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Raising the Bar for Acceptable Outcomes

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Pulmonary Arterial Hypertension in 2006: Treating to Goal

At a symposium chaired by C. Gregory Elliott, MD, FCCP, Professor of Medicine at the University of Utah School of Medicine and Chief of Pulmonary Critical Care and the Sleep Division at the LDS Hospital in Salt Lake City, UT, Dr. Elliott and three other pulmonologists discussed recent developments in our understanding of the pathophysiology and treatment of PAH.

Pulmonary Arterial Hypertension: Physiological Basis of Pharmacotherapeutic Intervention

Pulmonary arterial hypertension (PAH) is a chronic, progressive disorder that is difficult to diagnose, because the initial symptoms are often nonspecific. If the condition remains untreated, the increased pulmonary vascular resistance (PVR) associated with PAH can lead to right ventricular dysfunction and death. If untreated, the average life expectancy has been 2.8 years after establishing the diagnosis. Harold I. Palevsky, MD, FCCP, Professor of Medicine and Chief of the Pulmonary, Allergy, and Critical Care Division at Penn Presbyterian Medical Center and Director of the Pulmonary Vascular Disease Program at University of Pennsylvania Health System in Philadelphia, PA, introduced the audience to the pathophysiology of PAH and how it is the basis for PAH treatment.

Pathophysiology

PAH is defined as a mean pulmonary artery pressure greater than 25 mm Hg at rest, or greater than 30 mm Hg with exercise, with a normal left atrial pressure (pulmonary capillary wedge pressure) and a PVR greater than 3 Woods units. Dr. Palevsky noted that not all patients with elevated pulmonary arterial pressure have PAH. “If we have a patient with anemia who has a high cardiac output as a consequence of that anemia, the mean pulmonary artery pressure at rest could be greater than 25 and the wedge pressure could be normal,” adding, “This is not pulmonary arterial hypertension, because we would not have an elevated pulmonary vascular resistance.”

At present, our knowledge of the pathogenesis of PAH is limited but increasing. Dr. Palevsky noted that numerous factors seem to contribute to the disease. For example, pulmonary vasoconstriction is usually limited in PAH. Dr. Palevsky showed the audience numerous anatomic examples illustrating that the structural changes in the pulmonary arterial lumen may make it unresponsive to vasodilators, whereas they may be responsive antiproliferative agents.

Another pathogenetic process contributing to PAH is in situ thrombosis. “There are several factors, which are appearing to contribute to this,” stated Dr. Palevsky, including “loss of natural anticoagulant activity with decrease in certain factors, evidence of coagulation activation, enhanced von Willebrand’s factor, loss of endogenous fibrinolytic activity and, alterations in platelet function with serotonin release.”

There also appears to be a genetic component to some PAH. To date, two specific genes have been identified in familial PAH and PAH associated with hereditary hemorrhagic telangiectasia (HHT), and Dr. Palevsky said that these genes appear to code for receptors that most likely have a regulatory role in preventing the proliferation of cells in the pulmonary arterial microcirculation or controlling apoptosis.

Based on these pathophysiologic changes, as well as our current understanding of factors that control pulmonary microcirculation, Dr. Palevsky said treatment options for PAH have been developed. Dr. Palevsky confessed that current therapy is based on not what we may think is the most effective way to treat PAH but, rather, on what we know we can influence. Dr. Palevsky also noted that the basis of treatment is fairly simple. “If there is reduced activity to a mediator pathway, we try to replete it, and, if there is increased activity, we try to block it,” said Dr. Palevsky. For example, endothelin levels (ET-1) are high in PAH. “We don’t know whether this is chicken or egg,” admitted Dr. Palevsky, but the levels of endothelin do correlate with disease severity, and one treatment option available is to block endothelin receptors (ET-A and/or ET-B). Patients with PAH also have reduced production of nitric oxide and prostacyclin, and both of these are targets for therapy.

Dr. Palevsky noted that treatment strategies are currently in use to treat the disease after it has developed, but he is hopeful that earlier interventions will be developed in the future. “Our goal, ultimately, is to work toward early genetic and clinical detection so we are instituting our therapies at the point when it’s most likely to be advantageous,” concluded Dr. Palevsky.
Pulmonary Arterial Hypertension: Prognostic Factors and Goals of Therapy

The mean life expectancy of a diagnosed patient with PAH left untreated is 2.8 years. With treatment, PAH can survive longer, but, with or without treatment, there is a large variance in survival rates. Some patients die within months, while others survive for many years. In recent years, risk factors associated with a higher mortality rate have been studied and were discussed by Nicholas S. Hill, MD, FCCP, Professor of Medicine at Tufts University School of Medicine and Chief of the Pulmonary, Critical Care and Sleep Division at Tufts–New England Medical Center in Boston, MA. A better understanding of prognostic factors associated with treatment response and/or survival can help clinicians decide on a treatment strategy best suited for their patient.

Risk factors of PAH can be categorized into one of two ways: factors that identify a person at risk for PAH and factors that place a person at higher risk for mortality. In the first category, identification of the BMPR2 gene in patients does indicate that these people have a 20% likelihood of developing PAH. Dr. Hill noted that most would agree that screening for this gene is not in the patient’s best interest, because no treatment can be offered at this stage (Table 1).

With regard to functional class, Dr. Hill stated that the World Health Organization/New York Heart Association classification correlates very well with survival. In patients with mild PAH (class I), the average survival is 6 years. For class 2 PAH, mean survival is 3 years. For class 3 PAH, mean survival is 1.8 years, and for class 4 PAH, mean survival is 6 months (Ann Intern Med 1991; 115:343). Dr. Hill added that the functional class is also useful for assessing the likelihood of response to therapy. Vallerie McLaughlin and colleagues (Circulation 2002; 106:1477) showed that the higher the class, the poorer the response to epoprostenol therapy. If patients do respond to therapy, however, prognosis can greatly improve. For example, one study (J Am Coll Cardiol 2002; 40:780) showed that class 3 or 4 patients who dropped back to a class 1 or 2 category after 3 months of treatment have a better prognosis than those patients who did not drop a category (ie, symptoms stayed the same or got worse). Dr. Hill said “Many clinicians now use this to decide whether a patient should be referred to a transplant center or not, because remaining at class 3 or 4 puts them at high risk, whereas if they’re class 1 or 2, they’re likely to do well and transplant referral may not be necessary.”

Another risk factor that can be quantified is functional capacity. There are numerous ways to measure functional capacity, but the most common is the 6-min walk test, and most centers use it routinely. “There is a very close correlation between 6-min walk distance and New Heart Functional Class,” said Dr. Hill, adding, “There is a strong association between the distance walked in 6 min and survival.” For example, in a study from Japan, patients who walked more than 332 meters had an excellent survival in the long term (Am J Respir Crit Care Med 2000; 161:487).

Hemodynamic studies can also be valuable prognosticators. Dr. Hill said the variable with the greatest prognostic value is right atrial pressure. The cardiac index is also a powerful tool to measure the likelihood of mortality, whereas mean PA pressure is less well correlated with mortality (Table 2) (Ann Intern Med 1991; 115:343).

Recently, there has been a lot of interest in the use of neurohormones and biomarkers as outcome measures. The most common marker is brain natriuretic peptide (BNP), and Dr. Hill noted that it is a good prognosticator. Dr. Hill discussed a study (Circulation 2000; 102:865) that showed, if the BNP level was less than 180 pg/mL at follow-up, the outcome was fairly good; but, if levels exceeded 180 pg/mL, the outcome was poor. This study also observed that if BNP levels declined during treatment, the outcome was greatly improved; whereas, if it continued to rise, that was a bad prognostic indicator. Other prognostic markers include uric acid, endothelin, norepinephrine, and troponin T.

