

High-Frequency Ventilation and the Prevention of Ventilator-Associated Lung Injury

To the Editor:

With great interest, we read the article by Jerry A. Krishnan and Roy G. Brower that appeared in a recent issue of *CHEST* (September 2000).¹ We fully agree that every effort should be undertaken to minimize the occurrence of ventilator-associated lung injury. By avoiding stretch-induced injury, which is caused by high end-inspiratory and low end-expiratory lung volumes, high-frequency ventilation (HFV) potentially offers a gentler mode of ventilation. The majority of randomized controlled trials of HFV have been conducted in preterm neonates, although three Cochrane Reviews²⁻⁴ have been published. Although the predominant underlying disease in these reviews was a homogeneous parenchymal lung disease (respiratory distress syndrome), therapeutic options were so heterogeneously modified as to render the reviewer's statements inconclusive. However, with respect to the specific techniques of HFV (high-frequency oscillatory ventilation vs high-frequency jet ventilation [HFJV]), a few comments are appropriate. First, HFJV in the treatment of respiratory distress syndrome in preterm infants has been associated with a greater risk for adverse outcome (*ie*, severe intracranial hemorrhage, cystic periventricular leukomalacia, or death).⁵ Second, the only study that demonstrated a reduced incidence of chronic lung disease in preterm infants was the Provo trial.⁶ This trial was performed with the use of an oscillatory device of the diaphragm type, and a high-volume strategy was applied. The term "high-volume strategy" refers to the degree of lung expansion achieved during HFV and corresponds to the lung protective concept of reduced end-inspiratory and increased end-expiratory lung volumes. Taken together, the neonatal data published so far have shown efficacy as well as safety exclusively for the oscillator type of HFV.

A more uniform lung expansion during HFV has additional advantages, which were not discussed by Krishnan and Brower. The distribution of inhaled nitric oxide (iNO), which is frequently used in ARDS treatment regimens, happens in a more homogeneous manner and therefore can be enhanced by HFV. The coadministration of HFV and iNO leads to an improved oxygenation compared to either HFV or iNO alone, which has been shown in preterm as well as in term newborns with acute lung injury (ALI) and pulmonary hypertension.^{7,8} In addition, a more uniform lung expansion prevents alveolar collapse and secondary surfactant inactivation in nonventilated lung areas. High-frequency oscillatory ventilation turned out to significantly reduce the number of redosing surfactant in the treatment of neonatal respiratory distress syndrome.⁶

Clearly, randomized controlled trials establishing the potential role of HFV in adult patients with ALI/ARDS are highly desirable. Data from animal models readily document a superiority of HFV over conventional ventilation once traditional ventilation strategies are employed (*ie*, tidal volumes of 8 to 10 mL/kg).⁹ Applying lung protective strategies during conventional ventilation may ultimately complicate the proof of HFV superiority but will certainly be beneficial for patients with ALI/ARDS.

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To the Editor:

We agree that additional studies are necessary to evaluate the clinical benefit of high-frequency ventilation (HFV) as a lung protective strategy in adults with acute lung injury and ARDS (ALI/ARDS). Studies in animals and neonates are particularly promising for the use of high-frequency oscillation (HFO), a form of HFV. Two studies^{1,2} in premature neonates with respiratory distress syndrome discussed in our review (one cited by Drs. Hoehn and Bührer¹) suggested that HFO reduces the incidence of chronic lung disease compared to conventional ventilation.

The study by Kinsella et al³ found that oxygenation was similar in neonates with persistent pulmonary hypertension randomized to conventional ventilation with inhaled nitric oxide (iNO) compared to HFO alone. Neonates without improved oxygenation ($\text{PaO}_2 < 60$ mm Hg with fraction of inspired oxygen = 1.0 at 2 h) following the initial treatment assignment were crossed over to the alternate strategy. Lack of improvement in oxygenation following crossover led to treatment with HFO and iNO. HFO combined with iNO improved oxygenation in 32% of neonates whose oxygenation did not improve with conventional ventilation and iNO or HFO alone following crossover. While the response to HFO with iNO is encouraging, the lack of prospectively identified control group for this combined strategy limits the interpretation of the results. We look forward to studies in adults with ALI/ARDS.

