The care of patients with acute respiratory distress syndrome (ARDS) is a challenge to even the most seasoned critical care nurse. The patient mortality rate associated with the syndrome remains high at 40% to 60%, and care is complex.1-3 Despite 30 years of clinical trials focused on improving patient outcomes, no therapeutic interventions have convincingly altered the treatment of the underlying pathophysiology of ARDS,4 which, consequently, remains supportive. The search for supportive therapies has recently focused on the severe hypoxemia and pulmonary hypertension of ARDS, and has led to renewed interest in the use of the prostacyclin epoprostenol (Flolan), a naturally occurring prostaglandin and pulmonary vasodilator.5 This article discusses the use of the medication, especially the inhaled route of administration, in the treatment of pulmonary hypertension in patients with ARDS, and its implications for the critical care nurse.

**ACUTE RESPIRATORY DISTRESS SYNDROME**

ARDS, a severe form of acute lung injury caused by a direct or systemic insult, such as pulmonary contusion or sepsis, is characterized by the acute onset of inflammatory lung injury. The resultant increased alveolar capillary permeability causes noncardiogenic pulmonary edema, left atrial hypertension that is not evident (pulmonary artery wedge pressure 18 mmHg or lower), bilateral pulmonary infiltrates seen on chest X-ray, and severe hypoxemia,6, 7 in which the ratio of arterial partial pressure of oxygen (PaO₂) to fraction of inspired oxygen (FIO₂) is 200 mmHg or lower (the normal range is 300 to 400 mmHg). Without adequate pulmonary oxygen uptake and delivery to cells, ARDS patients quickly die.

**Pathophysiology.** Central to the pathophysiology of ARDS is the activation of the inflammatory response leading to ventilation–perfusion (V/Q) mismatch, intrapulmonary shunting of blood, microemboli, severe hypoxemia, and pulmonary hypertension1, 4 (see The Pathogenesis and Pathophysiology of ARDS, above). V/Q mismatch occurs when some alveoli fill with protein exudates and are not ventilated. Right-to-left intrapulmonary shunting occurs when blood is shunted past these fluid-filled or collapsed alveoli, resulting in substantial amounts of unoxygenated blood, sometimes as much as to 50%, being returned to the central circulation.7 Poor V/Q and occlusion of pulmonary capillaries from microemboli
result in severe hypoxemia (PaO₂–FIO₂ ratio lower than 200 mmHg) that is progressive and refractory. As a consequence of progressive hypoxemia, the pulmonary circulation, unlike the systemic circulation, becomes constricted through a poorly understood reflex mechanism, causing an increase in pulmonary vascular resistance and pulmonary hypertension.

**Pulmonary hypertension (PH)**
can be classified as either primary or secondary. Primary PH, a disease with an unexplained cause, is uncommon, but the causes of secondary PH are known (PH secondary to ARDS, for example). Whether primary or secondary, PH is defined as having a mean pulmonary arterial pressure (PAP) greater than 30 mmHg (the normal mean range is 20 to 30 mmHg at rest or greater than 30 mmHg with exercise), and when secondary to ARDS, it is associated with poor clinical outcomes.

PH causes changes in the smooth muscle of the arterial wall, leading to muscle hypertrophy, thrombosis formation, and small vessel occlusion. The elevation of PAP increases right ventricular afterload (pulmonary vascular resistance) and right ventricular dysfunction, leading to reduced right ventricular output, decreased blood flow to the lungs, and a worsening of already severe hypoxemia. Progressive, refractory, severe hypoxemia coupled with PH are hallmark clinical manifestations of ARDS.

**EPOPROSTENOL**
Epoprostenol is a prostanoyclin, a metabolite of arachidonic acid, and one of several naturally occurring prostaglandins—prostaglandin I₂ (PGI₂)—that is produced in all vascular tissues, particularly in endothelial cells and smooth muscle cells. This agent produces important effects in patients with ARDS. Epoprostenol causes vasodilation of pulmonary and
systemic vasculature in a dose-dependent manner,\(^\text{11}\) and by this action can reduce postcapillary vasoconstriction in the lungs and thereby decrease microvascular pressure, reducing the formation of lung edema.\(^\text{14}\) In addition, it has an inhibitory effect on platelet aggregation, thereby preventing adhesion of platelets to the vascular endothelium.\(^\text{16}\)

Finally, it can inhibit the activation of leukocytes and monocytes during the inflammatory reaction and reduce the release of lysosomal enzymes. In other words, epoprostenol can play a role in reducing the inflammation that occurs in ARDS.\(^\text{14, 17}\)

Epoprostenol was discovered in 1976 during studies of thromboxane production.\(^\text{18}\) Its use leads to potent relaxation of smooth muscle cells induced by a receptor-mediated increase in intracellular adenosine \(^3\)'\(^5\) cyclic monophosphate cAMP.

