure, high heart rate, low heart rate, hemodialysis catheter, inpatient admission, and a variety of diagnoses (eg, acute pulmonary insufficiency, pneumonia, asthma, sepsis, infectious disorder, hematologic disorder, oncologic disorder, metabolic disorder, immunologic disorder, neurologic disorder, rheumatologic disorder, organ transplantation, poisoning or drug overdose, head trauma, and nonhead trauma). The number of patients receiving mechanical ventilation from each unit was also included in the model to account for variability among units. Missing values for the risk factors included in the model were imputed using predictive mean matching with 5 multiple imputations.16,17 Propensity score matching was performed using the estimated probability of receiving HFOV based on 1-to-1 HFOV and CMV matching of patients with similar demographic and clinical characteristics (model 1). Similar propensity score matching was performed to obtain the 1-to-1 matching of early HFOV and CMV patients (model 2) (eAppendix in the Supplement).

Comparisons
Comparisons between unmatched samples were performed using the 2-sample t test for continuous variables and the χ² test for categorical variables. Comparisons between matched samples were performed using the paired 2-sample t test for continuous variables and the McNemar test for categorical variables. Frailty models were fitted to compare the ICU LOS and duration of mechanical ventilation between the paired samples.18 The Cox proportional hazards assumption was checked using the methods proposed by Grambsch and Therneau.19 Kaplan-Meier curves were plotted for the ICU LOS and duration of mechanical ventilation for HFOV and CMV, respectively.

Sensitivity Analysis
Sensitivity analysis was performed by fitting the multivariate logistic regression model for mortality as a function of ventilation group (HFOV or CMV) after adjusting for the prespecified potential confounding factors listed in the propensity score matching based on unmatched samples. Similarly, the Cox proportional hazards regression models were fitted for the duration of mechanical ventilation and the ICU LOS as a function of ventilation group after adjustment for other confounding factors based on the unmatched samples. To account for the potential correlation among admissions from the same unit, we further fitted the generalized estimating equation for the mortality and frailty models for the duration of mechanical ventilation and ICU LOS. An exchangeable covariance structure was used to account for the correlated admissions from the same unit. More detailed sensitivity analysis is described in the eAppendix and eTable 1 in the Supplement. The estimated odds ratios for mortality and the corresponding 95% CIs for all the variables in the logistic model based on the data after imputation are shown in eFigure 1 in the Supplement. The estimated hazards ratio for the duration of mechanical ventilation and ICU LOS and the corresponding 95% CIs are shown in eFigure 2 and eFigure 3 in the Supplement, respectively.

Results
Of the 208,456 patients in the VPS data set during the study period, 26,534 (12.7%) received mechanical ventilation. Of these patients, 25,208 (95.0%) received CMV, 1266 (4.8%) received HFOV, and 60 (0.2%) received liquid ventilation or jet ventilation. Only 9177 patients from 98 hospitals qualified for inclusion. Of these, 902 (9.8%) received HFOV, whereas 8275 (90.2%) received CMV. Of 902 patients receiving HFOV, 483 (53.5%) received early HFOV and 419 (46.5%) received late HFOV (Figure 1). With the use of propensity scoring matching, 1764 patients were matched for comparison of HFOV and CMV, whereas 942 patients were matched for comparison of early HFOV and CMV.

The mean (SD) age of the study population was 59.7 (66.0) months, with a mean (SD) weight of 20.5 (20.9) kg. There were 5477 males (56.1%) in the study population. The mean (SD) PIM-2 and PRISM-3 scores of the study cohort were -3.53 (1.51) and 7.45 (7.17), respectively. There was a center variation in the use of HFOV, with a median deployment rate of 9.5% (eFigure 4 in the Supplement).

The median time of HFOV initiation after intubation was 20.5 hours. The median duration of HFOV use was 4.7 days.

