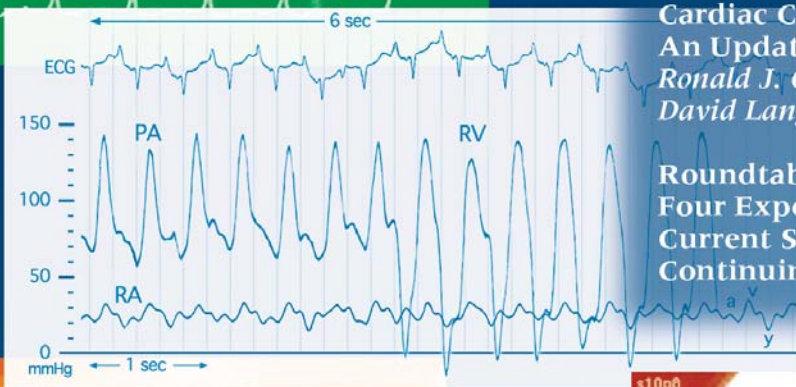
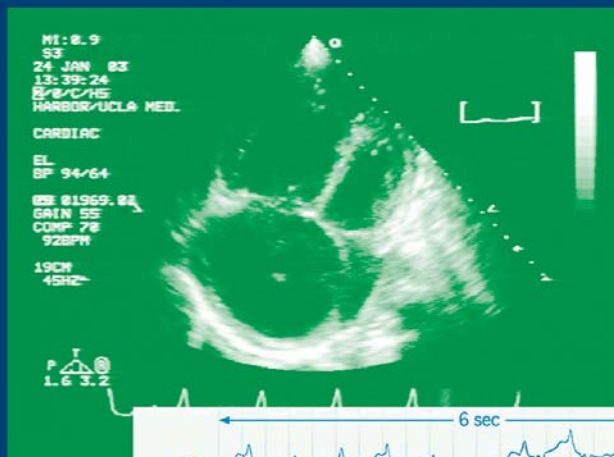


Advances in
Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

Autumn 2005
Vol 4, No 3



Focus in This Issue: Essential Guide to Diagnosing PAH

**Physical Exam: What Findings
Are Most Characteristic?**

Todd M. Bull, MD

Initial Diagnostic Testing

Terence K. Trow, MD

**Cardiac Catheterization:
An Updated Guide to Proper Use**

Ronald J. Oudiz, MD

David Langleben, MD

**Roundtable Discussion With
Four Experts on Integrating
Current Strategies for
Continuing Assessment**



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Advances in Pulmonary Hypertension is circulated to cardiologists, pulmonologists, rheumatologists and other selected physicians by the Pulmonary Hypertension Association. The contents are independently determined by the Editor and the Editorial Advisory Board.

Cover image:

Top: Apical four chamber view on two dimensional echocardiogram illustrating severe right atrial and ventricular dilatation as well as posterior bowing of interatrial septum pulmonary arterial hypertension. **Center:** Hemodynamic pressure tracings from pulmonary artery (PA), right ventricle (RV), and right atrium (RA) with simultaneous electrocardiogram (ECG). RA, PA, and RV pressures are severely elevated in patient with pulmonary arterial hypertension. **Bottom left:** AP chest x-ray demonstrating cardiomegaly. **Bottom right:** sagittal oblique short axis cine-MRI image of RV (anterior) and LV (posterior) demonstrating right ventricular hypertrophy and dilatation with flattening of inter-ventricular septum.

Editor's Memo

PHA Achieves Educational Breakthrough With New Interactive CD-ROM



Imagine an interactive, virtual diagnostic assessment of a patient with pulmonary arterial hypertension reconstructed for you step by step with every essential aspect covered, from history and physical, including heart tones, to echocardiograms, x-rays, lung scans, and catheterization. It is animated, contains videos, and allows you to interact with the diagnostic assessment to determine your next move. All captured on a CD-ROM

by the world's leading experts in diagnosing pulmonary hypertension. Better yet, all you need do to obtain this CD-ROM is request a complimentary copy via a Web site, as indicated on page 5.

For most of this year the Pulmonary Hypertension Association (PHA) has been developing this dynamic multimedia project on the diagnosis of pulmonary hypertension through the support of a \$25,000 grant from the Centers for Disease Control and Prevention. Leading cardiologists and pulmonologists have posted their insights and findings of diagnostic assessments on a Web site established specifically to create the information on the CD-ROM. This project was recently completed, enabling PHA to offer the only CD-ROM of its kind to guide physicians through the myriad situations arising in clinical practice, exactly as presented by a patient suspected of having pulmonary arterial hypertension.

Working with multimedia specialists David Criley and John Criley of Blaufuss Medical Multimedia, San Francisco, a PHA committee has contributed a wealth of information from real-life scenarios. Complete with real-time videos and allowing the viewer to interact, even at the level of moving a stethoscope's chestpiece on screen to elicit different heart tones, the CD-ROM is part of a growing resource of educational materials available to physicians and patients at no charge from PHA. For example, free copies are available of the new American College of Chest Physicians PAH Practice Guidelines. Six programs this fall, entitled *Shedding Light on Pulmonary Arterial Hypertension: The Journey Toward a Brighter Future*, will be held at regional locations around the country, with Continuing Medical Education credit offered.

