Pulmonary Hypertension in the Critical Care Setting

Perioperative Management
Ronald G. Pearl, PhD, MD

Right Ventricular Failure
Teresa De Marco, MD
Dana McGlothin, MD

Cases from the PH Service
Roxana Sulica, MD
Ramona Doyle, MD

Roundtable Discussion:
Acute Care Management
Editor’s Memo

PHA Web Site—www.phassociation.org—Best Kept Secret on the Internet

Whether you like to casually surf the Web and explore various medically oriented sites or directly seek specific information on a topic of interest, the Web site of the Pulmonary Hypertension Association (PHA) is an often overlooked treasure trove of valuable content. I say overlooked because we often view Web sites as part of a serendipitous search, as merely a means toward an end of retrieving the information we seek; but PHA’s site is a destination as well, a virtual labyrinth waiting to be discovered. And more people are discovering it—115,000 visitors per month to its 3000 pages, and 500 messages posted per week on its main message board. Physicians are always telling me how helpful it has been in directing them—or their patients and staff—to nuggets of information they could not have found otherwise.

Where else, for example, could you find information on such diverse topics in pulmonary hypertension as active clinical trials, the latest meeting on how patient advocates will discuss key concerns with their congressional leaders, an interactive map to search for a prominent physician in any state specializing in pulmonary hypertension care, or special events like a Christmas tree fundraiser that benefits the pulmonary hypertension community?

Navigating the site is easy. The topics are conveniently arranged to appeal to the visitor’s particular query or need. The links for healthcare professionals are clearly delineated and easily accessed. As the pulmonary hypertension community has grown, so has the need for an efficient roadmap with specific points of interest and signposts along the way to guide one toward a connection or network one seeks. This is extremely important at a time when improved communication at all levels—among patients, physicians, families, and allied healthcare personnel—can help in promoting clinical trial enrollment, an exchange of ideas on new treatment approaches, and an overall sense of where we stand in making such progress. In facilitating this communication PHA’s site serves as a forum and a vehicle to keep the pulmonary hypertension community working together.

Proof of the site’s value comes from numerous tributes to its role in the lives of the pulmonary hypertension community. Consider this comment from a patient, Marilyn Haney, posted in the “Our Journeys” section of the site: “I was diagnosed in mid 2004 with primary pulmonary hypertension. ‘I have what?’ Honestly, I had never heard of this disease. I dove right in to educate myself, beginning with my pulmonologist who referred me to PHA. The Web site, as well as A Patient’s Survival Guide, gave me a clear understanding of what PH is, what treatments are available, and what is currently happening to find a cure.”

As helpful as the PHA site is, PHA acknowledges its limitations and advises everyone by posting this message: “The information provided on the PHA website is provided for general information only. It is not intended as legal, medical or other professional advice, and should not be relied upon as a substitute for consultations with qualified professionals who are familiar with your individual needs.” Yet the information provided on the site is perhaps the next best thing to a consultation in that it points patients and caregivers alike to the appropriate source or resource. By fulfilling that role, the site has become an integral part of the pulmonary hypertension community and we are grateful for its continuing evolution and the benefit it provides to us all.

Vallerie V. McLaughlin, MD
Editor-in-Chief
The Scientific Leadership Council of the Pulmonary Hypertension Association

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- **The Mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA by:**
  - Developing and disseminating knowledge for diagnosing and treating pulmonary hypertension
  - Advocating for patients with pulmonary hypertension
  - Increasing involvement of basic and clinical researchers and practitioners
Bertron M. Groves, MD: Visionary Builder of Bridges Between Cardiologists and Pulmonologists Through Hemodynamics

Whether voluminous or brief, a curriculum vitae (CV) serves as a road map to one’s medical career, charting the stepping stones through internship, fellowship, appointments, awards, publications, and speaking engagements.

But the CV of Bertron M. Groves, MD, Professor of Medicine, University of Colorado Health Sciences Center, Denver, is much more. The entries—namely, the distinguished list of peer-reviewed and landmark publications—not only track the path he followed but signify milestones for all clinicians in the study of the relationship between hemodynamics and pulmonary hypertension.

Much of the work done by Dr Groves sprouted from the legacy of his mentor, John T. Reeves, MD, a legendary figure in pulmonary hypertension at the University of Colorado Health Sciences Center, who died in a bicycle accident last year. Soon after joining the faculty at the University of Colorado in 1979, Dr Groves was managing the catheterization laboratory when he began doing research influenced by Dr Reeves. “It was obviously becoming critical to have someone involved in the hemodynamics of pulmonary hypertension, to get deeply involved,” recalled Dr Groves. “Jack Reeves took me under his wing and was my mentor for many years. We had a very rich collaboration and he really pulled me into the pulmonary hypertension world, and it felt right because my home was the catheterization lab at that time and still is.”

Remembering the bench research of the early 1980s, he notes: “A lot of the studies we did were considered very risky and sort of on the fringe of what perhaps was appropriate. Some of my colleagues were openly critical of some of these studies because they feared that the likelihood of success would be too small to warrant the risk. In fact, 15 years later we got prostacyclin approved by the FDA, and now it is influencing the management of pulmonary hypertension in a pretty broad spectrum.”

Describing himself as “a purebred catheterization guy from the start,” Dr Groves explained how he began relating the work he was doing in the catheterization lab to pulmonary hypertension. “A lot of the studies that had been done were noninvasive and trying to use estimations of pulmonary pressure by various means, including echocardiography. As one who emphasized hemodynamics, that did not satisfy me, and I thought we could do the studies invasively and do them safely, even though there was a track record in the literature that some of these patients had sudden death in the catheterization procedures. That’s how I brought the two together and it has worked out very well for 20 years.”

Operation Everest: A Landmark Study in Pulmonary Hypertension

Dr Groves said he considers himself “a bridge” between the pulmonologist and the cardiologist, applying lessons from interventional cardiology to the management of pulmonary hypertension. One of his most exciting research projects was the “Operation Everest” expedition in which an Everest-like environment was simulated in a hyperbaric chamber in Massachusetts at the US Army Research Institute. The concept was to take normal volunteers into the hypoxic chamber for 40 days and nights and pattern their exposure to hypoxia and altitude.

“We were going to use echocardiographic estimation of the pulmonary hypertension they developed. I convinced them that instead of doing noninvasive assessments we should do serial cardiac catheterizations,” he added. “I agreed to do all the catheterizations on all of the subjects, and I commuted back and forth from Denver to Natick, Massachusetts, during those 40 days to do the serial studies that led to the hemodynamic definition of pulmonary hypertension. It was a fantastic experience with these numerous scientists who put it all together.”

Returning to His Roots, Interventional Cardiology

Today Dr Groves has returned to his roots, so to speak, interventional cardiology, having turned over the direction of the pulmonary hypertension center and clinic to his protégé, David B. Badesch, MD, whom he trained. “I continue to do the hemodynamic work to make sure I train other cardiologists to do what I have been doing for him.” For Dr Badesch, the arrangement has been mutually beneficial, and he refers to Dr Groves as “a fantastic educator, always willing to share time and expertise as one of the true pioneers 20 years ago. He is one of the true experts on obtaining right heart hemodynamics and has been my mentor.”

Looking toward new horizons in pulmonary hypertension, Dr Groves sees the trend toward trying to monitor the ongoing pulmonary pressure as the next focus. “The reason pulmonary hypertension was neglected for so long was that you couldn’t put your pulmonary artery in a cuff and go into the grocery store and measure what it was. Systemic hypertension has always been so easy to monitor and pulmonary hypertension has been so difficult. But now we have the invasive-type devices that are being developed to monitor chronic pulmonary artery pressure to see what happens over the full course of daily living. I’m expecting that there will be more of an emphasis on that in the next decade.”
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Pulmonary Hypertension: An Interactive Guide to Diagnosis

This companion piece to the Fall issue of Advances in Pulmonary Hypertension assists with diagnosis of pulmonary hypertension and is an invaluable resource for medical professionals in pulmonology, cardiology, rheumatology and primary care.

Featuring comprehensive diagnostic information on:

**Physical examination**

**Introduction on jugular venous pulse**

7 cases providing comprehensive diagnostic information on:
- Valvular pulmonic stenosis
- Patent ductus arteriosus with pulmonary hypertension (Eisenmenger syndrome)
- Restrictive ventricular septal defect (VSD)
- Non-restrictive VSD with pulmonary hypertension (Eisenmenger)
- Hypertensive heart disease, atrial fibrillation, PH, and tricuspid regurgitation
- Pulmonary arterial hypertension with tricuspid regurgitation
- Pulmonary arterial hypertension with tricuspid and pulmonic regurgitation

**Initial Diagnostic Testing**
Includes comprehensive and interactive information on:
- ECG
- Chest x-ray
- V/Q scan
- MRI
- Echocardiography
- Computed tomography
- Right heart catheterization
Advances in Pulmonary Hypertension

The pulmonary circulation is normally a low pressure, low resistance circulation. In patients with pulmonary arterial hypertension, altered vascular endothelial and smooth muscle function lead to a combination of vasoconstriction, localized thrombosis, and vascular growth and remodeling. These processes increase pulmonary vascular resistance, resulting in right ventricular failure, inadequate oxygenation, and ultimately death. Pulmonary hypertension markedly increases morbidity and mortality among patients undergoing surgery.1-6

Understanding the pathophysiology and etiology of pulmonary hypertension in the individual patient allows accurate risk assessment, optimization prior to surgery, and rational intraoperative and postoperative treatment.7-12

An approach to understanding the pathophysiology of an individual patient with pulmonary hypertension is derived from the equation for pulmonary vascular resistance: \( PVR = \frac{(PAP - LAP) \times 80}{CO} \), where \( PVR \) represents pulmonary vascular resistance (in dynes.s.cm\(^{-5}\)), \( PAP \) represents mean pulmonary artery pressure (in mmHg), \( LAP \) represents left atrial pressure (in mmHg), and \( CO \) represents cardiac output (in L.min\(^{-1}\)). Rearranging this equation for \( PAP \) demonstrates that \( PAP = LAP + \frac{(CO \times PVR)}{80} \).

Thus, the three factors that account for increased \( PAP \) are increased left atrial pressure, increased cardiac output, and increased pulmonary vascular resistance. Therapy of the perioperative patient with pulmonary hypertension should involve an assessment of the qualitative contribution of each of these three components. For example, patients with mitral stenosis who have increased \( PAP \) due solely to increased left atrial pressure have uncomplicated perioperative courses, but patients with mitral stenosis who have increased \( PAP \) due to increased \( PVR \) from pulmonary vascular modeling commonly have severe right ventricular failure after mitral valve replacement and may not succeed in weaning from cardiopulmonary bypass. Pulmonary vasodilator therapy would be inappropriate in one patient but life-saving in the other.

Similarly, patients with chronic left ventricular failure who undergo heart transplantation tend to do well perioperatively if the pulmonary hypertension is due solely to elevated left atrial pressure but may have severe right ventricular failure after transplantation if there is also a significant component of increased \( PVR \). In patients with pulmonary arterial hypertension, analyzing whether cardiac output is maintained or is markedly decreased has significant prognostic value in assessing perioperative risk (see section on risk assessment).

The current World Health Organization classification of pulmonary hypertension involves five major categories (pulmonary arterial hypertension, pulmonary venous hypertension, pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia, chronic thrombotic and/or embolic disease, and pulmonary hypertension due to disorders directly affecting the pulmonary vasculature). For the physician who is treating a perioperative patient with pulmonary hypertension, the equation for pulmonary artery pressure can be used to review the common etiologies. Increased left atrial pressure includes left ventricular failure and valvar heart disease (particularly mitral stenosis and/or regurgitation). Increased cardiac output includes patients with congenital heart disease with cardiac shunts such as ventricular septal defects. The major categories of chronically increased \( PVR \) are pulmonary disease (parenchymal or airway), hypoxia without pulmonary disease (hypoventilation syndromes, high altitude), pulmonary arterial obstruction (thromboembolism, schistosomiasis), and idiopathic pulmonary arterial hypertension. Because of pulmonary vascular remodeling, all these etiologies of pulmonary hypertension can result in increased \( PVR \).

In addition to these etiologies of chronic pulmonary hypertension, acute increases in \( PVR \) may result from hypoxia, hypercarbia, acidosis, increased sympathetic tone, and endogenous or exogenous pulmonary vasoconstrictors such as catecholamines, serotonin, thromboxane, and endothelin.13 Most perioperative patients with decompensated pulmonary hypertension have a combination of chronic pulmonary hypertension with an acute increase in \( PVR \) and therapy should be directed at reversing this acute \( PVR \) increase.