### Table 1. PAH: Measuring Risk Factors for Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Functional class</td>
<td></td>
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<tr>
<td>Functional capacity</td>
<td></td>
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<tr>
<td>Pulmonary function</td>
<td></td>
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<tr>
<td>Hemodynamics</td>
<td></td>
</tr>
<tr>
<td>Neurohormones/biomarkers</td>
<td></td>
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<tr>
<td>Right ventricular dysfunction</td>
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</table>

The final factor discussed by Dr. Hill was right ventricular dysfunction. Numerous parameters of cardiovascular function have been measured, and Dr. Hill said some of them, such as the Tei index, the TAPSE (tricuspid annular planar systolic excursion) index, and pericardial effusions, may be valuable tools to predict survival and/or serve as treatment outcome.

### Concluding Remarks

There are numerous quantitative methods to help clinicians assess risk of PAH progression and mortality. To date, these markers cannot help us to prevent the disease from developing, but we hope that future treatment strategies will be developed to perform that task. At present, proper treatment and prognostic indicators can help us determine which patients are more likely to respond to therapy and which patients will require more aggressive treatment.
Assessing the Evidence: Clinical Applications of Therapeutic Interventions in the Treatment of Pulmonary Arterial Hypertension

Treatment of PAH is designed for survival, functional capacity, exercise capacity, quality of life, and improved hemodynamics. Recently, pharmacologic advancements have emerged that may allow us to achieve these treatment goals and were the subject of the presentation by Aaron B. Waxman, MD, PhD, FCCP, Assistant Professor of Medicine at Harvard Medical School and Director of the Pulmonary Vascular Disease Program in the Pulmonary Critical Care Unit of Massachusetts General Hospital, Harvard Medical School in Boston, MA.

General Medical Management

The general medical management of PAH is summarized in Table 3. Dr. Waxman acknowledged, “These are things we do, really not based on clinical trials, but [they] have become part of the standard of care for these patients.” For example, many of these patients require oxygen and, while data are limited, it does help the patients who require it. As for anticoagulation, Dr. Waxman said that the risk-benefit ratio has to be considered for each patient, and it is only recommended for moderate-to-severe patients with PAH. In regard to the use of diuretics, Dr. Waxman said, “Diuretics are an important part of treating these patients, mostly for symptomatic goals but also when patients progress to right heart failure, in attempts to try to reverse that.” As for the use of digoxin, Dr. Waxman noted that there really is no good data on its use in PAH but acknowledged that most clinicians use it hoping that it adds the same benefit we would expect with use for left heart failure. Finally, Dr. Waxman said, “As with any chronic cardiopulmonary disease, there are certain lifestyle adjustments we ask our patients to work on and, hopefully, this has some positive impact on their functional status.”

In addition to these general treatment strategies, recent pharmacologic advances that more specifically address the alterations in pulmonary vascular function have emerged. The standard use of calcium channel blockers has been replaced by safer and more effective treatment options. Dr. Waxman stressed that “It’s an extremely rare event that a patient is going to have a long-term benefit from calcium channel blockade. We no longer advocate the use of calcium channel blockers as first-line or empiric therapy for PAH.”

Current and Emerging Treatment Options

There are three types of treatment options available to PAH patients (Table 4):

<table>
<thead>
<tr>
<th>Table 3. General Medical Management of PAH</th>
</tr>
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<tbody>
<tr>
<td>- Oxygen</td>
</tr>
<tr>
<td>- Warfarin (if not contraindicated)</td>
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<tr>
<td>- Diuretics</td>
</tr>
<tr>
<td>- Digoxin</td>
</tr>
<tr>
<td>- Lifestyle adjustment</td>
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</tbody>
</table>

Prostacyclins

The first prostacyclin to be used for PAH treatment was epoprostenol. Studies have shown that it is effective in improving the 6-min walk test and survival rates. Unfortunately, it must be given intravenously. Dr. Waxman said, “It has to be delivered as a continuous infusion, so it requires a Hickman catheter, a pump, and the patient needs to learn how to do this and become self-sufficient in the mixing and preparation of the drug,” adding, “Once that’s achieved, the drug is highly effective.”

The second-generation prostacyclin developed was treprostinil. Treprostinil has a half-life of 4.5 h compared with epoprostenol, which has a half-life of about 3 min. It was initially approved to be given subcutaneously. “Unfortunately, prostacyclin is an inflammatory mediator, and patients can have complications with site pain from this delivery system,” noted Dr. Waxman. It can also be given intravenously, and, in addition to the longer half-life, another advantage over epoprostenol is that treprostinil can be kept at room temperature and does not require an ice pack, like epoprostenol does. Thus far, the efficacy appears comparable.

The third prostacyclin that came out was iloprost, which is delivered as an inhaled formulation. It is more convenient than an IV preparation, but Dr. Waxman notes that patients must take the medication 6 to 9 times per day, and each preparation takes about 15 min. “That can be quite a chunk of time for somebody who wants to have an active lifestyle,” said Dr. Waxman.

Endothelin Antagonists

The first endothelin antagonist developed was bosentan, which is a nonselective endothelin antagonist. Clinical trials have shown it can significantly improve the 6-min walk test, with some marginal improvement in hemodynamics and delayed clinical worsening. Currently, bosentan is the only endothelin antagonist approved by the FDA for PAH, but two other antagonists will likely be approved soon. They are sitaxsentan and ambrisentan. Of these, sitaxsentan, a highly selective endothelin antagonist, will likely be the first approved, and phase III clinical trials have shown it to be a safe and effective treatment.

A comparative study of all three endothelin antagonists has not been performed, but all three appear to be equally effective for 6-min walk test improvements in short-term, 12-to-18 week, clinical studies. Concern for abnormal liver function
Pulmonary Arterial Hypertension in 2006: Treating to Goal

Assessing the Evidence: Use of Current and Emerging Treatments for Patients With Pulmonary Arterial Hypertension

Ramona L. Doyle, MD, FCCP, Associate Professor of Medicine at Stanford University and Co-Director, Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford University Medical Center in Palo Alto, CA, concluded the symposium by furthering the discussion of treatment options available for patients with PAH. Dr. Doyle began by saying that one of the limitations of our knowledge of PAH is in the less sick patients with PAH. Dr. Doyle said, “By the time patients actually develop symptoms and they come to our attention, about 70 to 80% of the pulmonary vascular bed is already probably involved in the process. We would be delighted to see patients who were NYHA functional class I in whom we knew they had pulmonary hypertension and in whom we could initiate treatment.” At the other extreme, for NYHA IV patients, Dr. Doyle said, “My own bias is, for patients who are functional class IV, really the ideal treatment is intravenous epoprostenol.” She added, “It has been shown to improve survival in these patients, and, I think, for the really sick patients, that would be my first step.” If the patient cannot handle the infusion therapy, then Dr. Doyle stated that another prostanooid should be considered.

As for how to treat class II and III patients with PAH, Dr. Doyle noted that several options are available, and the choice should be based on the patient’s health. For example, a patient with portopulmonary hypertension probably should not be put on endothelin antagonists because of the potential for liver toxicity. Other patients may be taking medications that interact with sildenafil, such as HIV-positive patients who require protease inhibitors. Dr. Doyle said, “I think in this arena, the class II and III patients, you really have to start to think about what the patient can actually handle.” In contrast, patients with class III or IV PAH, the symptoms are more severe and other considerations need to be addressed. If the patient is not getting better, the questions that occur include: (1) Do we switch to another class of medications? (2) Do we add another therapy to the existing therapy? (3) Do we consider the patient for a transplant? All of these questions need to be addressed if the patient is not getting better. Concerning the transplant option, Dr. Doyle cautioned that the lung transplant rating system does not favor patients with PAH and said, “Refer patients early if you think they might need lung or heart/lung transplant for PH. Don’t wait until they’re dying in the hospital.”

