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Pulmonary Vasodilators—Treating the Right Ventricle

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Pulmonary vasodilators are typically employed to improve right ventricular (RV) function in the setting of pulmonary hypertension (PH) or in an effort to enhance regional pulmonary blood flow and improve intrapulmonary shunt. In PH, pulmonary vasodilators are used acutely and chronically. Because patients who have chronic PH may require operative intervention, a working knowledge of these vasodilators by anesthesiologists is relevant.

PH is defined as an elevation of mean pulmonary artery pressure (PAP) to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise [1]. The World Health Organization Venice conference (2003) classification system attempts to base its classification of disease on underlying pathology and pathophysiology rather than on whether the disease is primary or secondary (Box 1) [2]. In addition, primary PH is now referred to as idiopathic pulmonary arterial hypertension. The classification further distinguishes pulmonary arterial hypertension from the broader definition of PH by excluding those diseases that are associated with primary cardiac or pulmonary diseases. Diseases that are grouped along with idiopathic pulmonary arterial hypertension in this new schema include connective tissue disease, HIV, portal hypertension, and drug-related causes [3]; however, this classification is likely to change because a pulmonary arteriopathy may be present in a broader series of causes for PH.

It has long been held that PH is characterized by a regional imbalance between vasodilation and vasoconstriction. Reductions in the nitric oxide (NO) pathway and prostacyclin and increases in thromboxanes and endothelin have been described [4,5]. These homeostatic imbalances are probably

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Box 1. Classification of pulmonary hypertension

Idiopathic
Associated with
- Connective tissue disease
- Left-to-right intracardiac shunt
- Portal hypertension
- HIV
- Drug/toxin
- Other (thyroid disease, hereditary hemorrhagic telangectasia, myeloproliferative diseases, hemoglobinopathies)

Venous or capillary
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

PH of the newborn
PH with left heart disease
PH associated with lung disease or hypoxemia
- Chronic obstructive lung disease
- Pulmonary fibrosis
- Hypoventilation syndromes/obstructive sleep apnea
- High altitude

Venous thromboembolism–related
- Proximal or distal
- Nonthrombotic embolism (tumor, parasite, talc)

Miscellaneous (sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, hyposplenism, compression of mediastinal vessels)

Data from Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5S–12S.

the consequence of pulmonary endothelial cell dysfunction or injury [6,7]. More recently, there has been a shift in focus and an appreciation that the major alterations in PH extend beyond simple vasoconstriction. Alterations in growth inhibitors, mitogenic factors, and antithrombotic and prothrombotic determinants have been described. The benefits of the use of pulmonary vasodilators in the chronic setting likely extends beyond their vasodilator properties and relates more to their effects on smooth muscle proliferation, apoptosis, and modification of the intracellular matrix.

In the acute care setting, it is these agents' pulmonary vasodilatory effects that are being exploited. In the setting of PH, it is worth emphasizing that it is the consequences of an elevation of pulmonary vascular resistance (PVR), namely the ensuing RV dysfunction, that should be considered the primary goal of therapy with pulmonary vasodilators. The right ventricle,

unlike the left ventricle, is very susceptible to increases in afterload. Owing to the contractile properties of the naïve right ventricle, attempts at improving its contractility are not very effective. Therefore, principles of management of acute RV dysfunction center on reducing RV afterload while preserving coronary perfusion by avoiding reductions in systemic blood pressure.

This article provides a brief review of pulmonary vasodilators and a review of the literature as it relates to the use of therapies to treat various clinical conditions that may be relevant to the reader. The authors have attempted to keep the focus on the acute care setting.

Pulmonary vasodilators

Intravenous vasodilators

Intravenous vasodilators such as sodium nitroprusside and nitroglycerin mediate their effects on PVR through the release of NO. Both agents are nonselective and, as a consequence, can concomitantly decrease systemic blood pressure. In the setting of poor RV function, this reduction in systemic blood pressure may impair RV coronary perfusion and cause ischemia [8]. With PH, the failing right ventricle is made more susceptible to ischemia through an attendant increase in the right ventricle's intracavitary and transmural pressure.