Perioperative Risk Assessment

In the face of increased impedance to right ventricular ejec-
tion, the compensatory reserves of the right ventricle are limited. Reduction in right ventricular stroke volume and cardiac output as well as ventricular interdependence, with decreased left ventricular filling and output, occur. In the patient with pulmonary hypertension, anesthesia and surgery may produce progressive hemodynamic deterioration and death due to additional increases in PVR combined with decreases in right ventricular function. For example, patients with pulmonary hypertension undergoing cardiac surgery may fail to wean off cardiopulmonary bypass due to inadequate myocardial right ventricular protection during the ischemic period of aortic cross-clamping, increased endogenous pulmonary vasoconstrictors, and decreased endogenous pulmonary vasodilators from pulmonary endothelial injury during cardiopulmonary bypass. Thus patients with pulmonary hypertension have markedly increased perioperative morbidity and mortality. For patients with Eisenmenger syndrome undergoing cesarean section, mortality is as high as 70%. Patients undergoing liver transplantation with pulmonary arterial hypertension have increased mortality related to the severity of the pulmonary hypertension, with mortality rates as high as 80% when mean PAP >45 mmHg. Reports of successful outcomes of surgery in patients with severe pulmonary hypertension include curative procedures such as lung or heart-lung transplantation, cesarean section, and relatively brief procedures with minor blood loss such as lung biopsy, cholecystectomy, femoral artery repair, and laparoscopic tubal ligation.

Survival in pulmonary arterial hypertension correlates with the ability of the right ventricle to compensate for the increased PVR as assessed by cardiac output, right atrial pressure, and functional status. These factors also appear to be major predictors of perioperative risk in the surgical patient. However, perioperative risk is also highly correlated to the surgical procedure. Major procedures that result in the systemic inflammatory response syndrome may exacerbate pulmonary hypertension and increase the perioperative risk. Procedures with rapid blood loss may result in fatal hypotension in the patient requiring adequate venous return as compensation for increased right ventricular afterload. Finally, some procedures may pose special risks for the patient with pulmonary hypertension. For example, hip replacement surgery commonly involves pulmonary embolization of air, bone marrow, and cement during placement of the femoral component. Overall, the risk assessment requires balancing the functional reserve of the patient against the anticipated increased demands of the surgical procedure.

Progressive or acute increases in pulmonary artery pressure leading to acute right heart failure are the major complications of anesthesia and surgery. A pulmonary vasodilator trial may provide additional prognostic information and guide therapy if perioperative right ventricular failure occurs. This approach is used in the evaluation for heart transplantation and has been advocated in occasional patients with pulmonary hypertension undergoing noncardiac surgery. Because of pulmonary selectivity inhaled nitric oxide is an ideal agent for screening for pulmonary vascular reactivity.

In patients at an unacceptably high risk following optimization of therapy, consideration should be given to lung or heart-lung transplantation or chronic prostacyclin treatment to decrease the pulmonary hypertension to acceptable levels.

Preparation of the Patient for Anesthesia and Surgery
Whichever anesthetic technique is chosen, surgery and anesthesia in patients with pulmonary hypertension are associated with significant morbidity and mortality. Prior to anesthesia and surgery such patients should be evaluated with electrocardiography, chest x-ray, arterial blood gas (ABG) measurement, and echocardiography. Evidence of significant right ventricular dysfunction should prompt reevaluation of the need for surgery. All attempts to reduce PAP prior to surgery should be performed, such as the administration of oxygen, bronchodilators, antibiotics, and steroids in the patient with lung disease, and vasodilators and inotropes in the patient with cardiac disease. Reduction of PAP is more likely to succeed prior to surgery than after the induction of anesthesia. Digoxin may have beneficial short-term effect on cardiac function and sympathetic activation in pulmonary arterial hypertension. Patients receiving chronic therapy for pulmonary arterial hypertension should continue such therapy throughout the perioperative period. Discontinuation of continuous epoprostenol infusion (Flolan) can precipitate an acute pulmonary hypertensive crisis. Although prostacyclin inhibits platelet aggregation, excess surgical bleeding is not usually a problem. It is important to coordinate continuation of the prostacyclin infusion with the nursing staff that will care for the patient after surgery. Patients receiving chronic prostacyclin infusion should have the infusion continued throughout the perioperative period, and management of hypotension should be with additional therapy rather than with discontinuation of the prostacyclin infusion.

Anesthetic Management
The anesthetic management of patients with pulmonary hypertension undergoing noncardiac surgery has received relatively little attention in the literature. Most discussion has been limited to obstetrical anesthesia case reports in adults and case series of repair of congenital heart defects in pediatrics. Most authors agree that the management of a specific anesthetic technique is as important as the choice of the technique. In the absence of evidence-based recommendations anesthesiologists need to focus on basic hemodynamic principles.

Physiologic Considerations and Goals
The anesthetic plan for the patient with pulmonary hypertension is designed to account for the underlying pathophysiology. The major abnormality is the elevated PVR, which increases right ventricular afterload, thereby increasing right ventricular work and decreasing right ventricular, and thus left ventricular, output. Based on the underlying pathophysiology, the major anesthetic considerations include:

1) Preload: Maintenance of preload (intravascular vol-
ume) at normal or increased levels is essential to maintain cardiac output in the face of increased ventricular afterload.

2) Systemic vascular resistance: In normal hemodynamic states, this is a major determinant of left ventricular afterload (and, therefore, cardiac output). In pulmonary hypertension, cardiac output is limited by right ventricular function and is, therefore, independent of systemic vascular resistance. Since systemic blood pressure is related to the product of cardiac output and systemic vascular resistance, it is important to maintain systemic vascular resistance in the normal-to-high range, because cardiac output is unable to increase when systemic vascular resistance decreases.

3) Contractility: Maintenance of normal-to-high contractility is essential to maintain cardiac output in the face of increased right ventricular afterload.

4) Heart rate and rhythm: Sinus rhythm is important for adequate filling of a hypertrophied right ventricle. Stroke volume is limited by right ventricular afterload, so bradycardia should be avoided.

5) Avoidance of myocardial ischemia: Right ventricular subendocardial ischemia due to myocardial oxygen supply-demand imbalance is common in pulmonary hypertension. Systemic hypotension and excessive increases in preload, contractility, and heart rate must be avoided.

The above five physiologic considerations for pulmonary hypertension are similar to the considerations in the patient with aortic stenosis (since both situations involve excessive ventricular afterload, specifically right ventricular afterload in pulmonary hypertension and left ventricular afterload in aortic stenosis). Although many physicians are skilled at the management of aortic stenosis, a final consideration applies only in the case of pulmonary hypertension:

6) Pulmonary vascular resistance: In pulmonary hypertension, this is the major factor governing right ventricular afterload and cardiac output. Therefore, increases in pulmonary vascular resistance must be avoided and therapy to decrease pulmonary vascular resistance may be required.

Perioperative Monitoring
Monitoring during anesthesia must be adequate to detect the causes and complications of increased pulmonary vascular resistance. Arterial oxygen saturation should be continuously monitored by pulse oximetry. Arterial catheterization is required both for beat-to-beat blood pressure monitoring and for frequent arterial blood gas measurements. Monitoring of preload requires consideration of the altered physiology in pulmonary hypertension. In the absence of pulmonary hypertension, cardiac output is determined by left ventricular function, and the relevant preload is left ventricular filling, which is usually monitored by pulmonary artery occlusion pressure (PAOP). However, with severe pulmonary hypertension, cardiac output is limited by right ventricular function, and the relevant preload is right ventricular filling, which may correspond to right atrial or central venous pressures. Therefore in severe pulmonary hypertension, volume administration should be governed by central venous pressure rather than PAOP. However, with moderate pulmonary hypertension, cardiac output varies with both left and right ventricular performance. In these cases, the normal relationships between central venous pressure and PAOP may be altered, so that central venous pressure is no longer an indicator of left ventricular preload. Monitoring both central venous pressure and PAOP and observing the response to volume administration is the best method for accurately assessing preload in patients with pulmonary hypertension. Intraoperative volume assessment can be performed with transesophageal echocardiography, which demonstrates the filling of both ventricles.

Pulmonary artery catheterization may be valuable for perioperative management of the pulmonary hypertension patient. First, it allows measurement of both central venous pressure and PAOP and determination of preload. Second, it allows measurement of cardiac output and calculation of pulmonary and systemic vascular resistance. Third, it allows measurement of pulmonary artery pressure, which is necessary for proper management of systemic hypotension or the use of pulmonary vasodilator therapy. The measurement of mixed venous oxygen saturation allows continuous assessment of arterial oxygenation and cardiac output in patients with pulmonary hypertension. The risk of pulmonary artery catheterization in patients with pulmonary hypertension is increased because of the high mortality of associated arrhythmias, pulmonary artery rupture, and venous air embolism or thromboembolism. In addition, thermodilution cardiac output determinations may be misleading when pulmonary hypertension is associated with anatomic shunting or significant tricuspid regurgitation. If there is a left-to-right shunt, thermodilution will measure pulmonary, rather than systemic, blood flow since the cold indicator will be diluted by shunted blood. If there is a right-to-left shunt, thermodilution will measure systemic rather than pulmonary blood flow, since some of the cold indicator will pass through the shunt. Pulmonary artery catheterization is usually not indicated in patients with intracardiac shunting because of the high risk of catheter misdirection and the limited additional information over measurement of central venous pressure alone.

Choice of Anesthetic Technique
All types of anesthetic techniques have been successfully used in individual pulmonary hypertension patients. The choice of anesthetic technique is usually based on pathophysiological considerations. Since general anesthesia in pulmonary hypertension patients has significant risks, limited regional anesthesia (eg, axillary block for upper extremity surgery, ankle block for foot surgery) should be considered when appropriate. The use of neuraxial regional techniques (spinal or epidural block) with sympatholytic effects may decrease systemic vascular resistance and produce systemic hypotension when cardiac output is fixed due to pulmonary hypertension. Thus, spinal anesthesia may be contraindicated in most patients. Epidural anesthesia has been successful in selected patients, particularly when the magnitude of the block is limited, eg, in management of labor. Epidural anesthesia allows a slow onset of block and titration of the extent of block so that adverse hemodynamic effects may be recognized early and corrected. However, extreme caution is mandatory to avoid excessive sympatholytic effects.
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INDICATIONS AND USES: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension in patients with World Health Organization (WHO) Functional Class III or IV symptoms, who have evidence of either right ventricular hypertrophy on echocardiography or a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest, and who are in need of additional therapy to improve functional capacity, exercise tolerance, and survival. In patients with WHO Functional Class III, a decrease in the mean pulmonary artery pressure of at least 10 mm Hg has been observed.

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PRECAUTIONS: Hematologic Changes: TRACLEER® is associated with decreases in hemoglobin, primarily after the first year of treatment. In placebo-controlled trials of patients with pulmonary arterial hypertension, a dose-related decrease in hemoglobin was observed. The decrease was more pronounced in patients treated with bosentan 250 mg b.i.d. compared to patients treated with bosentan 125 mg b.i.d. Patients with symptomatic anemia should be managed, and if indicated, transfusion therapy may be considered. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferase and bilirubin levels.

Elevations in Bilirobin: In two placebo-controlled studies of patients with pulmonary arterial hypertension, decreases in bilirubin levels of more than 2 x upper limits of normal (ULN) were observed in 1% of bosentan-treated patients and 0% of placebo-treated patients. The elevations were transient and usually were not clinically relevant. However, clinicians should monitor these patients closely, and if necessary, monitor bilirubin levels at least every 2 weeks. If bilirubin levels increase to more than 2 x ULN, the dose of bosentan should be reduced or treatment interrupted. If bilirubin levels remain at or above 2 x ULN after the dose has been reduced, bosentan treatment should be stopped.

Treatment of Hematologic Changes: If a decrease in hemoglobin to ≤ 10 g/dL occurs, the treatment should be interrupted or stopped, and the dose of bosentan should be reduced. If the decrease is ≥ 2 g/dL, bosentan treatment should be stopped. If the decrease is ≥ 3 g/dL, bosentan treatment should be stopped, and the dose of bosentan should be reduced. If the decrease is ≥ 4 g/dL, bosentan treatment should be stopped.

Hepatic Injury: TRACLEER® is associated with elevations in serum aminotransferase levels. In placebo-controlled studies of patients with pulmonary arterial hypertension, elevations of ALT and/or AST by more than 5 x ULN were observed in 1% of bosentan-treated patients and 0% of placebo-treated patients. The elevations were transient and usually were not clinically relevant. However, clinicians should monitor these patients closely, and if necessary, monitor aminotransferase levels at least every 2 weeks. If ALT or AST levels increase to more than 5 x ULN, treatment should be stopped. If ALT or AST levels increase to more than 3 x ULN, the daily dose of bosentan should be reduced by 25% or treatment should be interrupted. If ALT or AST levels increase to more than 2 x ULN, treatment should be interrupted. If ALT or AST levels increase to more than 1 x ULN, treatment should be stopped.

If aminotransferase levels increase to more than 2 x ULN, treatment should be stopped. If aminotransferase levels increase to more than 3 x ULN, the daily dose of bosentan should be reduced by 25% or treatment should be interrupted. If aminotransferase levels increase to more than 4 x ULN, treatment should be stopped.

If aminotransferase levels increase to more than 5 x ULN, treatment should be stopped. If aminotransferase levels increase to more than 3 x ULN, the daily dose of bosentan should be reduced by 25% or treatment should be interrupted. If aminotransferase levels increase to more than 2 x ULN, treatment should be interrupted. If aminotransferase levels increase to more than 1 x ULN, treatment should be stopped.