The newly published *Pulmonary Hypertension: A Patient's Survival Guide* may be obtained through the PHA Web site, www.phassociation.org/Store/, or call (301) 565-3004. It is a 280-page guide for patients and medical professionals. And from September 30 to October 1, the 2005 PH Resource Network Symposium will be held in Bethesda, Maryland. For more information and registration please access www.phassociation.org/PHRN/Symposium.

On behalf of PHA and its Scientific Leadership Council, I urge you to take advantage of the growing network and library of educational offerings as we work together toward a cure for pulmonary hypertension.

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Advances in Pulmonary Hypertension is committed to help physicians in their clinical decision making by informing them of important trends affecting their practice. Analyzing the impact of new findings and covering current information in the peer-reviewed literature, *Advances in Pulmonary Hypertension* is published four times a year. *Advances in Pulmonary Hypertension* is the official journal of the Pulmonary Hypertension Association.

Each article in this journal has been reviewed and approved by members of the Editorial Advisory Board.

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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



Profiles in Pulmonary Hypertension

Never Wavering From a Long Commitment to a Cure for PH, Stuart Rich, MD, Aims to Stop the Disease in Its Tracks



Stuart Rich, MD

When the next breakthrough in treatment for pulmonary hypertension emerges it will probably come from the research centers where teams of investigators have pursued it with a single-mindedness of purpose that for 27 years has characterized the work of Stuart Rich, MD. Beginning early in his career Dr Rich has focused on the disease with a special intensity and

commitment; proof of that commitment could be seen in the outpouring of appreciation, numerous expressions of gratitude from patients at last year's meeting of the Pulmonary Hypertension Association, and praise accorded him by his colleagues.

Throughout his involvement with pulmonary hypertension research, his "goal has been to cure this disease, and I have not lost sight of the goal line." During that time he has benefited from an extraordinary vantage point—as principal investigator on numerous pivotal trials, staunch and vocal patient advocate in the litigation over the fen-phen liability cases, and recently, as Chief Medical Advisor for United Therapeutics. On the academic side he is Professor of Medicine at the University of Chicago, an appointment that he says absorbs 60% of his time.

He characterizes his work now as one of moving into a new era, a departure from "the conventional approach of treating the disease, which traditionally has been one vasodilator after another. On the academic side, we are starting to pursue the approach of therapies that stop the disease process and reverse it. We are trying to better characterize who gets pulmonary hypertension, how sick they are, and how to better manage them. On the industry side, I am helping United Therapeutics to develop prostacyclin analogs to treat pulmonary hypertension. This is my single focus within the company."

After graduating from Loyola University, Stritch School of Medicine, Chicago, Dr Rich completed his internship and residency at the Jewish Hospital at Washington University, St. Louis, before accepting his fellowship in cardiology at the University of Chicago

Hospitals and Clinics. Later in his career he became Chief of the Cardiology Section at the University of Illinois at Chicago Medical Center and from 1996 to 2004 served as Director of the Rush Heart Institute, Center for Pulmonary Heart Disease. In a distinguished career, Dr Rich is the author or coauthor of 134 manuscripts published in the medical literature and of work appearing in 15 books, book chapters, or monographs.

A Time to Refocus the Field of Treating Pulmonary Hypertension

Assessing the progress toward finding the elusive cure of pulmonary hypertension, Dr Rich sums it up: "We've developed drugs that make people walk farther on a 6-minute walk test, but that's all we've done. We have not developed the drugs that reverse the disease, normalize pulmonary pressure, or prolong survival. Just coming up with another vasodilator that allows people to walk 20 more meters is missing the whole point. It's time to refocus the entire field of treating pulmonary hypertension and to start attacking the disease process. It's very much like research in cancer."

At United Therapeutics his team is working on the development of newer forms of prostacyclin, including an oral form of Remodulin that he says will be a breakthrough. Studies have been completed in normal volunteers to determine optimal dosing and a formal clinical trial is planned for 2006.

Looking Toward the Next Decade

Angered by the tragedy of seeing many of his patients die of the use of fen-phen, a diet medication quickly withdrawn from the market, Dr Rich was a key figure in helping the families of patients recover damages from the misuse of this drug. "It may seem ironic that even though I have been one of the most vocal critics of the pharmaceutical industry, I still work for one. Within the company I try to stress the ethics of drug development and this company has been very responsive to it. I'm constantly reminding them of a certain commitment they must hold themselves to—and they're doing it."

He is hopeful that in the next 5 to 10 years there will be a major breakthrough in the treatment of the disease. "It's an exciting time to be involved with pulmonary hypertension. There are great discoveries being made at the molecular biologic level. A lot will be done in the next decade to really turn this disease around and I'm hopeful that physicians and pharmaceutical companies have a clear vision of what is required to accomplish this. My guess is that in about 5 years we will see the initiation of clinical trials that are designed based on some molecular biologic discoveries. We need to look at survival in a multiyear trial and characterize patients differently based on their biologic criteria, and start to tailor their treatment in much the same way that oncologists do for cancer." ■

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A Breakthrough in Medical Education

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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.

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Physical examination

Introduction on jugular venous pulse

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- Patent ductus arteriosus with pulmonary hypertension (Eisenmenger syndrome)
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Please go to www.phassociation.org/medical/cd.asp to request your complimentary copy or check the box on the reply card found at the front of the journal.