Combination Therapy

The use of combination therapy for PAH is controversial. Dr. Doyle noted that from a theoretical perspective, combining drugs that work on different pathways is an efficient method to treat PAH. “Also, I think combining the vasodilator properties and the antiproliferative effects, based on our understanding of the pathophysiology, has a lot of appeal,” adding, “Then the question becomes, are we reducing or enhancing adverse side effects?” Dr. Doyle added that from a practical point of view, all of these medications are expensive and doubling the treatment costs is difficult to justify without clinical data to back it up. At present, Dr. Doyle said, “There are a lot of combination trials underway,” but until those trials are completed and we have sufficient data to make decisions, the clinician is forced to examine each patient individually and decide what treatment or treatment combination is likely best suited for them. One caveat about combination therapy, stated by Dr. Doyle, is that some combinations may not go well together. For example, sildenafil and bosentan interact, and you may end up having to increase the dose of sildenafil and decrease the dose of bosentan due to a bidirectional pharmacokinetic drug interaction between these two agents. In contrast, sitaxsentan and sildenafil do not appear to have any interactions that require dose adjustments.

Concluding Remarks

Dr. Waxman ended his presentation by reminding the audience that treatment options for PAH are available. Dr. Waxman concluded his symposium with the question that continues to trouble chest physicians, “What do you do when you’ve started one drug, and the patient is either starting to decline again or not getting the response that was hoped for?” With that question, he introduced Dr. Ramona Doyle to present the final presentation of the symposium.

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PDE-5 Inhibitors

The final class of vasodilator discussed by Dr. Waxman was the PDE-5 inhibitors. Of these, the only one approved for PAH treatment is sildenafil at a dose of 20 mg tid, but Dr. Waxman stated that higher doses are commonly used (80 mg tid). Dr. Waxman said these drugs are effective in improving performance on the 6-min walk test and are relatively safe. Dr. Waxman cautioned that PDE-5 inhibitors are contraindicated for patients taking nitrates.

Concluding Remarks

Dr. Doyle ended the symposium by referring back to a statement made earlier by Dr. Hill who said that the ultimate goal of PAH therapy is to get the patient normal again. Unfortunately, that treatment is not available yet, but Dr. Doyle is optimistic for the future and hopes that the audience realizes that at present, our treatment goals are to help the patient with PAH function at a higher capacity, walk further, have better hemodynamics, help their heart to function better, and ultimately, to live longer.
Optimizing Management of Persistent Asthma: Reinforcing the Role of Appropriate Antiinflammatory Therapy

At a conference chaired by Richard J. Martin, MD, FCCP, Head of the Pulmonary Division and Vice Chair of the Department of Medicine at the National Jewish Medical Center in Jackson, CO, three leading pulmonologists discussed the important role that inhaled corticosteroids have in the management of asthma.

E. Regis McFadden, Jr., MD, Professor of Medicine at Case Western Reserve University in Cleveland, OH, began the symposium with a quick overview of the burden of asthma. Dr. McFadden noted that in the United States, there are 31 million people with asthma, and they accrue 10.4 million outpatient visits, 1.8 million urgent care requests, 1.9 million emergency department visits, and 465,000 hospitalizations, at an estimated cost of $6 billion per year.

Most of these medical visits and expenses can be dramatically reduced if patients achieve better control of their asthma. At present, the essential elements of controlling asthma are as follows: (1) maintenance antiinflammatory medications (inhaled corticosteroids, antileukotrienes, and cromolyn) and (2) rescue inhalants for exacerbations. Of these medications, inhaled corticosteroids (ICS) are the preferred choice for maintenance therapy and the subject of Dr. McFadden’s presentation.

Ideal Inhaled Corticosteroids

There are currently, seven available, or soon to be available, ICS: (1) beclomethasone dipropionate; (2) budesonide; (3) flunisolide; (4) fluticasone propionate; (5) triamcinolone acetonide; (6) mometasone furoate; and (7) ciclesonide. All of these have slightly different pharmacokinetic and pharmacodynamic (PK/PD) properties that determine their overall safety and efficacy. In theory, the characteristics of the ideal ICS are:

- High pulmonary deposition
- Low oral bioavailability
- High systemic clearance
- Optimized pulmonary residence time
- Selective binding to glucocorticoid receptors

The fate of any ICS is dependent on many factors, and each of the above characteristics can affect the amount of ICS that affects the lungs and the rest of the body (Figure 1). For example, pulmonary deposition is the amount of the drug that enters into the lungs. The development of HFAs, as well as improvements in inhalers, has dramatically improved the amount of lung deposition, but Dr. McFadden warned that high pulmonary deposition alone is not sufficient to make an ideal ICS. High pulmonary deposition can lead to increased levels of alveolar compartmentalization, increased drug in the systemic circulation, and increased side effects.

Low oral bioavailability is also important. Dr. McFadden showed that the range

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**Figure 1. Fate of ICS**

*With permission from Derendorf H. Resp Med 1997;91 (suppl A):22–28.*
of oral bioavailability varies greatly with ICS—with ciclesonide, fluticasone, and mometasone having percentages lower than 1% (Table 1).

A third important characteristic is systemic clearance. The higher the systemic clearance, the lower the systemic side effects. Several factors are important for systemic clearance. Dr. McFadden noted that in a recent review article, the clearance of ciclesonide was substantially higher than other tested ICS (fluticasone, beclomethasone, and budesonide) (J Allergy Clin Immunol 2003; 112:S1-S40). Another important factor is plasma protein binding. By increasing the percentage of drug that binds to plasma proteins, only unbound drugs can have any systemic side effects. As shown in Table 1, ciclesonide, fluticasone, and mometasone have protein binding that approach 99%.

Optimizing pulmonary residual time refers to the amount of time the active drug remains in the lung. This can be accomplished in several ways. For example, fluticasone has a slow dissolution from the lung to increase pulmonary residual time. In contrast, budesonide attaches to a lipid conjugate that traps the drug in the lung to also increase pulmonary residual time. Dr. McFadden pointed out that ciclesonide has both of these properties.

The final characteristic discussed by Dr. McFadden was selective receptor binding. As shown in Table 1, the high affinities observed with ciclesonide, fluticasone, and mometasone make them more potent medications.

Summarizing the presentation, Dr. McFadden stated that comparing the PK/PD properties of the ICSs indicate that ciclesonide, fluticasone, and mometasone are theoretically approaching the “ideal ICS.” Whether this is translated into real clinical differences was the subject of the next two presentations.

### Improving Asthma Outcomes: Efficacy, Safety, and Adherence

The symposium continued with a discussion by Gene L. Colice, MD, Professor of Medicine at George Washington University and Director of Pulmonary Care and Respiratory Services at Washington Hospital Center in Washington, DC, on the ways in which advances in ICS formulations and delivery systems can improve the efficacy, safety, and adherence to asthma therapy.