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Lipid-Lowering Agents and Artery Endothelial Function

To the Editor:

We read with interest the recent article by Houghton and colleagues (September 2000),¹ which indicated an improvement in coronary resistance artery function in hypercholesterolemic patients after treatment with pravastatin. After reading the article, we would like to know whether such endothelial function is improved by treatment with other types of lipid-lowering agents, such as bezafibrate and clofibrate. Bezafibrate and clofibrate are recognized not only as hypolipidemic drugs, but as pharmacologic ligands of peroxisome proliferator-activated receptor α (PPAR- α), one of the ligand-activated nuclear receptor transcriptional factors.² Inoue et al³ demonstrated the expression of PPAR- α in human vascular endothelial cells by reverse transcriptase-polymerase chain reaction. They also demonstrated the increased expression of PPAR- α in these cells after exposure to bezafibrate, suggesting that PPAR- α in endothelial cells plays a regulatory role in the pathogenesis of hyperlipidemia and atherosclerosis, and also in the processes of inflammation and coagulation. Another study⁴ reported that inflammatory activation of aortic smooth muscle cells, which is a hallmark of atherosclerosis, is inhibited by the activation of PPAR- α by these fibrates. In addition, the activation of PPAR- α by these fibrates leads to the induction of apolipoprotein (apo)-AI and apo-AII expression in hepatocytes, resulting in an increase in circulating high-density lipoprotein cholesterol.⁵ Therefore, further study of resistance artery endothelial function in relation to such fibrates might result in more interesting data.

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To the Editor:

Inoue and colleagues are correct in bringing to attention the possible role of fibrate drugs, a different class of lipid-lowering agent than that employed in our study (September 2000),¹ for use in treatment of endothelial dysfunction. Seiler et al² showed that cholesterol-lowering therapy with bezafibrate, over a 7-month period, resulted in improved exercise-induced vasomotion of angiographically normal and previously dilated stenotic coronary arteries.

Evans et al³ recently reported that after 3 months of treatment with ciprofibrate, improvement was demonstrated in fasting and postprandial brachial artery endothelial function among subjects with type 2 diabetes mellitus. The comments of Inoue et al regarding the vascular biology of fibrate drugs are topical. Evidence mounts that not only cholesterol-lowering but nonlipid effects of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor drugs are important elements in the ultimate clinical benefit. For example, one important collateral effect of these agents, which was initially unexpected, is the apparent reduction of endothelial inflammation. Ridker et al⁴ found, in the Air Force/Texas Coronary Atherosclerosis Prevention Study, that treatment with lovastatin among subjects with average low-density lipoprotein (LDL) cholesterol levels independently lowered levels of C-reactive protein (CRP), the prototypic marker of vascular inflammation. Retrospective analysis showed that this translated into an improved cardiovascular event rate in subjects with elevated CRP levels even among those with low LDL cholesterol levels. A number of large randomized clinical trials^{5,6} have shown clinical benefits in patients after treatment with HMG-CoA reductase inhibitors resulting in significant reductions in myocardial infarction, stroke, and death during follow-up. The benefits have been conjectured to be out of proportion to the observed LDL reduction.⁷ This further supports the notion that lipid-lowering agents have other actions that independently lead to the repair of endothelial dysfunction. Ultimately, expanded indications for the use of lipid-lowering agents are likely in both the primary and secondary prevention of clinically significant coronary artery disease. In the future, the selection of lipid-lowering agents may be complexly dictated by factors such as the degree of vascular inflammation and the presence of postprandial lipemia in addition to the classical quantitative assessment of high-density and LDL cholesterol and triglyceride levels.

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