BRIEF REPORT

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Heterogeneous Treatment Effects of High-Frequency Oscillatory Ventilation for Acute Respiratory Distress Syndrome: A Post Hoc Analysis of the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) Trial

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OBJECTIVES: We sought to evaluate whether different subgroups of adults with acute respiratory distress syndrome (ARDS) respond differently to high-frequency oscillatory ventilation (HFOV).

DESIGN: The Oscillation for ARDS Treated Early (OSCILLATE) trial was a randomized controlled trial of HFOV vs. conventional ventilation that found an increased risk of in-hospital mortality (primary outcome) with HFOV. In a post hoc analysis, we applied three different approaches to evaluate heterogeneity of treatment effect for in-hospital mortality: 1) subgroup analyses based on baseline Pao_2:Fio_2 ratio and oxygenation index (OI); 2) a risk-based approach using a multivariable outcome prediction model; and 3) a clustering approach via multivariable latent class analysis. We used multivariable logistic regression models to assess for interaction.

SETTING: Thirty-nine ICUs, five countries.

SUBJECTS: Five hundred forty-eight adults with moderate to severe ARDS.

INTERVENTIONS: HFOV vs. conventional mechanical ventilation with low tidal volume and higher positive end-expiratory pressure.

MEASUREMENTS AND MAIN RESULTS: The effect of HFOV on in-hospital mortality was consistent across categories of Pao_2:Fio_2 ratio (adjusted odds ratio [aOR], 2.04; 95% CI, 1.32–3.17 and aOR, 1.16; 95% CI, 0.49–2.75 for groups with Pao_2:Fio_2 above or equal to 80, vs. below 80, respectively; interaction $p = 0.23$) and OI (aOR, 1.78; 95% CI, 0.67–4.70; aOR, 3.19; 95% CI, 1.44–7.09; aOR, 1.73; 95% CI, 0.82–3.65; and aOR, 1.33; 95% CI, 0.61–2.90 for quartiles of baseline OI, respectively; interaction $p = 0.44$). Point estimates for the effect of HFOV were consistent across risk categories (aOR, 2.44; 95% CI, 0.40–14.83; aOR, 1.69; 95% CI, 0.75–3.85; and aOR, 2.10; 95% CI, 0.59–7.54 for the lowest, moderate, and highest risk categories, respectively; interaction $p = 0.32$). Using a clustering approach, point estimates for HFOV were also consistent (cluster 1: aOR, 1.85; 95% CI, 1.15–3.00 and cluster 2: aOR, 1.75; 95% CI, 0.91–3.38; interaction $p = 0.75$).

CONCLUSIONS: We did not identify heterogeneity in the effect of HFOV across different subgroups of patients with ARDS.

KEYWORDS: acute respiratory distress syndrome; high-frequency oscillation ventilation; latent class analysis; randomized controlled trial; treatment effect heterogeneity

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KEY POINTS

Question: Do different subgroups of adult patients with acute respiratory distress syndrome (ARDS) respond differently to a high-frequency oscillatory ventilation (HFOV) strategy compared with conventional mechanical ventilation?

Findings: In this secondary post hoc analysis of a multicenter nonblinded randomized controlled trial, there was no heterogeneity in the effect of HFOV on in-hospital mortality by subgroups defined by oxygenation, a risk score, or latent class analysis. In all subgroups, point estimates for HFOV suggested increased mortality or were neutral.

Meaning: This analysis did not identify a patient subgroup for whom HFOV was associated with lower in-hospital mortality.

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome of hypoxemia and bilateral infiltrates on chest imaging, not primarily due to heart failure or volume overload, that is common in critically ill adults (1). Many trials evaluating therapeutic interventions for patients with ARDS have been indeterminate, arguably due to biological heterogeneity of enrolled patients (2). Recent studies have identified sub-phenotypes within ARDS that may respond differently to interventions such as statins and ventilation with higher positive end-expiratory pressure (PEEP) (3, 4).

