Prostaglandin $E_1$: Not the Magic Bullet in ARDS

Researchers throughout the country are diligently searching for new therapeutic agents that could be effective in treating patients with the adult respiratory distress syndrome (ARDS). The prognosis for patients with this syndrome remains dismal, with survival rates generally reported to be approximately 35 to 40 percent.\(^1\)\(^2\) Fifty percent of all patients with this syndrome die by day 13 after onset.\(^3\) Effective drug therapy to change the course of ARDS has been evaluated and includes corticosteroids, heparin, non-steroidal anti-inflammatory drugs, and vasopressors. To date, none of these various agents has produced any real differences in the outcome of ARDS patients. Although many of these treatments have produced measurable changes in pulmonary vascular or parenchymal physiology, the mortality rate for drug treated-patients has remained the same as that for placebo-treated patients.

This issue of Chest (see page 114) contains the summary report by Bone et al evaluating the use of parenterally infused prostaglandin $E_1$ (PGE\(_1\)) as a therapeutic agent in patients with ARDS. PGE\(_1\) is a monenoic prostaglandin that acts as a potent vasodilator of pulmonary veins. This vasodilator capacity is minimized in the pulmonary vascular bed under resting conditions but becomes much more active in vessels with increased tone induced by hyperoxia. PGE\(_1\) is also effective in preventing platelet aggregation in vivo, and the agent has been shown to block the pulmonary hypertensive effects of infused adenosine diphosphate.\(^4\)\(^5\) Systemic arterial pressure falls following PGE\(_1\) infusion, and this effect is thought to be a result of both decreased peripheral vascular resistance and decreased systemic venous return.

Dr. Bone’s study group was formed in response to a single center report by Holcroft et al,\(^6\) which found an improvement in survival of ARDS patients treated with PGE\(_1\) compared with a placebo-treated group. The Holcroft group’s 41 patients were obtained from a surgical ICU and they reported that 71 percent of the 21 PGE\(_1\)-treated patients survived 30 days postinfusion, with only 35 percent of the 20 placebo-treated patients surviving for 30 days. Of note, seven of the patients who were alive at 30 days did ultimately die by 70 days (four of the control subjects died between days 30 and 37).

The present study in Chest by Bone et al was a larger (50 PGE\(_1\), 50 placebo) randomized, double-blind clinical trial that included patients in both medical and surgical ICUs. These authors found that PGE\(_1\) did not enhance ARDS patient survival, with 60 percent of the PGE\(_1\)-treated patients and 48 percent of the placebo-treated patients dying in the first 30 days following infusion. Similar changes in hemodynamic parameters were reported by both Holcroft’s and Bone’s groups in PGE\(_1\)-treated patients with decreases in systemic and pulmonary vascular resistances, but these changes did not translate into differences in mortality in the patients with ARDS.

Why did these two studies produce such different results despite using the same therapeutic agent given in an identical fashion? The answer may lie in differences in patient populations entering into the trials. The Holcroft study was heavily weighted with trauma patients who have a higher ARDS survival than medical ARDS patients with sepsis or the septic syndrome. The prevalence of congestive heart failure (CHF) in the Holcroft ARDS patients was also not documented as clearly as the Bone multicenter study, which used pulmonary artery wedge pressures to eliminate patients with CHF from entering into the trial. Finally, the severity of ARDS as estimated by the PaO\(_2\):FiO\(_2\) ratio was different in these two studies, with the Bone study requiring this ratio to be 150 or less without PEEP before entry, and the Holcroft study including 22 patients with ratios >150 on entry.