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If aminotransferase levels increase to more than 5 x ULN, treatment should be stopped. If aminotransferase levels increase to more than 3 x ULN, the daily dose of bosentan should be reduced by 25% or treatment should be interrupted. If aminotransferase levels increase to more than 2 x ULN, treatment should be interrupted. If aminotransferase levels increase to more than 1 x ULN, treatment should be stopped.
Thoracic epidural blockade has only minor hemodynamic effects but must be titrated slowly to avoid bradycardia. Excess sedation, which may decrease systemic vascular resistance and produce respiratory depression, should be avoided when regional anesthesia is used. Intrathecal and epidural narcotics may provide excellent pain relief postoperatively or during labor without sympathetic blockade or respiratory depression.

General anesthesia remains the method of choice for major surgery in patients with pulmonary hypertension. Several techniques of general anesthesia are possible. Potent inhalational agents may decrease systemic vascular resistance, contractility, and heart rate, thereby producing hypotension and low cardiac output. The marked reduction in contractility and the increased incidence of dysrhythmias that occur with halothane are poorly tolerated. Isoflurane, sevoflurane, and desflurane have less effect on contractility and may result in beneficial pulmonary vasodilation; however, the marked reductions in systemic vascular resistance may result in systemic hypotension. In patients with adequate functional reserve sevoflurane can be used as it is shorter-acting and more readily titratable than isoflurane and unlike desflurane does not produce tachycardia during rapid increases in concentration. Narcotic-nitrous oxide techniques maintain systemic vascular resistance, but may produce hypoxia and decreased contractility; in addition, nitrous oxide increases pulmonary resistance in patients with pulmonary hypertension.

“Balanced” anesthetic techniques may have all the above disadvantages but are frequently chosen as a means of limiting the adverse effects of a single technique. One anesthetic technique that maintains preload, systemic afterload, and contractility without increasing pulmonary vascular resistance is the high-dose narcotic-oxygen technique used in cardiac anesthesia. This appears to be the technique of choice in the patient with severe pulmonary hypertension undergoing major surgery. In addition to producing hemodynamic stability, the use of 100% oxygen may produce pulmonary vasodilation in some patients. In patients undergoing short procedures with intense stimulation such as bronchoscopy a remifentanil infusion can provide short-acting analgesia. The choice of induction agents for general anesthesia is based on similar considerations. Anesthetic induction of the patient with pulmonary hypertension is an unstable period during which patients are prone to develop systemic hypotension and cardiovascular collapse. In addition, patients with right-to-left anatomic shunting have markedly increased responses to intravenous agents and delayed response to inhalation agents. For rapid-sequence induction etomidate maintains systemic hemodynamics without affecting pulmonary resistance. In contrast, propofol produces some systemic hemodynamics, questions have been raised about possible increases in pulmonary vascular resistance with this agent. Studies suggest that there is little or no increase in pulmonary vascular resistance when ventilation is controlled, and that any increase that may occur with ketamine will be less than the increase in systemic vascular resistance. Ketamine is therefore unlikely to produce systemic hypotension or reverse a left-to-right anatomic shunt.

Ventilatory management may markedly affect pulmonary vascular resistance. Alveolar hypoxia is a potent pulmonary vasoconstrictor and use of high inspired oxygen concentrations may result in additional pulmonary vasodilation in some patients. Hypercarbia is a potent pulmonary vasoconstrictor, and hypocarbia is a pulmonary vasodilator. Hyperventilation may decrease the pulmonary hypertensive responses to various stimuli. Pulmonary vascular resistance is dependent on functional residual capacity (FRC), such that it is increased whenever FRC is increased from its normal value. Pulmonary vascular resistance increases when lung volumes above normal FRC result in compression of small intra-alveolar vessels. Pulmonary vascular resistance also increases when lung volumes below normal FRC produce increased large-vessel resistance due to hypoxic pulmonary vasoconstriction. Ventilatory parameters may affect both FRC and peak lung volume. FRC is usually decreased during general anesthesia. This reduction in FRC can be reversed with positive end-expiratory pressure (PEEP), resulting in a decrease in pulmonary vascular resistance. However, excessive PEEP will increase FRC above optimal values, and result in an increase in pulmonary vascular resistance. The effect of tidal volume on pulmonary vascular resistance may similarly be bimodal. At low tidal volumes increased resistance occurs due to alveolar hypoxia and hypercarbia. At high tidal volumes lung volume intermittently exceeds normal FRC, resulting in compression of intra-alveolar vessels and increased pulmonary vascular resistance. Therefore, ventilation of the patient with pulmonary hypertension should use high concentrations of oxygen, moderate tidal volumes, rates sufficient to achieve hypocarbia, and low levels of PEEP (5-10 cm H₂O). High-frequency ventilation has been advocated as a means of achieving adequate gas exchange, while maintaining lung volume continuously at normal FRC.

Management of emergence from anesthesia requires maintaining hemodynamic stability and adequate alveolar ventilation. The major factor responsible for hemodynamic stability is the ratio of pulmonary to systemic vascular tone. Extubation in a deep plane of anesthesia to avoid pulmonary vasoconstriction may be complicated by decreased systemic vascular resistance, decreased contractility, and inadequate ventilation (producing hypoxemia or hypercarbia and exacerbating pulmonary hypertension). In addition, reductions in FRC can increase pulmonary vascular resistance. Extubation in a light plane of anesthesia can result in marked sympathetic tone and severe pulmonary vasoconstriction. The addition of narcotics to a primarily inhalational technique may allow extubation in a light plane of anesthesia without increasing sympathetic tone. A narcotic-oxygen anesthetic technique followed by postoperative mechanical ventilation appears to be the safest technique for major surgery.

Pulmonary hypertension patients have limited ability to tolerate any further increase in pulmonary vascular resistance and it is important to avoid introduction of air or particulate matter (eg, precipitated drugs) into the venous system. In patients with anatomic shunting, such venous
embolization may result in systemic embolization, as well as provoking hemodynamic decompensation.

**Treatment of Perioperative Hypotension**

Pulmonary hypertension patients should have hemodynamic therapy aimed at maintaining blood pressure, cardiac output, and low pulmonary vascular resistance. When inotropic therapy is required agents such as dobutamine and milrinone, which increase cardiac output, maintain systemic blood pressure, and decrease pulmonary vascular resistance, are indicated. The management of systemic hypotension in the patient with pulmonary hypertension is based on principles of hemodynamic management. As shown in Table 1, systemic hypotension may result from four etiologies, each of which has a specific hemodynamic pattern.

Pulmonary artery catheterization allows differentiation among these etiologies. Decreased preload is the only etiology that decreases central venous pressure; volume therapy is the appropriate treatment. But volume loading of a failing right ventricle can result in further distention and progressive dysfunction and therefore must be monitored closely. Decreased contractility is the only condition that results in an increase in central venous pressure with a decrease in pulmonary artery pressure; inotropic therapy is indicated. Decreased systemic vascular resistance is the only condition in which cardiac output is maintained. Appropriate therapy may be a combination of systemic vasoconstrictors, inotropic agents, and pulmonary vasodilators. The use of vasopressin as a systemic vasoconstrictor has been recommended in some reports. A combined inotropic-vasopressor agent such as epinephrine or norepinephrine may be useful. Finally, if pulmonary artery pressure has increased or remained the same during systemic hypotension, then the elevated pulmonary vascular resistance is preventing generation of adequate cardiac output. The initial approach should be to detect any correctable causes of increased pulmonary vascular resistance such as hypoxia, hypercarbia, acidosis, increased sympathetic tone, and endogenous or exogenous vasoconstrictors. Patients without correctable factors should be considered candidates for acute pulmonary vasodilator therapy. Therefore, arterial blood gases should be measured and acid-base status corrected to baseline. When systemic hypotension occurs without a decrease in pulmonary artery pressure, cardiac output measurement will differentiate between a primary fall in systemic resistance (cardiac output increased or unchanged with no change in pulmonary vascular resistance) and worsened pulmonary hypertension (cardiac output decreased with increased pulmonary vascular resistance). A primary fall in systemic vascular resistance may be treated by either increasing cardiac output with inotropic agents or by achieving selective systemic vasoconstriction with phenylephrine, norepinephrine, or vasopressin.

When an increase in pulmonary vascular resistance produces decreased cardiac output and systemic hypotension, pulmonary vasodilator therapy is required to interrupt the cycle of pulmonary hypertension. This cycle is characterized by low cardiac output, systemic hypotension, and decreased right ventricular coronary perfusion with a further decrease in cardiac output; similarly, low cardiac output produces desaturation of mixed venous blood and acidosis, which result in increased pulmonary vasoconstriction. The goals of pulmonary vasodilator therapy are twofold: first, to reduce pulmonary vascular resistance and thereby decrease pulmonary artery pressure and/or increase cardiac output, and, second, to reduce the PVR/SVR ratio so that the increase in cardiac output will prevent hypotension by compensating for any reduction in systemic vascular resistance. Essentially all agents with systemic vasodilator activity (alpha-blockers, beta-agonists, acetylcholine, direct smooth muscle vasodilators, calcium channel blockers, prostacyclin, prostaglandin E1) are capable of producing pulmonary vasodilation. However, use of these agents as pulmonary vasodilators has frequently resulted in systemic hypotension. In pulmonary hypertension, cardiac output varies with right heart function. Both the pulmonary and systemic vasodilator effects of drugs are dose-dependent. For the majority of drugs, systemic vasodilator effects occur at doses that do not produce pulmonary vasodilation. Thus, with a decrease in systemic and no change in pulmonary vascular resistance, cardiac output cannot rise and systemic blood pressure must fall (BP = CO x SVR).

**Table 1. Hemodynamic Patterns of Four Etiologies of Systemic Hypertension.**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>CVP</th>
<th>PAP</th>
<th>PAOP</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased PVR</td>
<td>↓</td>
<td>→</td>
<td>or ↓</td>
<td>≠ or →</td>
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<tr>
<td>Decreased preload</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Decreased contractility</td>
<td>≠</td>
<td>↓</td>
<td>≠</td>
<td>↓</td>
</tr>
</tbody>
</table>

CO = cardiac output; CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

Advances in Pulmonary Hypertension
does not produce systemic vasodilation because any nitric oxide that is absorbed into the pulmonary circulation is inactivated by binding to hemoglobin. In addition, inhaled nitric oxide may improve ventilation-perfusion matching in lung disease. Unlike intravenous vasodilators, which may increase blood flow to poorly ventilated alveoli, inhaled vasodilators are preferentially distributed to ventilated alveoli. By increasing blood flow to ventilated alveoli, there is an improvement in ventilation-perfusion matching and gas exchange. Inhaled nitric oxide effectively decreases perioperative pulmonary hypertension in multiple settings, particularly following cardiopulmonary bypass when pulmonary vascular resistance may be elevated due to pulmonary endothelial dysfunction. Inhaled nitric oxide may be useful in patients with allograft dysfunction following lung transplantation since nitric oxide may decrease pulmonary hypertension, improve ventilation-perfusion mismatch, and decrease ischemia-reperfusion lung injury. Inhaled nitric oxide improves outcome in neonatal pulmonary hypertension with hypoxic respiratory failure as judged by a decreased frequency of death or extracorporeal membrane oxygenation use. Although inhaled nitric oxide improves oxygenation and decreases pulmonary hypertension in the acute respiratory distress syndrome, randomized studies have not demonstrated sustained improvement or improved outcome. Patients with hypoxemia may not improve oxygenation with inhaled nitric oxide if the vascular tone in well-ventilated segments is not increased above basal levels. In such cases, combination of inhaled nitric oxide with almitrine bis mesylate or possibly phenylephrine may improve hypoxemia without producing excessive pulmonary hypertension.

In general, the inhaled nitric oxide dose-response curve in patients with pulmonary hypertension demonstrates maximal responses at doses of 10 ppm or less and, in the perioperative setting, a trial of 20 ppm inhaled nitric oxide is usually sufficient to determine if the patient will have a beneficial response. Discontinuation of inhaled nitric oxide may produce rebound pulmonary hypertension, which limits its utility in the perioperative setting. Rebound pulmonary hypertension may be due to progression of underlying pulmonary hypertension, decreased endogenous nitric oxide synthesis, downregulation of guanylyl cyclase, or activation of endogenous vasoconstrictor pathways such as endothelin. Approximately one third of pulmonary hypertension patients have little or no response to inhaled nitric oxide. Possible explanations include an unreactive pulmonary circulation, rapid inactivation of nitric oxide, abnormalities in the guanylyl cyclase system, or rapid metabolism of cGMP. Inhibition of cGMP phosphodiesterase with sildenafil can increase the frequency, the magnitude, and the duration of response to inhaled nitric oxide.

