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CORRESPONDENCE

High-Frequency Oscillation for ARDS

TO THE EDITOR: In their article on the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) study, Ferguson et al. (Feb. 28 issue)[1] report increased mortality in patients with the acute respiratory distress syndrome (ARDS) who underwent high-frequency oscillatory ventilation (HFOV), probably because of elevated mean airway pressures. High levels of airway pressure may reduce venous return by elevating right atrial pressure, increasing venous resistance, and creating vascular waterfall conditions in the vena cava.[2,3] High levels of airway pressure may also increase pulmonary vascular resistance and right ventricular afterload through passive compression of alveolar vessels.[4] During HFOV, the mean airway pressure is a setup measure but is a dependent variable during conventional mechanical ventilation. It is influenced by inspiratory, expiratory, and total cycle times, alveolar pressure, tidal volume, inspiratory resistance, and positive end-expiratory pressure (PEEP)[5] (Fig. 1). The data presented by Ferguson et al. suggest that we should consider control of the mean airway pressure for circulatory protection of patients with ARDS who are undergoing mechanical ventilation, just as we learned to limit plateau pressure for lung protection.

$$\text{mean airway pressure} = \frac{Ri \times Vt}{Tt} + \frac{\left[\int_0^{Ti} PA \times dt\right]}{Tt} + PEEP \times \frac{Te}{Tt}$$

Figure 1. Determinants of Mean Airway Pressure.
The mean airway pressure is influenced by the inspiratory time (Ti), expiratory time (Te), and total cycle time (Tt), along with the time integral of the function of alveolar pressure (PA) during inspiration (dt), tidal volume (Vt), inspiratory resistance (Ri), and positive end-expiratory pressure (PEEP).

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TO THE EDITOR: Ferguson et al. found that the use of HFOV for the treatment of early ARDS was associated with an absolute increase of 12 per-

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centage points in the rate of death, as compared with conventional ventilation. We are concerned that systematic differences between the sedation strategies used in the two study groups may explain the findings, as we discussed regarding the study of neuromuscular blockers for early ARDS reported by Papazian et al.[1,2]

Perception of discomfort associated with HFOV may predispose physicians to prescribe higher doses of vasodilating sedatives and analgesics than with conventional ventilation (approximately 750 μg of fentanyl and 50 mg of midazolam more per day with HFOV), a finding that was associated with the administration of an additional liter of fluid over the first 3 days to maintain hemodynamic stability. In the Sepsis Occurrence in Acutely Ill Patients (SOAP) trial, investigators found an absolute increase in mortality of 10 percentage points for each liter of fluid accumulated during the first 72 hours,[3] a finding that approximated the increase in mortality reported in the study by Ferguson et al.

Perhaps if the anesthetic prescription included ketamine (similar to that used in the group receiving neuromuscular blocking agents in the study by Papazian et al.[1]), the combination of the opiate-sparing and vasoconstricting effects of ketamine[4] would attenuate sedation-related fluid requirements, and the benefit of HFOV would be realized.

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TO THE EDITOR: The OSCILLATE study and the Oscillation in ARDS (OSCAR)[1] trial by Young et al. have provided robust data on the outcome of HFOV among patients with ARDS. However, we wonder whether the key message — namely, the critical importance of lower tidal volumes in conventional ventilation — should be taken from considering the two studies together. Illness-severity scores were lower at randomization in the OSCAR study than in the OSCILLATE study. However, the control group in the OSCAR study had a rate of death of 41.1%, whereas the rate of death in the OSCILLATE study was 35%. Although the ventilation protocols in the control groups seem similar, in the OSCILLATE study, investigators were more successful in delivering low tidal volumes. In the OSCAR study, the delivered tidal volumes were just over 8 ml per kilogram of body weight. The original study by the ARDS Network[2] showed the importance of targeting a low tidal volume. Needham et al.[3] showed that ventilation with tidal volumes of less than 6.5 ml per kilogram was associated with a survival advantage, as compared with even modestly higher values (6.5 to 8.5 ml per kilogram). It would appear that the control groups in the OSCILLATE and OSCAR studies reveal a major difference in practice, which resulted in a survival difference.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In experimental models of lung failure, the use of HFOV improves oxygenation and reduces lung injury, as compared with low-tidal-volume ventilation.[1] However, neither the OSCILLATE study nor the OSCAR study was able to translate this benefit from bench to bedside. Two factors are at play. First, both the time of initiation of HFOV and the type of lung injury are crucial determinants of the potential for lung re-

