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Until recent years, the concept of treating pulmonary arterial hypertension through a variety of mediators and mechanisms seemed beyond our grasp. As much as it is routinely done in other illnesses, the possibility of applying this concept in pulmonary hypertension was remote. This picture has radically changed, however, with the introduction of new agents that may be used in conjunction with prostacyclin and its analogs. The revolution in therapy started with the man profiled in this issue, Sir John Vane, a Nobel Prize winner recognized for his work in prostaglandin research.

Perhaps the theme of this issue should be that the revolution continues. After paying a debt of gratitude to Dr Vane, our story about prostacyclin continues throughout this issue. We explore the need to develop prostacyclin analogs to overcome the limitations of the epoprostenol delivery system, elaborate on the intriguing work with inhaled iloprost, and round it up with a roundtable discussion ranging across the spectrum of issues involving prostacyclin. We are also grateful to Bruce Brundage, MD, president of the Pulmonary Hypertension Association, who provided the images for this issue’s cover.

Slowly, but with encouraging progress, we are getting to the point where we will better understand how to treat pulmonary arterial hypertension through a variety of mediators and mechanisms. There is still much to be discovered about prostacyclin—for example, how precisely does the medication work? When we discover its true mechanisms and determine how it can be used in combination with other treatments, perhaps the revolution in therapy will have achieved its goals.

Vic Tapson, MD
Editor-in-Chief

Profiles in Pulmonary Hypertension

A Nobel Prize Winner Who Triggered a Revolution in Therapy

Winner of the Nobel Prize in medicine. The researcher who discovered prostacyclin, the most widely prescribed drug in pulmonary hypertension. The pioneer who uncovered the mode of action of aspirin. Knighted in 1984 for his contributions to medical research. These achievements of Sir John Vane and the accolades received for them tend to dwarf those of even the most highly respected investigators in pulmonary hypertension.

It's been 20 years since Dr Vane shared the Nobel Prize for his studies of prostaglandins, and his discovery of one of them, prostacyclin, eventually ushered in a new era in the treatment of pulmonary hypertension. Ironically, the initial research involving the drug took a different direction.

“The first clinical trials on prostacyclin were not in pulmonary hypertension. They were in peripheral vascular disease,” recalled Dr Vane during a recent interview from his office in the United Kingdom. Dr Vane was cited by the Nobel committee for his “discovery of the prostaglandin known as prostacyclin in 1976, and for analyzing its biological effects and function.” Yet it was years before the drug epoprostenol (Flolan) was first used in pulmonary hypertension after Timothy Higenbottam, MD, documented its efficacy in the disease in 1987. Initially, however, Polish researchers who spent time with Dr Vane in his UK laboratory took a different track with prostacyclin when they returned to Poland.

“They reported striking and prolonged benefits following intra-arterial infusion of prostacyclin in five patients with advanced atherosclerotic lower-limb peripheral vascular disease. Rest pain disappeared, previously refractory ulcers healed, and muscle blood flow as measured by Xenon133 clearance was significantly increased for at least 6 weeks after prostacyclin infusion. They later reported striking improvements in some of 55 patients with advanced peripheral artery disease of the lower extremities.”

With the benefits also observed in pulmonary hypertension and Dr Vane later serving as Group Research and Development Director of the Wellcome Foundation, the path was cleared for the introduction of Flolan. Since the introduction of the drug, longer lasting analogs have been introduced, but no one has produced a compound with a half-life of more than 2 hours and this remains a barrier still to be overcome with the use of such agents.

Addressing this problem, Dr Vane said, “the answer must be that the prostacyclin molecule is unstable, and no matter what you do to it to try to add stability, you can’t add all that much. Since the analogs have to be based on the original structure of prostaglandin, they are going to have relatively short half-lives.”

Dr Vane's research on other medications are also milestones in the development of more effective treatments for a wide range of disorders. These include his discovery of (continued on page 20)
Continuous Intravenous Epoprostenol for Pulmonary Arterial Hypertension: Highlighting Practical Issues, Special Considerations

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Continuous intravenous epoprostenol sodium (Flolan®) is a long-term, complex, and expensive therapy. Its pivotal role in the management of pulmonary arterial hypertension (PAH) is based on randomized studies that clearly established clinical efficacy. Subsequent studies have confirmed its benefits with regard to symptomatic and functional improvement, sustained hemodynamic effect, and enhanced survival. Initial studies demonstrated both acute (Figure 1A) and short-term (Figure 1B) hemodynamic improvement.1,2 Exercise capacity in epoprostenol-treated patients, as measured by 6-minute walk test distance, improved during 12 weeks of follow-up compared with conventionally treated patients (Figure 2).2 Improved exercise capacity, as assessed by improvement in peak oxygen consumption, has also been documented (Figure 3).3 Importantly, increased survival has recently been reported in two large case series of patients with PAH (Figure 4).4,5 Although the US Food and Drug Administration (FDA) has recently approved alternative subcutaneous and oral drugs, intravenous epoprostenol remains the most effective agent in the therapeutic armamentarium for PAH patients with World Health Organization (WHO) Class III or IV symptoms.

Despite its proved efficacy and cumulative experience since the commercial availability of epoprostenol in 1996, intravenous epoprostenol remains a complicated and potentially dangerous therapy. With the approval of additional therapies for advanced PAH, the selection of appropriate candidates for epoprostenol treatment has become particularly challenging. Health care providers must assess the potential risks and benefits of epoprostenol therapy compared with alternative treatment for each patient. This assessment should consider the patient’s medical diagnosis, comorbidities, psychosocial status, support structure, financial resources, and stability.

Providers should also consider the available resources in their own facility to provide the comprehensive and intensive management that these patients require. Importantly, although epoprostenol therapy can be life-saving when used appropriately, it can potentially complicate, and in some cases worsen, symptoms with catastrophic results if it is incorrectly initiated, administered, or managed over the long term. Careful attention to four aspects of treatment is required when considering long-term use of epoprostenol: (1) patient eligibility, (2) patient education, (3) drug initiation, and (4) treatment maintenance and follow-up.

**Patient Eligibility**

The decision about whether a patient should be treated with epoprostenol requires consideration of a number of issues:

- Does the patient have appropriate clinical indications?
- Are there clinical contraindications?
- Are alternative medications more suitable?
- Have issues of medical coverage been defined?

![Figure 1](image1.png)

Fig. 1—(A, top). Acute hemodynamic response to intravenous epoprostenol in 23 patients1 and in 81 patients2 with PPH studied in the two original randomized efficacy studies. Although the change in mean pulmonary arterial pressure (PAm) was minimal, cardiac index (CI) increased and pulmonary vascular resistance (Rp) decreased (*P < .0003). (B, bottom). After 8 to 12 weeks of follow-up, hemodynamic benefit was maintained in patients treated with epoprostenol and was significantly better than in patients receiving conventional therapy (*P < .03 compared with baseline).
• Is the patient able and willing to learn and comply with the regimen?
• Can adequate follow-up be assured?

Clinical indications

Epoprostenol is currently FDA-approved for patients with symptomatic (WHO Class III or IV) primary pulmonary hypertension (PPH) or PAH associated with collagen-vascular disease (the scleroderma-spectrum of diseases). At present, there are no controlled data demonstrating its efficacy in patients with HIV infection, congenital heart disease, or portopulmonary hypertension. Because these indications are similar to those for oral bosentan (Tracleer®) and subcutaneous treprostinil (Remodulin®), additional considerations should be weighed in selecting epoprostenol over these other agents.