Prostanoids, located in the vascular endothelium [9], induce relaxation of vascular smooth muscle, inhibit growth of smooth muscle cells [10], and are powerful inhibitors of platelet aggregation [9,11]. Currently, epoprostenol (prostaglandin [PG]I_2) and prostin (PGE_1) are available for intravenous administration in the acute setting. When infused chronically, epoprostenol has been shown to improve survival in patients who have advanced pulmonary arterial hypertension. In the acute setting, however, the therapeutic benefits of parenteral prostanoids are often limited by their systemic effects. Similar to sodium nitroprusside and nitroglycerin, prostanoids can lead to systemic hypotension. Additional care needs to be considered with several prostanoids because they are unstable in unbuffered solutions and inactivated by light and heat.

In addition to their systemic effects, all parenteral vasodilators are hampered by their relatively nonselective actions in the pulmonary vascular bed. As a result, their administration may lead to perfusion of underventilated alveoli, worsen intrapulmonary shunt, and in turn, worsen oxygenation. The ideal pulmonary vasodilator would have a rapid onset of action and a short half-life. It would produce regional pulmonary vasodilation, thereby avoiding issues related to systemic hypotension and potential adverse effects on ventilation-perfusion matching that limit the utility of systemic agents in critically ill patients. In this regard, inhaled vasodilators are attractive because they preferentially dilate ventilated alveoli and have less systemic effects.

Inhaled vasodilators

Inhaled NO (iNO) is delivered primarily to ventilated lung units, thereby causing increased perfusion to areas that are able to participate in gas exchange, which in turn may lead to a decrease in intrapulmonary shunt [8]. Shortly after NO was identified as the ubiquitous endogenous pulmonary vasodilator, it was rapidly embraced as a therapeutic agent in acute lung injury. iNO has been shown to produce pulmonary vasodilation without any significant effect on systemic circulation. Despite these advantages, there are inherent problems with iNO, such as costs, concerns surrounding methemoglobinemia, modulation of the immune system (pro- and anti-inflammatory), and cytotoxicity from free radical production. There is also the possibility of rebound PH with abrupt cessation of iNO. At present, iNO is approved only for use in infants who have respiratory distress syndrome. This approval stems from large prospective placebo-controlled studies demonstrating that NO reduced the need for extracorporeal membrane oxygenation and reduced the requirement for oxygen therapy following ICU discharge [12,13].

Inhaled prostaglandins, by contrast, involve an aerosol delivery mechanism that is attached by a nebulizer to the ventilator circuit. Despite having biologic rationale in practical terms, treatment is limited by inefficiencies in aerosolization. One study reported that as little as 3% of the drug that is administered reaches the lung [5]. Owing to the short half-life of epoprostenol, the drug must be continuously nebulized. As a result, changes of dose delivery with alterations in ventilator volumes, fraction of inspired oxygen (FiO_2), airway pressures, and solvent evaporation are other disadvantages [8]. Treprostinil, a synthetic prostanoid, has a much longer half-life and, in theory, holds promise as an inhaled vasodilator because it may require only intermitted administration [14]. To date, beyond acute hemodynamic studies, there are no clinical trials comparing these agents.

Inhaled nitroglycerin has been shown to decrease PH without producing systemic vasodilation [15]. Milrinone, a cyclic AMP–selective phosphodiesterase enzyme (PDE) inhibitor has also been administered by nebulization. Haraldsson and colleagues [16] evaluated a cohort of post–cardiac surgery patients and reported on the hemodynamic effects of the combination inhaled milrinone and inhaled prostacyclins. The inhalation of milrinone selectively dilated the pulmonary vasculature without systemic effects. When combined with inhaled prostacyclin, there seemed to be a potentiation and prolongation of the pulmonary vasodilatory effect.

Oral vasodilators

PDE_5 inhibitors mediate their pulmonary vasodilatory effect by preventing the degradation of cyclic GMP, allowing the prolonged effect of cyclic GMP as a secondary signal messenger, thus potentiating the effects of NO. PDE_5 inhibitors such as zaprinast and sildenafil produce pulmonary

vasodilation and enhance the effect of iNO on pulmonary hemodynamics [17–19]. Lepore and colleagues [20] studied the hemodynamic effect of the addition of oral sildenafil to iNO in patients who had chronic congestive heart failure and demonstrated that PDE_5 inhibition improved cardiac output and augmented the hemodynamic effects of iNO.