#### Efficacy

ICS efficacy is dependent on many factors. Dr. Colice noted that Dr. McFadden’s presentation showed how PK/PD properties can influence efficacy. Equally important is the delivery system. Back in the 19th century, ceramic inhalers replaced such novelty items as atomizers, steam inhalers, asthma cigarettes and powders. In 1956, the treatment of asthma was revolutionized when 3M introduced the first metered-dose inhaler and, for the next 40 years, they delivered chlorofluorocarbon (CFC) medication. Unfortunately, CFCs have a significant impact on the ozone layer and, as a result, the Montreal Protocol (1989) began to ban the production of CFCs, except for essential uses, such as in metered-dose inhalers. This ban indirectly affected the design of inhalers, and, in recent years, the use of HFA inhalers has grown exponentially. The reason for this is simple: they are more effective. As shown in Figure 2, the percentage of drug that it deposited is much higher in HFA preparations. Dr. Colice also noted that the conversion to an HFA preparation alone will not necessarily increase lung deposition, but other factors are equally important, including:

- Inhaled particles (size, shape, density, hygroscopy, charge, velocity)
- Device (principle and design features, such as DPI/MDI/nebulizer, spacer vs nonspacer, HFA/CFC devices, etc)
- Patient (lung anatomy, breathing pattern, disease state, technique, mucociliary transport)
- Solution vs suspension MDI

A balance between all of these factors is necessary to deposit the drug appropriately in the patient’s lungs.

#### Table 1. Pharmacodynamic and Pharmacokinetic Properties of ICS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioavailability %</th>
<th>Plasma Protein Binding %</th>
<th>Receptor Binding %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>100</td>
<td>...</td>
<td>100</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>20</td>
<td>80</td>
<td>190</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>23</td>
<td>71</td>
<td>233</td>
</tr>
<tr>
<td>Budesonide</td>
<td>12</td>
<td>88</td>
<td>935</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>&lt;1</td>
<td>~99</td>
<td>1,200</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>40</td>
<td>...</td>
<td>1,022</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>&lt;1</td>
<td>90–99</td>
<td>1,800</td>
</tr>
<tr>
<td>Mometasone</td>
<td>&lt;1</td>
<td>98–99</td>
<td>2,700</td>
</tr>
</tbody>
</table>
administration of a prodrug has been the approach used for ciclesonide, and a poster presented at the American Thoracic Society, by Engelstaetter and colleagues (2004), showed that ciclesonide has very low incidence of oral side effects.

Adherence
The final aspect of ICS treatment discussed by Dr. Colice was adherence. In a study by Williams and colleagues (J Allergy Clin Immunol 2004; 114:1288-1293), the overall adherence to ICS treatment in adult patients with asthma was approximately 50%. Furthermore, adherence to ICS treatment was negatively correlated with the number of emergency department visits. The authors of the study also calculated that the number of hospitalizations could be reduced by 60% if the patients had adhered to their ICS treatment.

One method to improve adherence to treatment is to make the treatment schedule more convenient. Unfortunately, attempts to market a once-daily fluticasone formulation were not approved (Chest 2003; 124:1584-1593); however, a once-daily formulation of ciclesonide is in development.

Concluding Remarks
Dr. Colice ended his presentation by stating that numerous factors are required to determine the most effective and safest ICS for asthmatic patients. Continuous advancements in the PK/PD properties of ICS, as well as improvements in the delivery systems, have drastically improved our ability to manage asthmatic patients safely and effectively.

Newer Single Entity Inhaled Corticosteroids

Bradley E. Chippens, MD, FAAP, FAAAI, FCCP, Medical Director of the Respiratory Therapy, Medical Director of the Cystic Fibrosis Center, Sutter Medical Center and Associate Medical Director at Sutter Community Hospitals Sleep Laboratory in Sacramento, CA, concluded the symposium with a discussion on which ICS are best suited for monotherapy. The increased interest in the use of ICS monotherapy was largely based on the FDA warnings regarding ICS-long-acting beta agonist (LABA) combinations. Dr. Chippens said this warning was in response to the SMART (Salmeterol Multicenter Asthma Research Trial) results published by Nelson and colleagues (Chest 2006; 129:15-26). In this large (n = 26,355), 28-week, randomized, double-blind, placebo-controlled, observational study, the authors terminated the study after an interim analysis revealed that the use of the LABA salmeterol led to an increased risk of respiratory- or asthma-related death, especially among African-Americans.

There are several single-entity ICS on the market. Of concern for all of them are the systemic adverse events (especially on the HPA axis) that may develop with long-term use. To address this concern, pharmaceutical companies have tried to develop ICS that are effective inside the lung but ineffective outside of the lung. For example, oral bioavailability needs to be low, and, as shown in Figure 3, fluticasone propionate, ciclesonide, and mometasone furoate have

Oral Adverse Events
In addition to the systemic side effects that are a concern with the use of ICS, the delivery of ICS through the oral cavity can create discomfort. Hoarseness, oropharyngeal candidiasis, and pharyngitis/glossitis can occur due to a variety of ICS induced mechanisms (ie, myopathy of vocal cords, effects on local immunity or increased salivary gland glucose release, or local irritation by drug or excipients, stated Dr. Colice.

Gallivan and colleagues (J Voice 2007; 21:101-111) examined 38 patients who use ICS and complained of hoarseness, and they observed a large percentage of the patients had laryngeal dysfunction and/or oropharyngeal abnormalities. With regard to candidiasis, Dr. Colice noted that the incidence varies greatly among studies (ie, 0 to 77%), but reports of esophageal candidiasis are fairly common. In a study by Kanda and colleagues, 37% of patients with asthma being treated with inhaled fluticasone had esophageal candidiasis (Am J Gastro. 2003: 98;2148-2149).

Dr. Colice stated that there are several ways to reduce oral cavity side effects, including the following:

- Decrease oropharyngeal/laryngeal deposition with a spacer
- Decrease oropharyngeal retention by rinsing mouth
- Decrease oropharyngeal/laryngeal deposition with small particles (formulation)
- Administer a prodrug (pharmacologic)

With regard to the last option, the administration of a prodrug has been the approach used for ciclesonide, and a poster presented at the American Thoracic Society, by Engelstaetter and colleagues (2004), showed that ciclesonide has very low incidence of oral side effects.
low oral bioavailability. The drug should also have a high clearance rate. In this regard, ciclesonide appears to have the advantage (Figure 4). Another way to lessen systemic effects is to increase protein binding so that any drug in circulation would be bound to protein and ineffective, and, as shown in Figure 5, ciclesonide and mometasone furoate have high protein binding, and, as a result, the amount of “free” drug is extremely low. Combining these theoretical principles, it would appear that ciclesonide has the best safety profile, due to its decreased oral bioavailability, high protein binding, and high clearance. To test whether these PK/PD differences lead to real clinical differences, several studies have been performed. For example, Lipworth and colleagues (Ann Allergy Asthma Immunol 2005; 94:465-472) measured serum cortisol levels (in response to a cosynaptropin stimulation) in patients given ciclesonide (320 µg or 640 µg) or fluticasone propionate (440 µg) and found the patients given fluticasone had significantly larger changes in cortisol response, while the patients taking ciclesonide did not have different responses than those patients taking placebo. Examination of urinary cortisol levels also indicates that ciclesonide, even at high doses (1280 µg/day), has little effect on the HPA axis, compared with fluticasone (1760 µg/day) (Chest 2005; 128:1104-1114).

In a comparison of ciclesonide with budesonide, Boulet and colleagues (Respir Med 2006; 100:785-794) showed both medications to be equally effective in controlling respiration (FEV-1) and asthma symptoms scores, and they had similar adverse event profiles. The possible superiority that ciclesonide may have over budesonide was observed in the number of symptom-free days in the 12-week study. In the ciclesonide group, 43.6% of the days were symptom free, while only 25.8% of the days were symptom free in the budesonide group.