Patients with very advanced or rapidly progressive symptoms should be considered for early treatment with epoprostenol since it has proved to be the most effective medical therapy and improved mortality has been demonstrated with its use. Epoprostenol can be added to the medical regimen of patients whose condition has failed to adequately respond or who have not tolerated other medications. This drug should not be used in those with pulmonary venous hypertension as no benefit has been demonstrated and there is potential for worsening. Central venous access is essential for placement of a permanent catheter. The presence of superior vena cava or bilateral subclavian vein obstruction (usually in the setting of previous central catheters or pacemaker leads) may be a relative contraindication.

Medical coverage

Epoprostenol is far more expensive than most drugs, its use sometimes exceeding $100,000 per year. If prescribed for appropriate indications (WHO Class III and IV PPH and PAH associated with the scleroderma-spectrum of diseases), medical coverage is usually available. Prior insurance authorization is necessary and can be facilitated by the distributors of the medication. Awareness of reimbursement issues by caregivers is mandatory, and coordination between the patient and the distributor is a vital role of an active pulmonary hypertension clinic.

Patient capability and compliance

Although purely clinical issues regarding treatment selection are pivotal, other factors may take precedence in matching the patient to appropriate epoprostenol treatment. Despite the desire to provide optimal clinically indicated therapy to all patients, not all are safe candidates. In addition, health care
provider time is a valuable resource; care of one marginally compliant or competent patient may adversely affect the care of others. Thus, careful consideration of factors related to a patient’s willingness and ability to undergo therapy as well as the level of family and social support should be addressed before initiation. These factors are best explored by an experienced and sensitive nursing staff with specialization in the management of PAH patients.

Nursing interviews should be conducted with both the patient and a significant other who will assist and support the patient at the outset. A number of issues should be explored with careful questioning. Responses to these questions do not necessarily preclude therapy, but are extremely useful in planning for future patient and staff needs.

**Questions to ask after therapy has been explained include:**
- Are there physical limitations, such as digital loss because of collagen vascular disease or visual problems or hearing impairment, that may hinder the ability to manipulate syringes, operate the pump, or hear warning alarms?
- Are there problems with the home environment that may preclude safe drug administration and follow-up, such as absence of satisfactory plumbing, poor home sanitation, or lack of access to a telephone?
- Is there a reliable family or social support person to help prepare the medication and manage the infusion pump?
- Are the patient and support persons committed to taking the time each day (approximately 1 to 1.5 hours) to perform necessary procedures?

**Questions practitioners should ask themselves about the patient include:**
- Is the patient sufficiently at ease to be a receptive learner about a complex treatment strategy, or does stress and agitation warrant deferring?
- Has the patient demonstrated compliance and initiative by keeping scheduled clinic visits and following current treatment recommendations?
- Does the patient actively participate in his or her own care or allow a significant other to manage it?
- Does the patient have a history of substance abuse or mental illness, including depression, that has required medication or hospitalization, which would be risky in the setting of long-term complex intravenous medication infusion?

**PATIENT EDUCATION**

This process is important and should proceed in an orderly and compulsive fashion. Information for the patient must include the following components:
- Introduction to the concept of long-term drug infusion
- Discussion of realistic expectations
- Education about technical aspects of epoprostenol use
- Potential adverse effects of epoprostenol

**Introduction to therapy**

Prior to making the decision to proceed with epoprostenol therapy, patients should be shown the actual delivery system, have all procedures demonstrated, and ideally have an opportunity to meet another epoprostenol patient. This may dramatically reduce the anxiety associated with starting long-term intravenous therapy. Patients may be more likely to benefit if they have the opportunity to meet someone of the same sex, disease substrate, and age range. Patients can be given information about the Pulmonary Hypertension Association (PHA), which may assist them in locating another patient in their area.

With the advent of new drug therapy, it is feasible that some patients may ultimately be weaned from epoprostenol, but they should understand that it is very likely going to be part of their daily routine forever, unless they undergo lung or heart-lung transplantation. In our experience, patients must have control over the decision-making process to learn and properly care for the delivery system. To ensure success, written and visual (videotape or compact disc) material to review at home can be offered to supplement face-to-face teaching prior to making a final decision regarding epoprostenol therapy.
Realistic outlook
Patients should have realistic perceptions about the drug. Although epoprostenol has the potential for making a significant difference in quality of life and for improving survival, it has not proved to be a cure for PAH. It is inconvenient, has side effects, and has associated risks. Patients must realize that there may not be immediate improvement in symptoms.

Although the majority of patients improve, it is impossible to predict the magnitude or duration of the therapeutic response. Patients have to understand that initial improvement in symptoms does not guarantee continued improvement or preclude eventual decline. While it is essential to hear this information from the pulmonary hypertension center providers, patients also may benefit from discussion with other patients and caregivers through support groups. They should not, however, base their expectations on results of therapy in other patients.

Technical education
Although the approach to education and drug initiation differs among large centers based on experience and resources, there are some common practices. Patients should be taught by experienced health care providers and ideally by the same people who will be following their care over the long term. At the Mayo Clinic, patients are provided with preprinted step-by-step directions in a manual that covers pump operation, drug reconstitution, and cassette and tubing change. They are encouraged to share a copy of this information with their local physician. Teaching should occur in intensive blocks before and during the actual initiation of the drug. Whether the infusion is initiated on an inpatient or an outpatient basis, it must be done in a monitored setting with immediate access to emergency equipment and care. Long-term epoprostenol infusion should be initiated using CADD I or Legacy pumps.

The process of reconstituting epoprostenol and all facets of pump operation and catheter care must be fully explained and demonstrated. Patients and support persons should be able to demonstrate their proficiency in all phases of epoprostenol administration before they can be considered adequately trained. This ensures that the patient always has a back-up person trained, which reduces patient stress.

Adverse effects
Patients should also be aware of common potential side effects, including jaw pain, headache, hypotension, nausea, diarrhea, and flushing. More long-term side effects may include leg and foot pain, and skin rash. Others, such as high cardiac output failure, anemia, thrombocytopenia, pancytopenia, or weight loss, may be recognized by the clinician with careful follow-up over time. Some of the latter effects may also, however, be due to other underlying disease. Finally, certain adverse effects may be related to the delivery system, including catheter-related infection or sepsis, catheter-related thrombosis, pump failure, and rebound symptoms or death due to sudden discontinuation of epoprostenol.

Drug Initiation
A 6 or 9 French single-lumen tunneled central venous catheter in the subclavian or internal jugular vein is the preferred approach for long-term epoprostenol therapy. The central venous catheter should be tunneled to an exit site that will allow the patient to see the site in order to care for it independently. Sutures should be removed after 4 weeks. Catheters are changed only when they become dysfunctional or infected. Many patients maintain the same catheter for many years. If a tunneled catheter must be removed for a period of time (for example, because of infection) a short-term dedicated catheter, such as a percutaneous intravenous central catheter (PICC) or midline catheter, is appropriate for short-term use. Such catheters have limited stability and are difficult to care for using only one hand.

Epoprostenol infusion through the catheter is typically started in a monitored setting at an infusion rate of 2 to 3 ng/kg/min. Vital signs are obtained before and at least every half hour for at least 2 to 3 hours after drug initiation. Teaching sessions occur on a daily basis until patients and support persons demonstrate proficiency in the techniques of sterile preparation of the medication, operation of the infusion pump, and care of the central venous catheter. At the time of discharge, patients are provided with detailed contact information. Patients are instructed to see their local physicians within the first month of returning home, offering them the opportunity to become familiar with their current status, and to assist with their assessment and monitoring, including anticoagulation.