Endothelin is a potent vasoconstrictor and smooth muscle mitogen that exerts its effects on the vasculature by acting on two receptors. Bosentan and ambrisentan (nonselective endothelin receptor A and endothelin receptor B antagonists) and sitaxsentan (a highly selective endothelin receptor A antagonist) have been studied for treatment of chronic PH. To date, only case reports have showed potential benefit of oral bosentan working in combination with other agents to aid in the acute treatment of PH. Owing to these agents' slower onset of action and long half-life, they will likely not have a prominent role in the management of acute pulmonary hypertensive crisis or acute RV failure. Concerns about potential liver toxicity (that manifest as an elevation in transaminases) may preclude their use in the critical care environment.

Disease-specific applications of pulmonary vasodilators

Cardiac surgery

When present, PH remains a significant cause of morbidity and mortality in patients undergoing cardiac surgery for valvular replacement/repair or correction of congenital cardiac defects. It is unfortunate that there are few prospective controlled studies of pulmonary vasodilators in this population to guide the clinician.

In an observational study of atrioventricular canal defect repair, 25 children received NO and 39 received conventional treatment. Comparison between the two groups showed a significant difference in mortality (NO group, 24% [95% confidence interval: 7%–41%]; versus control, 56% [95% confidence interval: 37%–75%]; $P = .02$) [21]. A separate prospective randomized unblinded study of 62 cardiac surgery patients evaluated differences in PVR with varying doses of iNO ranging from 10 ppm to 40 ppm [22]. There were no statistically different effects on PVR among the groups with varying concentrations of iNO. The ability of iNO to prevent hypertensive crisis in children undergoing cardiac repair has been controversial; however, review of the available literature suggests that iNO may be efficacious in managing hypertensive crises when they do occur [23,24].

Fullerton and coworkers [25] showed that the response to iNO may be variable in different contexts. They demonstrated a decrease in PVR and PAP following coronary bypass, but no change in PVR and PAP following mitral valve surgery. It is important to recognize that the relative benefit derived form iNO depends on the baseline PAP. Two studies have reported

a correlation between vasodilator response with iNO and baseline PVR [26,27]. Rich and colleagues [27] found that the degree of NO-induced (20 ppm) pulmonary vasodilation was proportional to the severity of PVR at baseline. This effect did not appear to be altered by cardiopulmonary bypass (CPB), the presence of a ventricular assisted device, or infusion of nitrates.

Several studies have compared iNO with other vasodilators. Schmid and colleagues [28] compared iNO with intravenous PGE_1 and nitroglycerin in a randomized crossover study of 14 cardiac patients who had severe PH and preserved RV function. There was no difference between iNO and PGE_1 on cardiac index and RV performance; however, PGE_1 caused systemic vasodilation. Solina and colleagues [29] compared iNO to intravenous milrinone in a prospective randomized trial with 45 cardiac surgery patients. They found that, on separation from CPB, NO produced an improvement in RV ejection fraction and less need for vasopressors on arrival to the ICU. A prospective double-blind randomized trial of 58 patients undergoing mitral valve repair showed no difference between inhaled prostacyclin and iNO on PAP or on PVR. Both agents produced an increase in cardiac index and RV function [30].

Lamarche and colleagues [31] studied the possibility of using inhaled milrinone to reduce PH and to facilitate weaning from CPB. Seventy-three patients were enrolled, and their postoperative course was evaluated. Thirty received inhaled milrinone before CPB and 40 received inhaled milrinone after CPB. Patients receiving inhaled milrinone before CPB had lower pulmonary pressures and less frequent re-initiation of CPB (3%–23%) compared with those in whom inhaled milrinone was initiated late.