Other inhaled vasodilators may also produce selective pulmonary vasodilation. These include nitrovasodilators (nitroglycerin, nitroprusside) and prostaglandin derivatives such as prostacyclin, prostaglandin E, and iloprost. The use of a combination of agents that affect different mechanisms of vasodilation (eg, nitric oxide, which increases cGMP and prostacyclin, which increases cAMP) may produce additive pulmonary vasodilation. Patients undergoing cardiac surgery who develop intractable right ventricular failure due to pulmonary hypertension may be candidates for a right ventricular assist device, either on a temporary basis until right ventricular function recovers or as a bridge to transplantation.

**Postoperative Management**

Although the focus in the literature has been on intraoperative management of pulmonary hypertension, most patients who die in the perioperative period do so several days after surgery. Causes of death include progressive increases in pulmonary vascular resistance, progressive decreases in myocardial function, and sudden death. Patients should therefore be monitored in an appropriate setting. Deepening of the level of sedation/anesthesia may be effective in selected patients. The use of epidural narcotics, limited thoracic epidural local anesthetics, continuous regional anesthesia, and non-narcotic analgesic adjuvant should be considered for pain management when appropriate.

In summary, pulmonary hypertension patients have markedly increased morbidity and mortality during anesthesia and surgery. However, management based on physiologic principles can allow the majority of patients to safely undergo required surgical procedures.

**References**

Managing Right Ventricular Failure in PAH: An Algorithmic Approach

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Pulmonary arterial hypertension (PAH) is a disorder characterized by progressive elevation of pulmonary artery pressure (PAP) and vascular resistance in the absence of left-sided cardiac disease, pulmonary vein compression, respiratory disorders, or thromboembolic disease. It is defined by a mean PAP over 25 mmHg at rest or over 30 mmHg with exercise and a pulmonary artery occlusion pressure (PAOP) of less than 15 mmHg. PAH is associated with a poor prognosis. The estimated median survival from diagnosis is 2.8 years and the 1-year and 5-year survival rates are only 68% and 34%, respectively. More than 70% of PAH patients will die as a result of right ventricular failure and most of the remainder from dysrhythmia. Predictors of a poor prognosis in PAH are related to the development of right ventricular failure. The objectives of this review are to examine the pathophysiologic mechanisms leading to the development of right ventricular failure due to PAH, the diagnostic features of right ventricular failure, and the management of chronic right ventricular failure with emphasis on acute decompensation in this setting.

Pathophysiology

Clinical Manifestations and Hemodynamic Derangements

The normal right ventricle is a thin-walled (less than 0.6 cm), trabeculated, roughly triangular structure that weighs less than 65 g in men and less than 50 g in women. It is designed to empty its volume into a low-impedance, high-capacitance, pulmonary circulation by contracting sequentially from inflow to outflow. The pulmonary circulation can tolerate three- to fourfold increases in right-sided cardiac output without significant increases in PAP. In healthy individuals, pulmonary vascular resistance (PVR) decreases as the cardiac output rises with exercise. In the setting of PAH, PVR does not sufficiently decrease with exercise, resulting in dyspnea and poor exercise capacity.

Progressive PAH presents a pressure overload state to the right ventricle, increasing right ventricular workload leading to concentric hypertrophy (Figure 1). The right ventricle compensates: the walls hypertrophy while maintaining a normal or smaller chamber size, resulting in normal or reduced right ventricular wall stress. During this compensated phase of adaptive hypertrophy and normal to reduced wall stress, the ventricle is able to eject blood against the high PVR while maintaining an adequate right-sided cardiac output and normal right atrial pressure. During this phase patients exhibit few symptoms.

The right ventricle can compensate only so long, initiating the symptomatic/declining phase (Figure 1). During this phase, with marked, maladaptive right ventricular hypertrophy and variable degrees of interstitial fibrosis, diastolic function may be impaired, altering the right ventricular diastolic pressure-volume relationship and leading to increases in right ventricular end-diastolic and right atrial pressures. With persistent pressure overload, the right ventricle undergoes a remodeling process eventually leading to right ventricular failure. The right ventricular chamber dilates and the concentric hypertrophy transitions to eccentric hypertrophy, resulting in increased wall stress and systolic dysfunction. Increased heart rate and right ventricular wall stress lead to significant increases in right ventricular myocardial oxygen consumption. This, in combination with reduced right ventricular endomyocardial coronary perfusion (due to reduced right coronary artery pressure, rising right ventricular end-diastolic pressure, and increased right ventricular mass), leads to right ventricular ischemia and worsening right ventricular diastolic and systolic function. The right ventricular ischemia may be clinically manifest as chest pain. As the right ventricle and the tricuspid valve annulus dilate, functional tricuspid regurgitation progressively worsens. Tricuspid regurgitation further compromises right ventricular forward output, and ultimately, left ventricular filling. During this phase of right ventricular remodeling, cardiac output does not meet peripheral demands and right atrial pressure rises further as reflected clinically by exercise intolerance, progressive dyspnea, elevated jugular venous pressure, and fluid retention with edema (the hallmarks of right ventricular failure). These clinical signs reflect both a low cardiac output and the detrimental activation of neurohormones and other mediators. Natriuretic peptide levels become significantly elevated in patients with right heart failure even in the absence of left ventricular dysfunction. B-type natriuretic peptide levels become significantly elevated in patients with right heart failure even in the absence of left ventricular dysfunction.
ic peptide (BNP) levels increase in proportion to the extent of right ventricular dysfunction in PAH and are predictive of mortality in right ventricular failure.\textsuperscript{10,11}

Progressive right ventricular dilation in the setting of pericardial constraint and diastolic ventricular interdependence compromise left ventricular filling via several mechanisms.\textsuperscript{7,12,13} A shift of the ventricular septum during diastole toward the left ventricle reduces left ventricular compliance and diastolic filling. As the right ventricle dilates in association with increases in right ventricular and right atrial diastolic pressure, a marked rise in intrapericardial pressure ensues. The transmural left ventricular end-diastolic pressure (end-diastolic pressure minus intrapericardial pressure), the true preload of the left ventricle, is reduced and by the Frank-Starling relationship results in low systemic cardiac output. Furthermore, with marked elevation in right atrial pressure the coronary sinus pressure also rises, resulting in left ventricular myocardial congestion and wall dimensions that limit left ventricular compliance. This mechanism appears to act independently of diastolic ventricular interaction due to pericardial constraint.\textsuperscript{14} As a consequence of decreased left ventricular preload, systemic cardiac output is further compromised, first with exercise only but eventually even at rest. It should be noted that with extreme right ventricular failure and dilation, left ventricular compliance can be so severely impaired that at a certain point the left ventricular end-diastolic pressure (LVEDP) and PAOP may rise due to a shift of the left ventricular diastolic pressure volume relationship upward and to the left such that even with low left ventricular volume the left ventricular pressure is increased.

The \textit{decompensated phase} of right ventricular systolic failure is manifest as symptoms with minimal activity or at rest. It is marked by elevation in right atrial pressure and systemic venous hypertension leading to hepatic congestion, which combined with tricuspid regurgitation, leads to an enlarged, pulsatile liver and ascites. A right ventricular S\textsubscript{3} gallop may be audible and renal and splanchnic congestion can cause diuretic resistance. Renal venous congestion combined with decreased renal arterial perfusion will be exhibited as diuretic resistance, reduced urine output, and prerenal azotemia.\textsuperscript{15} Also evident is a low cardiac output state resulting in fatigue and syncope or pre-syncope. In acute decompensated right ventricular failure (ADRVF) reduced cardiac output is evident by a narrow pulse pressure and hypotension with peripheral tissue and vital organ hypoperfusion. The latter increases the arterio-venous oxygen difference. Hypoxemia may also be the consequence of right to left shunting in PAH patients with a patent foramen ovale and elevated right atrial pressure. Further, the destruction of the cross-sectional pulmonary vascular bed (a pathologic consequence of protracted PAH) also contributes to
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  Marc Humbert, M.D., Ph.D., Service de Pneumologie, Centre des Maladies Vasculaires Pulmonaires, Hôpital Antoine Béclère

- **MR Imaging in Pulmonary Arterial Hypertension**
  Valentín Fuster, M.D., Ph.D., Zena and Michael A. Wiener Cardiovascular Institute, Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center

- **Current Experiences with Stress Echocardiography in Pulmonary Arterial Hypertension**
  Ekkehard Grünig, M.D., University of Heidelberg

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  John Newman, M.D., Vanderbilt Medical School

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hypoxemia and with reduction in peripheral oxygen delivery, acidosis, which can lead to life-threatening dysrhythmias, may ensue.

**Diagnostic Findings in Right Ventricular Failure in PAH**

Chest radiographs typically show enlarged pulmonary arteries and distal tapering of the peripheral vessels and on lateral view an enlarged right ventricle can be visualized by filling of the retrosternal space. The electrocardiogram in advanced stages of pulmonary hypertension and right ventricular failure may reveal right axis deviation, RBBB, p wave amplitude of more than 2.5 mm, and/or S1Q3T3 pattern reflective of pressure overload state on the right ventricle. The R wave will be prominent in V1 with deep S waves in the lateral precordial leads indicating right ventricular hypertrophy. Increased p wave amplitude in lead II, qR pattern in lead V1, and right ventricular hypertrophy are associated with an increased risk of death.16

Transthoracic echocardiography is the most useful and readily available noninvasive tool to evaluate right ventricular failure due to PAH. Typically the right ventricle is hypertrophied and dilated with poor systolic function and the right atrium is enlarged while the left ventricle is small and underfilled. In a cross-sectional view, the left ventricle appears “D” or crescent shaped as the ventricular septum displaces or “flattens” toward the left ventricle. Septal flattening during systole suggests right ventricular pressure overload, whereas septal flattening during diastole occurs with volume overload (tricuspid regurgitation). Typically in right ventricular failure, septal flattening occurs throughout the cardiac cycle due to both right ventricular pressure and volume overload. The left ventricle contracts normally or is hyperdynamic. However, the diastolic transmitral filling characteristics are abnormal due to reduced left ventricular compliance. Patients with right ventricular failure have Doppler evidence of significant tricuspid regurgitation and moderately to severely elevated pulmonary artery systolic pressure (PAPs). The PAPs is estimated from the peak tricuspid regurgitant velocity and an estimate of right atrial pressure based on inferior vena cava size and respiratory dynamics. In right ventricular failure, the inferior vena cava is plethoric and does not collapse with inspiration, indicative of high right atrial pressure. Pulse wave Doppler in the right ventricular outflow tract typically reveals a reduced velocity-time integral suggestive of low forward output. Agitated saline contrast not only will aid in the diagnosis of some congenital systemic-to-pulmonary shunts, but may also detect a patent foramen ovale in one third of patients. Echocardiographic predictors of a poor prognosis include an enlarged right atrium, the presence of a pericardial effusion, and a higher Doppler global right ventricular index.3,4,17

**Pulmonary Artery Catheterization**

In right ventricular failure associated with PAH pulmonary artery catheterization will reveal high right atrial, right ventricular, and pulmonary arterial pressures with a PAOP of greater than 15 mmHg. The cardiac and stroke volume indices are reduced and the mixed venous oxygen saturation is generally markedly reduced. With end-stage right ventricular failure, paradoxically the PAP may not be severely elevated and may actually fall as right ventricular ejection and the cardiac output are so compromised that the right ventricle cannot generate a high pulmonary pressure in the setting of high PVR.18 Ultimately in the throes of severe right ventricular dilation and failure, the PAOP may be elevated as left ventricular compliance is severely compromised with perturbation of the left ventricular diastolic-pressure volume relationship.

Pulmonary artery catheterization is useful not only for the diagnosis of right ventricular failure due to PAH but also for its management. In the case of systemic hypoperfusion and hypotension, catheterization can often identify the hemodynamic mechanism for the hypotension. Blood pressure is the product of cardiac output and SVR and hypotension in patients with PAH may be a result of either low cardiac output from right ventricular failure or reduced SVR from overvasodilation or infection. Precise identification of the operative hemodynamic derangement will guide therapy in right ventricular failure due to PAH.