Dr. Chipps noted that the above studies focused on patients with mild or moderate asthma. In patients with severe asthma, comparative studies have also been performed. To date, this data have only been presented in abstract form (Busse W et al. J Allergy Clin Immunol 2005; 115[2, suppl 1]:S213; Bernstein D, et al. J Allergy Clin Immunol 2005; 115[2, suppl 1]:S210), but the data do indicate that ciclesonide (160 µg bid or 320 µg bid) and fluticasone propionate, CFC (440 µg bid), are equally effective at improving a variety of outcome measures (eg, total airway symptom scores, FEV₁, PEFR, beta-agonist use, quality of life).

Dr. Chipps concluded the symposium showing that the three presentations given at this symposium reveal that ciclesonide has many qualities that theoretically make it a safe and effective option for treating asthma (Table 2). Among the ICS available, clinicians need to examine each ICS quality separately to make an informed decision as to what is best for their patients. Dr. Chipps noted that current NHLBI guidelines emphasize first-line utilization of ICS therapy for the treatment of mild to moderate persistent asthma and that a FDA Black Box Warning regarding the use of LABAs as first-line therapy for mild-to-moderate persistent asthma is present. Improvements in the PK/PD properties of ICS and in their delivery systems have made some of them, especially ciclesonide, attractive options to help asthma patients adhere to a treatment program that is safe and effective.
The Current State of Pulmonary Arterial Hypertension Treatment: Current Findings From New Databases

Michael D. McGoon, MD, FCCP, Professor of Medicine at the Mayo Clinic College of Medicine in Rochester, MN, began the symposium with an overview of registry databases involved in pulmonary arterial hypertension (PAH). Dr. McGoon reminded the audience that registries are not clinical trials. “Registries are observational by nature. They tend to generate hypotheses, although they can lead to specific conclusions on their own. They have descriptive goals, in terms of helping us understand populations of interest,” said Dr. McGoon, adding, “Clinical trials provide evidence for how to practice medicine based on a control comparison, using placebos and tight definitions of populations of interest, whereas registries are broader and have looser control to allow general observations about the real world” (Figure 1).

Over the years, PAH registries have provided us with many important medical contributions. For example, the initial NIH primary pulmonary hypertension (PPH) registry in the mid-1980s (Ann Intern Med 1987; 107:216-223) that monitored 187 patients with PPH utilized a definition for PAH that continues to be used today (mean pulmonary artery pressure of 25 mm Hg at rest or 30 mm Hg with exercise). This initial registry also showed that women were generally more prone to PAH, and the age group of most patients was 20 to 40 years. Dr. McGoon added, “It also made the important observation, which has subsequently led to a tremendous amount of progress, that 6% of patients with PPH had other family members who were also affected.” One final observation in this study that continues to haunt physicians is that the time from the initial symptoms to a diagnosis averaged 2 years.

The second study discussed by Dr. McGoon was a case-control study published by Abenhein and colleagues (N Engl J Med 1998; 335:609-616) in which the records of 95 patients with PPH were evaluated and compared with a control population (n = 355). A disproportionate number of patients with PPH had taken fenfluramine appetite suppressants. This study led to further registries. One registry was the Surveillance of North American Pulmonary Hypertension (SNAP) study. Dr. McGoon said, “This was a somewhat unique registry in that it was entirely voluntary on the part of 12 centers with no funding available, and it was not audited. It was intended to see whether there was evidence of anorexigenic-induced pulmonary arterial hypertension.” This study also noted that there appeared to be an
association between fenfluramine and PPH, but the study recognized its own potential for referral bias of patients who had been diet drug users tested for PAH without having any symptoms of PAH (Chest 2000; 117:870-874). A subsequent registry, the SOPHIA (Surveillance of Pulmonary Hypertension in America) study (American Heart Journal 2006; 152:521-526) used more specific and audited criteria for enrolling patients. It also showed an association between fenfluramine use and PPH. Dr. McGoon noted, however, that because a high prevalence of fenfluramine use was noted in referral patients who were, subsequently, discovered to not have PAH, patient selection bias was likely present.

“REVEAL (Registry to Evaluate Early And Long-Term PAH Disease Management) is a multicenter, observational, US-based study of the clinical course of disease management of patients with PAH.”

Michael D. McGoon, MD, FCCP

Dr. McGoon also discussed a recently published study (Am J Respir Crit Care Med 2006; 173:1023-1039) by Humbert and colleagues who enrolled 674 adult patients with PAH from 17 centers in France. In this registry, the patients were WHO category 1 patients (ie, patients with pulmonary arterial hypertension), while patients with evidence of underlying lung disease were excluded. Their key findings were that women continue to be slightly more predominant (62% of patients) and that peak age may be rising (mean peak age was 50 years [range 18 to 85 years]). Two disheartening findings from this recent study were: (1) the time of initial symptoms to diagnosis continues to be long, and (2) they observed a few new cases that were associated with anorexigenic, use even though the anorexigenics had been used over 4 years previously. Dr. McGoon said, “This may suggest there is a delayed effect that could occur, even as long as 4 years afterwards.”

Dr. McGoon finished his presentation with the REVEAL (Registry to Evaluate Early And Long-Term PAH Disease Management) registry, of which he is currently involved. Dr. McGoon said, “I’m very enthusiastic about the potential for it really advancing our understanding,” adding, “It is a multicenter, observational, US-based study of the clinical course of disease management of patients with PAH.” When completed, they hope to enroll 3,000 patients diagnosed with WHO group 1 PAH, making it the largest registry to date. It will also be one of the longest registries, because they plan to follow patients for a minimum of 5 years. Dr. McGoon stated, “The objectives, specifically, are to characterize the demographics and clinical course of the patient population with PAH, to evaluate differences in patient outcomes according to the different subgroups within PAH, and to compare patient outcomes in patients who do and do not meet prespecified hemodynamic criteria for the diagnosis of PAH.” Dr. McGoon is also hopeful that the registry will identify baseline clinical predictors of short-term and long-term outcomes and will assess outcomes of different PAH treatment strategies. Specific outcomes measured are shown in Table 1.

In March 2006, the first patient was enrolled, and Dr. McGoon is hopeful that they will reach their 3,000-patient goal by the end of 2007. To date, 545 patients had enrolled and preliminary data had shown the whole spectrum of PAH medications being used (ie, 41% are taking a prostacyclin, 50% are taking a PDE-5 inhibitor, and 51% are taking an endothelin receptor antagonist). Furthermore, Dr. McGoon noted that the percentages added up to more than 100% for the simple reason that almost half of the patients are on combination therapy.

Dr. McGoon is hopeful that many questions will be answered with the REVEAL registry, and he looks forward to presenting more results at future ACCP meetings.

### Laying the Foundation: Pathogenesis and Diagnostic Approach

C. Gregory Elliott, MD, MACP, FCCP, Professor of Medicine at the LDS Hospital and the University of Utah in Salt Lake City, UT, continued the symposium with a discussion on PAH pathogenesis which he described as a pathogenetic triad (thrombosis, vasoconstriction, and cellular proliferation) (Figure 2).

**Table 1. REVEAL: Outcomes To Be Assessed**

- Modified NYHA/WHO functional class
- 6-min walk distance
- Change in pulmonary function test results
- Change in hemodynamic measurements, when available
- Functional status, including employment, student status, level of independent function
- Occurrence of hospitalizations
- Occurrence of death

**Figure 2. PAH Pathogenesis**

**Thrombosis**

To illustrate the thrombotic element in PAH pathogenesis, Dr. Elliott showed the audience a cross-section of a small pulmonary artery from a patient with PAH that revealed the thrombotic material that recanalizes within the pulmonary arteries. “The mechanisms for these in situ thrombi, we think, are largely related to a loss of the natural anticoagulant activity of the normal pulmonary vascular endothelium, some enhancement of the activity of von Willebrand factor, and both stimulating active coagulation at the endothelial surface,” said Dr. Elliott.

