

Health-related quality of life and seizure control in temporal lobe epilepsy. *Ann Neurol* 1997;41:482-9.

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The editorialist replies:

To the Editor: St. George and Plowman call attention to the new gamma-knife radiosurgical approach for treating surgically remediable epilepsy. Unfortunately, space constraints prevented me from discussing alternative therapies still under investigation, and it is too early to comment authoritatively on indications for these procedures. I agree that a randomized, controlled trial comparing gamma-knife radiosurgery with standard resective surgical treatment in a selected population of patients, yet to be identified, would be in order at some future time.

Richards's letter is most welcome, because it so clearly illustrates the prejudice against surgical treatment for epilepsy that persists among physicians, despite overwhelming evidence of its effectiveness. Richards has a valid point about probable adverse effects of limbic resection on memory and emotion, but he minimizes the devastating consequences of continued disabling seizures on these functions. It is the appearance of serious, seizure-induced developmental, psychological, and social compromise — not the number of medications tried — that should trigger consideration of surgical intervention. Although hippocampal resection can impair memory, it has long been known that memory deficits also result from continued complex partial seizures and that surgical treatment can reverse seizure-induced dysfunction of the contralateral hippocampus to improve cognitive function.¹

No studies have suggested that emotional disturbances or adverse changes in personality result from unilateral mesial temporal resections when these structures are already damaged (although Richards is correct in stating that our tests may not be able to measure such changes accurately). However, the bilateral limbic disruption caused by recurrent unilateral temporal-lobe seizures is often associated with behavioral problems.² Furthermore, the disastrous psychological and social consequences of disabling complex partial seizures exert a much more potent negative influence on emotional well-being than surgical treatment, as clearly indicated by patients' own reports in the form of standardized, health-related quality-of-life measures.³ Finally, uncontrolled seizures greatly increase the risk of death,⁴ the ultimate personality change.

Nevertheless, we now need randomized, controlled trials of early surgical intervention, undertaken before the disabling psychological and social consequences of recurrent epileptic seizures become irreversible, to confirm our logical assumption that early surgery is more likely to rescue patients from a lifetime of social isolation, unemployment, and dependency than it is to produce unwanted personality changes. Without such studies, Richards and those who share his views will continue to see surgery for epilepsy as a drastic last resort.

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Prone Positioning of Patients with Acute Respiratory Failure

To the Editor: Gattinoni et al. (Aug. 23 issue)¹ reported that placing patients with acute respiratory failure in a prone position improved their oxygenation but not their survival. One reason why improved oxygenation did not translate into a reduction in mortality might be that the duration of pronation was too short — only seven hours per day on average — as pointed out by Slutsky in his editorial.² In our nine-year experience with prone positioning of patients during ventilation, we have used a different protocol.^{3,4} We use the same indications and timing that Gattinoni et al. used, but we do not return our patients to the supine position before their gas-exchange deficit has resolved. Therefore, patients do not have decreased oxygenation while they are in the supine position. Adverse events related to the turning procedure are avoided. The nursing workload is decreased, enhancing adherence to the protocol.

Ongoing ventilator-induced lung injury may also contribute to the death of some patients with acute respiratory failure.⁴ Matching the ventilator settings to the patients' respiratory demands is conceivably easier when gas exchange is more stable during continuous prone positioning. The use of the prone position for longer periods should be studied.² This approach appears feasible and safe in our experience. Studies are also required of patients with acute lung injury before they require mechanical ventilation, since prone positioning might obviate the need for ventilation.⁵

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To the Editor: As our understanding of the pathophysiology and clinical course of the acute respiratory distress syndrome (ARDS) in both adults and children has evolved, it has become evident that the syndrome is confoundingly

heterogeneous. In our view, the case mix of patients who qualify as having the syndrome is too heterogeneous for them to be studied as patients with a single entity.

Gattinoni et al. have argued that one can differentiate between ARDS induced by pulmonary problems and ARDS induced by extrapulmonary problems.¹ In children, the rates of death from ARDS vary widely in various patient groups. The rates are under 10 percent in patients with ARDS related to respiratory syncytial virus infection² and 86 percent in pediatric bone marrow recipients.³ ARDS cannot be viewed as a single disease entity.

Prone positioning may be effective in a particular subgroup of patients with ARDS. Should we not use more disease-specific criteria when stratifying studies to evaluate particular treatments or management strategies, even at the price of complicating recruitment?

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To the Editor: Since the benefits of open-lung protective ventilation (involving a high positive end-expiratory pressure [PEEP] and a low tidal volume)^{1,2} were less clear at the conception of the trial by Gattinoni et al., their negative results should be interpreted with caution.

We believe that prone positioning results in lung recruitment (that is, the opening of collapsed alveoli), although this is not certain to be the case.^{3,4} In ARDS, there is an exaggeration of the pleural-pressure gradients, with anterior pleural pressures of roughly -8 cm of water and posterior pleural pressures of 7 cm of water (as compared with -5 and -1 cm of water, respectively, in normal subjects). During prone positioning, these pleural pressures are more uniform, yielding a relatively homogeneous distribution of lung volume. While patients are prone, the sternum supports the cardiac weight, and diaphragmatic curvature limits the influence of abdominal pressure on the risk of caudal lung collapse. During mechanical ventilation of patients in the prone position, collapsed alveoli are recruited and open alveoli are minimally overdistended. The sustained improvement in gas exchange (lasting hours after the termination of prone positioning) reported by Gattinoni et al. supports the existence of these recruitment phenomena.