The potential additive role of combination therapy in cardiac surgery has also been studied. Stocker and colleagues [32] combined iNO with intravenous sildenafil in a prospective trial in 15 infants after cardiac surgery. They demonstrated that the combination produced a greater decrease in PVR compared with iNO alone. This improvement, however, was at the expense of a reduction in systemic blood pressure and worsening arterial oxygenation and alveolar-arterial gradient. Santini and colleagues [33] showed that after the addition of dipyridamole (a cyclic GMP–specific PDE inhibitor) to iNO, there was a decrease in pulmonary pressures and PVR from baseline and an increase in cardiac index. Further studies are required to look at other vasodilators and possible combinations of therapy. Although inhaled and intravenous prostaglandins have been studied in cardiac transplant patients, they have not been extensively evaluated in other cardiac surgeries.

Although there seems to be some evidence to support the notion that iNO administered perioperatively can control PH and facilitate CPB weaning, definitive studies are lacking. Furthermore, the optimum dose and duration of therapy has not been established. Prospective comparison to other agents in a controlled fashion is required. This need has been made more relevant given the expense of iNO and ongoing theoretic concerns

about the generation of potential proinflammatory mediators. Although improvements in pulmonary hemodynamics following cardiac surgery are reported with pulmonary vasodilators, it is unclear whether these agents lead to an improvement in outcomes that are of meaning to patients (eg, duration of ICU stay, hospitalization, ventilator days, or mortality). Consequently, it is difficult to advocate for the routine use of any specific pulmonary vasodilator.

Cardiac transplant

The adverse effects of high PVR on the naïve right ventricle may lead to significant morbidity and mortality following heart transplantation [34,35]. Post and colleagues [36] attempted to risk stratify 21 congenital adult cardiac patients to midterm outcomes based on response to iNO. The primary end point was cardiopulmonary death, and mean follow-up was 5 years. Four of the 11 patients who did not respond acutely to iNO died. None of the 10 responders to iNO died. The results suggest that patients who have an elevation in PVR may be further risk stratified and, more important, they raise the possibility that an elevation of PVR in these patients may be a modifiable risk factor. The current view is that the preoperative differentiation of fixed and reversible PH is essential to predict the response to vasodilator therapy and risk stratification of cardiac transplant candidates. A fall in mean PAP of more than 25% or a fall of more than 33% in PVR indicates reversibility in vascular resistance and may identify patients who would benefit from preoperative vasodilator therapy and subsequent heart transplantation [8] Recent studies suggest that regardless of severity, when PH can be reversed, these patients may have acceptable post-transplant survival [37].

Other vasodilators have been evaluated in the heart transplant patient. Haraldsson and colleagues [38] evaluated 10 pretransplant candidates and reported on the response of PVR to iNO at 40 ppm compared to inhaled prostacyclin. The results suggested that the effects of inhaled prostacyclin on pulmonary pressures and on PVR were comparable to iNO. There was no effect on systemic blood pressure with either drug. Kieler-Jensen and colleagues [39,40] performed studies of hemodynamic measurements post cardiac transplantation in the ICU with iNO, intravenous prostacyclin, PGE_1, sodium nitroprusside, and nitroglycerin. The greatest effect on cardiac output, stroke volume, RV end-diastolic volume, and central filling pressures was with prostacyclin. Intravenous prostacyclin, however, also produced a systemic effect by lowering systemic vascular resistance. Only iNO produced a selective pulmonary effect.

Although several studies have evaluated the acute hemodynamic responses to various pulmonary vasodilators, there are no randomized trials that have evaluated the effect of specific vasodilators on patient relevant outcomes.