**Chronic and Acute RV Failure in PAH**

**Goals of Therapy**

The goals of treating chronic right ventricular failure due to PAH are to 1) relieve symptoms, improve exercise capacity, and quality of life; 2) reduce morbidity and mortality; and 3) improve cardiopulmonary hemodynamics to prevent worsening of right heart failure (ie, delay disease progression). The immediate goals of treating acute decompensated right ventricular failure (ADRVF), especially with hemodynamic compromise, are to 1) restore oxygenation; 2) treat volume overload; and 3) restore vital organ perfusion. The intermediate and long-term goals are to optimize the medical regimen to alleviate symptoms, prevent further disease progression, reduce morbidity and mortality, and successfully bridge the patient to lung or heart-lung transplantation in appropriate individuals.7,8

**Chronic RV Failure: Medical Therapies**

The long-term goals of managing chronic right ventricular failure in PAH can be reached by applying the approaches delineated in Table 1 that have been reviewed elsewhere.8,19-21 Strategies to prevent and treat chronic right ventricular failure are aimed at reducing right ventricular wall stress, thereby minimizing myocardial oxygen consumption and ischemia, and to improve the inotropic state of the right ventricle. To reduce wall stress, one must lower right ventricular afterload. This is accomplished with chronic pulmonary arterial vasodilators: O2 therapy, endothelin receptor antagonists, prostanooids, and phosphodiesterase V inhibitors as described in recent reviews.19,20 Calcium channel blockers should be avoided in patients with marginal blood pressure and significant right heart failure as manifest by right atrial pressures greater than 15 mmHg and low cardiac index (less than 2.0 L/min/m²). Chronic anticoagulation is recommended to prevent pulmonary arterial thrombosis in situ, which contributes to narrowing and remodeling of the pulmonary arterial bed, consequently increasing right ventricular outflow impedance.22

Reduction in right ventricular preload and tricuspid regurgi-
Invasive interventions

- Percutaneous blade-balloon atrial septostomy
- Heart-lung transplantation for complex congenital heart disease
- Pulmonary vasodilators (endothelial receptor antagonists, prostanoids, PDE-5 inhibitors)
- Supplemental oxygen
- Anticoagulation (maintain INR 2-3)

Interventions for treatment of pulmonary arterial hypertension

- Pulmonary vasodilators (endothelial receptor antagonists, prostanoids, PDE-5 inhibitors)
- Supplemental oxygen
- Anticoagulation (maintain INR 2-3)

Table 1. Management of Chronic Right Ventricular Failure in Pulmonary Arterial Hypertension.

<table>
<thead>
<tr>
<th>Diet and lifestyle considerations</th>
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<tbody>
<tr>
<td>• Sodium restriction</td>
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<tr>
<td>• Smoking cessation</td>
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<tr>
<td>• Weight loss</td>
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<tr>
<td>• Avoidance of physical exertion in setting of pre or frank syncope</td>
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<td>• Avoidance of pregnancy</td>
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<td>• Avoidance of high altitude</td>
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<tr>
<th>Pharmacologic interventions for right ventricular failure</th>
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<tbody>
<tr>
<td>• Reduction of wall stress by decreasing excessive preload</td>
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<tr>
<td>– Diuretics: loop, thiazide, and aldosterone antagonists</td>
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<td>• Improve inotropy and reduce neurohormonal activation</td>
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<td>– Digitalis glycosides</td>
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<th>Invasive interventions</th>
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<td>• Lung transplantation</td>
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Diet and lifestyle considerations:

- Sodium restriction
- Smoking cessation
- Weight loss
- Avoidance of physical exertion in setting of pre or frank syncope
- Avoidance of pregnancy
- Avoidance of high altitude

Interventions for treatment of pulmonary arterial hypertension:

- Pulmonary vasodilators (endothelial receptor antagonists, prostanoids, PDE-5 inhibitors)
- Supplemental oxygen
- Anticoagulation (maintain INR 2-3)

Pharmacologic interventions for right ventricular failure:

- Reduction of wall stress by decreasing excessive preload
  - Diuretics: loop, thiazide, and aldosterone antagonists
- Improve inotropy and reduce neurohormonal activation
  - Digitalis glycosides

Invasive interventions:

- Lung transplantation
- Heart-lung transplantation for complex congenital heart disease
- Percutaneous blade-balloon atrial septostomy

Atrial septostomy. It is well known that patients with PAH and a patent foramen ovale have a better prognosis compared to those without a patent foramen ovale. The interatrial communication allows right to left shunting, thus reducing right atrial pressure and improving left ventricular filling and cardiac output, delaying progression of right ventricular failure. Percutaneous blade-balloon atrial septostomy is a catheter-based technique that allows the creation of a perforation in the atrial septum allowing shunting of blood from right to left. It has been utilized in select patients with right ventricular failure and syncope. Atrial septostomy has been shown to improve clinical status and produce beneficial long-lasting hemodynamic effects. The procedure is limited by systemic arterial oxygen desaturation, spontaneous closure of the atrial septal aperture, the potential for paradoxical embolic events, and a high procedure-related mortality. This investigational procedure should be performed only by experienced operators. It should not be performed in moribund patients or in those who have severe right ventricular failure and are on maximal cardiopulmonary support. A right atrial pressure greater than 20 mmHg, a PVR index greater than 55 u/m² and a predicted 1-year survival less than 40% are significant predictors of procedure-related death. Furthermore, patients should have an acceptable baseline systemic oxygen saturation (greater than 90% on room air). The procedure is indicated for recurrent syncope or right ventricular failure, despite maximal medical therapy, when no other options exist and/or as a bridge to lung transplantation. Extracorporeal membrane oxygenator systems in conjunction with atrial septostomy in a low cardiac output patient with hypoxemia have not been studied, but could theoretically be of value.

Transplantation. Bilateral lung transplantation or heart-lung transplantation for patients with complex congenital heart disease may be indicated for suitable candidates with chronic right ventricular failure who continue to deteriorate with poor quality of life despite aggressive pharmacologic therapy. With bilateral lung transplantation, survival is 70%, 45%, and 20%; with heart-lung transplantation, it is 65%, 40%, and 25% at 1 year, 5 years, and 10 years, respectively. Long-term survival is predominantly limited by the development of post-transplant bronchiolitis obliterans.

ADRVF: Identification and Correction of Precipitating Factors

Factors that may precipitate ADRV in patients with chronic right ventricular failure must be sought and corrected (Figure 2). These include dietary indiscretion, intercurrent infection, anemia/erythrocytosis, thyroid disorders, concomitant pulmonary embolus, and dysrhythmias. Infection must be considered in patients presenting with decompensated right ventricular failure and hemodynamic compromise, especially in patients with an indwelling central venous catheter for epoprostenol infusion. Infection is poorly tolerated in patients with right ventricular failure and limited right ventricular contractile reserve. The increase in right ventricular work associated with reduction in SVR will result in systemic hypotension. This scenario, beta- and alpha- agonists such as dopamine or norepinephrine are indicated as initial therapy to stabilize hemodynamics. Anemia also increases right ventricular work and it has been shown to be associated with worse quality of life and increased mortality in patients with PAH.
Erythrocytosis is associated with higher viscosity and more cardiovascular events in patients with Eisenmenger syndrome and cor pulmonale from respiratory disorders.8 Specifically, higher hemoglobin levels are associated with worse cardiopulmonary function. Ventricular dysrhythmias usually occur in end-stage right ventricular failure.

Atrial tachyarrhythmias should be slowed with digoxin, amiodarone, or diltiazem. The use of beta-blockers or the calcium blocker verapamil should be avoided as their negative inotropic effects may exacerbate the low cardiac output state while vasodilatory effects may reduce the SVR and cause hypotension. Amiodarone is relatively safe in this setting and is useful for the management of atrial fibrillation with rapid ventricular response to slow the rate as well as to facilitate electrical or chemical cardioversion to sinus rhythm. With symptomatic bradydysrhythmias, temporary and/or permanent pacemaker insertion should be considered in the appropriate situation. Ventricular dysrhythmias usually occur in end-stage right ventricular failure.

Identify and treat underlying precipitating factors
- Dietary indiscretion
- Infection
- Anemia/erythrocytosis
- Thyroid disorders
- Pulmonary embolus

Restore oxygenation
- Supplemental O₂
- Vapotherm
- Mechanical ventilation - Avoid acidemia

Restore vital organ perfusion
- Pulmonary vasodilators:
  - IV epoprostenol
  - Combination therapy
  - Inotropes and vasopressors:
    - Adrenergic agonists
    - Add or Δ to IV epoprostenol

Treat volume overload
- IV bolus + IV infusion loop diuretic
- IV or oral thiazide diuretic
- Oral aldosterone antagonist
- Addition of β-adrenergic inotropic agent
- Mechanical fluid removal

Stabilization achieved

Transition to chronic therapy
- Wean NO with IV epoprostenol
- Wean IV inotropic agents
- Optimize chronic therapies (Table 1)

Unstable and/or refractory cases (not candidates for lung transplantation)
- Palliation of symptoms
  - Oxygen supplementation
  - Diuretics
  - Continuous infusion inotropes
  - Liberal use narcotic analgesics
  - Hospice care

Bridge to lung transplantation (suitable candidates)
- IV epoprostenol + other pulmonary vasodilators
- Inotropic support (digoxin, β-adrenergic agonists)
- Diuretic therapy
- Percutaneous atrial septostomy

Figure 2.—Factors that may precipitate ADRVF in patients with chronic right ventricular failure must be sought and corrected.

ADRVF: Restoration of Oxygenation and Prevention of Acidemia
Oxygen is a pulmonary vasodilator and maintenance of adequate oxygenation in right ventricular failure due to PAH is of paramount importance. High-flow oxygen has been shown to reduce PVR and increase cardiac index even in normoxic patients with pulmonary hypertension30 and should be applied liberally in patients with right ventricular failure or hypoxemia. Vapotherm is a high-flow oxygen delivery device that heats and humidifies oxygen for use with a nasal cannula, face mask, or tracheostomy mask at flow rates of 6 to 14 L/min that may provide adequate oxygen delivery without having to use positive pressure.31 Mechanical ventilation may be required for cardiorespiratory collapse due to ADRVF in order to maintain adequate oxygenation. However, by increasing transpulmonary pressures, especially with positive end expiratory pressure (PEEP), mechanical ventilation may increase right ventricular afterload and decrease right ventricular stroke volume, aggravating right ventricular failure and potentially exacerbating hepatic, splanchnic, and renal congestion.7 The ventilator should be set to the lowest possible PEEP and acidemia, a potent pulmonary vasoconstrictor, should be
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_Fernando Torres, MD_  
Director Pulmonary Hypertension Clinic  
UT Southwestern Medical Center- Dallas

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_Myung H. Park, MD, FACC_  
Director, Pulmonary Hypertension Vascular Disease Program  
Assistant Professor of Medicine  
University of Maryland School of Medicine  
Baltimore, Maryland

Allied Health Professionals… please go to page 29 for information on PH Resource Network, PHA’s membership section for non-physician medical professionals.
avoided. Small degrees of alkalemia may be beneficial.32

**ADRVF: Restoration of Vital Organ Perfusion**

In the setting of ADRVF with hypotension once emergent measures have been applied to stabilize the patient, pulmonary arterial catheterization should be considered to identify the hemodynamic mechanism for the hypotension and to guide therapy. Pharamacologic therapy to reduce right ventricular afterload and/or increase inotropy should be promptly and aggressively administered to avoid vital organ damage. Inhaled nitric oxide (via endotracheal tube or by face mask) up to 40 ppm can be administered.33,34 Inhaled nitric oxide is a selective pulmonary vasodilator that reduces the PVR via the cyclic guanosine monophosphate system without affecting the SVR as it is quickly inactivated by hemoglobin.33 With the reduction in pulmonary afterload the cardiac output increases and the blood pressure can stabilize.34 Alternatively, inhaled epoprostenol or iloprost may be considered, but unlike inhaled nitric oxide, these agents can exert systemic vascular effects.35-37 Once stabilized patients can be transitioned to intravenous epoprostenol which has pulmonary vasodilator properties and may exert inotropic effects on right ventricular function.38 Continuous intravenous infusion of epoprostenol should be started at 1 ng/kg/min and titrated by 0.5 to 1 ng/kg/min every 30 minutes while maintaining a systolic blood pressure of greater than 80 mmHg, until a maximum tolerated dose is reached. This point is usually marked by the development of hypotension or other dose-limiting side effects such as headache, nausea/vomiting, diarrhea, myalgias, arthralgias, and trismus. If the patient maintains an adequate systemic blood pressure and cardiac output, inhaled nitric oxide can be weaned slowly by 5 ppm increments until a dose of 5 ppm is reached. Thereafter, nitric oxide should be weaned by 1 ppm increments until off to prevent rebound increases in pulmonary hypertension. While administering nitric oxide, methemoglobin levels must be monitored every 6 hours and maintained at less than 5% of hemoglobin to avoid methemoglobin toxicity.39

Nitric oxide and epoprostenol may be used together in refractory cases, given that the combination may be additive as they exert their effects via different cyclic nucleoside pathways. It must be emphasized that if an acute effect to epoprostenol is not apparent, the therapy should not be abandoned (provided multiorgan failure has not occurred) as its benefits may be delayed. The effects of epoprostenol on the pulmonary circulation will take time (weeks) and prove to be effective while the cardiac output and blood pressure are supported with inotropic agents to avoid vital organ hypoperfusion. In addition to its pulmonary vasodilator effects epoprostenol may exert positive right ventricular inotropic effects via activation of the cyclic adenosine monophosphate pathway.38 It should replace or be added to any chronic oral or inhalational pulmonary vasodilator agent the patient may already be receiving for PAH when ADRVF supervenes. Intravenous epoprostenol can assist with the weaning process from inhaled nitric oxide and beta-adrenergic inotropes in severe right ventricular failure.