cruitment. The inclusion of patients receiving mechanical ventilation for up to 1 week and the high prevalence of direct lung injury may have contributed to the reported lack of benefit for HFOV. Second, HFOV is a complex technique requiring high levels of expertise and is associated with a considerable learning curve. Although we note the efforts to train personnel at the experimental sites, for the studies to be credible, there needs to be a verifiable demonstration of skill in the use of HFOV by all operators.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We think that the methods that were used to set mean airway pressure in the OSCAR and OSCILLATE trials were sufficiently different to be clinically meaningful. In the OSCAR trial, the mean airway pressure was set at 5 cm of water above the pressure recorded in conventional ventilation, whereas it was set according to levels of the fraction of inspired oxygen in the OSCILLATE trial. Therefore, in the OSCILLATE trial, the mean airway pressure was greater in the HFOV group at day 1 than in the control group, and the difference persisted during the first week. We have found that the use of a mean airway pressure of more than 5 cm above the level of airway pressure recorded during conventional ventilation was not associated with better oxygenation but was associated with a decrease in cardiac output by worsening right ventricular function.[1] This mechanism probably occurred in patients in the OSCILLATE study, in which the HFOV group had higher use of vasopressors after initiation of the protocol than did the control group.

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DR. FERGUSON AND COLLEAGUES REPLY: Different ventilatory strategies have varying consequences on many physiological and biologic processes, including gas exchange, hemodynamics, ventilator-induced lung injury, and patient comfort, which often makes it difficult to predict the effects of these strategies on outcome. Each of the correspondents highlights this fact and shows why clinical trials are necessary to weigh the positive and negative effects of different aspects of any given ventilatory strategy.

As discussed in our article, we agree with Liaudet and with Guervilly and colleagues that higher mean airway pressures in the HFOV group may have contributed to excess mortality. After the publication of the study by Guervilly et al., which suggested worsening right ventricular function on echocardiography with HFOV, the OSCILLATE steering committee discussed whether there should be any changes to the protocol.[1] Given the uncertain clinical relevance of their findings, the potential benefits of higher mean airway pressures in mitigating ventilator-induced lung injury, and expert recommendations underlying our protocol,[2] we did not change the protocol but recommended that investigators consider performing echocardiography in study participants receiving HFOV.

We agree with McDermid and Csányi-Fritz that increased sedation and fluid administration could have contributed to the increased mortality in the HFOV group, although the relative importance of this mechanism is unclear. Observational data such as those obtained in the SOAP study may be confounded by severity of illness. Indeed, data from randomized trials have shown that large differences in sedative administration were not associated with differences in mortality.[3]

We agree with MacDuff and Holland that the conventional ventilation strategy used in the control group in our study (i.e., low tidal volumes and higher PEEPs) may have contributed to our finding of better outcomes for conventional ventilation. However, we urge caution in comparing the outcomes in control groups across studies, since even subtle differences in methods may

have important implications. For example, in the OSCAR study, severity of illness was calculated on admission, whereas we used data obtained 24 hours before randomization, which may have resulted in systematic differences in scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II between the studies.

As Muellenbach and colleagues point out, both the timing of HFOV initiation and the expertise of the personnel using the device may have important implications. We specified that patients be enrolled within 72 hours after meeting study inclusion criteria, and we enlisted centers in which there was substantial experience in using HFOV. Although we cannot attest to the expertise of every clinician who cared for patients in the trial, we found no relationship between the number of patients studied per site (as a rough measure of experience) and mortality.

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Since publication of their article, the authors report no further potential conflict of interest.

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DR. YOUNG REPLIES: MacDuff and Holland suggest that the lower mortality in the OSCILLATE control group, which they attribute to the use of smaller tidal volumes in conventional ventilation than were used the OSCAR study, may have unmasked the harm that HFOV was causing. This may be the case, although there might also have been differences between the two control groups that were not captured in the severity scores, demographic characteristics, or other recorded data that would account for the differences.

In the OSCAR study, we spent a considerable amount of time training participating critical care staff in the use of HFOV. It would not have been appropriate to introduce a new mechanical ventilator to critical care units without this training, whether in the context of a trial or not. In clinical trials of interventions that require training, it is not uncommon to look at the results to see whether the effect size changes as units recruit more patients, suggesting a learning effect. We are currently looking into this issue.

Guervilly and colleagues suggest that in the OSCILLATE study, the higher mean airway pressure in the HFOV group than in the control group may account for the increased early use of vasoactive drugs in this group. In the OSCAR study, the mean pressure was not recorded in the control group, so we cannot determine whether it was the same as that in the HFOV group. There was no significant between-group difference in the use of vasoactive drugs in the OSCAR study, as recorded as the proportion of patients receiving these drugs.

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Myths, Presumptions, and Facts about Obesity

TO THE EDITOR: Casazza et al. (Jan. 31 issue)[1] state that the common notion that "regularly eating (versus skipping) breakfast is protective against obesity" because people who skip breakfast may overeat later in the day is currently nothing more than a presumption. However, the evidence they cite in support of this statement is more complex than they intimate. Examination of this evidence implies overcompensation (with increased food consumption later in the day after having skipped breakfast), but also undercompensation depending on timing of meals.[2,3] In addition, Casazza and colleagues do not acknowledge the short-term nature of the available experimental research on which they focus exclusively. Several surveys and a longitudinal study have negatively correlated body-mass index (BMI) with the frequency of eating breakfast, and mul-