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The following letters are in response to Point:Counterpoint: High-frequency ventilation is/is not the optimal physiological approach to ventilate ARDS patients.

To the Editor: Mechanical ventilation (MV) may aggravate lung injury due to two primary types of injury: volu- and atelectrauma. There is a variety of experimental data clearly showing that avoidance of alveolar overdistension and repetitive collapse and reopening of damaged alveolar lung units leads to lung protection (3). In clinical studies the application of lower tidal volumes (V_T) was associated with improvements in outcome (1). Outcome was not affected by the level of positive- end-expiratory pressure (2). Thus low-V_T ventilation seems to be the key factor to reduce mortality, whereas the optimal V_T remains unclear. At this point, there is growing evidence to suggest that a further V_T reduction might be beneficial for ARDS patients. Due to a number of different CO_2-removal mechanisms, V_T during high-frequency oscillatory ventilation (HFOV) may further be decreased (in the range of 1.0–2.0 ml/kg), thereby minimizing the potential of volutrauma (4, 5, 6). During conventional MV, a further V_T reduction (<4 ml/kg) would inevitably result in an unacceptably high level of hypercapnic acidosis. Therefore, alternative techniques of ventilation, such as arteriovenous extracorporeal CO_2 removal (av-ECLA), must be considered during conventional MV to achieve the same low-V_T that is possible during HFOV. However, a further minimization of V_T with maximal oscillatory frequencies (10–15 Hz) would also be possible if av-ECLA is combined with HFOV. Thereby, av-ECLA may contribute significantly to the goals of lung-protective ventilation strategies, raising the following question: What is the optimal ventilatory strategy during av-ECLA—conventional MV or HFOV?

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To the Editor: Although mammals are scaled similarly and have a tidal volume of ~6.3 ml/kg body wt (6), it is possible to adequately ventilate small and medium body sized mammals and humans of all ages with healthy or diseased lungs using very small volumes (less than anatomic dead space) (5). The use of small tidal volume is the key to lung-protective conventional mechanical ventilation (CMV). On the basis of an abundance of published data, Ferguson and Slutsky (2) and Kacmarek (3) disagree with tenacity on the issue of optimal ventilatory management for ARDS.

In medicine, there are many "correct" theories for the same issue, but what is true in theory may not be true in nature. Many alternatives to CMV that were successfully tested in animal models of ARDS, failed in humans (e.g., partial liquid ventilation) (4). From a physiological perspective, HFO is an excellent way of ventilating ARDS patients. However, most studies comparing HFO with CMV used non-clinically relevant models, lacked adequate sample size, and ventilation lasted just a few hours. In addition to differences in anatomy, pattern of respiration, and the chest shape across species (1), these experiments did not meet equipoise: the CMV arms did not provide lung protection.

If HFO is theoretically better than CMV, it is time to prove it! An RCT comparing HFO to our best approach to CMV in patients with established ARDS is needed. Until then, there is no clinical data to support HFO as the optimal physiological approach to ventilate ARDS.

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To the Editor: Ferguson and Slutsky (3) used abundant experimental data to support the view that HFOV is the optimal physiological approach to ventilate patients with ARDS. In his Counterpoint, Kacmarek (4) stated that although HFOV should theoretically be more protective than conventional ventilation, definitive clinical evidence is still lacking.

Clinical evidence favoring HFOV is particularly scarce in the pediatric (non-neonatal) ARDS population. A single pediatric randomized controlled trial, performed before the era of conventional ventilation with reduced tidal volumes, showed that HFOV was associated with decreased pulmonary morbid-

ity (1). HFOV has since become an important tool in managing pediatric ARDS, based on solid experimental data and anecdotal clinical observations. As such, a well-powered multicenter randomized pediatric trial would probably not be feasible in North America, since many pediatric intensivists would now have ethical concerns about depriving the sickest patients from receiving HFOV sometime along the course of treatment. Furthermore, even if such a trial were to be conducted in the current era of lung protective ventilation, it would be unlikely to show superiority of HFOV over a conventional strategy, as a properly applied protective strategy should not be more protective than another (6).

A truly protective conventional ventilation strategy generally results in hypercapnia and elevated mean intrathoracic pressures. Although well tolerated in adults (2), this approach has been associated with significant hemodynamic instability in models of pediatric ARDS under tight experimental conditions (5) and in pediatric clinical practice. As such, all else being equal, HFOV should be the optimal physiological approach to ventilate the pediatric patient with ARDS.

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To the Editor: One of the major issues in the management of patients with ARDS is whether high-frequency ventilation is the optimal physiological approach to ventilate them (2, 4). Also in preterm neonates with acute pulmonary dysfunction, there is no clear evidence that elective high-frequency oscillatory ventilation (HFOV), as compared with conventional mechanical ventilation (CMV), offers important advantages when used as the initial ventilation strategy (3). In particular, the bronchopulmonary dysplasia rate is only reduced with HFOV in some trials where a high lung volume strategy (HLVS) was used. The question is: was lung volume optimization equally effective in all "HLVS" trials? In our experience (6) an $F_{I_{O_2}} < 0.26$ was chosen as an index of optimal lung volume. It is not reasonably correct to consider an $F_{I_{O_2}}$ of 0.40 or more, used in other trials (5), as marker of ideal lung volume, because in this situation an important V/Q alteration exists. The objectives of future research in both neonatal and adult patients should be: *1*) to explore the importance of specific patient-level factors (for neonates: antenatal corticosteroids, gestational age, birth weight, severity of lung disease, postnatal age at start of HFOV) as effect modifiers, to outline a risk profile of each infant and then target those patients who could have maximal benefit from being ventilated in HFOV modality; *2*) to reexamine the importance of trial design-level factors (HFOV device/settings, HFOV strategy-optimal lung volume and CMV strategy-lung protective ventilation adopted), to explain the heterogeneity of the trials (6).