In ADRVF, low dose beta-adrenergic agents such as dobutamine or dopamine at 1 to 2 mcg/kg/min may improve cardiac output and restore vital organ perfusion.7 In the initial treatment of hypotension/hypoperfusion, dopamine or norepinephrine should be considered to restore right ventricular function, systemic hemodynamics and coronary perfusion. These agents may be more beneficial than phenylephrine alone, which is a selective alpha-agonist.40 Phenylephrine with low-dose dobutamine is a combination that may be desirable in tachycardic patients with vital organ hypoperfusion. Manipulating these drugs separately will allow the clinician to attain specific hemodynamic effects. The institution of inotropic and vasopressor agents is a double-edged sword as they can increase right ventricular work and exert vasopressor effects on the pulmonary circulation. However, in the appropriate clinical situation they are essential to restore and maintain systemic perfusion. The lowest possible dose of these drugs should be utilized to minimize tachycardia, proarrhythmia, myocardial oxygen consumption and ischemia, and pulmonary vasoconstriction.

In patients with ADRVF, central venous congestion, and hypotension **volume infusion should not be employed**. The failing right ventricle is operating on the flat to descending portion of its Frank-Starling curve and further increase in right ventricular preload will not improve cardiac output and blood pressure. Volume loading will further dilate the right ventricle, resulting in worsening tricuspid regurgitation and right ventricular wall stress. In addition, as a result of diastolic ventricular interdependence imposed by pericardial constraint, volume loading will exacerbate the low systemic cardiac output state due to compromised left ventricular filling as previously discussed.41,42

The phosphodiesterase-3 inhibitor, milrinone, is an intravenous inodilator that should be avoided in right ventricular failure from PAH as its vasodilatory properties may overwhelm its inotropic effect. Milrinone may reduce the SVR without affecting the PVR in this patient population and may exacerbate systemic hypotension. By the same token, nitric oxide donors such as nitroprusside or nitrates should not be used in ADRVF due to PAH as they can exacerbate systemic hypotension.15

Although the recombinant B-type natriuretic peptide nesiritide is effective in pulmonary hypertension due to left-sided heart failure, it has not been shown to decrease PVR when administered acutely in patients with PAH with or without right ventricular failure.43 Data are lacking for this agent in PAH and concerns for systemic hypotension do not support use of nesiritide in this patient population at this time.

**ADRVF: Treatment of Volume Overload**

In severe right heart failure when diuretic resistance is operative, aggressive intravenous and combination diuretic therapy should be instituted. Diuretic resistance may result from 1) poor intestinal absorption of oral diuretic secondary to bowel wall edema; 2) pre-existing renal disease; 3) low cardiac output with renal arterial hypoperfusion and inadequate delivery of solute to the distal renal tubule; 4) renal arterial hypoperfusion combined with renal venous congestion resulting in reduced glomerular filtration; 5) tubular cell hypertrophy due to chronic diuretic use; 6) intense neurohormonal activation; and/or 7) concomitant administration of nonsteroidal anti-inflammatory agents or COX-2 inhibitors.44,45 Intravenous bolus loop diuretic therapy or a continuous infusion of loop diuretic (furosemide 5 to 20 mg/h, bumetanide 0.5 to 1 mg/h, and torsemide 5 to...
10 mg/h) after a priming bolus dose often overcomes the diuretic resistance. The constant infusion strategy will maintain a continuous renal threshold of drug without the peak and valleys of the higher dose intermittent bolus administration and effect a constant diuresis with less ototoxicity. If loop diuretic drip alone is ineffective, then intermittent intravenous chlorothiazide (not to exceed 2 gm over a 24 hour period) can be instituted. Intermittent metolazone can also be administered provided that absorption of the oral drug is felt to be adequate. The use of an aldosterone antagonist in conjunction with loop or thiazide diuretics will often be effective. Aldosterone antagonists should be avoided in patients with hyperkalemia and significantly compromised renal function. Electrolytes should be monitored closely with these agents.

In the patient who is markedly volume overloaded and not responding adequately to aggressive diuresis, or in whom the blood urea nitrogen and creatinine are rising, low dose dobutamine and dopamine should improve renal perfusion and potentiate diuresis. If diuretic manipulation with inotropic assistance fails to adequately deal with the volume overload, mechanical fluid removal usually with continuous venous-venous hemodialysis or other methods of ultrafiltration should be promptly employed to decompress the right ventricle, improve right ventricular performance and left ventricular preload, and reduce vital organ congestion.

Once hemodynamic stabilization has been achieved with the maneuvers delineated above, optimization of chronic therapy should be instituted. For patients who are suitable candidates for lung or heart-lung transplantation, strategies should be put in place to successfully bridge them to surgery. For those who are unstable and/or have refractory right ventricular failure and are not candidates for transplantation, the emphasis of care should shift to palliation of symptoms and hospice care when appropriate.

Conclusions
In patients with PAH, right ventricular failure is associated with a poor prognosis. Established therapies for PAH should be instituted early and optimized to prevent right ventricular failure. Diuretics are the mainstay of therapy for right ventricular failure and should be optimized. For patients who present with ADRF an aggressive approach should be undertaken. Pharmacologic therapy including oxygen, inhalational nitric oxide, epoprostenol, and inotropic support must be instituted rapidly to prevent vital organ hypoperfusion. Volume overload must be treated promptly to decompress the right ventricle and promote left ventricular filling. Sequential nephron blockade with intravenous loop and thiazide diuretics as well as aldosterone antagonists should be instituted. Mechanical fluid removal should be applied if diuretic therapy fails. In suitable patients who continue to deteriorate despite optimal medical therapy, prompt evaluation and listing for lung or lung-transplantation is indicated. At specialized centers, atrial septostomy should be considered for severe right ventricular failure, recurrent syncope, or as a bridge to lung transplantation. Intravenous epoprostenol and beta-adrenergic inotropic agents may be utilized in combination as a bridge to transplantation. For end-stage right ventricular failure, when all treatment options are exhausted or are inappropriate, the focus of management should transition to palliative care.

References


CASE 1:
A 42-year-old woman with HIV-related pulmonary arterial hypertension (WHO class II) presented to the emergency room with a 2-day history of fever, dysuria, lightheadedness, and increased abdominal girth. Her medications at home included continuous intravenous epoprostenol at a rate of 25 ng/kg/min, furosemide 80 mg po qd, and co-trimoxazole for PCP prophylaxis. Her heart rate (HR) was 140/min regular, blood pressure (BP) was 72/45 mmHg, she had an oxygen saturation of 95% on 3L/min nasal cannula and a temperature of 38 Celsius degrees. Her mucous membranes were moist; she had elevated jugular venous pressure and evidence of ascites. Cardiac examination revealed a right ventricular heave, loud P2, murmur of tricuspid regurgitation, and right-sided gallop. Lungs were clear to auscultation bilaterally, the liver was slightly enlarged, and she had suprapubic tenderness. Hickman line insertion site had no evidence of erythema or discharge. Electrocardiographic examination showed sinus tachycardia at a rate of 138/min, right axis deviation, and incomplete right bundle branch block. Chest radiography demonstrated cardiomegaly, but neither lung parenchymal infiltrates nor pleural effusions. Total white blood cell count was 14.5 x 1000/dL with 95% polymorphonuclear cells, and urinalysis showed numerous white blood cells, positive leukocyte esterase and nitrite. Blood urea nitrogen (BUN) was 32 mg/dL and serum creatinine (Cr) 1.8 mg/dL (baseline BUN/Cr = 16/0.9). Blood and urine cultures were collected. She was immediately given one liter of crystalloid infusion over 90 minutes, followed by a continuous infusion of normal saline at 100 mL/h and one dose of intravenous Piperacillin-Tazobactam. HR remained elevated at 135/min and BP remained low at 70/45 mmHg; she had minimal urine output and complained of worsening shortness of breath. Her pulmonary hypertension physician was called, the patient was transferred to the CCU, and intravenous fluids were discontinued. Repeat BUN at 4 hours was 38 mg/dL and Cr was 2.2 mg/dL. Urine Na was 25 mEq/L, with a fractional excretion of sodium of 0.22. Bedside echocardiogram showed right ventricular dilatation and severe dysfunction, enlarged right atrium, and a small pericardial effusion without tamponade physiology. She received 80 mg of furosemide intravenously and continuous infusion of dopamine at 2 mcg/kg/min and dobutamine at 3 mcg/kg/min. After 2 hours, BP increased to 85/55 mmHg, and she urinated 250 cc of urine. Dobutamine was increased in 1 mcg/kg/min increments to 5 mcg/kg/min over 3 hours and the patient was initiated on standing dose of intravenous furosemide 80 mg intravenously every 12 hours. Upon urine culture results that showed growth of *Klebsiella pneumoniae* sensitive to fluoroquinolones, the patient was transitioned to oral ciprofloxacin, after receiving 48 hours of intravenous antibiotics. Blood cultures were negative. Over the next 3 days, her BP remained stable at 95-100 mmHg/50-60 mmHg, HR of 95-110/min (sinus tachycardia), she was afebrile, and her respiratory status improved. She had good urine output, her oxygen supplementation requirement decreased and renal function returned to normal. Dopamine and dobutamine were tapered to off, intravenous furosemide converted to oral form, and she was discharged home on oral antibiotics after a 7-day hospital stay.

Discussion:
This case provides an example of acute right heart failure precipitated by an intercurrent urinary tract infection in a patient with pulmonary arterial hypertension who was relatively well controlled with intravenous epoprostenol. Patients with pulmonary arterial hypertension have little tolerance for any comorbidity, which can easily precipitate acutely decompenated right heart failure (ADRVF), particularly in cases with significant baseline right ventricular dysfunction. Even with another obvious source of infection (in this case, a urinary tract infection) patients receiving continuous intravenous prostacyclin through a central catheter who present with fever should have blood cultures done and receive empiric coverage for gram-positive organisms. Patients with ADRVF are usually hypotensive and tachycardic and in a low flow state. Any further increase in the right ventricular preload (such as with intravenous fluid administration) may
exacerbate right ventricular dysfunction, as it did in this case. The systemic hypotension that follows is due to decreased left ventricular filling from interventricular septal shift and decreased right ventricular output. Intravenous fluid administration should be done with great caution in patients with pulmonary hypertension and requires clear evidence of true intravascular fluid depletion, such as a history of recent fluid loss, dry mucous membranes, or drenching sweats with large insensible fluid loss. Patients who present in septic shock, particularly if it is complicated by cardiogenic shock, may be extremely difficult to manage and likely will require pulmonary artery catheterization to guide management. Decreased urinary output and evidence of pre-renal azotemia can be due to low cardiac output and cannot be considered evidence enough to begin intravenous fluid administration, as was the case in our patient.

The goal of BP support is to decrease the right ventricular dilatation and to directly improve the right ventricular contractility. Right ventricular dilatation is primarily decreased by administration of intravenous loop diuretics. Because of bowel edema, orally administered diuretics may be ineffective. By decreasing the right atrial size and pressure diuretics improve right ventricular filling and contractility, and in some cases, may be the only intervention required to improve systemic hemodynamics. Most patients, however, will benefit from direct right ventricular inotropic support and vasopressors, as in this case where low-dose dopamine and dobutamine were used. In patients with right ventricular failure dobutamine is the inotropic agent of choice, despite some potential direct pulmonary hypertensive effect. Milrinone may be more beneficial as a pulmonary vasodilator, but the pronounced systemic hypotensive induction by this agent has the potential to decrease venous return to the already insufficient right heart, worsening the right ventricular failure. All vasopressors may have a direct pulmonary vasoconstrictor effect, but low-dose dopamine, phenylephrine, norepinephrine, or vasopressin may be used to sustain the systemic blood pressure. Improved systemic hemodynamics are usually translated in improved renal function, increased diuresis, and further increased right ventricular contractility. In conclusion the mainstay of therapy in cases of hypotension from right ventricular failure dobutamine is the inotropic agent of choice, despite some potential direct pulmonary hypertensive effect. Milrinone may be more beneficial as a pulmonary vasodilator, but the pronounced systemic hypotensive induction by this agent has the potential to decrease venous return to the already insufficient right heart, worsening the right ventricular failure. All vasopressors may have a direct pulmonary vasoconstrictor effect, but low-dose dopamine, phenylephrine, norepinephrine, or vasopressin may be used to sustain the systemic blood pressure. Improved systemic hemodynamics are usually translated in improved renal function, increased diuresis, and further increased right ventricular contractility. In conclusion the mainstay of therapy in cases of hypotension from right ventricular failure in pulmonary arterial hypertension is not intravenous fluid administration, but rather inotropic support, diuretics, and vasopressors.

CASE 2:
A 58-year-old man with hepatitis C-cirrhosis (MELD = 32, refractory ascites, recurrent variceal bleeds, episodes of hepatic encephalopathy, and hepato-renal syndrome) and porto-pulmonary hypertension was called for cadaveric orthotopic liver transplantation (OLT). He had been deemed an appropriate candidate for OLT after 9 months of therapy with subcutaneous treprostinil. His initial cardiac catheterization at the time of diagnosis of porto-pulmonary hypertension revealed the following hemodynamics: mean pulmonary artery pressure (mPAP) of 55 mmHg, pulmonary artery occlusion pressure (PAOP) of 10 mmHg, cardiac output (CO) of 6 L/min and pulmonary vascular resistance (PVR) of 600 dynes s cm⁻⁵. He lived alone, was mildly encephalopathic, and his wife, who had multiple sclerosis, resided in a nursing home. With hemodynamics that posed a prohibitive operative risk for OLT, and an inappropriate social situation for intravenous epoprostenol therapy, treatment was initiated with subcutaneous treprostinil. Six months after initiation a follow-up right heart catheterization on 36 ng/kg/min of treprostinil showed the following hemodynamics: mPAP of 33 mmHg, PAOP of 15 mmHg, CO of 8.7 L/min, and PVR of 166 dynes s cm⁻⁵. On the basis of these numbers he was listed for liver transplantation and because of rapidly progressing liver disease he received a graft after 3 months.