Acute respiratory distress syndrome and acute lung injury

It is known that acute respiratory distress syndrome (ARDS) is frequently associated with PH due to increased vascular resistance [41]. There are a variety of factors in ARDS that contribute to PH, including lung parenchymal destruction, microthrombi, airway collapse, and pulmonary vasoconstriction related to hypoxemia, hypercarbia, and mechanical ventilation with high positive end-expiratory pressure settings [42–44]. In the face of demonstrable acute improvements in oxygenation, no controlled trials have demonstrated a benefit in patient outcome when NO is used in all comers who have ARDS. Adhikari and colleagues [45] performed a meta-analysis and, after reviewing the literature, concluded that NO had limited improvement in oxygenation, conferred no mortality benefit, and may cause harm. In this meta-analysis, NO was associated with an increased risk of renal insufficiency. In term infants who had acute lung injury (a disease characterized by more severe PH), the use of NO has may have more merit [12,13]. More recent studies suggest that NO may lead to an improvement in late sequelae (bronchopulmonary dysplasia) in some premature infants who have mild to moderate respiratory distress syndrome without significant increase in short-term side effects such as pulmonary hemorrhage, intracranial hemorrhage, pneumothorax, or acute deterioration [46,47]. This beneficial effect, however, has not been seen across all baby weights or studies [46–49]. Caution about the use of NO in this population needs to be exerted based on the findings of a recent Cochrane review in which it was suggested that iNO may not be a reasonable treatment in the ill preterm infant and may increase interventricular hemorrhage [50].

One of the difficulties with the use of iNO relates to rebound worsening of PAP or oxygenation on weaning. To this end, PDE_5 inhibitors have been shown facilitate weaning. In a case report by Giacomini and colleagues [51], vardenafil, a PDE_5 inhibitor was used to successfully wean an ARDS patient off iNO without significant systemic hypotension. In the pediatric population, Namachivayam and colleagues [52] investigated the role of sildenafil in preventing rebound PH after discontinuation of iNO. Thirty ventilated patients receiving 10 ppm or more of iNO were randomized to sildenafil or placebo 1 hour before discontinuing iNO. Rebound PH occurred in 10 of 15 placebo patients, whereas 0 of 15 patients in the sildenafil group had rebound PH.

Other therapeutic options may still be available for the treatment of hypoxemia in ARDS. Levosimendan exerts a positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C. It also has a vasodilatory effect by opening ATP-sensitive potassium channels in vascular smooth muscle to cause smooth muscle relaxation. Morelli and colleagues [53] studied the effects of levosimendan versus placebo on RV afterload in patients who had ARDS. Compared with placebo, levosimendan decreased mean PAP, increased cardiac index, and produced a reduction

in PVR. Dahlem and colleagues [54] showed that aerosolized prostacyclin compared with placebo in children who had acute lung injury improved oxygenation by 26%, with no significant adverse side effects, although long-term outcomes were not assessed during this trial. Van Heerden and colleagues [55] performed an unblinded interventional prospective trial that compared different doses of prostacyclin and their effect on oxygenation. The study showed that there was a significant dose-related improvement in the Pao_2/Fio_2 ratio and in the alveolar-arterial difference in partial pressure of oxygen, without any significant side effects. Further studies are needed to determine whether inhaled prostanoids are advantageous in long-term outcomes; as of yet, this has not been evaluated. It is likely, however, that inhaled prostanoids will be susceptible to the same shortcomings as iNO use in ARDS.

Although acute physiologic studies are encouraging, the use of pulmonary vasodilators has not been shown to confer a survival benefit in ARDS. The use of strategies aimed solely at improving oxygenation and RV function in ARDS is hampered by the fact that most patients who have ARDS do not succumb to refractory hypoxemia or RV failure, rather they die as the result of multisystem organ failure. Insofar as vasodilators are able to reduce the required intensity of mechanical ventilation, they have theoretic benefit. Although the routine use of vasodilators for ARDS cannot be advocated, they may still have a role in certain patients who have refractory hypoxemia or RV failure.

Lung transplant

With the advent of targeted therapies for PH, many patients have been successful in deferring time to transplantation; however, the clinical condition of these patients (who deteriorate in the face of receiving targeted therapies such as epoprostenol) at transplantation may be precarious. As a rule, these medications are continued until the grafts are perfused or the patient is placed on bypass. Some centers resume epoprostenol postoperatively if PH persists or cardiac dysfunction occurs [56]. In general, however, cardiac function improves significantly post lung transplantation, allowing the discontinuation of pulmonary vasodilators without sequelae [57].