Comparison Between Unmatched HFOV and CMV Patients
Patients in the CMV group vs the HFOV group were younger (59.2 vs 63.6 months, P = .06) and smaller (20.2 vs 22.7 kg, P = .003) (eTable 2 in the Supplement). Patients in the CMV group vs the HFOV group had lower PIM-2 (-3.6 vs -3.2, P < .001) and PRISM-3 scores (7.1 vs 11.3, P < .001). Patients in the CMV group vs the HFOV group had a lower presence of arterial line catheters (48.1% vs 89.5%, P < .001), central venous access (78.1% vs 96.7%, P < .001), and dialysis catheters (4.1% vs 13.9%, P < .001). Patients in the CMV group vs the HFOV group also had lower institution of CPR (6.5% vs 16.7%, P < .001) and use of ECMO (0.9% vs 7.9%, P < .001). In the unmatched sample, the outcomes, including the length of mechanical ventilation (12.3 vs 20.6 days, P < .001), ICU LOS (16.5 vs 24.9 days, P < .001), and mortality (3.3% vs 18.2%, P < .001), were better in the CMV group compared with the HFOV group. The SMR in the HFOV group was 2.07 (95% CI, 1.77–2.41) compared with the SMR in the CMV group of 0.51 (95% CI, 0.46–0.58).

Comparison Between Unmatched Early and Late HFOV Patients
Early HFOV patients vs late HFOV patients were older (69.2 vs 57.1 months, P = .006) and larger (24.5 vs 20.6 kg, P = .01) (eTable 2 in the Supplement). In the early vs late HFOV patients,
Comparison of Matched HFOV and CMV Patients

The patients in the 2 groups were similar in baseline characteristics, severity of illness scores, hemodynamic parameters, institution of CPR and cardiopulmonary support, laboratory data, and interventions in the ICU (Table). The most common diagnoses associated with the matched study population are represented in eTable 3 in the Supplement. The estimated log odds for different intervals from intubation to initiation of HFOV was associated with increased mortality ($P = .01$). The most common diagnoses associated with the matched study population are represented in eTable 3 in the Supplement. The estimated log odds for different intervals from intubation to initiation of HFOV based on the logistic regression model for mortality as a function of interval from intubation to initiation of HFOV based on the logistic regression model for mortality as a function of interval from intubation to institution of HFOV and increased standard mortality, increased length of mechanical ventilation, and increased ICU LOS compared with CMV. In addition, in survivors, early use of HFOV within the first 24 hours for different ventilator modalities. We demonstrated that application of HFOV and early HFOV is associated with increased standardized mortality, increased length of mechanical ventilation, and increased ICU LOS compared with CMV.

Discussion

This study compared the efficacy of HFOV and CMV in children with acute respiratory failure from 98 nationally diverse pediatric ICUs in the United States. To our knowledge, this report is the largest study to date comparing these 2 ventilation modalities in children with acute respiratory failure. With the use of propensity score matching, children with similar demographic and clinical characteristics were compared for their outcomes for different ventilator modalities. We demonstrated that application of HFOV and early HFOV is associated with increased standardized mortality, increased length of mechanical ventilation, and increased ICU LOS compared with CMV.

**Figure 1. Study Design and Outcomes**

<table>
<thead>
<tr>
<th>Model 1: HFOV vs CMV</th>
<th>Model 2: “Early” HFOV vs CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFOV vs CMV</strong></td>
<td><strong>“Early” HFOV vs “Late” HFOV</strong></td>
</tr>
<tr>
<td>902 HFOV 164 (18%) Mortality</td>
<td>483 Early HFOV 93 (19%) Mortality</td>
</tr>
<tr>
<td>8275 CMV 269 (3%) Mortality</td>
<td>419 Late HFOV 71 (17%) Mortality</td>
</tr>
<tr>
<td><strong>Matched between HFOV and CMV group</strong></td>
<td><strong>Matched between “Early” HFOV and CMV group</strong></td>
</tr>
<tr>
<td>882 Matched between HFOV and CMV group</td>
<td>471 Matched between “Early” HFOV and CMV group</td>
</tr>
<tr>
<td>152 (17%) HFOV mortality</td>
<td>74 (8%) CMV mortality</td>
</tr>
<tr>
<td><strong>P &lt; .01</strong></td>
<td><strong>P &lt; .01</strong></td>
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CMV indicates conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