A proactive approach has been successful with this patient population. Once the patient is fairly comfortable with the procedures and has minimal jaw pain, mild diarrhea, or headache, the epoprostenol dosage is increased by 1 to 2 ng/kg/min. The patient is called or instructed to call within the next week or sooner if dyspnea decreases or the side effects cause discomfort.

Treatment Maintenance and Follow-up
Important issues in long-term management include:
• Communication
• Dose modification
• Interaction with the referring physician
• Follow-up at the clinic
• Emergencies

Communication
While large pulmonary hypertension centers have different communication protocols, virtually all include telephone contact as part of management. At the Mayo Clinic, patients are instructed to call at least every two weeks. The following information is always obtained:
• Verification of current pump rate
• Number and type of vials that are being mixed
• Current weight
• Interim change in symptoms (including functional status) or side effects, and relationship to dose changes
• Verification of prothrombin time monitoring, including recent international normalized ratio (INR)

Dose adjustment
When epoprostenol was FDA-approved, experienced clinicians felt that frequent and consistent dose escalations were advis-
able in order to “stay ahead” of symptoms, rather than to try to catch up once they recur or worsened. As a consequence of this dosing strategy and because of extended patient survival, substantial numbers of patients began to receive epoprostenol infusion rates of 100 ng/kg/min and higher. Over time, it became apparent that the consequences of high epoprostenol doses in some patients included high output states and fatigue.5

Epoprostenol dosing should be individualized to the patient, taking into consideration severity of symptoms, side effects, and underlying disease. Some patients who experience improvement in symptoms during initiation of epoprostenol in the hospital or monitored outpatient setting will report increased symptoms on returning home to a more physically challenging environment. Thus, close regular contact with these patients is imperative.

Role of referring physicians
Local medical providers, including primary care physicians, specialists, and emergency personnel, should be informed about patients’ need for epoprostenol and its implications. Patients’ current symptoms, medications and doses, the target range for the INR, potential complications, and plan for the future should be provided to primary care and other local practitioners. Local providers should also know how and when to contact the pulmonary hypertension center, particularly for problems that occur after clinic hours. Laminated instruction cards inserted into the pump pack are useful in emergency situations.

Clinic follow-up
Patients are generally seen for follow-up examination in the clinic 1 month after initiation and then every 3 to 6 months, depending on response to treatment. They are called or advised to call every 2 to 4 weeks to report symptoms and side effects, or sooner if problems arise. The frequency of contact depends on the stability of the patient, side effects, and overall comfort level.

During follow-up telephone surveillance, new or worsening symptoms should prompt a visit to the clinic for evaluation. Many centers repeat hemodynamic assessment after 1 year of therapy. Right-heart catheterization is the gold standard for assessment of pulmonary hemodynamics. The expectation at 1 year should be improvement in pulmonary hemodynamics but not normalization of them. Echocardiographic evaluation after approximately 3 to 6 months of treatment can provide useful interim estimation of pulmonary hemodynamics.

Emergencies
All potential emergency situations and proper responses should be discussed and “role-played” with patients during initial teaching. Ideally, local emergency rooms or emergency medical staff should be informed about PAH and its treatment and emergency requirements. Patients sometimes take on this responsibility themselves. If necessary, a letter can be provid-
ed to emergency services about the importance of maintaining the infusion at all times and even via a peripheral vein if necessary. Stickers located on the infusion pump show the current dose of epoprostenol as well as warn that the pump cannot be turned off for any reason. Patients are also encouraged to wear a medic alert bracelet or carry a laminated card listing their health problems as well as pump warnings. Urgent situations include central catheters being inadvertently pulled out, a torn or leaking catheter, pump malfunction, and central line infection (particularly tunnel infection or sepsis). Patients need to call 911 or proceed to an emergency room and be certain that the ambulance or emergency personnel are aware that interrupted epoprostenol delivery constitutes an emergency and that intravenous access must be established immediately. The pulmonary hypertension center should be contacted for further instructions if at all possible. A backup medication cassette and supplies should be brought to the hospital. Infections related to long-term indwelling central lines can be minimized by strict attention to aseptic care.

References
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Canterbury: pick up from first issue
Epoprostenol therapy has revolutionized the treatment of pulmonary arterial hypertension (PAH).\textsuperscript{1-3} Patients realized an improvement in quality of life, hemodynamics, and survival and this therapy has offered hope to patients with advanced disease.\textsuperscript{1,4} However, these attributes must be balanced against the complicated nature of the intravenous delivery system. Infections may range in severity from local exit-site infections easily treated with oral antibiotics to life-threatening sepsis. Because of the short half-life of epoprostenol, interruptions in therapy related to catheter displacement or pump malfunction may be life-threatening. Rare adverse events associated with the delivery system include pneumothorax, deep venous thrombosis, and paradoxical embolus. Additionally, the patient’s life is radically changed by the need to mix the medication on a daily basis, store the medication under refrigerated conditions, and carry a mechanical pump. The success of epoprostenol coupled with the limitations of the delivery system has provided the impetus to develop prostacyclin analogs with alternative routes of delivery. This article will focus on the analogs beraprost and treprostinil (the analog iloprost is discussed in another article in this issue).

### Beraprost

Beraprost sodium is an orally administered prostacyclin analog. When taken with food the half-life is approximately 3 to 3½ hours, requiring dosing four times daily. Enthusiasm for the treatment of PAH with beraprost arose from the initial experience in Japan and subsequent experience in Europe. In 1999 Nagaya and colleagues reported the benefit of beraprost on survival in patients with primary pulmonary hypertension (PPH).\textsuperscript{5} They followed 58 consecutive patients with PPH between 1981 and 1997. The 34 patients diagnosed before December 1992 were treated with conventional therapy alone, and the 24 patients diagnosed after January 1993 were treated with beraprost in addition to conventional therapy. Oral beraprost was initiated at a rate of 60 mcg per day and increased by increments of 60 mcg per day over 1 to 2 weeks to the highest tolerated dosage. Survival was estimated from the date of initial diagnosis until the conclusion of the study in November 1998. Of the 34 patients in the conventional therapy group, 27 patients died of cardiopulmonary causes after a mean follow-up of 44 ± 45 months. In contrast, only 4 of the patients in the beraprost group died of cardiopulmonary causes during a mean follow-up of 30 ± 20 months. Kaplan-Meier survival curves demonstrated the 1-, 2-, and 3-year survival rates in the beraprost group to be 96%, 86%, and 76%, respectively, compared with 77%, 47%, and 44%, respectively, in the conventional therapy group, differences that were statistically significant.

A subgroup of 15 patients treated with beraprost underwent repeat cardiac catheterization after receiving therapy for a mean of 53 days. There was a reduction in mean pulmonary artery pressure of 13% and in total pulmonary resistance of 25% as well as an increase of 17% in cardiac output. Sixty-seven percent of the patients treated with beraprost demonstrated an improvement in New York Heart Association (NYHA) Functional Class. Although these results suggested an improvement in survival with beraprost therapy, several limitations of the study bear mention. These include the small size of the cohort and retrospective analysis. Other medical therapies were not controlled and there was a significant difference in the use of calcium channel blockers and digitalis between the conventional therapy group and the beraprost group. The mean follow-up was substantially longer in the conventional therapy group than in the beraprost group. Additionally, a larger proportion of the patients in the beraprost group went on to treatment with intravenous epoprostenol.