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To the Editor: This debate (2, 3) has not arisen from flaws in the physiological principles, but from a growing inappropriateness of the populations enrolled in ventilator trials.

In the 1980s and 90s, early randomization was advocated to limit exposure of the HFO-managed patients to the injurious CV patterns then in use. As CV became more lung protective, the "start line" for both clinical and animal RCTs should have moved progressively to include only subjects with lungs that proved resistant to the reversal of ongoing atelectasis despite lung-protective CV. Instead, 1994 Consensus Guidelines for the diagnosis of ARDS have directed most human study enrollment, with successfully recruitable lung injury models dominating animal studies.

In Villar's (6) recent study, patients meeting the classic 1994 $Pa_{O_2}/F_{I_{O_2}}$ criterion for ARDS (i.e., without specific $F_{I_{O_2}}$ and PEEP requirements) had mortality rates varying from 6.3% to 45.5%. A ventilator effect would be improbable in the first subgroup, but worth looking for in the latter patients.

Despite major advances, lung-protective CV protocols cannot achieve optimal aeration in all patients with ARDS. Terragni et al. (5) report a population in which alveolar reexpansion could not be achieved and maintained in a substantial volume of lung, and tidal hyperinflation occurred while using the ARDSnet protocol. In two large neonatal HFO trials, benefit occurred only in the study limiting enrollment to sicker babies (4). Bollen et al. (1) hypothesized that an HFO treatment effect will likely occur only in patients with more severe disease.

The flaw is not in the physiology, but in existing study design.

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To the Editor: In their debate, Ferguson and Slutsky and Kacmarek refer to two studies published by our research group (1, 2). Using apparently the same evidence, they reach opposite conclusions about whether high-frequency ventilation (HFV) is the optimal physiological approach to ventilate ARDS patients (3, 4). A similar discussion has been conducted among neonatologists (1). There is overwhelming theoretical and animal evidence in support of HFV, on the other hand this has not been confirmed in randomized trials. This apparent gap between theory and practice could be because of heterogeneity of the disease. We propose a different starting point. There may be ARDS patients with either such a favorable or such a poor prognosis that HFV will not make a difference. The same line of reasoning has been used to explain differences between trials comparing low with high tidal volumes (5). The theoretical existence of a safe window between atelectasis and over inflation of the lung supports this view (6). This safe window may limit tidal volumes to an extent that only HFV can be used for adequate ventilation. It is not yet clear how to assess this safe window. In our randomized trial, patients with a low oxygenation index and patients with a very high oxygenation index did not seem to benefit from HFV. Mortality in patients with an oxygenation index in between, however, showed a trend in favor of HFV (2). Therefore, we propose to reverse the question to: Which ARDS patients are the optimal candidates for high-frequency ventilation?

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To the Editor: Both supporter (4) and detractor (6) agree that high-frequency oscillation (HFO) theoretically should be more lung protective than conventional ventilation (CV). The main point to be debated is whether HFO can really modify outcome in ARDS patients. To answer this question we have to consider that clinical knowledge and operative learning in intensive care medicine are complex and extremely time consuming phenomena. Since Dreyfuss et al.'s (3) experimental studies on animals, a decade passed until lung protective CV was applied in clinical practice (1). However, even if intensivists are nowadays confident in all aspects of CV, being such ventilation mode part of the daily routine in intensive care patient treatment, still in ARDS patients CV must be tailored because "one size does not fit all" (2): each patient needs specific assessment of his/her clinical condition and a personalized setting of a coherent ventilation strategy.

Animal studies suggest that HFO reduces ventilation-induced lung injury (VILI) in neonatal and adult models (5). Discordant results at the moment are coming from scanty randomized clinical trials on ARDS patients (4, 6). HFO is a complex ventilatory technique with many variables (measurement of tidal volume delivery and its dependence on endotracheal tube size). Moreover, clinical experience on HFO is limited to specialized ICU settings and a commercially available ventilator has been introduced only ten years ago. Before discarding HFO, enough time must be allowed for the development of this technique to its full potential.

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To the Editor: A central feature of this debate (2, 4) is the disparity between studies in animal models, which have provided a physiological rationale for HFO, and clinical studies, which have been hard pressed to show an advantage. One of the main physiological rationales for HFO is its avoidance of atelectrauma. In clinical studies (3) and laboratory studies, the usual way to assess potential for cyclical recruitment and derecruitment (R/D) is to measure the amount of atelectasis at end-inspiratory and end-expiratory breath-holds and extrapolate these values to tidal breathing. This approach assumes that the instantaneous airway pressure is the only relevant parameter, which is implicitly assuming that R/D are nearly instantaneous. Recent studies in animal models, however, have suggested that the time constants for R/D are not zero (5, 6). The result is that cyclical recruitment is profoundly sensitive to respiratory rate, even at conventional respiratory rates (1). No measures to assess R/D dynamics have been applied in ARDS, and the time constants for recruitment and derecruitment are not currently known. If the time constants are faster in ARDS than in experimental models, the usual assumptions will give good approximations. If, on the other hand, the time constants are on par with experimental models, or slower, then the usual assumptions might infer a particular patient is undergoing atelectrauma, when in fact they are not. It is perhaps not so surprising that an optimum frequency for ventilation has been difficult to define in clinical studies, given that the dynamics of recruitment and derecruitment are so poorly characterized in ARDS.

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