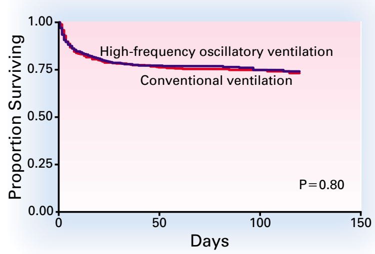
This Week in the Journal

August 29, 2002

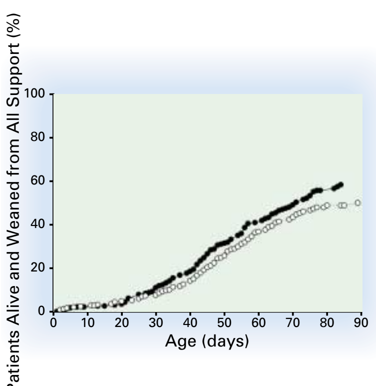


High-Frequency Oscillatory Ventilation in Premature Infants

Respiratory distress is common in premature infants. Many of these infants require mechanical ventilatory support for the first few weeks of life, but the best way to deliver this support is not known. In this randomized trial performed in the United Kingdom, there was no difference between the two ventilatory strategies in terms of survival, the need for oxygen treatment at 28 days of life, or other benefits or complications of ventilation.

The risks and benefits associated with high-frequency oscillatory ventilation are not significantly different from those associated with conventional mechanical ventilation in very preterm infants requiring mechanical ventilatory support. The choice of a mode of ventilation for such infants is best guided by the experience of the medical staff caring for the neonate.

see page 633 (Perspective, page 630; editorial, page 682)



High-Frequency Oscillatory Ventilation for Very-Low-Birth-Weight Infants

This randomized study, performed at multiple centers in the United States, compared high-frequency oscillatory ventilation with synchronized intermittent mandatory ventilation in babies who required mechanical ventilatory assistance. Ventilators were adjusted according to strict validated protocols. Among 234 infants assigned to high-frequency oscillatory ventilation, as compared with 250 assigned to synchronized intermittent mandatory ventilation, a small but significantly greater proportion were alive and not requiring supplemental oxygen at 36 weeks of postmenstrual age ($P=0.046$); there was no significant difference in the incidence of adverse events between the two groups.

This study shows that high-frequency oscillatory ventilation, when delivered in centers experienced with the technique, offers a small advantage over synchronized intermittent mandatory ventilation. In experienced centers, high-frequency oscillatory ventilation offers a small advantage compared to conventional ventilation.

see page 643 (Perspective, page 630; editorial, page 682)

PERSPECTIVE

Ventilation with Small Tidal Volumes

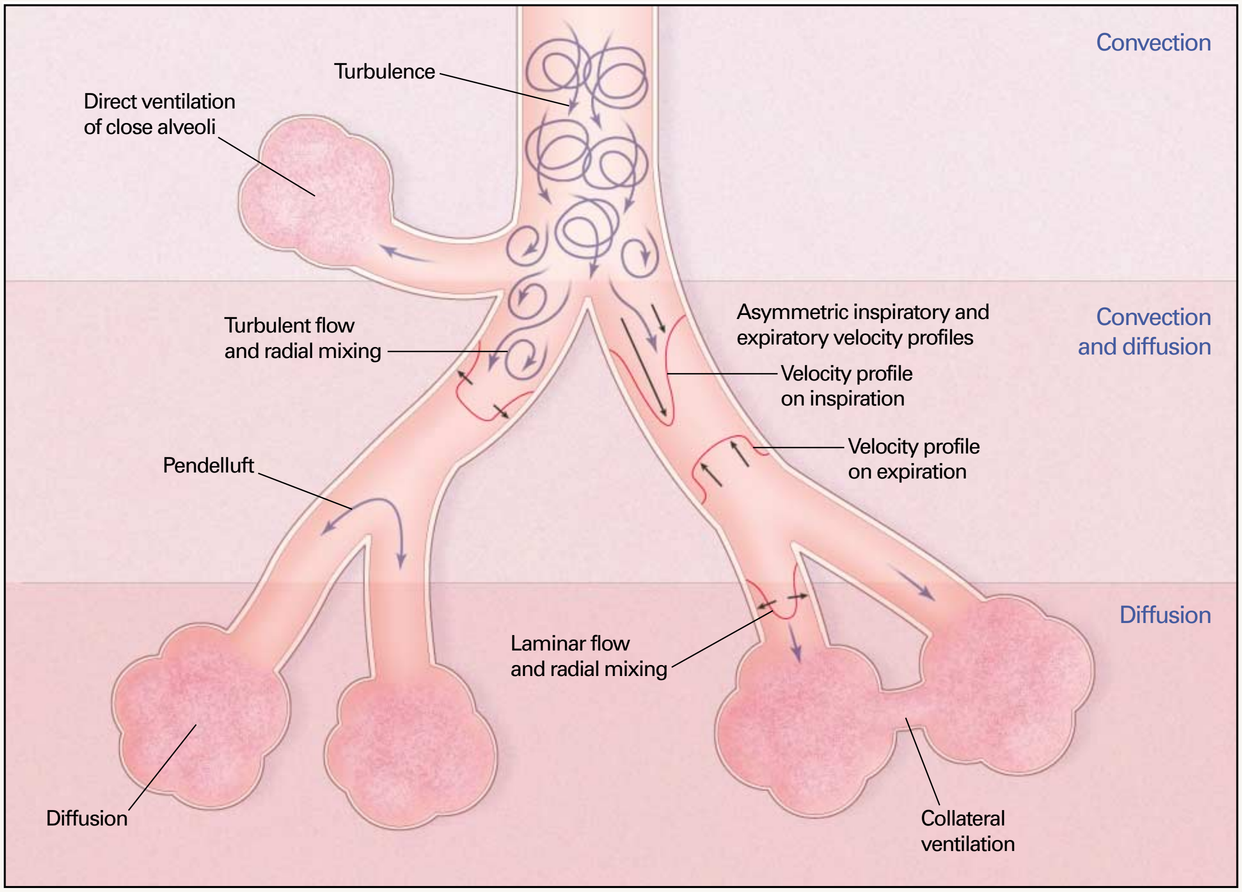
Human survival depends on the exchange of fresh air with carbon dioxide in the blood. Since this exchange takes place in the alveoli, one of the first concepts taught in respiratory physiology is that the size of each breath, the tidal volume, must exceed the volume of the conducting airways, also known as the dead space. However, this construct is not strictly accurate, since we know that adequate gas exchange can be achieved when tidal volumes smaller than that of the dead space are taken in at sufficiently high frequencies, a technique termed high-frequency ventilation.