Despite advances in organ procurement, primary graft dysfunction (PGD) remains a common problem after lung transplantation. PGD is a consequence of endothelial and epithelial dysfunction following reperfusion and is characterized by hypoxemia, bilateral airspace disease, and PH. In addition to its vasodilatory properties, NO may have important anti-inflammatory effects. NO has been shown to reduce the frequency and severity of ischemia reperfusion and PGD in animal models [58]. Although early uncontrolled studies of NO to prevent PGD appeared promising, a prospective randomized placebo-controlled trial in 84 patients from the authors' center showed no difference in the incidence or severity of

PGD, ventilator-free days, or postoperative survival when NO was administered at the time of reperfusion [59]. Whether earlier administration of NO (before reperfusion) affects outcome is still a matter of debate. More commonly, iNO has been advocated for the treatment of established PGD [60,61]. Used in this context, it has the same acute effects as in those seen in ARDS: an improvement in oxygenation and concordant reduction in pulmonary pressures.

Based on similar acute hemodynamic effects and potential anti-inflammatory effects, other agents have been evaluated to treat PGD. Some animal studies have shown a beneficial effect of intravenous prostacyclins in preventing lung transplant injury [62,63]. Wittwer and colleagues [64] looked at pretreatment of the donor lung with iloprost to optimize postischemic function of non–heart beating donor lungs in asystolic pigs. Compared to a control animal that did not receive iloprost, it was found that inspiratory pressure, dynamic compliance, and wet-to-dry ratio were significantly superior. Another study investigated the effects of iNO and PGI_2 on single porcine transplanted lungs. Parameters such as PVR, mean PAP, and blood flow distribution were investigated. Animals were divided into three groups: iNO, PGI_2, and a control group. The results concluded that iNO initially decreased PVR more than PGI_2 within the first hour and that both reduced PVR compared with control [65]. Fiser and colleagues [66] published a case report of the use of inhaled prostacyclin in the management of lung reperfusion injury post single lung transplant. The case report indicated that inhaled protacylcin is as effective as iNO and could potentially be used instead of iNO thereby reducing concerns related to costs and lack of potential toxic metabolites. At present, however, definitive studies are lacking; therefore, additional studies are needed to determine the best management options for PH and PGD in the lung transplant population.

Obstetrics

In a normal pregnancy, maternal cardiac output increases by 30% to 50%, blood volume by 40% to 50%, and oxygen consumption by up to 20% [67,68]. Reduced vascular tone, increased arterial compliance, and arterial load alterations help to accommodate the increased circulating volume and to maintain the efficiency of ventricular-arterial coupling and perfusion pressure [68]. With a progressively increasing uteroplacental blood flow, fetal growth, and ''peripheral'' oxygen consumption with limited oxygen delivery in the third trimester [69], the demands on the cardiac system may exceed the patient's adaptive capabilities. Historically, these physiologic demands have translated into high maternal mortality rates ranging from 30% to 56% in patients who have PH [70].

Weiss and colleagues [71] performed a systematic review of outcomes in vascular disease in pregnancy and completed an analysis of neonatal outcomes. When only patients in the late stages of pregnancy were included,

they found a surprisingly good infant survival rate of 90%. With the inclusion of patients who had Eisenmenger's syndrome, the infant survival rate was 82%. The largest obstetric series, conducted by Gleicher and colleagues [72], was less optimistic. In 70 pregnancies in women who had Eisenmenger's syndrome physiology, these researchers reported a disturbing 52% maternal mortality rate. There were no differences in maternal mortality between primiparous or multiparous women. Neonatal outcome was also discouragingly low: only 25.6% of pregnancies reached term, and at least 54.9% of all deliveries occurred prematurely [73]. The difference in neonatal mortality rates between Weiss and colleagues [71] and Gleicher and colleagues [72] may be due to the fact the former group included only women in the later stages of pregnancy. In general, the presence of hemodynamically significant PH is considered an absolute contraindication to pregnancy. Most experts recommend termination of the pregnancy in these patients.