More recently Vissa and colleagues reported their results of long-term treatment of PAH with beraprost.\textsuperscript{6} They studied 13 patients, 9 with PPH, 3 with thromboembolic pulmonary hypertension, and 1 with PAH related to congenital heart disease. The mean daily dose of beraprost was 116 ± 24 mcg after the first month of treatment and 193 ± 74 mcg at the end of 12 months. One patient died at 40 days of treatment and 1 patient was lost to follow-up. Twelve-month follow-up data were achieved in 11 patients. Patients demonstrated an improvement in NYHA Functional Class from 3.4 ± 0.7 at baseline to 2.9 ± 0.7 at the end of 1 month ($P < .016$). No further improvement was noted after a full year of therapy. The 6-minute walk distance increased by 63 ± 47 meters from a baseline distance of 213 ± 64 meters. This improvement was noted at 1 month and was maintained over the...
12-month period. This prospective uncontrolled trial suggested that beraprost improved symptoms and exercise capacity in patients with PAH.

The only prospective, double-blind, placebo-controlled, randomized study of beraprost in the study of PAH has recently been completed in Europe. Galie and colleagues studied 130 patients with PAH, including PPH and PAH associated with collagen vascular disease, congenital heart disease, portal hypertension, and human immunodeficiency virus infection. Patients were randomized to receive the maximal tolerated dose of beraprost or placebo for 12 weeks. The primary end point of distance walked in 6 minutes improved by 25.1 meters ($P = .036$) in the active treatment group. They also noted an improvement in symptoms as measured by the Borg dyspnea index, which decreased by 0.94 in the beraprost group ($P = .009$). Subgroup analysis demonstrated that patients with PPH realized the greatest improvement, with a mean change in 6-minute walk distance of 46.1 meters. They noted no statistically significant differences in cardiopulmonary hemodynamics or NYHA Functional Class. The median dosage of beraprost in the study was 80 mcg four times per day.

The most common side effects of beraprost reported in these studies were headache, flushing, jaw pain, diarrhea, leg pain, and nausea. Side effects can be minimized when the drug is taken with a meal. Beraprost is currently available in Japan and may become available in Europe. A placebo-controlled trial with beraprost in the United States was terminated prematurely and this drug will not likely become commercially available in the United States. Presumably the early termination was because of a lack of efficacy estimation by the Data and Safety Monitoring Board.

**Treprostinil**

Treprostinil is a prostacyclin analog with a half-life of 3 hours when administered subcutaneously. The drug is stable at room temperature. Animal studies suggest that the hemodynamic effects of treprostinil are similar to those of epoprostenol. To test this hypothesis in humans, we studied 14 patients with PPH acutely with intravenous epoprostenol and then intravenous treprostinil. Both drugs had similar effects on hemodynamics. There was no difference in reduction in pulmonary vascular resistance (22% with epoprostenol versus 20% with treprostinil).

To then test the alternative subcutaneous delivery method, we compared the effects of intravenous and subcutaneous treprostinil in 25 patients with PPH. In the intravenous treprostinil and subcutaneous treprostinil groups there was a 6% and 13% decline in mean pulmonary artery pressure and a 23% and 28% decline in pulmonary vascular resistance respectively.

Having demonstrated that the drug favorably affects cardiopulmonary hemodynamics when given subcutaneously acutely, we embarked on an 8-week, placebo controlled, randomized trial of subcutaneous treprostinil. Twenty-six patients with PPH were enrolled. Two patients in the treprostinil group did not complete the study because of intolerable side effects. The remaining 15 patients randomized to active drug were receiving a mean dosage of 13.0 ± 3.1 ng/kg/min of treprostinil, and the 9 patients randomized to placebo were receiving 38.9 ± 6.7 ng/kg/min at the end of the 8-week period. There was an improvement of 37 ± 17 meters in the 6-minute walk distance in patients receiving the active therapy (from 373 meters to 411 meters) compared with a 6 ± 28 meter reduction in those receiving placebo (from 384 meters to 379 meters), which was not statistically significant. There was a favorable, but again not statistically significant trend in hemodynamics, with a 20% reduction in pulmonary vascular resistance index over the 8-week period in the group receiving active treprostinil. Adverse events, including headache, diarrhea, flushing, jaw pain, and foot pain, were as common in the treprostinil-treated as in the epoprostenol-treated group.

An unexpected adverse effect was pain at the site of the subcutaneous infusion. This pain was occasionally severe, was often associated with erythema, and occurred in nearly all the patients undergoing active therapy. This proof-of-concept trial demonstrated that this novel subcutaneous agent could be given safely and effectively on an outpatient basis and paved the way for a larger pivotal trial.

Subsequently, the largest placebo-controlled randomized study involving PAH patients was an international trial assessing the efficacy of subcutaneously delivered treprostinil in patients with PAH, either primary or associated with collagen vascular disease or congenital systemic-to-pulmonary shunts. Patients were enrolled between November 1998 and October 1999 in 24 centers in North America and 16 centers in Europe, Australia, and Israel. Four hundred-seventy patients were randomly assigned to receive either continuous subcutaneous infusion of treprostinil plus conventional therapy or continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. Because of the infusion-site pain and reaction noted in the proof-of-concept trial, the dosing strategy called for lower doses at initiation and a maximal allowable dose at the end of 12 weeks of 22.5 ng/kg/min. The primary end point of this trial was exercise capacity as measured by the 6-minute walk distance, which improved in the treprostinil group and was unchanged with placebo. The median between treatment group difference was 16 meters ($P = .006$). This effect on exercise tolerance appeared to be dose-related. The patients in the lowest two quartiles of dosing experienced little improvement in 6-minute
intravenous epoprostenol for both PPH and PAH related to the less than the improvements demonstrated in the trials with treatment in 6-minute walk distance was relatively modest and site pain. Eight percent of the patients in the active infusion site pain and 83% had erythema or induration aspiration site were common. Eighty-five percent of patients experi-
enced infusion site pain and 83% had erythema or induration at the infusion site. Eight percent of the patients in the active treatment group were withdrawn from the study because of nausea, rash, and jaw pain. Side effects related to the infu-
sion of 36 meters (greater than 13.8 ng/kg/min) demonstrated a mean improve-
ment of 36 meters ($13.8$ ng/kg/min) demonstrated a mean improvement of 36 meters (Figure 1). Secondary end points, including the dyspnea fatigue rating and the Borg dyspnea scale, confirmed an improvement with treprostinil therapy. Treprostinil also demonstrated a significant improvement in the hemodynamic parameters of mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation (Table 1). Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common. Eighty-five percent of patients experienced infusion site pain and 83% had erythema or induration at the infusion site. Eight percent of the patients in the active treatment group were withdrawn from the study because of site pain.