the PIM-2 ($-2.9$ vs $-3.6$, $P < .001$) and PRISM-3 scores ($13.5$ vs $8.7$, $P < .001$) were higher. No difference was seen in the presence of arterial line catheters ($89.1\%$ vs $89.9\%$, $P = .64$), central venous access ($95.9\%$ vs $97.6\%$, $P = .14$), and dialysis catheters ($14.5\%$ vs $13.2\%$, $P = .55$) in the early HFOV patients vs late HFOV patients. In the early HFOV group vs the late HFOV group, institution of CPR was higher ($19.5\%$ vs $13.3\%$, $P = .01$), but the use of ECMO ($7.7\%$ vs $8.1\%$, $P = .37$) was similar. Although raw mortality was similar in the early vs late HFOV groups ($19.3\%$ vs $16.9\%$, $P = .37$), length of mechanical ventilation ($16.3$ vs $25.5$ days, $P < .001$) and ICU LOS ($19.6$ vs $31.1$ days, $P < .001$) were shorter. The SMR in the late HFOV group ($3.06$; $95\%$ CI, $2.43$-$3.86$) compared with the early HFOV group ($1.65$; $95\%$ CI, $1.35$-$2.03$) was $2.00$ ($95\%$ CI, $1.71$-$2.35$) compared with the SMR in the CMV group ($0.85$; $95\%$ CI, $0.68$-$1.07$). Figure 2 depicts the Kaplan-Meier curves for the ICU LOS and duration of mechanical ventilation for CMV and HFOV patients, respectively. The effects of age and PIM-2 score on mortality are depicted in eFigure 6 in the Supplement. Age was not found to be a significant factor affecting mortality in either the HFOV or CMV group ($P = .77$).

**Comparison Between Matched Early HFOV and CMV Patients**

Patients in both groups were similar in baseline characteristics, severity of illness scores, hemodynamic parameters, institution of CPR and cardiopulmonary support, laboratory data, and interventions in the ICU (Table). After appropriate matching, length of mechanical ventilation ($14.6$ vs $15.9$ days, $P < .001$), ICU LOS ($19.3$ vs $19.5$ days, $P = .03$), and mortality ($8.3\%$ vs $18.1\%$, $P < .001$) were significantly lower in the CMV vs the early HFOV group. The SMR in the early HFOV group was $1.62$ ($95\%$ CI, $1.31$-$2.01$) compared with the SMR in the CMV group ($0.76$; $95\%$ CI, $0.62$-$1.16$).
hours of acute respiratory failure was associated with shorter length of ventilation and shorter ICU LOS compared with late use of HFOV.

Given the paucity of data on this topic and issues of designing and conducting large prospective, multicenter, randomized controlled trials in pediatrics, we conducted a post hoc analysis of data from an existing national database with a large sample size. Although patients were not classically prospectively randomized, children receiving HFOV were matched with children receiving CMV using propensity score matching. One potential advantage of this quasi-experimental outcomes research using databases is that data are generated from all patients during routine health care services; therefore, the results can be applied more generally, mitigating the effects of study design and selection bias.

To date, only one randomized, multicenter study in children has compared HFOV with CMV for acute respiratory failure. Although this trial was a randomized multicenter trial that involved 5 centers in North America, the sample size was small, with only 29 patients in each arm. In addition, there was a significant crossover between the 2 groups because of treat-
though raw mortality was similar in the 2 groups, standard-
and decreased ICU LOS when compared with late HFOV. Al-
comes, including decreased length of mechanical ventilation
HFOV group, early use of HFOV was associated with better out-
illness. Our study demonstrated similar results. Within the
sequently advised that HFOV should be considered early in the
ration of vasoactive medications.10 In our study, increased use of
HFOV for acute hypoxemic respiratory failure is controver-
sial. Arnold et al21 reported increased mortality in children 5
respiratory failure, infants randomly assigned to HFOV were
noncrossover clinical trial in very low-birth-weight infants with
respiratory failure, infants randomly assigned to HFOV were
successfully extubated earlier than infants assigned to CMV,
with improved mortality and less need for supplemental oxygen.22 In our study, we did not find any association of mor-
tality with age (eFigure 2 in the Supplement). However, our
study did not include premature neonates and children younger than 1 month.

In a single-center trial that involved 26 children, early use of HFOV within the first 24 hours of acute hypoxemic respi-
atory failure was associated with better survival.23 It was sub-
sequently advised that HFOV should be considered early in the
illness. Our study demonstrated similar results. Within the
HFOV group, early use of HFOV was associated with better out-
comes, including decreased length of mechanical ventilation and
decreased ICU LOS when compared with late HFOV. Al-
though raw mortality was similar in the 2 groups, standard-
ized mortality was higher in the late HFOV group compared
with the early HFOV group. However, children in the early
HFOV group were younger, smaller, and sicker (as demon-
strated by higher PIM-2 and PRISM-3 scores) when compared
with the late HFOV group.