The management of PH in the peripartum period has not been well studied, with most of the literature confined to case reports [74]. Several case reports have used iNO in the operating room and ICU for emergency cesarean section to decrease pulmonary pressures in parturient patients [74–76]. Other reports focusing on the postpartum period in the ICU have commented on the use of intravenous prostacyclin and nebulized iloprost [73,76]. Although animal studies have raised concerns about potential teratogenicity of these agents, there are no data to suggest that they confer fetal harm when used at term [70]. Endothelin antagonists such as bosentan, however, have shown to be teratogenic and are avoided during pregnancy [77]. To date, there is no good evidence to suggest that one vasodilator is better than another in the treatment of PH during the peripartum period.

In Eisenmenger's syndrome, there are no established guidelines on peripartum treatment. There are two case reports that attempted to use NO to control the hypoxemia during the third trimester and labor. In both cases, the patient died in labor or post partum [78,79].

Pulmonary embolism

The mortality of acute massive pulmonary embolus causing hemodynamic instability is approximately 31% [80]. Aims of therapy include reducing PVR and, if possible, relieving the mechanical obstruction through thrombolysis or pulmonary endarterectomy. Current guidelines support the use of thrombolysis of pulmonary embolus when associated with hemodynamic instability unless contraindicated. If thrombolysis has failed, then surgical embolectomy can be performed with an experienced surgical team [81]. Although data supporting pharmacologic treatment of increased PVR and right heart failure with pulmonary vasodilators are very limited, there have been case reports of iNO improving gas exchange [82].

Studies evaluating the use of pulmonary vasodilators post pulmonary thromboendarterectomy weakly advocate for the use iNO or iloprost in

improving of oxygenation and hemodynamics. Imanaka and colleagues [83] performed a prospective crossover study following seven patients immediately after pulmonary endarterectomy for chronic thromboembolism. iNO was given at 30-minute intervals for 30 minutes following surgery until extubation. Although iNO improved oxygenation and decreased vascular resistance, the changes were small and of uncertain clinical relevance [83]. Inhaled iloprost was also studied post pulmonary endarterectomy to control residual PH. Twenty-two patients were randomized to a single dose of 25-μg aerosolized iloprost or to normal saline. Iloprost enhanced cardiac index and reduced mean PAP and PVR [84].

Portopulmonary hypertension

Portopulmonary hypertension (PPHTN), an uncommon (<1%) complication of cirrhosis and portal hypertension, is defined as a mean PAP greater than 25 mm Hg with a normal pulmonary capillary wedge pressure (<15 mm Hg) and an increase in calculated PVR of greater than 240 dyne·s·cm^{-5} [85]. Moderate PPHTN (mean PAP >35 mm Hg) results in a significantly higher perioperative risk, and severe PPHTN (mean PAP >50 mm Hg) is frequently considered an absolute contraindication for liver transplantation [86].

For patients who have suspected PPHTN, a right heart catheterization is required, as is hemodynamic assessment to determine whether the patient can safely undergo transplantation [85]. In the perioperative period, preservation of RV function through control of pulmonary pressures is a critical component of the overall management goals [86]. Formerly considered an absolute contraindication to liver transplantation, new therapeutic options have become available that may alter these patients' eligibility for liver transplantation [87]. In a multicenter survey, Krowka and colleagues [88] provided some rationale for the use of epoprostenol to improve pulmonary pressures in patients who have PPHTN. The use of iNO has not been shown to be of any benefit during the perioperative management of these patients [89]. In the postoperative period, epoprostenol is generally continued for at least 6 months until it can be gently weaned as tolerated by the patient [87]. There is scant literature in this regard, however, and patients must be judged on their own merits. It is difficult to determine whether the pulmonary pressures will continue to be elevated after successful liver transplantation.

There is even less experience with other vasodilators in this population. The use of sildenafil has been reported in the preoperative and postoperative period [90,91], and there is one case report on the use of bosentan [92]. Based on the authors' experience and that of others, the authors believe that there is some merit in attempting to reduce pulmonary pressures in patients who have PPHTN to improve their surgical risk.

Summary

Hemodynamically significant PH remains a significant challenge. The goal of treatment should focus on improving RV function by reducing afterload and by augmenting RV coronary perfusion. Inhaled agents appear to have the most attractive physiologic and pharmacologic profile, although PDE_5 inhibition may provide additional benefit in some instances.

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