High-frequency oscillatory ventilation (HFOV) has shown no benefit for the average patient with ARDS, and may be harmful (5–7). However, there is plausible physiologic rationale that the most severely hypoxemic patients may benefit from HFOV, a finding also suggested by an individual patient data meta-analysis (5–7). As rescue therapy, HFOV has been used in selected patients with ARDS, despite increased deployment of prone positioning and extracorporeal membrane oxygenation (8). Hence, we sought to identify clinical subgroups of adult patients with ARDS enrolled in the Oscillation for ARDS Treated Early (OSCILLATE) randomized trial, which found increased in-hospital mortality in patients receiving HFOV compared with conventional mechanical ventilation. We then explored the existence of heterogeneity of the effect of HFOV on in-hospital mortality in the different subgroups.

MATERIALS AND METHODS

We analyzed demographic, clinical, and physiological data from a multicenter nonblinded randomized controlled trial as a post hoc study (ClinicalTrials.gov numbers: NCT00474656 and NCT01506401) (6). The OSCILLATE trial included 39 centers in Canada, the United States, Saudi Arabia, Chile, and India between July 2007 and August 2012. The pilot trial was first approved by the University Health Network research ethics board (study title: The Oscillation for ARDS Treated Early (OSCILLATE) Trial; approval date May 3, 2007; reference 07-0158-B) and by the ethics committee at each center. Patients' legal representatives provided informed consent, and the study was conducted according to the amended declaration of Helsinki. Briefly, 548 adults with new-onset, moderate to severe ARDS were randomized to either HFOV or a conventional ventilation strategy comprised of low tidal volume and a higher PEEP target. The primary endpoint was all-cause in-hospital mortality; details can be found elsewhere (6).

We aimed to evaluate the presence of heterogeneity of treatment effect (HTE) of HFOV on mortality by clinically distinct subgroups defined at baseline. We used three approaches: 1) separate subgroup analyses based on Pao_2:FIO_2 ratio and oxygenation index (OI = 100 × mean airway pressure/[Pao_2/FIO_2]) at baseline (9); 2) a risk-based approach using a multivariable outcome prediction model; and 3) a statistical clustering approach via multivariable latent class analysis. First, we stratified the cohort by Pao_2:FIO_2 ratio (either ≥ 80 or < 80), with the threshold selected based on the previous meta-analysis (7). Separately, we stratified by quartile of OI, a measure that incorporates mean airway pressure to reflect the intensity of mechanical ventilation and thus may have superior prognostic ability in ARDS compared with measures of hypoxemia alone (10, 11). In a sensitivity analysis, we considered baseline Pao_2:FIO_2 ratio thresholds of 50, 60, and 70. In the second approach, we created a multivariable model for hospital death using baseline demographic, clinical, ventilator, and laboratory data (**eTable 1**, http://links.lww.com/CCX/B430). Data for all variables were obtained before or at randomization and

chosen based on subject matter knowledge. We stratified the cohort by the quintile of predicted probability of hospital death. Finally, in the clustering approach, we selected potentially useful variables a priori (eTable 1, http://links.lww.com/CCX/B430). Continuous variables were standardized on a z scale with mean of zero and SD of one. We excluded variables with correlation coefficients greater than 0.5 (12). We then applied multivariable latent class analysis; the optimal number of clusters was based on the Bayesian information criteria, entropy, size of the smallest cluster, and biological plausibility (**eTable 2**, http://links.lww.com/CCX/B430).

Our main outcome of interest was in-hospital mortality. To assess for HTE, we fitted both univariable and multivariable logistic regression models; we adjusted for covariates including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score (13), Pao_2:FIO_2 ratio (except for the first analytic approach), vasopressor use, prone positioning before randomization, and corticosteroid prescription before randomization. To address missing data, we used multiple imputation implemented in the mice package in R statistical software (14). To test for HTE, we created interaction terms between the randomized treatment and the different subgroups. We present estimates of association across different strata using adjusted odds ratios (aORs) with 95% CIs.

All analyses were performed using R, Version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and Stata, Version 15.1 (Stata Corp, College Station, TX). We considered two-sided *p* value of less than 0.05 as the threshold for statistical significance.