Preoperatively his mPAP was 40 mmHg, his central venous pressure (CVP) was 18 mmHg, PAWP was 20 mmHg, and CO was 8.5 L/min, with a PVR of 188 dynes s cm⁻⁵. During abdominal preparation the subcutaneous treprostinil administration was discontinued. Systemic blood pressure was 85/55 mmHg before induction of general anesthesia and decreased to 70/35 mmHg after induction. This fall in blood pressure responded to a phenylephrine bolus of 0.2 mg. Approximately half an hour after treprostinil discontinuation a continuous intravenous epoprostenol infusion was started at 2 ng/kg/min and adjusted to keep mPAP = 30-40 mmHg, with up-titration in 1-2 ng/kg/min increments every 30 to 60 minutes. Cardiac output was constantly monitored and remained at 6.5-8.5 L/min. Inhaled nitric oxide (NO) was kept on stand-by for potential rebound pulmonary hypertensive episodes, but was not used. After removal of ascites, mPAP, PAOP, and CVP decreased by 10 mmHg. Intermittent boluses of phenylephrine (0.2 mg) and vasoressin (2-4 U) were used to maintain the mean systolic BP above 45-50 mmHg. During the procedure the patient received a total of 6 L crystalloid infusion, 10 U of fresh frozen plasma, and 5 units of packed red blood and he was placed on continuous veno-venous hemofiltration (CVVH). He remained stable hemodynamically throughout the transplant, including during the anhepatic phase. Upon graft revascularization during a 2 minute hypotensive episode (with a decrease in the mean systemic BP to 30 mmHg and a rebound mPAP to 45 mmHg) he received 4 U of vasoressin and this increased the mean systemic BP to 50 mmHg, without significant change in mPAP. On completion of the transplant operation he was receiving 15 ng/kg/min of continuous intravenous epoprostenol. He was transferred to the surgical intensive care unit, where he remained hemodynamically stable. The next day subcutaneous treprostinil was reintitated and up-titrated in 3-4 ng/kg/min increments, with simultaneous down-titration of intravenous epoprostenol in 1-2 ng/kg/min decrements, until a dose of 30 ng/kg/min of treprostinil were reached. Prior to discontinuation of the pulmonary artery catheter the mPAP was 32 mmHg, the CO was 7.5 L/min, the PAOP was 12 mmHg, and the calculated PVR was 213 dynes s cm⁻⁵.

Discussion:
This case illustrates the strategy that may be employed for the perioperative hemodynamic management of patients with porto-pulmonary hypertension who require OLT. Porto-
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There are many reasons to join this group, but the benefit I have truly enjoyed is being able to ‘tap’ into everyone’s collective knowledge with the listserv. Many changes are taking place in this field right now and it would be difficult for even the most seasoned veterans to have all the answers. With this, my patients and I can benefit from everyone else’s experiences and expertise.

Ginger R. Ward, RN
Duke University Medical Center
Durham, North Carolina

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Stephanie Harris
University of Washington Medical Center
Seattle, WA

Physicians and Researchers… please go to page 23 for information on PH Clinicians and Researchers, the membership section for physicians and researchers.
pulmonary hypertension is a type of pulmonary arterial hypertension that develops in patients with end-stage liver disease, characterized by the presence of a true pulmonary arteriopathy (elevated PVR) and (potential for) right ventricular dysfunction. Perioperative mortality is significantly increased in the presence of moderate to severe pulmonary hypertension. These patients require chronic therapy for pulmonary hypertension for hemodynamic optimization prior to OLT, and case series in the literature support the use of continuous intravenous epoprostenol in these circumstances. This patient was treated with subcutaneous treprostinil instead because of the lack of social support and his own inability to manage the complexities of intravenous epoprostenol therapy. With the advent of alternative therapeutic options for pulmonary arterial hypertension, it is likely that physicians will use other forms of chronic prostacyclin therapy, ideally in the setting of organized clinical trials. This patient had a good hemodynamic response to treprostinil, rendering him an OLT candidate, but the particular challenge in his case was the timing of transition from subcutaneous to intravenous prostacyclin during the surgical procedure. Given the relative unpredictability of the time of OLT, it is not possible to transition these patients in advance. Liver transplantation surgery is associated with hemodynamic instability, rebound pulmonary hypertension, and precipitation of right ventricular failure, particularly after induction of general anesthesia, after graft revascularization, and during the first postoperative days. Transitioning from one to another form of prostacyclin therapy during OLT may increase the risk of hemodynamic instability. In this case, transition from subcutaneous treprostinil to prostacyclin infusion was successfully achieved with guidance from pulmonary artery catheterization.

As a general rule, prostacyclin deficiency may be associated with rebound pulmonary hypertension and prostacyclin excess with systemic hypotension. There is a difference in half-lives between epoprostenol and treprostinil (2 to 3 minutes and 2 to 4 hours, respectively) and anecdotal evidence suggests that approximately two to three times more treprostinil (in nanograms) is required for an equivalent effect. Inhaled NO may be used for the pulmonary vasodilator effect, particularly in cases with systemic hypotension, because of its selectivity for the pulmonary vasculature. Inotropic agents and vasopressors, as well as volume replacement or volume removal, may be used as needed for the hemodynamic management during liver transplantation.
This discussion was moderated by Roxana Sulica, MD, Assistant Professor of Medicine, Mount Sinai School of Medicine, and Director, Mount Sinai Pulmonary Hypertension Program, Mount Sinai Medical Center, New York, New York. The participants included James R. Klinger, MD, Pulmonary Hypertension Center, Rhode Island Hospital, Providence, and Associate Professor of Medicine, Brown University Medical School, Providence, Rhode Island; Ronald G. Pearl, PhD, MD, Professor and Chair, Department of Anesthesia, and Associate Director, Intensive Care Units, Stanford University Medical Center, Stanford, California; and Fernando Torres, MD, Director, Pulmonary Hypertension Clinic, University of Texas Southwestern Medical Center, Dallas, Texas.

Dr Sulica: Thank you for joining us for this discussion today. I’ll start by asking how you would manage a patient with the following: recently diagnosed pulmonary hypertension, as suggested by an echocardiogram, with estimated right ventricular systolic pressure of 90 mmHg, right ventricular dilatation and severe dysfunction, pericardial effusion, and an enlarged right atrium. The patient has a systemic blood pressure of 80/50 mmHg with a heart rate of 120 bpm and is very short of breath with activities of daily living. There are a few episodes of impending syncope with minimal exertion for the past two or three weeks. What would you do or what is your first choice of treatment?

Dr Torres: The first thing I would try to find out is why the patient developed cor pulmonale. One of the first illnesses we will try to rule out is chronic pulmonary emboli. I would try to sort things out very quickly either by a ventilation perfusion scan or by a CT angiogram. I would get a chest x-ray and make sure the patient doesn’t have interstitial lung disease, etc., as an etiology of cor pulmonale. While I am waiting for other tests, obviously the patient seems to be in right ventricular failure, and in such patients we want to make sure to start diuretics fairly quickly. I usually use furosemide at about 10 to 20 mg per hour even though they are hypotensive. Most of the time, the right ventricle is able to compensate better and work more efficiently when the preload decreases. Another intervention that we tend to do fairly quickly is to try to get a right-sided catheterization to make sure the patient has cor pulmonale. This will help manage the patient. Obviously, with the heart rate of 120 bpm this may be somewhat challenging, but it is very important to monitor pulmonary pressures and right ventricular function in a patient who has hypotension and tachycardia. Most of the time when I use diuretics in these patients they seem to stabilize to the point where we can start epoprostenol therapy. Usually, when the patients seem to be decompensated, a challenge with epoprostenol, adenosine, or nitric oxide is not going to be useful given that their cardiac index is going to be so low that it would be inappropriate to consider them for calcium channel blocker therapy. A lot of times, fairly soon, for these patients treatment is going to be started with a prostacyclin, usually epoprostenol.

Dr Sulica: And your choice is epoprostenol despite the current availability of other forms of prostacyclins?

Dr Torres: You know, I don’t think there are enough data on patients with decompensated cor pulmonale, class IV, for me to feel comfortable enough to start using inhaled therapy at this point. At this point, the drug of choice for the decompensated phase of cor pulmonale is intravenous epoprostenol. Intravenous treprostinil is also available, but we do not have as much experience using it in acute right ventricular failure.

Dr Sulica: Absolutely, Ron, do you see placement of a pulmonary artery catheter in critical care settings as riskier than in patients with no pulmonary hypertension?

Dr Pearl: Certainly placing a central line in a decompensated patient who is hypoxemic, is very dyspneic, and may not tolerate lying flat may have increased risks. I don’t view the passage of a pulmonary artery
catheter by itself as being particularly risky in a patient with pulmonary hypertension. It may be much more difficult to do with just pressure waveform guidance, but we have never had complications from passing the catheter itself. Obtaining a wedge pressure may not be feasible in many of these patients, but it may not be particularly important to measure the wedge pressure because with ventricular interdependence the wedge pressure may no longer reflect left ventricular filling. So, people just try to get into the pulmonary artery and are happy with looking at pulmonary artery pressures. I think that is being safely done.

**Dr Sulica:** How about the reliability of cardiac output determinations? Do you confidently rely on thermodilution cardiac output, given the fact that frequently these patients have significant tricuspid regurgitation or maybe open PFOs?

**Dr Pearl:** If there is no intracardiac shunting, and if we are not talking about a patent foramen ovale, but simply pulmonary hypertension, our experience has been that the cardiac output seems to be reliable, and it does provide a useful trend. We often supplement the cardiac output values by using a continuous cardiac output catheter with venous oximetry, or at least getting some intermittent mixed venous oxygen saturations to be sure that what we think cardiac output is doing seems to be reflected in the trend in mixed venous oxygen saturation. I would like to mention that as the cardiac output gets very low, thermodilution may be less reliable.

**Dr Sulica:** Great point. What do you think about the role of transesophageal echocardiography and transthoracic echocardiography in the critical care area or intraoperatively?

**Dr Pearl:** In the intensive care unit we have been extensively using portable transthoracic echocardiography for diagnosis, but we would use it in the patient you described to be sure that what we are dealing with is clearly right heart failure and not from the insult that has occurred, and that there are no major valvular abnormalities. We would want to see if there is shunting going on that we would want to know about. I think in the intensive care unit setting, transesophageal echocardiography is likely not all that useful in the nonintubated patient. I would be concerned about potentially decompensating a patient as described. In the operating room it is effective, because we are leaving a probe in for the entire duration of many of the marked changes that we might expect to occur.

**Dr Torres:** Do you have vasovagal episodes during the procedure with transesophageal echocardiography?

**Dr Pearl:** I think in the nonintubated patient who is already decompensating I would worry about it. In the operating room the patient would already be asleep and anesthetized.

**Dr Sulica:** What do you think about the reliability of pulmonary artery catheterization determinations in patients with an acute lung injury or ARDS (acute respiratory distress syndrome) associated with signs of right heart dysfunction, low urine output, or systemic hypotension? How useful and reliable is the information obtained from placing a pulmonary artery catheter?

**Dr Klinger:** I think I would approach it two ways. One is the person we don’t think has pulmonary hypertension and now has a Swan-Ganz catheter placed for acute lung injury and is found to have pulmonary hypertension. In that situation, what we need to stress is that an acute lung injury normally causes a certain degree of pulmonary hypertension, so that should be anticipated, not as pulmonary arterial hypertension, but as pulmonary hypertension secondary to the acute lung disease. This should resolve as the lung disease improves. The second situation is someone who has pulmonary arterial hypertension and then develops an acute lung injury, and has a Swan-Ganz catheter inserted. Now the pulmonary pressures may actually be less if the cardiac output is decreased compared to baseline. High levels of PEEP will decrease right-sided return and right ventricular filling, and decrease cardiac output. So the pulmonary arterial pressure may come down. Occasionally there will be patients who have high wedge pressure because they are being volume resuscitated or who have a lot of pressure transmitted from the airways, causing a falsely elevated wedge pressure with a true transmural left ventricular diastolic pressure that is normal. These patients may appear to have elevated pulmonary venous hypertension when they actually don’t. So, pulmonary artery pressure measurements may be confusing in someone that has established pulmonary hypertension who develops an acute lung injury, goes on mechanical ventilation and PEEP, and then has a Swan-Ganz catheter coming in. The other issue to consider is if patients have enough hypcapnea that they are acidic. For any level of hypoxia, pulmonary vasoconstriction is increased in the presence of acute hypcapnea or acidosis. So there may be some degree of elevation in pulmonary arterial pressure in response to acute hypcapnea. I would add that in many of these settings one can administer inhaled nitric oxide diagnostically to see to what extent the acute pulmonary vasoconstriction is really contributing to any hemodynamic problems. Inhaled nitric oxide can be effective in blunting the increased pulmonary vascular resistance from acute hypcapnea.