The production of this CD-ROM was supported by Grant Number Purchase Request (PR)# HCL33-2005-23060 and Contract Award # 254-2005-M-13200 and Purchase Request (PR)# HCL33-2004-09925 and Contract Award # 200-2004-M-10076 from the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the Pulmonary Hypertension Association and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

The distribution of this CD-ROM is being made possible by an unrestricted educational grant from Myogen, Inc.



Physical Examination in Pulmonary Arterial Hypertension



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The physical examination is an integral to the evaluation of any patient with suspected cardiopulmonary disease. This is particularly true of patients with pulmonary arterial hypertension (PAH) as careful attention to physical signs will not only alert the clinician to the presence of PAH, but guide assessment of disease severity and provide important clues regarding underlying pathogenesis. This paper will focus on the physical findings most characteristic of patients with PAH, with a brief discussion of normal physical findings where appropriate. Descriptions in the text link directly to the audio and video examples of the relevant physical findings on the CD-ROM Pulmonary Hypertension: An Interactive Guide to Diagnosis. A complimentary copy is available through the Pulmonary Hypertension Association at (see page 5).

Jugular Venous Pulse

Important information regarding the condition of the right heart can be obtained from observation of the jugular venous pulse.¹ Discriminating the internal jugular vein from the external jugular vein and the carotid pulsation is an important part of this evaluation. The internal jugular vein is located deep in the neck, covered by the sternocleidomastoid muscle, but its pulsations are transmitted to the skin of the neck. It is both easier and more clinically useful to evaluate the internal jugular pulse on the right side of the neck. It is a relatively straight path from the right atrium to the right internal jugular via the innominate vein, and therefore assessment of the right internal jugular gives a more accurate account of right atrial pressures. By convention, most patients are examined at a 45° angle; however, in patients with very high venous pressures a more acute (60° to 90°) angle may be required to adequately discriminate the jugular pulsations. It is helpful to make a note of the height of the jugular venous pulsations and the angle at which they were measured during each evaluation to track changes in this physical finding during subsequent visits.

The internal jugular vein is usually not visible as a discrete structure except in the presence of significant right heart pressure elevation. However, transmitted pulsations of the internal jugular are visible at the surface of the neck in many patients. The first important step in evaluating the

internal jugular wave forms is discriminating them from the carotid pulsations. There are a number of clues to assist with this discrimination. The venous wave can often be dampened or suppressed by firm placement of a palpating finger below the pulsation at the base of the neck (this may not be true if severe elevation of right heart pressures exists), while arterial pulsations continue despite firm palpation. Arterial pulsations do not change location in relation to patient position while venous waves increase and decrease in height depending on the angle of incline of the patient. Lastly, the venous pulse has two peaks and two troughs, while the arterial pulse has a single upstroke.²

Two aspects of the jugular venous pulse should be assessed in the evaluation of the patient with PAH: 1) the height of the jugular venous distension above the sternal angle (angle of Louis), and 2) the quality of the venous wave pattern.³

Height of jugular venous distension (Case 7 2L). PAH results in an elevation in jugular venous pressure, indicating an increase in right atrial pressure. To measure jugular venous distention, identify the top of the oscillating jugular vein waveforms with the patient in a semirecumbent position (usually a 45° angle). The distance from the sternal angle to the top of the waveform is measured in centimeters. By convention, 5 cm is then added to this measurement, as the right atrium is approximately 5 cm below the sternal angle. Four centimeters above the sternal angle is the upper limit of normal for jugular venous distension and this corresponds to a jugular venous pressure of 9 cm H₂O (4 cm + 5 cm).

Quality of jugular venous waves. The jugular venous wave is composed of three peaks or positive deflections (*a*, *c*, and *v*) and two descents (*x* and *y*) (Figure 1). The morphology of these waves can be altered by a number of cardiovascular diseases, including PAH. The *a* wave results from venous distension during right atrial contraction. The *x* descent occurs during right atrial relaxation. The *c* wave is generated by the bowing of the tricuspid valve into the right atrium during ventricular systole. The *v* wave occurs due to increased right atrial pressure as venous blood fills the right atrium during ventricular contraction when the tricuspid

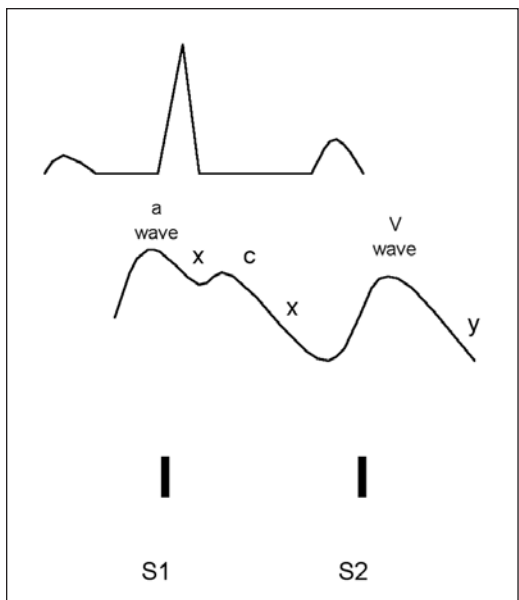


Fig 1a. Jugular venous pulse waves and descents and their relation to the ECG and heart sounds.