Although statistically significant, the 16-meter improvement in 6-minute walk distance was relatively modest and less than the improvements demonstrated in the trials with intravenous epoprostenol for both PPH and PAH related to the

Table 1—Hemodynamic Response to Subcutaneous Treprostinil

<table>
<thead>
<tr>
<th></th>
<th>Treprostinil</th>
<th>Placebo</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean right atrial pressure, mmHg</td>
<td>-0.5 ± 0.4</td>
<td>+1.4 ± 0.3</td>
<td>.0002</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>-2.3 ± 0.5</td>
<td>+0.7 ± 0.6</td>
<td>.0003</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>+0.12 ± 0.04</td>
<td>-0.06 ± 0.04</td>
<td>.0001</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, units/m²</td>
<td>-3.5 ± 0.6</td>
<td>+1.2 ± 0.6</td>
<td>.0001</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation, %</td>
<td>+2.0 ± 0.8</td>
<td>-1.4 ± 0.7</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Adapted from Simonneau et al.11

Table 2—Subgroup Analysis of Treprostinil Trial

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Treatment Effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>+2 m</td>
</tr>
<tr>
<td>III</td>
<td>+17 m</td>
</tr>
<tr>
<td>IV</td>
<td>+54 m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Walk</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 – 150 m</td>
<td>+51 m</td>
</tr>
<tr>
<td>151 – 250 m</td>
<td>+33 m</td>
</tr>
<tr>
<td>251 – 350 m</td>
<td>+16 m</td>
</tr>
<tr>
<td>351 – 450 m</td>
<td>-2 m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary pulmonary hyperten-</td>
<td>+13.0 m</td>
</tr>
<tr>
<td>sion</td>
<td></td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>+10.4 m</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>-1.0 m</td>
</tr>
</tbody>
</table>

*Refers to primary end point of 6-minute walk distance.

walk distance, and patients in the highest quartile of dosing (greater than 13.8 ng/kg/min) demonstrated a mean improvement of 36 meters (Figure 1). Secondary end points, including the dyspnea fatigue rating and the Borg dyspnea scale, confirmed an improvement with treprostinil therapy. Treprostinil also demonstrated a significant improvement in the hemodynamic parameters of mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation (Table 1). Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common. Eighty-five percent of patients experienced infusion site pain and 83% had erythema or induration at the infusion site. Eight percent of the patients in the active treatment group were withdrawn from the study because of site pain.

Although statistically significant, the 16-meter improvement in 6-minute walk distance was relatively modest and less than the improvements demonstrated in the trials with intravenous epoprostenol for both PPH and PAH related to the who were in NYHA Functional Class III or IV. Fifty-three patients who were in NYHA Functional Class II were enrolled in the treprostinil trial. Their treatment effect in the 6-minute walk distance was only two meters in the Functional Class II patients compared with 17 meters for the 382 patients who were in Functional Class III and 54 meters for the 34 patients who were in Functional Class IV. The baseline 6-minute walk distance in the treprostinil study was 326 ± 5 meters in the active treprostinil group and 327 ± 6 meters in the placebo group.

In comparison the baseline 6-minute walk distance in the PPH epoprostenol trial was 315 meters in the epoprostenol plus conventional therapy group versus 270 meters in the conventional therapy group alone.1 In the scleroderma epoprostenol trial the baseline 6-minute walk distance was 272 meters in the epoprostenol plus conventional therapy group and 240 meters in the group receiving conventional therapy alone.3 This demonstrates that the patient population was less ill in the treprostinil trial, which may have contributed to the less impressive treatment effect.

The treatment effect was also related to the baseline walk distance in the treprostinil trial (Table 2). Patients who were able to walk between 351 and 450 meters did not demonstrate a treatment effect at all, whereas those patients who were able to walk in the lowest category of 50 to 150 meters demonstrated a treatment effect of 51 meters. The etiology of PAH was also more broad in the treprostinil trial. In addition to the inclusion of PPH patients and PAH associated with collagen vascular disease, PAH associated with congenital heart disease was included. This group had been untested in the past and in the treprostinil study did not demonstrate any treatment effect at all. This may in part be related to the patients’ long-standing disease and the difficulty of making an impact on such a process over a short 12-week period.

The nemesis of subcutaneous treprostinil has been pain and erythema at the infusion site (Figure 2). A variety of therapies have been used to control this adverse effect, although none has emerged as uniformly successful. Local remedies such as topical hot and cold packs, topical analgesics and anti-inflammatory agents have been variably effective. Some patients also responded to oral analgesics, such as non-steroidal anti-inflammatory drugs. More recently, a pharmaceutical transdermal delivery vehicle, pluronic lecithin organogel, has been compounded with a variety of analgesic and anes-

(continued on page 15)
Elective Initiation of Epoprostenol

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Duke University Medical Center  
Durham, North Carolina

Footnotes
1. A few large centers initiate epoprostenol therapy in an outpatient setting; patients stay at local facilities that are provided for by the medical center.
2. These include Hickman and Groshong catheters. In some patients it may be appropriate to start with an antecubital PICC line. Epoprostenol should not be infused through a Mediport—this is not an appropriate catheter for continuous infusions, only for intermittent infusions, ie, antibiotics, chemotherapy.
3. Rarely, patients may not tolerate this and the dose may have to be decreased to 1 ng/kg/min.
4. Rarely, patients may not tolerate this and dosage may have to be increased at a slower rate. Other, sicker patients may warrant more aggressive titration, ie, 2-3 ng/kg/min dose increases daily.
5. Rarely, patients may not tolerate this and dosage may have to be increased at a slower rate. Other, sicker patients may warrant more aggressive titration, ie, 2-4 ng/kg/min dose increases weekly.
6. The policy regarding listing for transplantation and moving to inactive list varies substantially at different centers.
thetic therapies for local application in patients treated with treprostinil. Initial observations appear promising, although the therapy has yet to be studied in a controlled fashion.

A common observation has been that site pain and erythema improve after several months of therapy. Additionally, the pain is not related to the dose of treprostinil. Given the dose-response relationship, it is important to increase the dose regularly, so that patients realize an improvement in dyspnea. Under such circumstances, patients are more likely to tolerate site discomfort. Some patients have found that moving the infusion site every 3 days as opposed to every day is useful. The infusion site most commonly used was subcutaneous abdominal fat, although some patients were able to use the outer hips and thighs and underside of the upper arm with some success.

Because of the longer half-life of treprostinil, interruptions of drug due to dislodgment of the catheter or pump malfunction are less serious than with epoprostenol. In such instances, either the catheter could be replaced or a backup pump, which all patients had, could be exchanged without any serious consequences. The Mini-Med pump, used to administer treprostinil, is smaller than the CADD pump used to administer epoprostenol and is about the size of a pager. The drug comes in a premixed-prefilled syringe and therefore patients need only to place the syringe in the pump and do not have to mix the medication in a sterile fashion on a daily basis.

The Food and Drug Administration has approved subcutaneous treprostinil for patients with Functional Class II, III, and IV PAH. One should consider the use of subcutaneous treprostinil in patients who are not candidates for or decline therapy with intravenous epoprostenol, for example someone with poor venous access or recurrent catheter infections. In addition, patients who have contraindications to or transaminase elevations with the oral endothelin-receptor antagonist bosentan might be candidates for subcutaneous treprostinil. Treprostinil has not been studied in combination with bosentan; however, there may be a theoretical benefit to such a combination.

References
Inhaled therapy for pulmonary hypertension is an interesting concept as it offers selectivity of hemodynamic effects for the lung vasculature, thus avoiding systemic side effects. Selective pulmonary vasodilatation has been described for inhaled nitric oxide (NO) but use of this agent has several drawbacks. Most importantly, there are no data demonstrating improved survival with long-term inhaled NO treatment, and there is evidence that this agent possesses less vasodilator potency than do the prostanoids in primary pulmonary hypertension (PPH) patients. The intravenous prostacyclin epoprostenol (Flolan) has been shown to improve survival, exercise capacity, and hemodynamics in patients with severe PPH. Epoprostenol has been approved for treatment of PPH in the United States and several European countries.

Iloprost, a Stable Prostacyclin Analog
Iloprost is a prostacyclin analog that has the same biologic profile as the natural substance with respect to prostaglandin receptor binding and cellular effects. This explains why during continuous intravenous use its effects as well as its side effects are the same as those of epoprostenol. In contrast, the chemical stability is considerably different. Epoprostenol has to be freshly dissolved, continuously cooled, and protected from light to provide full activity, while iloprost is stable at room temperature and normal light. Epoprostenol has a half-life in vivo of 3 to 5 minutes, while iloprost has a serum half-life of 20 to 25 minutes.