**Administration.** Epoprostenol is administered both intravenously and by inhalation but is approved by the FDA for IV use only. It is indicated for long-term IV treatment of primary PH and secondary PH resulting from intrinsic precapillary pulmonary vascular disease or PH associated with scleroderma in New York Heart Association Class III and Class IV patients who don’t respond adequately to conventional therapy.\(^\text{16, 19}\)

The IV route, however, has limited utility in critically ill patients with ARDS because of its side effects—systemic hypotension and increased right-to-left shunting in the lung, the first of which, caused by arterial vasodilation, can lead to a reduction in coronary perfusion and compromised ventricular performance, and the second of which, resulting in less oxygenated blood being supplied to the left side of the heart, can worsen hypoxemia.\(^\text{20}\) In contrast, inhaled epoprostenol reaches only the well-ventilated areas of the lungs, causing greater vasodilation in these regions than the IV route does, while not causing systemic hypotension.\(^\text{7}\)

**INHALED (AEROSOLIZED) EPOPROSTENOL**

Case reports and descriptive and randomized trial research in the last six years suggest that administration of epoprostenol by inhalation decreases shunting while improving oxygenation and decreasing P\(_{\text{a}}\)\(_{\text{O}}\)–\(\text{FIO}_2\) ratio while improving ventilation–perfusion matching in secondary PH.\(^\text{11, 15, 17, 21-24}\) (see *Studies of the Use of Inhaled Epoprostenol*, page 64CC). In addition to its direct vasodilative properties, inhaled epoprostenol can modulate vascular growth or vascular remodeling and modify platelet function, thereby improving oxygenation and reducing P\(_{\text{a}}\)\(_{\text{O}}\).\(^\text{15, 23}\)

Inhaled epoprostenol’s role as an inhibitor of platelet aggregation was noted in early trials.\(^\text{23}\) Max and Roissant suggest that IV-administered epoprostenol may induce a platelet aggregation defect with subsequent bleeding,\(^\text{25}\) an effect that has not been associated with the use of inhaled epoprostenol.\(^\text{21}\) The literature suggests that individually titrated doses of nitric oxide (NO) and inhaled epoprostenol have identical efficacy profiles in terms of selective pulmonary vasodilation and redistribution of blood flow in the lungs.\(^\text{15, 22, 24}\) However, the potential side effects of NO include direct lung injury, inhibition of platelet
aggregation, methemoglobinemia, and possibly mutagenesis or carcinogenesis. In contrast, epoprostenol produces none of the adverse effects of toxic metabolites and its potential side effects are uncommon, transient, and negligible in sedated, ventilated patients.

**INHALED EPOPROSTENOL AT BAYSTATE MEDICAL CENTER**

In August 2002 the Pharmacy and Therapeutic Committee at Baystate Medical Center in Springfield, Massachusetts, approved the use of inhaled epoprostenol for salvage therapy in patients with the hypoxemia and PH of ARDS and developed guidelines for its administration and patient selection (see **Criteria for Use in Adults**, page 64EE, and **Cautions in the Use of Inhaled Epoprostenol in Adults**, above). The information is not intended to supersede informed medical judgment applied to specific patient cases.

**Dosage.** Recent data indicate that a broad range in dosage of inhaled epoprostenol has been found to be effective. One study found that dosages ranged from 2 ng/kg/min to a maximal dosage of 40 ng/kg/min. Another, in a single dosage response curve for a patient with ARDS, demonstrated that a dosage of 20 to 30ng/kg/min is as effective as 30ng/kg/min. Baystate’s pharmacy mixes an epoprostenol solution of 1.5 mg/100 mL, which results in a dose based on ng/kg/min. The center’s dosage guidelines are still in development in accordance with the trend toward administering lesser amounts of the agent, given adequate patient response.