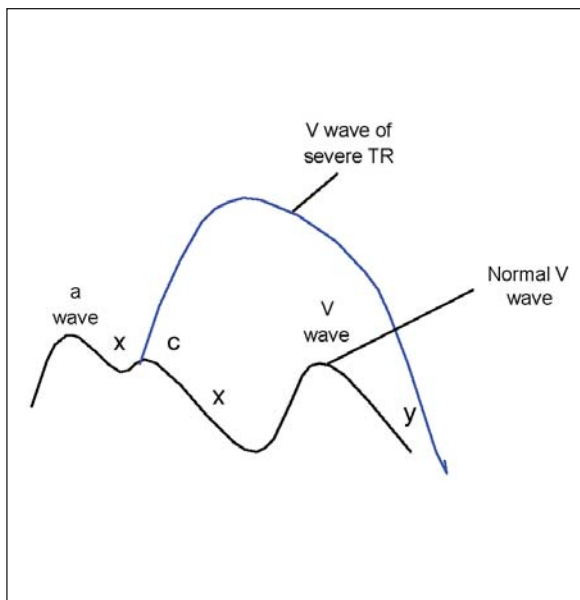


Fig 1b. Jugular venous wave forms in a normal individual and in a patient with severe tricuspid regurgitation (TR). Note the significant increase in size of the "c-v" wave.

valve is closed. The y wave is related to the decrease in right atrial pressure as the tricuspid valve opens.

Pulmonary hypertension can affect the a wave and the v wave as well as their associated descents. Contraction of the right atria against increased downstream resistance (such as occurs in PAH) results in an increased a wave (**Case 2: 3L**). Significant tricuspid regurgitation (common in PAH) increases the amplitude of the v wave (**Case 7: 2L**). Typically in severe PAH, the v wave is the more prominent of the two waveforms.

Cardiac Sounds

Normal Findings

S1 and S2. The first heart sound (S1) is generated by the closing of the mitral (M1) and tricuspid (T1) valve, while the second heart sound (S2) is produced by the closure of the aortic (A2) and pulmonic (P2) valves, respectively. Normally, S1 is heard as a single sound as the mitral and tricuspid valves close essentially simultaneously. The second heart sound (S2) varies within the respiratory cycle. During expiration, S2 is heard as a single sound as the aortic and pulmonic valve close together. However, during inspiration, negative intrathoracic pressure generated by the diaphragm causes increased blood flow to the right heart. This increased flow delays the closure of the pulmonic valve and a "split" second heart sound, which is an audible differentiation of A2 and P2, can be detected (**Figure 2a**).

Findings in PAH

S2 (Case 6 or 7: 3L). The second heart sound is frequently accentuated in patients with pulmonary hypertension. This is because the intensity of P2 is dependent on the velocity of blood coursing back toward the right ventricle after ventricular contraction and the suddenness in which that motion is arrested by the closing valve. In patients with PAH, the diastolic pressure within the pulmonary artery is high

and therefore the velocity of blood moving toward the tricuspid valve is increased, resulting in an accentuated P2.

Widened splitting.

This refers to a longer than expected interval between S1 and S2 and can be caused by pulmonic valve stenosis (this is not a true form of PAH but can present with right heart failure and is easy to misdiagnose by history as well as by echocardiography). A widened split S2 can be an important clue to pulmonic stenosis (**Figure 2b**).

Fixed splitting.

This refers to an audible separation between A2 and

P2 that persists through both inspiration and expiration (**Figure 2c**). This finding frequently indicates the presence of an atrial septal defect. The fixed splitting is due to the continuous delay of P2 closure throughout the cardiac cycle related to increased blood flow to the right ventricle. The blood flow to the right ventricle is increased in inspiration for the reasons discussed above and increased in expiration from the volume of blood shunted from the left to the right heart through the septal defect.⁴

Extra Cardiac Sounds in PAH

S3. An S3 occurs in early diastole during the ventricular rapid filling stage, following the opening of the atrioventricular valves. While an S3 heard in children or young adults is often a normal finding, in older individuals, patients with a depressed left ventricular ejection fraction, and patients with PAH an S3 is a sign of increased diastolic ventricular filling pressure and ventricular failure.⁵ The sound is generated by the tensing of the chordae tendineae. A right-sided S3 (more typical of patients with PAH) is best appreciated with the bell of the stethoscope placed over the tricuspid region with the patient in the supine position and during inspiration.³

S4. An S4 occurs late in diastole and is caused by contraction of the atria as they force the last of the blood from the atria into a stiffened ventricle just prior to ventricular systole. The presence of an S4 indicates decreased ventricular compliance, often due to hypertrophy. An S4 is heard best with the bell of the stethoscope with the patient lying in the left lateral decubitus position.

Cardiac Murmurs

Heart murmurs are caused by turbulent blood flow. Pathologic changes in patients with PAH can result in a variety of murmurs detectable and distinguishable by careful auscultation.