For these reasons iloprost has practical advantages for daily use compared with epoprostenol, and it has been approved for treatment of pulmonary arterial hypertension (PAH) in New Zealand. While epoprostenol is available in the United States and Europe, iloprost is not approved for use in the United States.

The dosages used with continuous epoprostenol range between 10 and 50 ng/kg/min, while the dosages for continuous intravenous iloprost range between 1 and 5 and rarely up to 10 ng/kg/min. The reasons for this huge difference have not been fully elucidated but probably result from a higher potency of iloprost (about 5:1) and the different delivery method, as well as from more aggressive dosing with intravenous epoprostenol in the United States compared with Europe.

Prostanoid Inhalation
Patients receiving prostanoids are prone to side effects such as headache, jaw pain, leg pain, and diarrhea, and there may be complications with the delivery system. These findings are well documented for continuous intravenous epoprostenol therapy and have also been reported with the subcutaneous delivery of the prostacyclin preparation treprostinil.
Oral application of prostanoids (beraprost) may decrease delivery-associated risks, but this therapy has not yet proved effective in severe disease, although in moderately ill PPH patients there was a significant benefit in a controlled study.12

In order to selectively treat the pulmonary vessels in the ventilated areas of the lung, inhaled prostacyclin and iloprost were ultimately considered as treatment options. Due to the fact that the intraacinar pulmonary arteries are tightly surrounded by alveolar surfaces (Figure 1), it is possible to vasodilate these vessels via the alveolar deposition of a prostanoid. For acute vasodilator testing with inhaled prostacyclin or iloprost, a special inhalation device with a drug-saving reservoir for delivery of aerosols is utilized.

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repetitive inhalations with iloprost, six to nine times per day are required (Figure 2). Each inhalation takes approximately 10 to 15 minutes. With newer devices, it is possible to reduce the inhalation time to about 4 minutes13 and to avoid noisy delivery by using ultrasound energy for nebulization.

In patients with severe PAH, we have demonstrated that inhalation of aerosolized iloprost results in a substantial decrease in pulmonary artery pressure and pulmonary vascular resistance. This decrease is concomitant with an increase in cardiac output, in the absence of a significant decrease in mean arterial pressure (Figure 3) or worsening ventilation-perfusion mismatch.14,15

In a statistical comparison of the effects of intravenous epoprostenol and inhaled iloprost, the mean acute effect on pulmonary vascular resistance was equal. However, during treatment with inhaled iloprost, pulmonary artery pressure decreased significantly and systemic artery pressure remained stable, whereas during treatment with intravenous epoprostenol, systemic pressure decreased significantly and pulmonary artery pressure was minimally changed.14 These observations were consistent with preceding findings in mechanically ventilated patients with acute respiratory failure.16-22 In uncontrolled studies, inhaled iloprost was effective in decompensated right heart failure23 and led to favorable long-term hemodynamic improvement.24

**AIR Study**

A large randomized double-blind placebo-controlled multicenter study in Europe with inhaled iloprost has been performed (Aerosolized Iloprost Randomized, AIR).25 A total of 203 patients with PPH or other forms of PAH were enrolled. These included New York Heart Association (NYHA) Functional Class III or IV patients with PAH due to appetite suppressants or collagen vascular diseases and those with associated or non-operable thromboembolic pulmonary hypertension. In the iloprost and placebo groups, about 50% had PPH and 50% had PAH of other causes. About 60% were in NYHA Functional Class III and 40% in Functional Class IV.

The primary end point of the study, defined as an improvement in NYHA Functional Class combined with at least 10% improvement in the 6-minute walk test and no prior deterioration or death (combined clinical end point), was reached by 3.4 times more patients in the iloprost group compared with the placebo group (16.8% vs 4.9%; P = .007). Treatment effects did not differ between subgroups. This effect was achieved with a mean inhaled iloprost dosage of 0.37 ng/kg/min (Figure 4).

In the 6-minute walk test the treatment effect was 36.4 meters in favor of iloprost (P < .004, Figure 5). There was a treatment effect with iloprost on NYHA Functional Class (P < .05), quality of life assessments by means of the EuroQoL visual analogue scale (P < .05), and on the Mahler Dyspnea Transition Index (P < .05). Hemodynamics significantly deteriorated in the placebo group, whereas in the iloprost group, although preinhalation values were unchanged compared with baseline, postinhalation values were significantly improved. Importantly, the number of patients remaining on study medication was significantly higher in the ilo-
prost than in the placebo group (Figure 6).

Over 3 months of therapy, there was no indication of tachyphylaxis. In the iloprost group, 1 patient (1.0%) died during the double-blind study period vs 4 patients (4.0%) in the placebo group. Overall, iloprost therapy was well tolerated. Cough, headache, and flushing occurred more commonly in the iloprost group. These adverse events were mild and mostly transient. Syncope occurring in the iloprost group was more often rated as serious, compared with the placebo group, but was commonly not associated with clinical deterioration. It can be concluded from this study that inhalation of iloprost is an effective and safe therapy for patients with severe (NYHA Functional Class III and IV) PPH and for patients with the other causes of PAH that were studied.

Future Perspectives
In addition to treatment of PPH, the pulmonary selectivity of inhaled iloprost provides the chance to safely apply prostanoids in patients who are prone to systemic hypoten-

sion, such as patients with portopulmonary hypertension, and in emergency situations. The intrapulmonary selectivity allows prostanoid application in patients who are prone to intrapulmonary right-to-left shunt, such as patients with pulmonary fibrosis.\textsuperscript{15} The inhaled application may be combined with other effective treatments for PAH, although this has not yet been studied in a controlled fashion.

A more specific positive interaction is the use of inhaled iloprost in combination with phosphodiesterase (PDE) inhibitors. The specific pulmonary vasodilating effects of iloprost that may be mediated by an intracellular increase of cAMP can be increased by blocking the breakdown of this second messenger by means of PDE inhibition.\textsuperscript{26-31} We noticed excellent clinical results with the combination of inhaled iloprost and sildenafil, a specific PDE 5 inhibitor\textsuperscript{32} and have been successfully using this combination for more than a year in a considerable number of patients. At present sildenafil is not approved for use as therapy for PAH, but clinical studies are under way. Inhalation intervals could be lengthened and pulmonary selectivity could still potentially be achieved with the concomitant use of PDE inhibitors. This approach could also lead to simpler delivery methods, such as via metered dose inhaler, for treatment of PAH.

Conclusions
Inhaled iloprost has been shown to be effective for the treatment of PAH and may provide an alternative to the use of intravenous epoprostenol. When the clinical effects of inhaled iloprost and intravenous epoprostenol are compared, iloprost inhalation has clear advantages but also certain drawbacks. Most importantly, inhalation provides potent pulmonary vasodilatation with minimal systemic side effects and no risk of catheter-related complications. Additionally, iloprost could be considered as therapy in patients with pre-existent ventilation-perfusion mismatch and in those who are prone to develop such a mismatch during systemic prostanoid application. The most important disadvantage is the fact that the hemody-
namic effects of inhaled iloprost last only 30 to 90 minutes, and that six to nine inhalations are needed to achieve good clinical results. In addition, sustained hemodynamic improve-
ment and long-term survival with long-term use of inhaled iloprost have yet to be demonstrated in more than a small num-
ber of patients.