How can we survive if we take such small breaths? In 1915, Yandell Henderson observed that panting dogs achieved adequate gas exchange, even though they had very small tidal volumes. He suggested that during each breath, a parabolic core of fresh gas penetrated deep into the lung and reached the alveoli. Although Henderson's hypothesis was not entirely correct, many theoretical and experimental studies have demonstrated that a number of convective and diffusive mechanisms (see Figure) act in concert to affect gas transport during high-frequency ventilation. The key concept underlying most of the proposed mechanisms is that the increased energy of the gas molecules at the high ventilatory frequencies and high flows leads to augmented mixing of gas in the airways. The net result is that fresh gas reaches the alveoli.

Pulmonary physiologists understandably take an interest in this counterintuitive approach to ventilation, but why should physicians in general and neonatologists in particular be interested in this mode of ventilation? One explanation might be that the dynamics of gas-flow distribution are altered during high-frequency ventilation, which may improve the matching of ventilation with perfusion. This property of ventilatory dynamics was first understood when isolated lungs ventilated with high-frequency ventilation were viewed with the use of stroboscopic filming techniques. The film showed a massaging motion that could enhance the mixing of gas in the conducting airways and at the interface between these airways and the alveoli. High-frequency ventilation may also facilitate the movement of gas through collateral pathways and through pendelluft (side-to-side ventilation), as illustrated in the Figure. (A video clip of this asynchronous motion is available with the full text of this article at http://www.nejm.org.) Better mixing of gas in diseased lungs should help to improve oxygenation and hence the clinical usefulness of high-frequency ventilation.

However, the major advantage of high-frequency ventilation over conventional ventilation does not appear to be its ability to distribute ventilation more uniformly, but rather its potential to prevent some deleterious consequences of mechanical ventilation. Infants with respiratory distress syndrome have problems with surfactant, predisposing some lung units to collapse. This collapse and the stress placed on the lungs when these units are repetitively reopened with each breath make them more susceptible to injury during tidal ventilation. Furthermore, since less of the lung is available for ventilation because of the collapse, the remaining lung can be overdistended with a normal-sized breath. These factors can lead to iatrogenic injury when mechanical ventilation is used — an effect called ventilator-induced lung injury. The importance of this mechanism can extend beyond the lung — it can lead to the translocation of mediators, endotoxin, and bacteria from the lung into the systemic circulation, which may lead to multiorgan dysfunction.