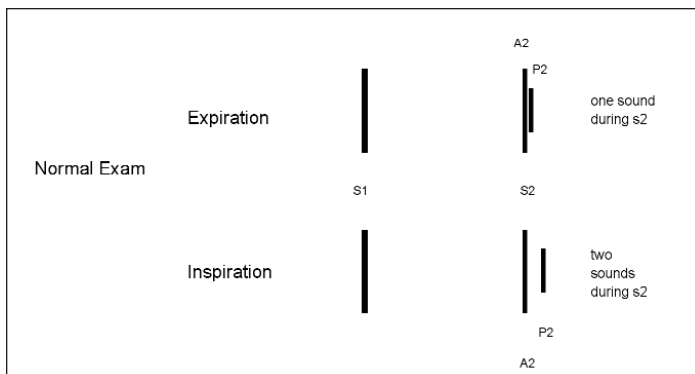


Fig 2a. Graphic representation of the normal cardiac auscultatory findings on physical examination. During inspiration P2 separates from A2 due to increased blood flow to the right heart and can be detected as a separate sound.

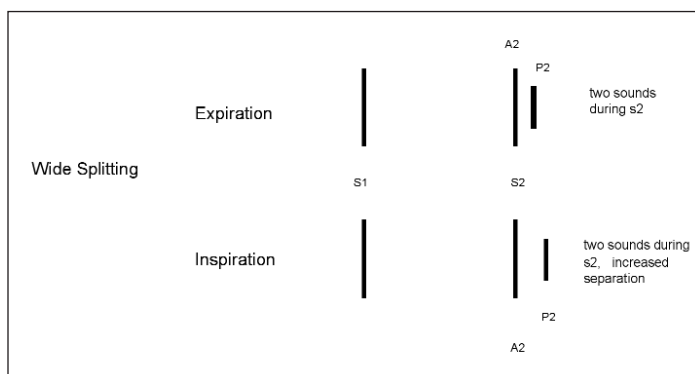


Fig 2b. Graphic representation of widened splitting of the second heart sound (S2). This can be heard in pulmonic stenosis.

Tricuspid Regurgitation (Case 7: 2L or 3L). Perhaps the most common and recognizable murmur of PAH is tricuspid regurgitation. A tricuspid regurgitation murmur is best heard along the lower left sternal border. It can radiate to the right of the sternum and is high pitched and blowing in quality. The murmur of tricuspid regurgitation is holosystolic and can be augmented by inspiration, increasing return of venous blood to the right ventricle.⁶

Ventricular Septal Defect (Case 3: 2R). The murmur of a ventricular septal defect is holosystolic. It is heard best at the 4th to 6th left intercostal space and is high pitched and may be associated with a palpable thrill. The intensity of a ventricular septal defect murmur does not change with inspiration and it does not radiate. Paradoxically, the smaller the ventricular septal defect, the greater the turbulence of blood flow moving from the high-pressure left ventricle to the low-pressure right ventricle, and thus the louder the murmur.^{7,8}

Pulmonic Stenosis (Case 1: 2L). The murmur of pulmonic stenosis is a systolic ejection murmur (crescendo-decrescendo). It is best appreciated at the left upper sternal border.⁹

Pulmonic Regurgitation (Case 2: 2L). This early diastolic murmur can occasionally be detected in patients with severe pulmonary hypertension. It occurs as the pulmonary artery dilates, resulting in pulmonic valve incompetence. It is a high-pitched, blowing murmur best heard using the diaphragm of the stethoscope and with the patient sitting

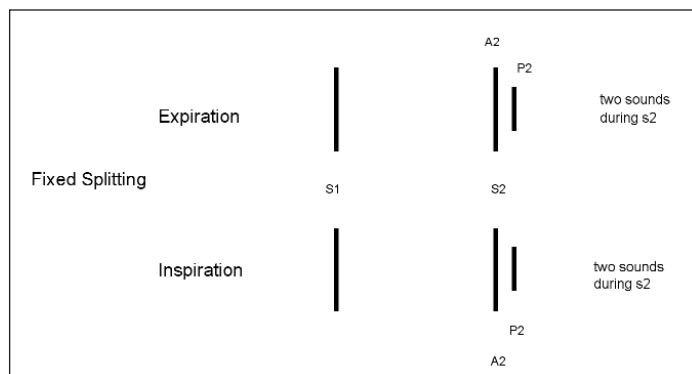


Fig 2c. Graphic representation of fixed splitting of S2 during inspiration and expiration. This is a common finding in patients with atrial septal defects.

up, leaning forward, and in fixed expiration. This murmur is also referred to as the Graham Steell murmur.³

A variety of other valvular diseases and intracardiac shunts can result in PAH; however, a discussion of all these physical findings is beyond the scope of this paper.

Other Physical Findings in PAH

Clubbing (Case 4: Insp Hands). Clubbing is a descriptive term, referring to the bulbous, uniform swelling of the soft tissue of the terminal phalanx of a digit resulting in the loss of the normal angle between the nail and the nail bed. Although clubbing is a common physical finding in many pathologic processes, the pathophysiologic mechanism of this finding remains unclear. The earliest forms of clubbing are characterized by increased glossiness of the distal skin of the finger and the root of the nail. There is then obliteration of the normal angle between the base of the nail and the skin. The soft tissue of the pulp becomes hypertrophied and the nail root floats freely. On examination one may note a spongy sensation as the nail is pressed toward the nail plate. The sponginess results from increased fibrovascular tissue between the nail and the phalanx. The skin at the base of the nail may be smooth and shiny.