References

(Sir John Vane, continued from page 3)

Dr Vane has also explored other avenues of research into the mechanisms of prostaglandin, including its cyto-

protective effects. “In models of myocardial infarction, it will reduce the infarct size. It will reduce oxygen demand and enzyme release from the infarcted areas. Other prostaglandins also share similar cytoprotective activity, distinct from the activity on platelet aggregation or vasodilatation.”

One of the intriguing questions still unresolved is the possibly synergistic relationship between prostacyclin—essentially a cyclic AMP agonist—and the phosphodi-

esterase inhibitor sildenafil (Viagra). Dr Vane suggested that the synergism could be related to the fact that silde-
nafil inhibits consumption of both cyclic GMP and cyclic AMP. This could enhance the effect of prostacyclin in pulmonary hypertension.


Advances in Pulmonary Hypertension

**Pulmonary Hypertension Roundtable**

**Bench to Bedside: Principles and Practice of Epoprostenol Therapy, from Maximizing Benefit to Minimizing Side Effects**

*Ivan Robbins, MD, Director, Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee, conducted this discussion. The panel included David Langleben, MD, Director, Center for Pulmonary Vascular Disease, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; Michael McGoon, MD, Consultant in Cardiology, Mayo Clinic, Rochester, Minnesota; and Abby Krichman, RRT, Pulmonary Hypertension Coordinator, Duke University Medical Center, Durham, North Carolina.*

**Dr Robbins:** I have always been interested in why investigators decided to try intravenous prostacyclin, or epoprostenol (Flolan), as long-term treatment.

**Dr McGoon:** It was recognized as a very potent vasodilator, with the additional theoretical benefits of being one of the most potent endogenous platelet inhibitors. So it made some sense to use it in a disease in which vasoconstriction was felt to be a predominant causal mechanism.

**Dr Langleben:** It was a serendipitous concurrence of a novel molecule and a pharmaceutical company that held very basic research in high regard. Prostacyclin, as an endogenous vasodilator was initially described in 1976. The major clinical phase in pulmonary hypertension began later in that decade, extending to the mid-80s. So it took a while to work its way down to clinical use. I think it was its potent vasodilator effect with a probable short duration of action that made it very attractive as an acute vasodilator for testing.

**Dr McGoon:** The other serendipitous aspect of this drug is that it came when we were getting disillusioned with other vasodilators, most specifically hydralazine. So the concept of a short-acting pulmonary vasodilating agent, which was actually replacing deficient endogenous production of prostacyclin, made a lot of sense.

**Dr Robbins:** How did you come up with the dosing scheme?

**Dr McGoon:** Initially it had been identified during the acute-stage dose-ranging studies that preceded our involvement. It became clear very soon when using epoprostenol that if you gave too big a dose you were going to get a lot of side effects and you had to creep up on the dose if you were going to get benefit over the long haul. About 2 to 3 ng/kg/min was the initial starting dosage in the early studies and is clearly the way to go. Typically, most patients, by the time they were dismissed from our initial care, were receiving around 6 ng/kg/min when they went home, and after that point we incrementally increased by 1 or 2 ng/kg/min every week or so, particularly if a patient was still symptomatic, which was frequently the case. Later, based on conversations with other clinicians nationwide, we evolved into more or less routinely increasing the dosage regardless of symptoms. The idea was that we wanted to stay ahead of symptoms preventively and continue to have a vasodilator effect that would hopefully impart some vascular remodeling and permanency to the decreased resistance. Eventually it was recognized that there was a state in which symptoms of high cardiac output could overtake the benefits of decreased resistance. It has always been observed that the predominant effect of administering epoprostenol was to increase cardiac output with modest decreases in pulmonary pressure at best, resulting in a decrease in calculated pulmonary resistance.

**Dr Robbins:** Abby, what has the experience been at Duke?

**Ms Krichman:** Initially, in the early days of epoprostenol dosing, the prevailing practice was to continue increasing dosages on a regular basis and just tolerate the adverse side effects. We certainly have come full circle. Now we try to maintain the lowest dose (of epoprostenol) possible to ameliorate symptoms but also to minimize the side effects.

**Dr Langleben:** Our practice was exactly as Mike described initially.

**Dr Robbins:** We were just looking at our 5-year experience, and our average dose is probably somewhere around 25 ng/kg/min. We have very few people receiving more than 50 ng/kg/min.

**Dr Langleben:** Our early patients, the ones who have had 10 or 11 years of treatment, have reached higher dosages. Most of the recent patients are not at that dose level, though. Our average is probably 45 to 60 ng/kg/min after many years. After a year of therapy most people are receiving about 20 ng/kg/min.

**Dr McGoon:** We are all over the board, to be perfect-
ly honest. It is such a moving target at this time, when we have the option of combining or transitioning to other medications. We can talk about averages, but at least in our case, the standard deviation of doses at any given time is extremely broad.

Dr Robbins: Should we talk a bit about combined therapy?

Dr McGoon: It is at an early stage. We are still learning about it. One pattern we have seen is that when we add another agent to epoprostenol, even one that is not a prostenoid, like bosentan, for example, there can be an exacerbation of what we would normally call epoprostenol side effects, such as flushing, headache, and gastrointestinal disquietude.

Dr Langleben: The concept of attacking an illness through a variety of mediators and mechanisms is standard for other types of illnesses. Perhaps, because of the relative rarity of pulmonary hypertension or the lack of availability of easy therapy, we have not been able to consider combined therapy until now.

Ms Krichman: There are a lot of physicians out there who think they can just give patients bosentan and completely wean them from epoprostenol. We may be able to accomplish that in some patients, but with very careful monitoring.

Dr Robbins: You are absolutely right.

Ms Krichman: We ought to make it clear that we are using combination therapy to hopefully improve outcomes, not solely to wean epoprostenol.

Dr Langleben: Would everyone agree that epoprostenol remains our gold standard for the medical treatment of advanced functional class III and IV patients?

Dr Robbins: Yes.

Dr Langleben: So, has everyone around the table seen failures of other therapies already and resorted to epoprostenol?

All: Yes.

Dr McGoon: Our prediction was, and I think it is coming true, that the oral therapy, bosentan, would be used widely, but that not all hopeful expectations would be met. There has been more recently the feeling that “Well, we haven’t seen all the benefit we want, so maybe we should think about adding or transitioning to epoprostenol.”

Ms Krichman: At our center, and probably for most of you as well, when somebody’s more of an early Class III patient, our preference is always oral therapy first, but for those with later Class III symptoms, we are initiating epoprostenol in most cases.

Dr McGoon: The key, particularly if you are going to start with conservative therapy, is the follow-up. The whole process of the pulmonary hypertension specialty clinic has to be geared to establishing communication with the patient about the treatment options, the pros and cons, and then to very intensive follow-up and reevaluation.

Dr Langleben: What are your standards for follow-up?

Dr McGoon: Of course, it varies from patient to patient. We follow patients in terms of clinical symptoms with 6-minute walk testing at intervals of 3 to 6 months and with echocardiography, usually at 6 months. If there is disparity among clinical impression, examination, and echocardiographic data, we will do right-heart catheterization.

Dr Langleben: We prospectively follow patients with echocardiography at least every 6 months. Our population numbers aren’t huge, but we can tell who is doing well on the basis of the Doppler echocardiography-derived index of myocardial performance (the TEI index)) and how their ventricles are coping.

Dr McGoon: At some centers, some clinicians clearly feel that regular, periodic right-heart catheterization for hemodynamically precise characterization provides additional information about cardiac output.