RESULTS

Overall, 548 patients were included in the OSCILLATE trial; median (interquartile range [IQR]) age was 57 years (44–66 yr) and 42% of patients were female. The median (IQR) APACHE II score was 29 (24–35); close to half of the study cohort presented with sepsis (47%), and 65% received vasopressor support before randomization. In-hospital mortality was 41% (225/548); HFOV was associated with increased mortality overall (unadjusted odds ratio, 1.63; 95% CI, 1.15–2.30 and aOR, 1.76; 95% CI, 1.21–2.58; **Fig. 1**).

Figure 1 summarizes the three distinct approaches to evaluate HTE. The Pao_2:FIO_2 < 80 group had 106 patients, of whom 55% died in hospital; the Pao_2:FIO_2 ≥ 80 group had 435 patients, of whom 38% died in hospital (**Table 1**). There was no evidence of HTE of HFOV for in-hospital mortality (Pao_2:FIO_2 < 80: aOR, 1.16; 95% CI, 0.49–2.75 and Pao_2:FIO_2 ≥ 80: aOR, 2.04; 95% CI, 1.32–3.17; interaction $p = 0.23$; Fig. 1). In the sensitivity analysis applying Pao_2:FIO_2 ratio thresholds of 70, 60, and 50, results were similar (**eFig. 2**, http://links.lww.com/CCX/B430). Additionally, there was no evidence of HTE of HFOV according to different baseline OI quartiles (interaction $p = 0.44$; Fig. 1).

In the risk-based approach, in-hospital mortality in the lowest ($n = 110$), moderate ($n = 110$), and highest risk ($n = 110$) groups were 6%, 36%, and 88%, respectively (Table 1; and for all five risk categories, **eTable 3**, http://links.lww.com/CCX/B430). There was no evidence of heterogeneity in the effect of HFOV across different risk categories (lowest: aOR, 2.44; 95% CI, 0.40–14.83; moderate: aOR, 1.69; 95% CI, 0.75–3.85; highest: aOR, 2.10; 95% CI, 0.59–7.54; interaction $p = 0.32$ by a likelihood ratio test; Fig. 1).

Finally, in the statistical clustering approach, we identified two subgroups via latent class modeling. The number of patients in clusters 1 and 2 was 342 and 206, respectively; there were no participants for whom the highest probability of belonging to a single class was poor (< 0.7). Groups differed across several clinical characteristics (Table 1; and **eFig. 1**, http://links.lww.com/CCX/B430). In-hospital mortality was 41% in both subgroups. Point estimates for HFOV favored increased hospital mortality in both clusters, with no evidence of heterogeneity (cluster 1: aOR, 1.85; 95% CI, 1.15–3.00 and cluster 2: aOR, 1.75; 95% CI, 0.91–3.38; interaction $p = 0.75$).

DISCUSSION

In this secondary analysis of the OSCILLATE trial, we did not find evidence of HTE of HFOV for in-hospital mortality using traditional subgroup, risk-based, or latent clustering methods. Point estimates for the effect of HFOV in all subgroups suggested increased mortality or were neutral.

Our data complements a previous individual patient data meta-analysis that reported potential HTE by Pao_2:FIO_2 ratio; patients with more profound hypoxemia (Pao_2:FIO_2 < 80) seemed to benefit from HFOV (7). Our results did not reveal similar HTE;