Clubbing of the digits is common in congenital heart diseases that cause pulmonary hypertension (atrial septal defects, ventricular septal defects). It is an unusual finding in other forms of pulmonary hypertension.

Edema (Case 6: Insp). Edema of the lower extremities is a common finding in advanced pulmonary hypertension resulting in right heart dysfunction. Firm pressure on the pretibial region for 10 to 15 seconds may be necessary for detection of edema in less severe disease.

Hepatojugular reflux. Firm pressure over the liver (or other areas of the abdomen) can cause an increase in jugular venous distension. This is indicative of right heart failure.

Ascites. Abdominal distension with shifting dullness or a fluid wave is a sign of ascites familiar to most clinicians. The presence of ascites tends to be a late finding in patients with PAH and is indicative of severe right ventricular dysfunction and elevated right atrial pressure. Ascites is a common finding in patients with portal hypertension related to hepatic disease. As portal hypertension is recognized as being associated with pulmonary hypertension, this physical finding

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We are often confronted with treatment issues with no clear answers. Those of us who practice in this field find ourselves navigating through uncharted territories, with the decisions we make on behalf of our patients impacting their outcome. It is so imperative to have a community of colleagues who you can rely on for sound and trusted advice and opinions—that's where PHCR comes in.

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may provide a clue toward the etiology of the elevated pulmonary pressures.

Raynaud Phenomenon (? Case 4: Insp Hands). The Raynaud phenomenon is an occasional finding in patients with idiopathic pulmonary arterial hypertension (IPAH) and a common finding in individuals with PAH associated with connective tissue disease, in particular, limited-stage scleroderma or CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia).

References

1. Butman SM, Ewy GA, Standen JR, Kern KB, Hahn E. Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. *J Am Coll Cardiol.* 1993;22:968-74.
2. Ducas J, Magder S, McGregor M. Validity of the hepatojugular reflux as a clinical test for congestive heart failure. *Am J Cardiol.* 52;1983: 1299-303.
3. Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* New York, NY: WB Saunders Company; 1997.
4. Perloff JK. *The Clinical Recognition of Congenital Heart Disease.* New York, NY: WB Saunders Company; 1994.
5. Van de WF, Geboers J, Kesteloot H, De Geest H, Barrios L. The mechanism of disappearance of the physiologic third heart sound with age. *Circulation.* 1986;73:877-84.
6. Rios JC, Massumi RA, Breesmen WT, Sarin RK. Auscultatory features of acute tricuspid regurgitation. *Am J Cardiol.* 1969;23:4-11.
7. Leatham A, Segal B. Auscultatory and phonocar-diographic signs of ventricular septal defect with left-to-right shunt. *Circulation.* 1962;25:318-27.
8. Newburger JW, Rosenthal A, Williams RG, Fellows K, Miettinen OS. Noninvasive tests in the initial evaluation of heart murmurs in children. *N Engl J Med.* 1983;308:61-4.
9. Kaplan S, Adolph RJ. Pulmonic valve stenosis in adults. *Cardiovasc Clin.* 1979;10:327-39.

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Initial Diagnostic Testing in the Evaluation of Pulmonary Hypertension



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Diagnosing pulmonary arterial hypertension (PAH) requires a high index of clinical suspicion from even the most astute clinician, especially given the lack of specificity of the symptoms offered by the PAH patient. In addition, even mild elevations in pulmonary arterial pressure may represent fairly advanced pulmonary vascular disease making early detection difficult.¹ As discussed by Dr Bull in the accompanying article, many clues from the history and physical may prompt further testing. In this segment, the noninvasive methods available to pursue a diagnosis of PAH will be reviewed.

The Electrocardiogram

While electrocardiography lacks sufficient sensitivity to serve as an effective screening tool for PAH, it can contribute important prognostic information and should be performed.¹ Right ventricular hypertrophy and right-axis deviation can be detected 87% and 79% of the time in PAH.² Findings suggestive of PAH include a tall R wave and small S wave (R/S ratio greater than 1) in lead V_1 , a large S wave and small R wave (R/S ratio less than 1) in lead V_5 or V_6 , a qR complex in V_1 , an rSR' pattern in lead V_1 , or an $S_1S_2S_3$ pattern. Right atrial enlargement should also be looked for, defined as a tall P wave in lead II, III, and aVF (greater than 2.5 mm) and a frontal P axis of 75 or greater. However, the absence of these findings does not exclude a diagnosis of PAH, with one study of 61 patients with PAH showing 8 with normal electrocardiograms despite severe PAH, and sensitivities of 73% for right-axis deviation and 55% for right ventricular hypertrophy noted.³ Specificity was only 70% in that population as well.³ The ECG may be helpful prognostically, independent of its role in diagnosis, in patients with established PAH since the presence of right atrial enlargement (P wave 0.25 millivolts or greater) has been associated with a 2.8-fold greater risk of death over a 6-year period of observation.⁴ The presence of electrocardiographic findings of right atrial enlargement, right ventricular hypertrophy, and right-axis deviation should prompt further evaluation in the patient with suspected PAH.