Ms Krichman: I think a lot of centers do that.

Dr McGoon: We don’t do it on everybody because the specific number doesn’t really help me too much, compared with the global assessment of a patient’s status, which includes many factors. I think all of us employ multiple criteria in deciding how patients are doing and what changes, if any, in therapy should be attempted.

Dr Langleben: The other thing we pay particular attention to on our echocardiograms is an estimate of cardiac output.

Ms Krichman: What is the prevailing thought about patients who continue to have severely enlarged right ventricles, but who symptomatically are doing okay?

Dr Langleben: With those patients, we follow the TEI index. In many of these patients the index is greatly and abnormally elevated. If the index is slightly improved, despite the fact that they have right ventricular dilatation, we gently increase the dosage. If the index hasn’t really improved with epoprostenol, we give them a couple of months, then that is an indicator to list them for early transplantation, regardless of...
Ms Krichman: Except for the very sickest patients, there is no probably done in a lot of centers. This is not an easy disease to manage. Patients on a regular basis and see them in clinic periodically. Who work very closely with physicians and who talk with extenders. There is clearly a role for healthcare professionals of epoprostenol patients without some kind of physician need to rapidly titrate epoprostenol.

Dr Robbins: Oh, I agree.

Dr Langleben: We do increase the dose more rapidly than we would in more stable patients. We don’t get a lot of epoprostenol side effects beyond jaw pain and a little bit of diarrhea.

Ms Krichman: We see a lot of musculoskeletal pain.

Dr McGoon: The problem is knowing in the individual patient whether you have reached the optimal dosage. I agree with David that if a patient is not doing well, then you don’t know that a higher dose won’t work until you have tried. So it does stimulate a strategy of going up on the dosage. If you find the side effects overwhelm the benefits, or if you really don’t get any additional benefits from the inconvenience or expense of a higher dosage, then it may make sense to try tapering off again.

Ms Krichman: I think we should talk about general dosing strategies for patients who have just started receiving epoprostenol. We usually have a 3- to 4-day hospitalization with a goal of sending patients home taking 4 to 6 ng/kg/min of drug, somewhere in that range. For sicker patients we’ll be more aggressive, titrating up during the initiation period. Once they are home, we call patients weekly for at least a month following initiation of therapy and go up 1 or 2 ng/kg/min a week. Dosing is very individualized, depending on symptoms and side effects. Once symptoms are somewhat under control, we back off on dose titration, typically to every 2 weeks and then every month. When we reach a dosage where there is a balance of symptomatic improvement and minimal side effects, we stop going up.

Dr Robbins: That is pretty close to what we do, and what is probably done in a lot of centers.

Ms Krichman: Except for the very sickest patients, there is no need to rapidly titrate epoprostenol.

Dr McGoon: I have no hesitation whatsoever in saying that our pulmonary hypertension clinic was established primarily to have nurses in a setting with focused interest.

Ms Krichman: Yes. And that has to be the message to community physicians or physicians who aren’t at tertiary care centers.

Dr Robbins: What about infection from the long-term indwelling catheters? How do you manage that at your centers?

Dr McGoon: The first step is obviously prevention, and that comes with education of the patient about strict aseptic control. But even under the best conditions, the catheter can get infected. Our response depends on the circumstances. If it is a localized exit-site infection, we will make substantial efforts to preserve the catheter and treat with antibiotics to prevent it from getting worse. Certainly if there is any evidence of systemic infection, the catheter is out and intravenous antibiotics are given.

Dr Robbins: Education is key. The only time we have had problems is with patients who didn’t understand or ignored the signs of the problem and then came in and were quite ill.

Ms Krichman: Overall, how many catheters have you had to pull because of systemic infection?

Dr McGoon: If I had to guess the percentage of patients who have had that, it would be 3% or 4% maybe. I have some patients who have been receiving the drug for more than 10 years who have never had a change in catheter. But then there are others who have had two or three infections in one year.

Dr Robbins: Have the indications for use of prostacyclin changed over the years for you?

Dr McGoon: Yes, it has evolved to broader indications. As published experience increased with secondary pulmonary hypertension and randomized studies increased with collagen vascular disease, the labeling expanded our options and we were able to use the drug more broadly. Now we consider its use in nonsurgical thromboembolic disease or interstitial pulmonary fibrosis and so on, in which pulmonary hypertension may be a big component. The more other things you have wrong, the less the beneficial effect.

Dr Langleben: I am not sure their longevity will be the same as that of primary pulmonary hypertension patients in the sense that the other medical issues related to their principal illness will likely affect survival.

Dr Robbins: Any other issues that anyone feels are important to bring up?

Dr McGoon: One source of problems for us has been when patients unexpectedly see other physicians who don’t know what to do in an urgent situation. You just have to listen to...
patients when dealing with epoprostenol. They actually know what they are doing.

Ms Krichman: That is an important part of the education of patients and caregivers that sometimes does not happen, really taking the time to explain what a peripheral IV is, when you need to get it put in, and that sort of thing.

Dr Langleben: We give patients a preprinted card that they carry with their pumps. It states in big bold letters, “DO THIS NOW.” Patients are instructed to go to their nearest hospital emergency room if they have a problem with the infusion lines or catheter, and to show the card immediately on arrival. The system works.

Ms Krichman: Another topic we might touch on is the side effects of prostacyclin and how we are treating them. The initial approach is to lower the dose of epoprostenol if tolerated. Musculoskeletal pain is a big issue. Mostly we are using gabapentin (Neurontin).

Dr Robbins: We have used COX-2 inhibitors. They help some people, and then we move on to amitriptyline with an occasional patient, and then to gabapentin.

Ms Krichman: Is anybody using tramadol (Ultram) or opioids?

Dr McGoon: Not in any routine way. We have a low threshold for using gabapentin.

Dr Langleben: What about for diarrhea?

All: Loperamide (Imodium).

Dr McGoon: We sometimes use jaw pain as an index of whether patients are getting enough. If they are not having jaw pain, we have serious concerns whether enough is being used.

Ms Krichman: We used to do that, and then there were those patients who did not have jaw pain but were doing great.

One thing I know we have all seen as a side effect is ascites. The important issue is determining whether ascites is from worsening heart failure or from epoprostenol. Those seem to be the most difficult to sort out.

Dr Robbins: Any other big side effects?

Ms Krichman: One thing I know we have all seen as a side effect is ascites. The important issue is determining whether ascites is from worsening heart failure or from epoprostenol. Those seem to be the most difficult to sort out.

Dr Robbins: We have seen it somewhat, but more often we have seen it in the face of severe right heart failure.

Ms Krichman: We certainly have seen such patients, but now we are seeing patients who are not in right heart failure and have significant ascites.

Dr McGoon: Yes, I agree, Abby. And patients require frequent paracentesis.

Dr McGoon: You know, I think it is a testimonial. To be frank, epoprostenol has never been exposed to what we would consider a scientifically rigorous clinical study. There was no placebo, there was no blinding involved and so on, and yet I think most of us are convinced, based on our experience, that it works. Part of the reason we are convinced is that in spite of what seem to be fairly horrendous side effects, patients still feel they are benefiting from the medication. The other reason I think it is physiologically beneficial is our experience when some patients’ infusions have been surreptitiously interrupted. For example, we’ve had a couple of instances when the line was inadvertently pulled out from the vein but remained subcutaneous, so the patient was unknowingly no longer getting an infusion. The patients felt worse, as though their symptoms had returned until the infusion was resumed. That was my “controlled” study.
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