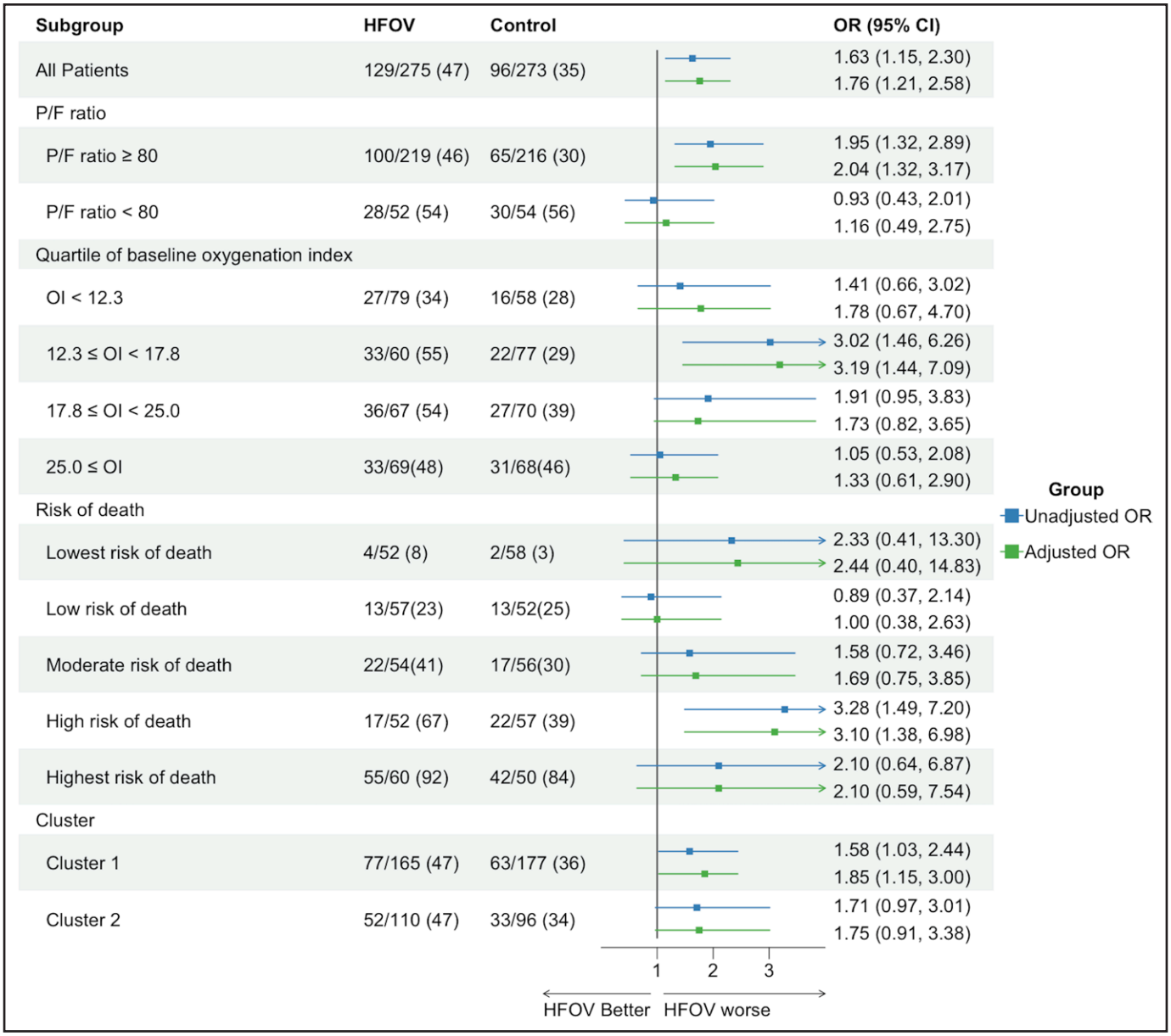

Figure 1. Hospital death and odds ratio (OR) of high-frequency oscillatory ventilation (HFOV) among subgroups. Data in the HFOV and control (conventional mechanical ventilation) columns indicates the number of patients who died/total number of patients randomized (%). Oxygenation index (OI) = 100 × mean airway pressure/(Pao_2/FIo_2). P/F ratio = Pao_2:FIo_2 ratio.

however, this study only includes OSCILLATE, which limits sample size and reduces statistical power to discover HTE. A post hoc calculation suggests that this analysis had a power of 39.4% to detect differential effects of HFOV by baseline Pao_2:FIo_2, dichotomized at 80 (15). Furthermore, we did not find HTE based on OI, a variable that reflects the intensity of mechanical ventilation. Our findings agree with the original trial report that showed no interaction with baseline lung compliance (6).

We also implemented a risk-based approach to HTE, as recommended (16). In contrast to prior data showing potential differential effects of statins in ARDS by baseline risk of mortality, we did not find differences in the effect of HFOV (17). Although baseline risk might have been expected to be associated with a differential response to HFOV, perhaps based on lung recruitability, point estimates for HFOV suggested no effect or harm in all subgroups, without statistically significant interaction.

