First, the data from animal experiments are compelling. Explanations for the contradictory findings between the human and animal studies are most likely related to (1) the timing of HFV initiation and (2) the heterogeneity of the human population.

In animal models of acute lung injury, the immediate application of HFV reduces barotrauma when compared with the continued use of conventional ventilation. Later "rescue" use of HFV is not as effective. Most human studies have evaluated the relatively late use of HFV. To achieve the dramatic results demonstrated in animal experiments, it may be that HFV intervention must be initiated early. In this October issue of Chest (1993; 104: 216-21), the study by Rosenberg et al supports this conjecture. Children who survived on HFV were treated earlier in their disease progression than children who died. When compared with nonsurvivors, survivors had a better initial response to HFV, suggesting that they had greater pulmonary reserve and less lung injury. Similar observations have been reported in neonates.

The second important difference between animal studies and human studies is the heterogeneity of human diseases. Animal experiments are conducted under precisely controlled conditions, and great effort is made to produce a consistent degree of lung injury. Human experiments are never so controlled. Factors such as age, diagnosis, duration of illness, immune response, cardiac function, and infection can have a profound effect on outcome and response to ventilator changes. In neonates, HFV appears to be most useful in the management of diffuse disease processes like hyaline membrane disease, pneumonia, and adult respiratory distress syndrome. High-frequency ventilation is less effective in patchy lung diseases, such as meconium aspiration syndrome. Most of the data on pediatric patients have been collected on patients with adult respiratory distress syndrome. In this setting, HFV appears to be an effective method for applying a high mean airway pressure to recruit lung volume and improve oxygenation without compromising ventilation or cardiac output. The use of HFV in pediatric patients with airway disease and/or patchy lung disease may not be as effective. In this setting, the time constant of the respiratory system is relatively long, and the propensity for gas trapping is high. The use of HFV in these patients may increase gas trapping. Future clinical studies must correct for these confounding variables and apply disease-specific ventilator strategies if they are to be successful.

Another confounding variable is the application of different types of HFV in the same study. As Rosenberg et al suggest, the outcome in patients managed with high-frequency flow interruption was not as good as in those treated with high-frequency oscillation. There are three types of high frequency ventilators: jets, flow

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**High-Frequency Ventilation in Acute Pediatric Respiratory Failure**

Mortality in pediatric patients with severe acute respiratory failure remains high, ranging from 60 to 92 percent. Animal studies comparing conventional and high-frequency ventilation (HFV) in the management of acute lung injury show that HFV can improve gas exchange and survival and reduce the occurrence of barotrauma. The results of "rescue" studies in humans are encouraging, but two large controlled clinical trials failed to show that HFV could improve outcome when compared with continued use of conventional ventilation.

Carlon and coworkers randomized 309 adults with acute lung injury to conventional ventilation (n = 157) or high-frequency jet ventilation (n = 152). A significantly higher percentage of patients treated with high-frequency jet ventilation met successful ventilation criteria (88 vs 76 percent, p<0.05), but there were no differences between the two groups with respect to survival or the number of days spent in the intensive care unit. The HIFI Study Group randomized 673 neonates with respiratory distress syndrome to high-frequency oscillation (n = 327) or conventional ventilation (n = 346). Survival, the average number of days spent on mechanical ventilation, and the occurrence of chronic lung disease were similar in both treatment groups. High-frequency oscillation was associated with an increase in the incidence of intracranial hemorrhage and periventricular leukoencephalomalacia. It is reasonable to ask why there is still interest in the use of HFV.

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6 Miller RF, Semple SJC, Kocjan G. Difficulties with sputum induction for diagnosis of Pneumocystis carinii pneumonia. Lancet 1990; 335: 112

interrupters, and oscillators. Each type has its own range of operating frequencies, mode of gas humidification, method of delivering tidal volume breaths, and patient circuit. The results achieved using HFV can be both device and strategy specific. The ventilator-associated differences in outcome reported by Rosenberg et al might also be explained by patient selection. Patients treated with high-frequency oscillation were younger and were treated earlier with HFV than patients offered high-frequency flow interruption.

The most important reason for the continued clinical use of HFV is that it is very effective at improving gas exchange when conventional ventilator adjustments fail. When faced with a dying child, we are all compelled to offer extraordinary support to promote survival. However, our enthusiasm for any new therapy must be tempered with academic discipline. Safety and efficacy can be demonstrated only by controlled randomized studies that are based on data collected in pilot studies like the one reported by Rosenberg et al. A number of therapies need careful study (eg, nitric oxide, surfactant, HFV, and extracorporeal membrane oxygenation).

While the study reported by Rosenberg et al presents important new data, it does not prove that HFV offers any long-term benefit with respect to survival or outcome. Adult and neonatal studies are useful, but the diseases affecting children and the recoverability from these disease processes are unique. Evaluation of the safety and efficacy of HFV will require carefully designed, randomized, controlled studies of patients admitted to the pediatric intensive care unit. I hope that the authors’ prospective clinical trial will provide some of these important answers.

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References
6 Mayes TC, Jefferson LS, David Y, Louis PT, Fortenberry JD.

Management of malignant air leak in a child with a neonatal high-frequency oscillatory ventilator. Chest 1991; 100:263-64

Angina Pectoris Caused by Pernicious Anemia

Pernicious anemia, expressed as megaloblastic anemia, exists in individuals who fail to produce a glycoprotein, Castle’s intrinsic factor (CIF). It is commonly thought that the parietal cells of the stomach do not secrete CIF due to autoantibodies, thus not allowing vitamin B12 (cobalamin) to bond with CIF and so to be absorbed by the distal ileum. The failure of CIF secretion is associated with achlorhydria and gastric mucosa atrophy. This acquired disease becomes symptomatic usually after the age of 50 and is most common in individuals of northern European descent, especially Scandinavians. It is diagnosed with the Schilling test.

Anemia of any cause may result in increased cardiac output, especially when the hemoglobin level drops to 7 g/dl or less. Tachycardia may not be present in chronic anemia, and the increased cardiac output at rest usually reflects an increased cardiac stroke volume. The increased cardiac output is achieved at the cost of increased work of the left ventricle. Right atrial, right ventricular, and pulmonary arterial pressures are usually normal unless cardiac decompensation develops. Left ventricular end-diastolic pressure remains unchanged.

Increased cardiac output in pernicious anemia and in other severe chronic anemias is of importance in maintaining an adequate oxygen supply to the tissues, and is facilitated by alterations in left ventricular afterload and myocardial contractility. Although ventricular end-diastolic volume, which is the preload of the left side of the heart, seems to be unchanged, myocardial contractility appears to increase. Afterload and left ventricular wall stress, having as major determinants vascular resistance and blood viscosity, are reduced. Decrease in peripheral vascular resistance in severe pernicious anemia is of great importance in producing increased car-