There are a number of tactical approaches to minimizing ventilator-induced lung injury. One can "rest" the lung using extracorporeal methods of gas exchange (e.g., extracorporeal membrane oxygenation). Another approach is to inflate previously airless regions of the lung and then minimize the stress on the lung by limiting end-inspiratory lung volume. These objectives can be achieved during conventional ventilation with the use of positive end-expiratory pressure and relatively small tidal volumes (such as those noted in adults in the recent Acute Respiratory Distress Syndrome Network trial sponsored by the National Institutes of Health). However, this strategy may not be effective in some patients, because relatively large tidal volumes are still required to ensure adequate gas exchange. During high-frequency ventilation, the tidal volumes and associated swings in alveolar pressure are very small; when applied in a recruited lung, this approach should theoretically limit ventilator-induced lung injury. Such is the promise of high-frequency ventilation, but like many promises, it



Gas-Transport Mechanisms during High-Frequency Ventilation.

The major gas-transport mechanisms that are operative under physiologic conditions in each region (convection, convection and diffusion, and diffusion alone) are shown. There are seven potential mechanisms that can enhance gas transport during high-frequency ventilation: turbulence in the large airways, causing enhanced mixing; direct ventilation of close alveoli; turbulent flow with lateral convective mixing; pendelluft (asynchronous flow among alveoli due to asymmetries in airflow impedance); gas mixing due to velocity profiles that are axially asymmetric (leading to the streaming of "fresh" gas toward the alveoli along the inner wall of the airway and the streaming of "alveolar" gas away from the alveoli along the outer wall); laminar flow with lateral transport by diffusion (Tayor dispersion); and collateral ventilation through nonairway connections between neighboring alveoli.

has been hard to fulfill. Two articles in this issue of the *Journal* (by Johnson et al., pages 633–642, and Courtney et al., pages 643–652) show that, at best, such ventilation helps a little in infants with respiratory distress. An editorial (see pages 682–684) addressing these articles provides insight into the similarities and differences in the trials and discusses the problems that must be addressed if high-frequency ventilation is to be a major therapeutic advance.

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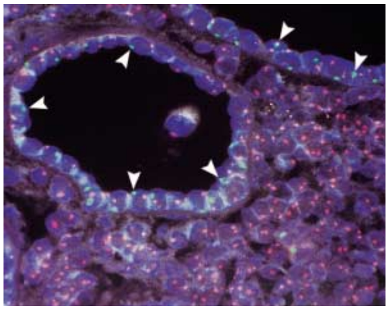
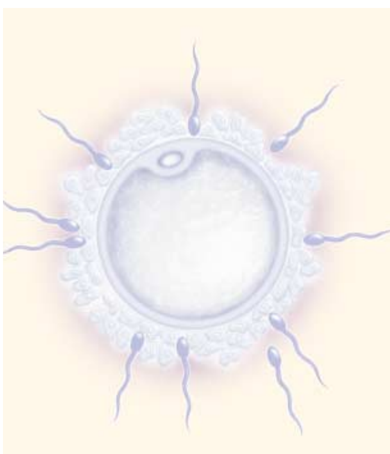


Nephrogenic Adenomas in Renal-Transplant Recipients

Nephrogenic adenomas are benign growths in the urothelial mucosa that can cause hematuria or dysuria. Their origin is unknown. This detailed study of nephrogenic adenomas from recipients of kidney grafts showed that in all cases the adenoma had the sex chromosomes of the donor kidney and the immunohistochemical features of renal tubular cells.

This study provides convincing evidence that the kidney sheds viable tubular cells that can seed the lower urinary tract, where they may grow into tumor-like masses. The authors' suggestion that such adenomas are really renal tubular satellites is both provocative and persuasive.

see page 653 (editorial, page 684)



Special Article: **Insurance Coverage and Outcomes of in Vitro Fertilization**

This study assessed associations between state requirements for insurance coverage of in vitro fertilization services and the utilization and outcomes of such services. Fertility clinics in states that required complete coverage performed significantly more in vitro fertilization cycles involving the transfer of fresh embryos than clinics in states that required partial coverage or none. The percentage of cycles that resulted in live births was lower in the states that required complete or partial coverage, but these states also had a lower number of embryos transferred per cycle and a lower rate of pregnancies with three or more fetuses.

Mandated insurance coverage for in vitro fertilization is associated with increased utilization of these services, suggesting an unmet need. These data also suggest that financial constraints in states that do not require insurance coverage may result in the transfer of more embryos to maximize the chance of pregnancy, with the attendant risk of high-order multiple gestations.

see page 661 (editorial, page 686)

"Adolescent depression is . . . an eminently treatable condition that responds to selective serotonin-reuptake inhibitors and specific psychotherapies."

Clinical Practice: **Adolescent Depression**

A 16-year-old boy is brought by his parents to his primary care physician because of a decline in school performance, which began at least three years earlier but has become more severe in the past year. He reports boredom, a lack of enjoyment and motivation, poor self-esteem, a feeling of hopelessness, difficulty sleeping, poor concentration, and passive thoughts of suicide without a plan or intent. How should he be treated?

About 5 percent of adolescents have major depression. This article reviews approaches to identifying and treating this disorder.

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