One needs to carefully evaluate the severity of illness and
etiologic factors to understand the results of any study.24 It is
conceivable that, despite careful matching and similarity of 2
widely accepted severity of illness scores, the patients in the
HFOV group were sicker than the CMV patients. Even if that
were the case, the question of whether HFOV is the solution
to preventing mortality and improving long-term outcomes in
children with acute respiratory failure remains. The possible
strategies for improving long-term outcomes can be the use of
either lung-protective low tidal volume ventilation or early
use of ECMO in patients with acute respiratory failure. Our
study was conducted during the period when most of the pe-
diatric ICUs are using lung-protective low tidal volume venti-
lation. It is possible that this may have led to improved out-
comes in the CMV group. However, our study lacked data on
certain key variables, such as partial pressure of oxygen in ar-
terial blood (PaO2), partial pressure of carbon dioxide in arte-
rial blood (PaCO2), fraction of inspired oxygen, ratio of PaO2 to
fraction of inspired oxygen, presence of focal vs diffuse lung
disease, use of nitric oxide, and presence of air leak, that could
have been used in the propensity score modeling. Our study
also lacked mechanical ventilator data, such as plateau, mean,
and end expiratory pressures, and data on inotropes, seda-
tives, and neuromuscular blocking agents, which could have
potentially affected outcomes. The use of HFOV has been dem-
onstrated to be associated with increased and longer use of va-
soactive infusions, higher doses of sedatives, and increased use
of neuromuscular blockers.25 In our study, increased use of

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Figure 2. Kaplan-Meier Curves for Intensive Care Unit (ICU) Length of Stay (LOS) and Duration of Mechanical Ventilation

A. ICU LOS for conventional mechanical ventilation (CMV) and high-frequency oscillatory ventilation (HFOV) patients (death times are marked in the plot). The median ICU LOS was estimated to be 14.6 days (95% CI, 13.8-15.2 days) for CMV patients and 21.9 days (95% CI, 20.9-23.4 days) for HFOV patients. A significant difference was seen in the ICU LOS between CMV and HFOV patients based on the frailty model (P < .001). B. Duration of mechanical ventilation for CMV and HFOV patients (death times are marked in the plot). The median duration of mechanical ventilation was estimated to be 10.3 days (95% CI, 9.5-10.9 days) for CMV patients and 16.8 days (95% CI, 15.7-18.1 days) for HFOV patients. A significant difference was seen in the duration of mechanical ventilation between CMV and HFOV patients based on the frailty model (P < .001).

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A, ICU LOS for conventional mechanical ventilation (CMV) and high-frequency oscillatory ventilation (HFOV) patients (death times are marked in the plot). The median ICU LOS was estimated to be 14.6 days (95% CI, 13.8-15.2 days) for CMV patients and 21.9 days (95% CI, 20.9-23.4 days) for HFOV patients. A significant difference was seen in the ICU LOS between CMV and HFOV patients based on the frailty model (P < .001). B, Duration of mechanical ventilation for CMV and HFOV patients (death times are marked in the plot). The median duration of mechanical ventilation was estimated to be 10.3 days (95% CI, 9.5-10.9 days) for CMV patients and 16.8 days (95% CI, 15.7-18.1 days) for HFOV patients. A significant difference was seen in the duration of mechanical ventilation between CMV and HFOV patients based on the frailty model (P < .001).
sedatives and neuromuscular blockers in the HFOV group may have led to worse outcomes.

Conclusions

Application of HFOV and early HFOV compared with CMV in children with acute respiratory failure is associated with worse outcomes, including increased standardized mortality, increased length of mechanical ventilation, and increased ICU LOS. The results from our large, multicenter study of children receiving mechanical ventilation for acute respiratory failure are similar to recently published studies in adults comparing these 2 ventilation modalities for acute respiratory distress syndrome. Further studies using large clinical databases may provide evidence of efficacy (or lack thereof) for other commonly used therapeutic interventions in critical care that may be difficult to study with classic prospective randomized controlled trials due to expense, logistics, and clinical balance. Use of such databases for comparative effectiveness research may in the future decrease the cost of discovery and guide us in improving outcomes for critically ill patients.

REFERENCES