Chest Radiography

Like the electrocardiogram, a chest radiograph should be

obtained in all patients with suspected PAH even though it lacks sensitivity and specificity to establish a diagnosis. Suggestive clues that should be sought include attenuated peripheral markings, enlarged main and hilar pulmonary artery shadows, and obscuration of the retrosternal clear space on a lateral view due to an enlarged right ventricle. Lupi et al described a radiologic index in PAH defined as the ratio of the summed horizontal measurement of the pulmonary arteries from the midline to their first division divided by the entire transverse chest diameter.⁵ The chest radiograph may also define concomitant pulmonary parenchymal disease, pulmonary venous congestion (seen in pulmonary veno-occlusive disease), hyperinflation changes of chronic obstructive pulmonary disease (COPD), kyphosis, or findings suggestive of chronic thromboembolic pulmonary hypertension (CTEPH) such as mosaic oligemia, right ventricular hypertrophy, or an enlarged descending right pulmonary artery.⁶ The extent of radiographic abnormalities and the degree of PAH in any given patient do not appear to be correlated.¹

Transthoracic Echocardiography

The reliability of Doppler echocardiography to quantify PAH has been extensively studied. While numerous studies report excellent correlation coefficients as a measure of accuracy, technical aspects of interrogation make tricuspid regurgitant jets (a requisite feature of systolic pulmonary arterial pressure estimates by the modified Bernoulli equation) analyzable in anywhere from 39%⁷ to 86%⁸ of patients. Patients with advanced lung disease may represent a challenge as estimates of systolic pulmonary arterial pressure were achievable in only 44% of 166 such patients in one study.⁹ When tricuspid and pulmonic valve regurgitant jets are not present or quantifiable, estimates of pulmonary diastolic pressures may be useful¹⁰ and these correlate well with right-heart catheterization measures.¹¹ While correlations are generally strong with catheterization data the magnitude of difference between estimated and true pulmonary arterial pressure as measured by right-heart catheterization can be significant, with mean differences ranging from 3 to 38 mm Hg.¹ Discordance is generally greatest at extremes, with

underestimation common when systolic pulmonary arterial pressure is greater than 100 mm Hg.¹² Advanced lung disease patients pose a special challenge, with 48% of patients misclassified as having PAH and 52% of pressure estimates inaccurate in a cohort of 374 patients being assessed for lung transplantation.⁹ Despite these caveats, the sensitivity and specificity of Doppler echocardiography range from 0.79 to 1.0 and 0.6 to 0.98, respectively.¹³⁻¹⁶

The role of exercise echocardiographic testing to unmask PAH remains controversial. One study examined the features of the resting echocardiogram (with normal resting systolic pulmonary arterial pressure) in those with exercise-induced PAH and found that tricuspid regurgitation and right ventricular outflow velocity time integral at peak velocity distinguished exercise PAH from normal PAH.¹⁶ Interestingly, recent studies of idiopathic pulmonary hypertension (IPAH) family members suggest that supine bicycle exercise echocardiography may identify a subgroup of asymptomatic carriers of the PAH gene.^{17,18}

Since false-positive testing is more common when the prevalence of disease is low, focused ordering of Doppler echocardiography in an asymptomatic population at risk is advisable,¹ as overestimation of systolic pulmonary arterial pressure is more likely in populations with normal pressures.^{15,19} Risk factors that warrant screening echocardiography include known genetic mutations associated with PAH, a first degree relative with familial PAH (FPAH), a diagnosis of scleroderma, portal hypertension prior to liver transplantation, or congenital heart disease with systemic-to-pulmonary shunts.¹ When PAH is suspected or estimated by Doppler echocardiography, a contrast “bubble” echocardiogram should be obtained to assess for left-to-right shunting.¹ In addition, left atrial enlargement, even in the absence of left ventricular dysfunction, should raise the possibility of elevated left-sided pressures that may be contributing to the pulmonary pressure elevation seen. When present, right-heart catheterization, and often left-heart catheterization, to measure transpulmonary gradient and to assess for diastolic dysfunction is crucial.¹

Serologic Testing

In order to define PAH association with certain connective tissue disease, a serologic assessment should be performed in conjunction with features of the individual patient's history and exam findings. Since the most common connective tissue disease associated with PAH, limited scleroderma, typically will not manifest interstitial disease on exam or chest radiography, patients with perceived IPAH should be carefully assessed for features of systemic sclerosis. Estimates of PAH prevalence in scleroderma range from 4.9%²⁰ to 38%.²¹ When PAH is present in association with diffuse scleroderma, U3-RNP antibodies are often positive.²² When PAH develops in those with limited scleroderma it usually does so slowly¹ and in association with 1) positive anticentromere antibodies,²³ 2) positive antinuclear antibodies including U3-RNP, B23, Th/To, and U1-RNP,²⁴⁻²⁶ and 3) marked reductions in diffusing capacity for carbon monoxide (DLCO) on pulmonary function testing.^{13,27} In fact, 20% of those with limited scleroderma and isolated

carbon monoxide diffusing capacity reductions of less than 55% of predicted values will acquire PAH within 5 years.²⁸