Substantial data suggest that a high PEEP can prevent cyclic opening and closing of collapsed alveoli and thus prevent lung injury. Although Gattinoni et al. did not specify the ventilator strategy, they used only moderate levels of PEEP (mean, 9.7 ± 2.9 cm of water) and relatively high tidal volumes (10.3 ± 2.7 ml per kilogram of predicted

body weight). Therefore, we speculate that a strategy of combining prone positioning and open-lung protective ventilation may have substantially different results. This simple, safe, and inexpensive technique should not be discarded until a combined strategy has been fully evaluated.

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1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
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The authors reply:

To the Editor: We share most of the writers' concerns and views about speculative issues. The prone position was introduced as a rescue technique for patients with severe hypoxemia. In this regard, it is effective in most patients, and its beneficial effects on oxygenation last beyond the duration of prone positioning.

Use of the prone position may improve survival by two main mechanisms. First, improved oxygenation may allow a lower fraction of inspired oxygen and lower airway pressures. Second, when the patient is prone, lung inflation is more homogeneous. Both mechanisms reduce the potential for ventilator-induced lung injury. These mechanisms suggest that the prone position should be more effective in patients with the most severe respiratory distress or in subgroups in which mechanical ventilation is expected to be more deleterious.

In our study, the time patients spent in the prone position was relatively short and was limited to 10 days. We plan to study the value of longer periods of prone positioning for more than 10 days in patients with severe ARDS. We will standardize mechanical ventilation in both the supine and prone groups according to a predefined lung-protective strategy. Thus, our current study should be regarded as a starting point for a better understanding of the role of the prone position in clinical practice.

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The editorialist replies:

To the Editor: The common theme of all the letters is that the use of prone positioning during ventilation should not be discarded on the basis of the negative study by Gattinoni and colleagues. The writers suggest that further studies should be performed that use the prone position for longer periods, in more homogeneous populations of patients, in combination with recruitment maneuvers to reexpand lung units, or before mechanical ventilation is needed. These are all excellent suggestions; however, the implications of these suggestions underscore the problems involved in performing randomized clinical trials of mechanical ventilation. The number of permutations and combinations of ventilator strategy (involving different modes of ventilation and different levels of PEEP, tidal volumes, and respiratory rates) in combination with the duration of pronation (e.g., 6, 12, 18, or 24 hours) plus the presence of underlying disease processes (e.g., trauma, sepsis, aspiration, and pneumonia), in addition to the diversity of coexisting conditions and the need for other interventions, means that any negative study will be followed by suggestions that a different study design would have been better. The chief obstacle is finding a practical way to implement these suggestions, given the costs of the studies and the difficulty in accruing patients.

The study by Gattinoni et al. included 304 patients from 30 centers and was conducted over a three-year period. The ARDS Network trial, which demonstrated a 22 percent reduction in mortality in patients with ARDS who were treated with a tidal volume of 6 ml per kilogram of predicted body weight, enrolled 861 patients, but it took three years to accrue this number, despite the fact that it had 10 well-funded centers and more than 70 participating intensive care units.¹ It would be difficult to test even a small number of the possibilities suggested.

Increased collaboration among centers and countries conducting studies of patients with ARDS will certainly be helpful and, indeed, will most likely be necessary. Perhaps we should focus on large, simple trials that collect far fewer physiological data and involve less stringent oversight. In the case of diseases that are relatively uncommon, for which there is a paucity of evidence of the efficacy of any given therapeutic option, and that are difficult to assess with the use of randomized controlled trials, perhaps we should accept less stringent P values (e.g., $P < 0.1$ or $P < 0.15$). Finally, the development of new experimental paradigms that are not based on randomized controlled trials may allow a more efficient evaluation of various therapeutic options.

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1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.

Diet and Risk of Type 2 Diabetes

To the Editor: In their article on diet, lifestyle, and type 2 diabetes mellitus in women (Sept. 13 issue),¹ Hu et al.

point out that obesity is an important cause of type 2 diabetes mellitus. I wish to point out that since diabetes does not develop in all overweight women (or men, of course), there must be other factors that predispose patients to the condition, as I illustrated in earlier reports.²⁻⁶ Therefore diet is certainly important, but particularly for women and men for whom this overlooked risk factor is involved.

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To the Editor: The recent article by Hu et al. concerning type 2 diabetes is misleading, since it implies that there is an association between diabetes and smoking. Has such an association been shown previously?

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The authors reply:

To the Editor: As shown in Table 1 of our paper, the majority of patients with diabetes were overweight or obese. In our cohort, approximately 60 percent of incident cases of diabetes were attributable to overweight and obesity. However, this does not mean that other factors are not important. We showed that even after adjustment for body-mass index, a poor diet, lack of exercise, and cigarette smoking were each associated with a significantly elevated risk of diabetes. In addition, among overweight and obese women, the combination of a healthy diet (a diet high in cereal fiber and polyunsaturated fat and low in trans fat and glycemic load), regular exercise, and abstinence from smoking could substantially lower the risk of type 2 diabetes. Furthermore, diet and exercise are the primary factors that determine body weight.

There is convincing evidence that cigarette smoking is a risk factor for type 2 diabetes. Cigarette smoking has been consistently associated with a relatively small but significantly increased risk of type 2 diabetes in both men^{1,2} and women³ in large prospective cohort studies. Cigarette smoking has also been associated with insulin resistance. Facchini et al. found that smokers had higher insulin concentrations as well as higher glucose concentrations after infusions of steady-state insulin than nonsmokers with similar ages, body-mass indexes, and family histories of diabetes.⁴ Although smoking is generally associated with a lower body-mass index, it is associated with a greater waist-to-hip cir-