Recent studies using latent class analysis have classified patients with ARDS to hyperinflammatory and hypoinflammatory subphenotypes, which might respond differently to interventions (3, 4). Although we identified two distinct clusters in our cohort, their relationship to

TABLE 1.
Baseline Characteristics and Outcome Among Subgroups in Three Approaches

Variable	P/F Ratio ≥ 80, *n* = 435	P/F Ratio < 80, *n* = 106	Lowest Risk of Death, *n* = 110	Moderate Risk of Death, *n* = 110	Highest Risk of Death, *n* = 110	Cluster 1, *n* = 342	Cluster 2, *n* = 206
Age, median (IQR), yr	56 (44–66)	54 (42–67)	38 (29–49)	61 (49–67)	64 (55–71)	56 (46–66)	55 (38–66)
Female, *n* (%)	175 (40)	52 (49)	47 (43)	48 (44)	42 (38)	147 (43)	81 (39)
Chronic health issues,[a] *n* (%)	143 (33)	28 (26)	9 (8)	31 (28)	70 (64)	121 (35)	57 (28)
Acute Physiology and Chronic Health Evaluation II, median (IQR)	29 (24–34)	33 (26–38)	25 (21–28)	30 (25–34)	36 (31–40)	29 (24–34)	30 (25–35)
Risk factors of acute respiratory distress syndrome, *n* (%)							
Sepsis	204 (47)	50 (47)	35 (32)	49 (45)	70 (64)	141 (41)	117 (57)
Pneumonia	266 (61)	72 (68)	62 (56)	72 (66)	64 (58)	342 (100)	0 (0)
Gastric aspiration	76 (18)	15 (14)	20 (18)	16 (15)	15 (14)	21 (6)	72 (35)
Trauma	13 (3)	2 (2)	6 (6)	2 (2)	1 (1)	3 (1)	12 (6)
Positive end-expiratory pressure, median (IQR), cm H_2O	12 (10–15)	15 (12–16)	14 (10–18)	14 (10–16)	12 (10–14)	14 (10–16)	12 (10–16)
Plateau pressure, median (IQR), cm H_2O	28 (24–33)	32 (30–35)	28 (24–32)	30 (26–33)	32 (26–34)	30 (25–34)	30 (25–33)
P/F ratio, median (IQR)	124 (103–150)	66 (55–74)	142 (111–170)	111 (87–136)	93 (70–119)	112 (84–139)	115 (87–147)
Vasopressors, *n* (%)	279 (64)	71 (67)	55 (50)	70 (64)	90 (82)	218 (64)	137 (67)
Glucocorticoids, *n* (%)	146 (34)	39 (37)	19 (17)	41 (37)	52 (47)	134 (39)	55 (27)
Hospital mortality, *n* (%)	165 (38)	58 (55)	6 (6)	39 (36)	97 (88)	140 (41)	85 (41)

IQR = interquartile range, P/F ratio = Pao_2:Fio_2 ratio.

Data on the low and high risk of death categories are in eTable 3 (http://links.lww.com/CCX/B430).

[a]The 'chronic health issues' variable was defined by the presence of any chronic health points in the Acute Physiologic and Chronic Health Evaluation II score, including severe organ insufficiency (liver, cardiovascular, respiratory, renal) and immunocompromised state.

these previously identified subphenotypes is unclear in the absence of biomarker data. From a clinical perspective, the diagnosis of pneumonia, which was present in all patients in cluster 1 and none in cluster 2, differentiated the clusters. HFOV was nonbeneficial in both clusters. The lack of differential effect could be related to the cohort characteristics in OSCILLATE, which included more patients with sepsis, vasopressor use, and higher plateau pressure compared with previous trials, or true consistent harm from HFOV.

Our study has additional limitations. As a secondary analysis of previous clinical trial, our findings should be taken as exploratory and hypothesis generating. Although our dataset included missing values, these were evident in only 3% of patients.

CONCLUSIONS

In adult patients with ARDS enrolled in the OSCILLATE trial, we did not find evidence of HTE of HFOV vs. conventional mechanical ventilation on the outcome of in-hospital mortality.

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