**Dr Sulica:** So, you would consider inhaled nitric oxide if the pulmonary vascular resistance is high?

**Dr Klinger:** Well, it depends on the type of patient. There is the patient who, as a result of acute lung injury, has pulmonary hypertension. It is rarely important to treat pulmonary hypertension in that situation. Then there is the patient who has established pulmonary hypertension, who now has a superimposed acute lung injury and develops worsening of the pulmonary hypertension because of acute hypoxia, acidosis, or hypcapnea. This is a very different setting and it is often not easy to know how much of the pulmonary hypertension in these patients is actually a problem versus a normal response to acute lung injury. So, sometimes we debate whether we should treat the pulmonary hypertension or not. In this setting, we often use inhaled nitric oxide diagnostically to see if we can lower the pulmonary pressures. If it is effective in doing that and cardiac output increases, this can tell you that the pulmonary hypertension itself is a problem.
Dr Sulica: And you also take into account the level of the right ventricular dysfunction.

Dr Klinger: Definitely!

Dr Sulica: Now, in patients already diagnosed with pulmonary hypertension who are presenting to the emergency room hypotensive and seeming septic, what will be the diagnostic and therapeutic maneuvers?

Dr Torres: If they have a fever, we get a urinalysis, CBC, chemistries, blood cultures, and a chest x-ray. If we do not identify the source of the infection fairly quickly, we are going to assume it is coming from the central line in a patient receiving intravenous epoprostenol and start intravenous antibiotics.

Dr Sulica: How about giving intravenous fluids when patients come in septic? Sometimes they are febrile and possibly fluid depleted. We discussed that we actually diurese patients in right heart failure even though they are hypotensive.

Dr Torres: For the most part, in patients with pulmonary hypertension, the right ventricle is not going to need more preload. We tend just to give them antibiotics, and we may even have to diurese them, as you are saying. We check their BUN and creatinine and it is usually higher than you think. You are right, even though they have a fever and their blood pressure is a little bit low, we tend not to give them any fluids. For the most part we continue giving them their diuretics or just cut back a little bit on the diuretics.

Dr Sulica: And even though they are hypotensive, you do not interrupt the intravenous epoprostenol.

Dr Torres: Exactly! We never interrupt the vasodilator therapy because then you may make the hypotension much worse.

Dr Sulica: Jim, do you have the same strategy of managing these patients?

Dr Klinger: Absolutely. I have very much the same strategy. We have done some laboratory studies showing that a lot of the catheters are infected with an organism called *Micrococcus*, which is a kind of *Staphylococcus*, that responds fairly well to treatment with antibiotics even though you might have to give treatment for a long period. While commonly considered a contaminant, *Micrococcus* should be treated as a real pathogen in these patients with indwelling lines.

Dr Sulica: What if the patient becomes hemodynamically unstable? What would be your favorite inotropic drug and favorite vasopressor, and what do you think would be the best management strategy for these patients with pulmonary hypertension in the operating room?

I think we are relatively liberal in allowing pulmonary hypertension when they have a compensated right ventricle. We are doing something that will eventually improve the outcome. We may have to temporarily support the right and left ventricle with pharmacologic and mechanical means, but normally when the cardiac problem is repaired, over time we will see things improve. Those are the patients in whom we may postoperatively use inhaled nitric oxide and transition to a phosphodiesterase-5 inhibitor such as sildenafil.

Dr Torres: I would echo your comments. I think your preferred therapy depends on where you were trained or what your subspecialty might be. If you are a pulmonologist, you tend to use a little bit more dopamine and if you are a cardiologist, then you tend to use more dobutamine. As a pulmonologist I tend to use a little bit more dopamine, especially in the hypotensive patient. Obviously, I use dopamine at the expense of patients developing tachycardia. I still go back and forth between dopamine and dobutamine, especially in the patient with hypotension. Dobutamine can still worsen the hypotension and the patient may not tolerate it.

Dr Pearl: The other setting is your sepsis patients, as you mentioned a little bit before. It is probably a good example. What has occurred often is not that cardiac output has fallen from exacerbation of the pulmonary hypertension, but that there has been some systemic vasodilation and they are not able to increase cardiac output because of the pulmonary hypertension. In those settings I am much more likely to use something that has the ability to give some inotropic effect and some systemic vasoconstriction, like dopamine. I am not as worried about adding on pulmonary vasodilation.

Dr Sulica: How about norepinephrine? What is your opinion about this?

Dr Klinger: I think Ron is right. The difficulty is really not so much treating the pulmonary hypertension as it is decreasing the drop in afterload on the systemic side. You need to do what you need to do to keep up that blood pressure. We do this sometimes in septic patients as well. When we think their volume is expanded to the maximum, we try to get away from volume expansion and go toward vasopressors. I think people get concerned that when they use vasopressors they are going to have pulmonary vasoconstrictive effects as well, but this is really very mild. As a result, once you have tried the inotropic route, and you fail, vasopressors would be the next thing to use. I would probably use Levaphed. I don’t know anyone who has tried vasopressin. Are there some case reports of it now?
Dr Sulica: Yes, although the effect of vasopressin in experimental pulmonary hypertension is controversial, there are few human case reports showing that low-dose vasopressin may be used to treat systemic hypotension with minimal consequences on pulmonary hemodynamics. How about combining those drugs with direct pulmonary vasodilator effect, such as inhaled nitric oxide or inhaled epoprostenol?

Dr Klinger: We have tried that infrequently, but if patients are going to die of hemodynamic collapse due to sepsis while they have pulmonary hypertension, I would like to see them treated with pretty high doses of epoprostenol intravenously, along with dobutamine. Then, if they are still hypotensive, I would add other pressors such as Levophed or vasopressin. I think that is probably the best approach that we have right now. Years ago, I would try nitric oxide for some of these patients, but I do not think it has any more vasodilatory effects than epoprostenol, and it doesn’t have some of the inotropic effects that epoprostenol has. So, those would be my three drugs of choice to have on even if the patient does not survive.

Dr Pearl: I do not think there is any advantage to using inhaled prostacyclin when you have someone with cardiogenic shock or other kinds of compromise. The area where we have seen advantages possibly with the drug’s performance is when we are trying to avoid hypotension. I don’t think it is going to contribute in sepsis. Just to clarify, when the patient is acutely hypotensive it is a pretty difficult setting to start intravenous epoprostenol. I would think about using an inhaled pulmonary vasodilator transiently. They usually don’t work in that setting more than anything else in terms of giving acute pulmonary vasodilation. I think in a hypotensive patient it is hard to initially and quickly get to high doses of prostacyclin. Once you get other pressors and inotropic agents on, it may be much easier.

Dr Sulica: And how would you look at the response of therapy? Would you place a pulmonary artery catheter in that situation?

Dr Pearl: I think you probably have to. If you can’t, then you would be looking at as much epoprostenol as you can start without the patient becoming hypotensive. It depends on the situation. If you start epoprostenol therapy, and as you go up, the blood pressure starts to drop, then you have defined the maximum dose the patient can tolerate.

Dr Sulica: Perioperatively, how would you manage a patient, let’s say, after having surgery for valvular heart disease, who still has elevated pulmonary vascular resistance?

Dr Pearl: I think in the intraoperative and perioperative setting, a lot of treatment has to be based on defining what goals you are trying to achieve. Many patients have pulmonary hypertension after cardiac surgery but do not have problems from the pulmonary hypertension. You have to figure out if the problem is they are hypotensive because of low cardiac output or if there is some gas exchange problem going on. Where people run into problems is when they treat the pulmonary artery pressures themselves as the problem. If the issue is one of low cardiac output without systemic hypotension, one can often treat that the same way we would commonly treat low cardiac output, using inotropes and vasodilators and optimizing the degree of volume. When we have pulmonary hypertension itself that is clearly resulting in hypotension, then choices become fairly limited. In the postcardiac surgery setting, inhaled nitric oxide has sometimes been useful where we will decrease pulmonary vascular resistance with the inhaled nitric oxide and then use additional agents to support both the right and the left ventricle. Sometimes the severe pulmonary hypertension is associated with left-sided problems, and you may have to go to an intraaortic balloon pump, left ventricular assist device, or sometimes a right ventricular assist device. It is hard to make broad generalizations on how to treat the perioperative pulmonary hypertension. The point I would emphasize is that often people get into trouble trying to treat it, when in fact it doesn’t need to be treated. We need to be sure that we identify what we are trying to improve.

Dr Sulica: How about perioperatively, for example, in patients with valvular disease or patients evaluated for heart transplantation? Do you have a cut-off of the preoperative pulmonary vascular resistance to proceed with surgery? Do you test for so-called reversibility?

Dr Pearl: If you are now talking about cardiac surgery, there are two very different settings, the patient who is having definitive repair of mitral valve disease or coronary disease, versus the patient who is having a heart transplant. In patients who are having corrective cardiac surgery, I think we are relatively liberal in allowing pulmonary hypertension when they have a compensated right ventricle. We are doing something that will eventually improve the outcome. We may have to temporarily support the right and left ventricle with pharmacologic and mechanical means, but normally when the cardiac problem is repaired, over time we will see things improve. Those are the patients in whom we may postoperatively use inhaled nitric oxide and transition to a phosphodiesterase-5 inhibitor such as sildenafil. In contrast are the patients who are having heart transplants where there is a high resistance pulmonary circulation, and we are putting in a donor heart that has no right ventricular compensatory mechanisms, and so for those patients, yes, we do consider pulmonary hypertension to be a contraindication to the surgery. In terms of the exact numbers, I think it is a combination of the pulmonary artery pressure, the gradient between mean pulmonary artery pressure and wedge pressure, the pulmonary vascular resistance, and the reversibility with pulmonary vasodilator therapy. I hesitate to give exact numbers because it is often the combination of them that we decide on, rather than using one specific number.

Dr Sulica: In terms of testing the vasoreactivity and reversibility...
ty, what agents are you using? In the catheterization lab when you test for vasoreactivity, if we have a patient with high wedge pressure we are reluctant to use inhaled nitric oxide or epoprostenol, being mindful of pulmonary edema.

**Dr Klinger:** We are always concerned. We actually had two patients whose cases we published years ago who developed acute pulmonary edema in a response to inhaled nitric oxide. They had wedge pressures that were pretty normal. They both had scleroderma, and we think they just had stiff ventricles and couldn’t handle it. On the other hand, we have a plethora of patients with long-standing congestive heart failure and diastolic dysfunction who we are called to see because they have pulmonary hypertension that appears to be out of proportion to their wedge pressure. In some cases, I have actually done vasodilator trials and have seen improved pulmonary pressure without an increase in the wedge pressure. What we generally try to do is to get as much diuresis as possible and get the wedge as low as possible. Then after that we will try to add a pulmonary vasodilator. In that situation, I think nitric oxide is really the best because, if we do see a rise in wedge pressure, we can turn it off pretty quickly and resolve the problem.

**Dr Sulica:** Although there are reports of pulmonary edema in patients with underlying left heart dysfunction, even with inhaled nitric oxide, it has a much shorter action, so you hope it is going to reverse faster.

**Dr Klinger:** I think it is a very interesting area of pulmonary hypertension that we don’t have a lot of data on. There are some people with elevated wedge pressure in whom we are hesitant to do vasodilator trials, yet other patients seem to tolerate it fairly well, and I don’t currently have a good way to differentiate what is going to happen.

**Dr Torres:** At the same time, should we be doing a vasodilator challenge in a patient with a high wedge, or should we measure a left ventricular end diastolic pressure to confirm that this was an accurate wedge?

**Dr Sulica:** Absolutely! It might sometimes be impossible to determine an accurate wedge in patients with pulmonary hypertension, at least severe pulmonary hypertension. Ron, are these issues still valid for the patient we were just discussing with high pulmonary vascular resistance? Presuming that there is a left heart failure so the wedge is high, are you concerned about putting the patient in pulmonary edema with the vasodilator challenge?

**Dr Pearl:** The preoperative testing concern is that the pulmonary vasodilation allows the right heart to overload the left heart because the patient is already in a volume overloaded state. In essence, the pulmonary hypertension is a protective mechanism. Our experience has been that there is less concern in the outpatient setting for the heart failure patient than in past years because these patients are so much better managed clinically now than they used to be. They have less volume overload and we don’t precipitate a lot of pulmonary edema with the challenge. In the acute intraoperative and postoperative setting we are normally very actively titrating volume, and although it is conceivable that the nitric oxide would produce the same effect of producing pulmonary edema, I think it is less likely to occur because we are often very focused on maintaining the appropriate volume status.

**Dr Sulica:** Great. Thank you Ron, Jim, and Fernando. I really appreciate your time.
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