**Vasoconstriction**

“The pathogenesis of the vasoconstrictive phenomena is often viewed in a very simple manner, as being an imbalance between factors that lead to vasodilation of the pulmonary circulation, such as decreases in
nitric oxide synthase, decreases in prosta-
cyclin or prostacyclin substances, and
decreases in endogenous nitric oxide being
secreted by the pulmonary endothelium,”
explained Dr. Elliott, adding, “In contrast,
there may be, with this imbalance, an
increase in factors that promote vasocon-
striction, such as endothelin or serotonin.”
To illustrate, Dr. Elliott discussed a series
of physiologic and anatomic studies show-
ing an imbalance of various factors that
control pulmonary microvasculature are
present (i.e., abnormal prostacyclin syn-
thease, nitric oxide synthase, and endothe-
327:70-75; Am J Respir Crit Care Med
333:214-221; Am J Respir Crit Care Med
328:1732-1739). Dr. Elliott also noted that
serotonin may be an important factor.
“When you look at healthy individuals,
you find very little serotonin in the plasma
of these individuals. In contrast, you can
see almost a 30-fold increase in patients
with idiopathic pulmonary arterial hyper-
tension,” said Dr. Elliott (Am J Med
99; 249-254).

The diagnosis of pulmonary arterial hypertension remains quite challenging. The diagnosis often requires a
multidisciplinary evaluation.”

C. Gregory Elliott,
MD, MACP, FCCP

Vascular proliferation
“Pulmonary arterial hypertension is very
much, in part, a disease of over-prolifera-
tion of endothelial and smooth muscle
cells,” stated Dr. Elliott. An examination of
the pulmonary vessels show a remodel-
ing of the vessel wall and “proliferating
cells within that lumen, obstructing the
lumen, then you see this plexiform lesion
with the rupture and the recanalization of
the muscular small pulmonary artery.” One
 genetic factor that is associated with vas-
cular proliferation is the gene that codes
for bone morphogenetic protein receptor
(BMPR2), which is linked to familial pul-
monary arterial hypertension. Mutations
of this gene are in most familiar PAH cases
and in 11 to 40% of patients with IPAH.

In addition to the supportive care that is
required for many patients with PAH
(Table 2), the PAH-specific care is based
largely on the severity of the PAH, and Dr.

If we could prevent the right
ventricle from failing, the vast
majority of these patients would
never die; we would certainly
have long-term survival.”

Victor F. Tapson, MD, FCCP
Pulmonary Arterial Hypertension Disease Management: Raising the Bar for Acceptable Outcomes

Prostacyclins

“Options available for less severe patients with PAH include the endothelin antagonists and PDE-5 inhibitors. For more severe patients with PAH, prostacyclins are recommended (Table 3). Only in the small percentage of patients who are vasodilator reactive are calcium channels blockers recommended.

Prostacyclins

“Our FDA-approved therapies that are prostaglandin-based are epoprostenol, treprostinil, and inhaled iloprost,” stated Dr. Tapson. Of these, epoprostenol is the most widely studied, and numerous clinical trials have shown it to improve exercise capacity, hemodynamics, dyspnea, and functional class. Survival benefit has been demonstrated, as well (N Engl J Med 1996; 334:296-301; Ann Intern Med 2000; 132:425-434; J Am Coll Cardiol 2002; 40:780-784). While the efficacy is promising, Dr. Tapson said that it is an intravenous preparation and, as such, “it is somewhat cumbersome; you have a pump, a central IV line; you may get infections, possibly sepsis, and if you’re disconnected from your line, its symptoms may worsen, occasionally resulting in death.” Dr. Tapson also noted that “we see unusual side effects with prostacyclins, including leukocytoclastic vasculitis in patients, especially on the higher doses of the drugs, although most patients tolerate this drug very well and deal with milder side effects, such as headache and loose stools. When someone comes to the hospital, and starts on epoprostenol, we tell them they’re probably going to get some jaw pain the first couple of days when they bite down on their food.”

The PAH-specific treatment options available for less severe patients with PAH include the endothelin antagonists and PDE-5 inhibitors. For more severe patients with PAH, prostacyclins are recommended.

Victor F. Tapson, MD, FCCP

Table 2. PAH: Supportive Therapy

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen (when indicated)</td>
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<tr>
<td>Diuretic therapy (when indicated)</td>
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<tr>
<td>Anticoagulation</td>
<td></td>
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<tr>
<td>Digoxin</td>
<td></td>
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<tr>
<td>Cautious exercise (cardiopulmonary rehabilitation)</td>
<td></td>
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<tr>
<td>ICU setting: dopamine, dobutamine, furosemide drip, CVVHD, mechanical ventilation</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. PAH: Specific Therapy

<table>
<thead>
<tr>
<th>Prostanoid therapy</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (Flolan) IV</td>
<td></td>
</tr>
<tr>
<td>Treprostinil (Remodulin) SC and IV</td>
<td></td>
</tr>
<tr>
<td>Iloprost (Ventavis) inhaled</td>
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</table>

PDE-5 Inhibitors

The only FDA-approved endothelin antagonist currently available is oral bosentan. Clinical trials show that it improves the 6-min walk test, dyspnea index, functional class, and time to clinical worsening (N Engl J Med 2002; 346:896-903). McLaughlin and colleagues have also shown that it likely improves survival (J Eur Respir 2005; 25:218-220). Two antagonists in development, sitaxsentan and ambrisentan, also show promise as safe and effective alternatives to bosentan.

Table 3. PAH: Specific Therapy

<table>
<thead>
<tr>
<th>Calcium channel blockers*</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan (Tracleer)</td>
<td></td>
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<tr>
<td>Sitaxsentan (Thelin)*</td>
<td></td>
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<tr>
<td>Ambrisentan*</td>
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</table>

Concluding Remarks

Dr. Tapson ended the symposium by stating that if PAH is suspected in a patient, “you’ve got to get the diagnosis and know the severity to make decisions on treatment.”

Victor F. Tapson, MD, FCCP
Minimizing Ventilator-Induced Lung Injury

At a symposium chaired by Leonard D. Hudson, MD, FCCP, Professor of Medicine and Endowed Chair in Pulmonary Disease Research in the Division of Pulmonary and Critical Care Medicine at the University of Washington School of Medicine in Seattle, WA, four leading pulmonologists discussed recent developments in our understanding of acute respiratory distress syndrome, ventilator-induced lung injury, and other lung injuries.

The Pathophysiology of Ventilator-Induced Lung Injury

Acute lung injury (ALI) is a serious condition that develops in 43,000 to 107,000 people per year (Crit Care Med 2003; 31: S276). The overall mortality rate regardless of treatment strategy is approximately 40%. Patients with acute respiratory distress syndrome (ARDS) require the use of mechanical ventilation that, if improperly used, can significantly increase mortality by 9 to 33%. Thus, inappropriate use of a ventilator can lead to further lung injury, including ventilator-induced lung injury (VILI).

To understand the options to treat ARDS and prevent VILI, it is first necessary to understand their pathophysiologies. To that end, the symposium began with a quick overview of the pathophysiology of ARDS and VILI by Gary Nieman, Assistant Professor in the Department of Surgery and Director of the Cardio-pulmonary and Critical Care Laboratory at SUNY Upstate Medical University in Syracuse, NY.