The bottom line concerning the use of PGE\(_1\) in ARDS revealed that in the larger, more tightly controlled multicenter study, PGE\(_1\) was not more effective in changing the mortality of ARDS than placebo. Since both the Holcroft and Bone studies reported a number of side effects in patients receiving PGE\(_1\), pulmonary physicians should not currently be using this agent to treat patients with ARDS because we have not identified any substantial differences in mortality from PGE\(_1\) infusion, although we have defined several significant risks. The bad news emerging from this latest trial is that PGE\(_1\) is not the magic bullet to change mortality in patients with ARDS. Research into new pharmacologic agents must be continued with the hope that an effective therapy will emerge in the future.
Asthma and Gastroesophageal Reflux

Gastroesophageal (GE) reflux is an extremely common clinical problem usually manifested by heartburn or acid regurgitation. These symptoms are estimated to occur daily in up to 10 percent of the US population and intermittently in 50 percent or more of otherwise healthy individuals. The typical postprandial occurrence of these symptoms usually makes the diagnosis readily apparent and the widespread use of over-the-counter antacid-type medications testifies to the high frequency with which these complaints plague our society. In recent times, we have begun to understand that there are a number of other manifestations of chronic and intermittent GE reflux, not the least of which are related to the respiratory tract. These are not new concepts. The older literature refers to the association of reflux with chronic hoarseness and posterior laryngitis (the Cherry-Donner syndrome “reflux laryngitis”) and the potential relationship between reflux and intermittent bronchospasm, particularly “intrinsic” or “nonallergic” asthma. Until recent times, however, techniques to specifically identify GE reflux as the causative factor in these conditions have been limited, creating uncertainty about the actual role of reflux in the production of these symptoms. Skeptics would appropriately remind us that GE reflux is a very common event and that its association with these atypical symptoms might be pure association, not causation; true/true and unrelated.

In this issue of *Chest*, the article by Perrin-Fayolle and colleagues (see page 40) presents their long-term experience with a group of 44 patients followed for greater than five years (average follow-up 7.9 years) after Nissen fundoplication as definitive therapy for asthma considered most likely due to GE reflux. This study represents the longest careful evaluation of a group of patients of this kind and provides some important insights into this clinical problem. Granted, the diagnosis of GE reflux was mainly based on clinical findings (“postural pyrosis and retrosternal pain or burning”), with only a few patients having more objective evidence of actual GE reflux (nine had isotopic scintiscan and seven pH monitoring). These more objective tests of reflux were not, however, readily available at the time that these patients were initially evaluated. The authors note that the symptoms of GE reflux cleared in 42 of 44 patients, indicating the effectiveness of fundoplication. Utilizing a clinical score based on asthmatic symptoms and the need for continued asthma therapy, they report very satisfying responses in the patients’ asthma following fundoplication; 29/44 (66 percent) patients showed improvement, and 18/44 (41 percent) evaluated as markedly improved or cured.

The most fascinating aspect of their observation relates to the clinical aspects of this condition which may help predict those patients who are truly suffering from reflux-related asthma and in whom definitive therapy for reflux should be most seriously considered. These investigators found no relationship between evidence of obstructive airway disease or duration and severity of asthma with the response to antireflux treatment. A positive and significant association, however, was found between cure of asthma following fundoplication and the presence of nocturnal attacks, nocturnal tracheitis, intrinsic asthma, or a clear history of reflux symptoms preceding the onset of asthmatic symptoms. These authors also found that the response to a trial of medical therapy helped predict patients who would be cures or failures following fundoplication.

In accepting the potential for GE reflux to produce respiratory manifestations such as chronic laryngitis or asthma, a critical question is, how common are these clinical conditions? Our recent experience with 24-hour esophageal pH monitoring has indicated that as many as 75 percent of patients with chronic hoarseness will show an abnormal amount of GE reflux. It has recently been suggested that 45 to 65 percent of adults with asthma will have reflux. One of the major difficulties with identifying the actual frequency of these relationships has been lack of specificity in the recognition of abnormal reflux. Many prior studies relating GE reflux to these clinical syndromes have relied on diagnostic indicators (hiatal hernia on x-ray, “typical” symptoms of heartburn) that suffer from questionable reliability. Even more specific techniques to establish its presence, such as identifying...