**Actions.** Inhaled epoprostenol’s action is site-specific to ventilated areas of the lung. Coupled with its short half-life and selective vasodilation, the drug’s actions result in redistribution of blood flow from unventilated to ventilated areas, leading to a decrease in the V/Q mismatch and improved hypoxemia without lowered systemic blood pressure.

**CASE STUDY**

Darryl Brightman, a 49-year-old with a history of high triglyceride levels and hypertension, presents to a local hospital with abdominal pain. Laboratory testing reveals a markedly elevated lipase level of 21,330 U/L and a triglyceride level higher than 2,000 mg/dL. Because Mr. Brightman is in shock and experiencing ARDS secondary to severe necrotizing pancreatitis, he is placed on mechanical ventilation (MV). Over the next two days the state of shock persists, the ARDS becomes more severe, and the patient develops anuric renal failure. He is transferred to Baystate Medical Center.

On admission, Mr. Brightman is afebrile (at 98.4°F), with a heart rate of 85 beats per minute. A phenylephrine infusion is necessary to maintain a mean arterial pressure of 69 mmHg, and the patient is pharmacologically sedated and paralyzed to facilitate optimal MV. There is generalized edema and mottling of the extremities, and a chest X-ray shows bilateral lung edema. Despite 100% oxygen and a positive end expiratory pressure of 18 mmHg, arterial PaO2 is 61 mmHg.

A solution of epoprostenol (1.5 mg/100 mL) is administered by continuous aerosol, and PaO2 rapidly increases to 83 mmHg. The FIO2 decreases to 83% within 24 hours and to 50% after 48 hours, indicating an improvement in PaO2/FIO2 ratio. The patient’s cardiac index increases from 1.8 to 2.3 L/min/m² immediately, and to 4.2 L after 24 hours. The PAP does not change substantially. At the same time, Mr. Brightman is supported with continuous venovenous hemofiltration and eventually taken to the operating room for debridement of a necrotic pancreas.

Epoprostenol is administered by continuous aerosol for 10 days, during which period the need for treatment is determined by the level of oxygenation and the hemodynamic response to withdrawal of the medication for
short intervals. Eventually, the patient no longer needs administration. After an ICU stay of about six weeks and an additional three weeks’ hospitalization for the healing of abdominal wounds, Mr. Brightman, ambulatory and no longer in need of MV, is discharged to a rehabilitation center.

**NURSING IMPLICATIONS**

The nursing care of patients receiving aerosolized epoprostenol for ARDS focuses on the end points of therapy, proper administration, and the monitoring of side effects. Hypoxemia should decrease, PaO2/FIO2 ratio should increase, and PAP should decrease without a decrease in the mean arterial pressure. Abruption withdrawal or interruption of drug delivery will result in the return of hypoxemia and PAP to pretreatment levels. The nurse, pharmacist, intensivist, and respiratory therapist should collaborate in the attainment of end points.

The proper administration is crucial. While institutions may maintain constant inhalation in a variety of ways, as determined by the type of nebulizer used, it is important that the bedside nurse and respiratory therapist set up, maintain, and continuously refill the nebulizer to ensure constant inhalation.

Finally, observation for side effects is critical to the safety of the patient. While the side effects of IV-administered epoprostenol vary and can be severe (bleeding, chills, tachycardia, nausea and vomiting, jaw pain, and dizziness), inhaled epoprostenol produces few side effects. Although cardiac arrhythmias may occur and bleeding related to the inhibition of platelet aggregation are of possible concern, research indicates otherwise. Baystate Medical Center’s guidelines underscore several cautions to be considered in the use of inhaled epoprostenol.

**Cost containment.** In 1996 inhaled epoprostenol cost about $2,000 a day at 20 ng/kg/min in a 70-kg adult, but in October 2002 Baystate ICU pharmacist Gary Tereso reported that the cost of the same treatment had decreased to as little as $70 a day.

The nursing care of patients receiving epoprostenol for the treatment of ARDS is crucial to the improvement of outcomes in critically ill patients, among whom there is a high mortality rate. The use of inhaled epoprostenol is a promising therapy for the severe hypoxemia and PH of ARDS, and the pursuit of its use requires the collaborative effort of nurses, physicians, pharmacists, and respiratory therapists.

**REFERENCES**