ARDS involves a cascade of events. It begins with an injury, such as sepsis or trauma, that in turn leads to the systemic inflammatory response syndrome (SIRS). SIRS activates polymorphonuclear neutrophils (PMNs), which sequester in the pulmonary capillaries and release reactive oxygen species (ROS) and proteases that damage the microvessels. This leads to an increase in capillary permeability, resulting in alveoli flooding with edema. This pulmonary edema deactivates surfactant, which results in alveolar instability. Mechanical ventilation is thrust into the complex pathophysiology of ARDS and can result in further tissue damage (ie, VILI).

While this description of the pathophysiologies of ARDS and VILI does not fully describe the complex nature of either problem, the simplified description does point out that the instability of the alveoli is one of the primary mechanisms of VILI (Figure 1) and attempts to make the alveoli more stable are being studied to reduce VILI.

Components that stabilize the alveoli include (1) intracellular cytoskeleton, (2) elastin and collagen support tissue, (3) pulmonary surfactant, and (4) alveolar interdependence. Of these, the latter two can possibly be manipulated to stabilize alveoli and reduce VILI. In regard to exogenous surfactant treatment, Dr. Nieman noted there have been a plethora of ARDS/surfactant clinical trials. To date, the results have been inconclusive. For example, Willson and colleagues (JAMA 2005; 294:898-899) looked at the effects of exogenous surfactant in children with acute lung injury and found that it did improve mortality and oxygenation, but it did not change the course of the acute lung injury. In a study by Spragg and colleagues (N Engl J Med 2004; 351:884-892), the effects of a protein-C-based surfactant in patients with ARDS was not found to change mortality. Other studies have shown similar results (ie, trends toward improvement or no improvement) when surfactants were added to the therapy regimen.

Dr. Nieman stated that at his research facility, they have performed studies based on the question “Are abnormal alveolar mechanics (ie, unstable alveoli) an important mechanism in the development of VILI?” Addressing this question, Dr. Nieman and his colleagues (Am J Respir Crit Care Med 2004; 169:57-63) designed a study based on the hypothesis that unstable alveoli increase the risk of lung damage and that by using elevated positive end-expiratory pressure (PEEP), the damage would decrease, as well as cytokine release would reduce and alveolar stability would improve. In their animal (porcine) study, the researchers were able to visually and histologically confirm that alveoli are unsta-
ble in the ARDS model and that elevated PEEP can convert abnormal unstable alveoli into normal, stable alveoli with resultant reduction in lung injury (Figure 1). Whether this also occurs in people remains to be determined, but Dr. Nieman is optimistic that improvements in our understanding of the pathophysiology of ARDS and VILI can lead to better understanding of how to best implement ventilation for these patients.

**Concluding Remarks**

Dr. Nieman ended his presentation by stating that alveolar instability is one of the main causes of tissue injury in VILI. Attempts to stabilize alveoli and reduce tissue injury with PEEP are recommended.

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**Protective Mechanical Ventilation in Preventing VILI**

The symposium continued with a summary of nonconventional and conventional approaches to using protective mechanical ventilation to prevent VILI by Arthur S. Slutsky, MD, of the Keenan Research Center, Li Ka-Shing Knowledge Institute at St. Michael’s Hospital, Interdepartmental Division of Critical Care Medicine at the University of Toronto in Toronto, Canada.

Despite recent clinical trials demonstrating improved outcome in ARDS, the overall mortality rate and incidence of VILI remains unacceptably high. As a result, adjunct therapy and/or alternatives to standard conventional mechanical ventilation continue to be evaluated. One of the issues with developing a strategy to treat these patients is the small window available to treat them without causing further damage (Figure 2). Dr. Slutsky discussed some of the recent nonconventional and conventional approaches that have been tested to prevent VILI.

**Non-Conventional Therapy**

**Partial Liquid Ventilation**

In partial liquid ventilation, the lungs are partially filled with a clear inert fluid, and perfluorocarbon (PFC) and mechanical ventilation occur with a standard ventilator. The rationale for this approach is that PFCs improve gas exchange by recruiting dependent lung regions, clearing retained secretions, and redistributing blood flow to ventilated regions in patients with ARDS. In animal models of acute lung injury, this approach has been shown to improve gas exchange and decrease lung injury compared with conventional mechanical ventilation. Based on this and other preliminary clinical data, a large, randomized, clinical trial was undertaken by recruiting dependent physicians, including Dr. Slutsky (*Am J Respir Crit Care Med* 2006; 173:882-889).

In this trial, patients with ARDS were randomized to receive (1) conventional mechanical ventilation (n=107); (2) low dose PFC (10 mL/kg, n = 99); or (3) high dose PFC (20 mL/kg, n=105). Patients in all three groups were ventilated using volume ventilation, VT ≤10 mL/kg predicted body weight, rate ≤25/min, inspiratory-to-expiratory ratio ≤1:1, FIO₂ ≥0.5, and positive end-expiratory pressure (PEEP) ≥13 cm H₂O. The primary outcome was ventilator-free days during the 28 days after randomization and in this study, there were more ventilator-free days in the control group (13 ± 9.3 days), compared with either the low-dose PFC (7.4 ± 8.6 days) or high dose PFC (9.9 ± 9.1 days). A secondary outcome of the study was mortality, and there were no significant differences in the three groups. The reason that the results of this study were negative, but Dr. Slutsky emphasized, until further studies can explain the results, the use of partial liquid ventilation in patients with ARDS should not be performed.

**High Frequency Ventilation**

High frequency oscillatory ventilation for patients with ARDS is based on the premise that the higher frequency allows for better lung volume to attenuate lung injury compared with conventional therapy. In a clinical trial testing this procedure, Derdak and colleagues (*Am J Respir Crit Care Med* 2002; 166:801-808) randomized patients with severe ARDS to high-frequency oscillatory ventilation (n = 75) or conventional ventilation (n = 73). Dr. Slutsky noted that in this study, no significant differences in hemodynamics, oxygenation failure, ventilation failure, barotrauma, or mucus plugging were observed between the two groups. However, the high-frequency oscillatory ventilation group did show a trend toward a greater survival rate. Thirty-day mortality was 37% in the high-frequency oscillation group and 52% in the conventional ventilation group (not significantly different).

**Conventional Therapy**

**ARDSNet Study**

Dr. Slutsky began his discussion of the conventional ventilation approach with a description of the ARDSNet study, which is a prospective, randomized, multicentered study comparing conventional ventilation strategy (12 mL/kg, predicted body weight [PBW]) with a smaller dose, “protective” strategy (6 mL/kg, PBW). This study was stopped early after 861 patients were recruited, because the lower Vt group had a significantly lower mortality rate than the larger Vt group.

Dr. Slutsky acknowledged that this trial has been criticized and the ARDSNet clinical design has been under great scrutiny. Questions that have been addressed include the following: (1) Was the control group Vt too large? (2) Was
the lower protective strategy (6 mL/kg) needed, or could VTs between 6 and 12 have been equally effective? (3) Will the small VT increase the need for sedatives? and (4) Was the approach used in this study not an individualized ventilation strategy for each patient? Dr. Slutsky dealt with each of these questions and said none of these negates the validity of the study.

**High PEEP**

Another conventional approach discussed by Dr. Slutsky was the use of high PEEP in acute lung injury. Several trials involving this are ongoing, including the LOVS (Lung Open Ventilation Strategy) trial with which Dr. Slutsky is involved. Presently, the only published study available is by the National Heart, Lung, and Blood Institute ARDS Clinical Trial Network (New Engl J Med 2004; 351:327-336). In this trial, patients were classified into low or high PEEP groups (mean low PEEP was 8.3 cm H2O; mean high PEEP was 13.2 cm H2O). A 28-day follow-up showed no significant differences in the two groups, including mortality.

**Concluding Remarks**

Dr. Slutsky summarized his presentation by stating that nonconventional approaches have not proven to be viable treatment options; however, high frequency ventilation is showing promise and more studies are underway. At present, conventional studies are the gold standard, and there are numerous trials underway to determine optimal PEEP value, but, to date, no differences have been seen, although Dr. Slutsky said that higher PEEP appears to have a slight advantage.

Dr. Slutsky ended the presentation with "An Ode to Ventilator Management" he and Dr. Tremblay wrote a few years ago, which is as follows:

**An Ode to Ventilator Management**

Ensure you’ve set the ventilator to go BEEP, should you have too much PEEP - else from the lungs the air will SLEEP.

Conversely, should you see ZEEP - or even worse, the infamous NEEP, the patient’s gratitude will not run DEEP.

But if between these two extremes you CREEP, you’ll find little cause to WEEP and many accolades you will REAP.

So remember - before you go to SLEEP, GIVE PEEP, listen for the BLEEP, and never, never, NEEP or ZEEP.

Tremblay and Slutsky. Am J Respir Crit Care Med 2001;164:2001

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**Prone Position and Protective Mechanical Ventilation**

The symposium continued with a discussion on patient positioning by Richard K. Albert, MD, FCCP, Professor of Medicine at the University of Colorado Health Sciences Center, Chief of Medicine at the Denver Health Medical Center and Adjunct Professor of Engineering and Computer Science, University of Denver in Denver, CO.

Most patients with ARDS are treated in a supine position, but Dr. Albert argued that a prone position may be more beneficial. Dr. Albert showed that the lungs fit better inside the thorax when patients are in the prone position, and this may make the lung less susceptible to further damage. These observations, as well as animal and preclinical studies, have led Dr. Albert to hypothesize that the prone position in patients with ARDS may (1) lower the inspiratory pressure needed to reach airway opening, (2) lower the end-expiratory pressure required to maintain airway opening, and (3) reduce cyclical air-space opening and closing. Assuming that VILI may be due to one of these factors, the prone position could reduce the incidence of VILI and reduce morbidity and mortality rates in patients with ARDS.

**Clinical Trials**

While animal studies and small observational studies may support the use of prone positioning for patients with ARDS, the results of large clinical trials have not been very robust. Dr. Albert argued that this is largely due to the poor design of these studies. In a study based in Italy (N Engl J Med 2001; 345:568-573), patients with ARDS were randomized to receive conventional therapy with patients in the supine position (n=152) or in a prone position for 6 to 10 h per day for 10 days [n=152]. The results of the study found no survival benefit for positioning patients in the prone position; however, a post hoc analysis did show that patients with a higher simplified acute physiology score (SAPS) did have some improvement in survival. Dr. Albert noted that there were several problems with the design of this study. For example, the duration of prone positioning was only 7 h (i.e., 17 h a day in the supine position). Dr. Albert also noted that the study was underpowered and had no protocols in place for ventilation or weaning.

In another trial, Guerin and colleagues (JAMA 2004; 292:2379-2387) examined the effects of prone positioning in hypoxic acute respiratory failure. In this trial, 791 patients with acute respiratory failure were randomized to receive conventional supine therapy (n=378) or therapy in the prone position (minimum of 8 h per day, n=413). As in the previous trial, this study observed no survival benefit (primary outcome was 28-day mortality rate); however, increased survival was observed in the patients with higher SAPS. Dr. Albert also pointed out the problems with the design of this study. Namely, the patient population was not specific, the study was underpowered, and the daily duration prone positioning was short (8 h). There was also no ventilation protocol in place.

The final, large trial discussed by Dr. Albert was a recent trial originating in Spain (Am J Respir Crit Care Med 2006; 173:1233-1239). In this trial, the researchers did include ventilation and weaning protocols, and the patients with severe ARDS (n=136) were placed in the prone position for 20 h per day. Dr. Albert noted that using this improved design, the mortality rate was 25% lower in the patients given the prone position therapy (34/456 mortality in supine patients vs 33/75 patients in the prone patients). However, this difference was not statistically significant, and the study was stopped early because of enrollment difficulties.

Summarizing the data, Dr. Albert said that while animal studies support the use of using the prone position to help patients with ARDS, the clinical trials involving the use of prone positioning have not been sufficiently well-designed or conducted and, as a result, are inconclusive. That said, Dr. Albert thinks that prone positioning a patient with ARDS is safe, and there is a very strong physiologic rationale by which it could reduce VILI and mortality. Consequently, more studies are needed.
The symposium concluded with a discussion by Clement Singarajah, MD, ICU Director at the Carl Hayden VA Medical Center in Phoenix, AZ. Dr. Singarajah began his presentation by stating that all treatment options should be evidence based. Unfortunately, most treatment options for ARDS (Figure 3) are based on limited evidence. One treatment option available is kinetic therapy, and Dr. Singarajah used this platform to discuss some of the clinical evidence for the use of kinetic therapy in ARDS and other pulmonary ailments.

Kinetic therapy, by definition, involves the use of a bed that slowly and continuously turns at an angle greater than 40° along its longitudinal axis.

**Kinetic Therapy: Clinical Trials**

A key element to a successful outcome with kinetic therapy is the angle of rotation (ie, > 40°) (Figure 4). For example, McIntyre and colleagues (Respir Care 1999; 44: 1447-1451) randomized 104 patients to receive standard ICU care or care with continuous rotation at 20°, and the authors observed no statistically significant difference between the two groups. In contrast, increasing the rotation to 40° or more improves outcome. In a study by Raoof and colleagues (Chest 1999; 115:1658-1666), 24 patients with respiratory failure (patients receiving mechanically ventilation or spontaneously breathing, who demonstrated segmental, lobar, or unilateral entire lung atelectasis were randomized to receive kinetic therapy (40°) combined with mechanical percussion

(\text{n}=17) or to receive manual repositioning and manual percussion every 2 h (\text{n}=7). In this study, partial or complete resolution of atelectasis was seen in 14 of 17 patients (82%) in the kinetic therapy + percussion group. In contrast, only 1 of the 7 patient taking conventional therapy showed improvement (14%).

Dr. Singarajah also discussed a study by Ahrens and colleagues (Am J Crit Care 2004; 13:376-383), which was a multicentered, prospective, quasirandomized trial involving 255 patients in which 121 patients received kinetic therapy (rotation to >40° for 18 h/day) and 137 patients received standard care (manual turning every 2 h). In this study, the patients receiving kinetic therapy had significantly reduced ventilator-associated pneumonia (kinetic therapy = 14% vs control = 33%) and lobar atelectasis (kinetic therapy=17% vs control=43%). For the other outcomes, no significant differences were observed (ICU/hospital length of stay, ventilation time, and mortality), but Dr. Singarajah noted that lower ICU charges were observed in the kinetic therapy group.

The final study discussed by Dr. Singarajah was a comparison of early vs late kinetic therapy in trauma. Pape and colleagues (Injury 1998; 29:219-225) performed a retrospective analysis comparing early (ie, before oxygenation deteriorated) (\text{n}=107) with late intervention (\text{n}=54) on pulmonary function and the incidence of ARDS. The study found that the group receiving the early intervention had better systemic oxygenation and lower incidence of ARDS (early, 34%, vs late group, 74%).

**Concluding Remarks**

Dr. Singarajah ended the symposium by stating that kinetic therapy may be an effective adjunct therapy for some patients with ARDS in the ICU but its use in these patients needs to be further studied. Dr. Singarajah further stated that at the very least, kinetic therapy has had no harmful effect in any study to date, which contrasts with many interventions in septic shock studies.