Other connective tissue diseases such as systemic lupus erythematosus, polymyositis, and rheumatoid arthritis are less commonly associated with PAH.^{29,30} In mixed connective tissue disease, however, one study found that PAH was the most common cause of death, occurring in 38% of these patients.³¹ Anticardiolipin antibodies have been associated with PAH in at least two studies of systemic lupus erythematosus patients.^{32,33} Human immunodeficiency virus (HIV) is associated with PAH in up to 0.5% of HIV infections,³⁴ and HIV testing is advised in all appropriate cases of unexplained PAH.¹ Evaluation for liver disease is also appropriate as 2% of these patients have been found to have PAH in one study.³⁵ Thyroid function abnormalities have also been suggested as a risk factor for PAH, although it is unclear at present whether thyroid disease is causally related to PAH.¹

Excluding Thromboembolic Disease

Since PAH develops as a complication of chronic thromboembolic disease (CTEPH) and can mimic IPAH, this potentially surgically remediable entity should be looked for in all patients with PAH.¹ Indeed, one recent study concluded that CTEPH occurs in up to 4% of patients surviving their pulmonary embolism, usually within 2 years of the event.³⁶ Ventilation-perfusion (V/Q) scanning is the screening method of choice, typically showing one or more segmental-sized mismatched defects.³⁷ A normal V/Q scan effectively rules out CTEPH.^{38,39} Perfusion scans alone tend to underestimate the severity of vessel obstruction in CTEPH.⁴⁰ While both contrast-enhanced computerized tomography and magnetic resonance imaging have utility in defining alternative diagnoses (eg, sarcoma, vasculitis, mediastinal fibrosis) and may be complementary to V/Q scanning, these techniques should not be used to exclude the diagnosis of CTEPH.¹ Pulmonary angiography is ultimately required for accurate diagnosis and anatomic definition of CTEPH and remains the procedure of choice.¹

Pulmonary Function Testing

Pulmonary function testing is an important adjunct in the initial evaluation of all patients with PAH. Restrictive defects are not uncommon in IPAH and CTEPH patients, with 20% demonstrating such defects at initial evaluation,^{2,37} and mild diffusing capacity for carbon monoxide impairment is likewise often observed in these patients.⁴¹ Isolated abnormalities in carbon monoxide diffusing capacity occur in limited scleroderma^{13,27} and, in fact, when severe (less than 55% of predicted), 35% of these patients will acquire demonstrable PAH within 5 years.²⁸ A fall in the carbon monoxide diffusing capacity values is suggestive of early development of PAH.²⁸ A widened alveolar-arterial oxygen gradient may also be suggestive of IPAH and CTEPH.³⁸ Desaturation during exercise occurs in all forms of PAH because of the inability of the failing right ventricle to increase cardiac output adequately.¹ Nocturnal oxygen desaturation, even in the absence of sleep-disordered breathing, is surprisingly common in PAH, occurring in up to 75% of IPAH patients.⁴²

Magnetic Resonance Imaging

Exquisite experimental work using MRI evaluation of right ventricular dysfunction in PAH has begun to appear in the literature,^{43,44} with some authors proposing it may be superior to echocardiography in estimating pulmonary arterial pressure.⁴⁴ In CTEPH, one report suggested that good correlation to V/Q results can be expected with MRI in experienced hands.^{45,46} Noninvasive measures of right ventricular chamber size,²⁰ shape, thickness, and mass can also be offered by MRI,⁴⁷ and mean pulmonary arterial pressure has been shown to correlate with MRI measurement of right ventricular thickness, main pulmonary artery diameter,⁴⁸ and right ventricular mass.⁴⁹ Nonetheless, the incremental clinical value of MRI and computed tomographic techniques to traditional echocardiographic assessments in PAH have not been reported.¹

Exercise Testing

Measures of exercise intolerance may be helpful in diagnosing early PAH (before it is present at rest) as well as in predicting survival and response to therapy.^{50,51} Because PAH patients are limited in the extent to which they are able to raise cardiac output in response to tissue oxygen demands, small increases in workload can result in significant hypoxemia. Reductions in maximum peak oxygen consumption ($VO_{2\text{ max}}$), anaerobic threshold, peak O_2 pulse, rate of increase in VO_2 , and ventilatory efficiency as assessed by cycle ergometry cardiopulmonary exercise testing correlate well with New York Heart Association functional class.⁵² In addition end-tidal partial pressure of carbon monoxide (P_{ETCO_2}) in IPAH patients is significantly reduced at rest and exercise in proportion to physiologic disease severity, and this finding on cardiopulmonary exercise testing when accompanied by arterial hypoxemia should trigger consideration of pulmonary vasculopathy.⁵³ Cardiopulmonary exercise testing has been found reproducible and safe without complications or fatalities in even the most severely exercise-intolerant PAH patient.⁵⁴ Peak VO_2 and peak systolic blood pressure during cardiopulmonary exercise testing have also been shown to independently predict survival in PAH patients.⁵⁵ Peak VO_2 measures and ventilatory efficiency by cardiopulmonary exercise testing also show progressive improvement in response to surgical thromboendarterectomy in CTEPH.⁵⁶

A simple and practical substitute for full cardiopulmonary exercise testing is the 6-minute walk test. This validated test shows strong correlation between the distance ambulated and peak VO_2 seen on cardiopulmonary exercise testing,⁵⁷ as well as to total pulmonary vascular resistance, mean right atrial pressure, baseline cardiac output, and New York Heart Association functional class.⁵⁸ The 6-minute walk test can also predict disease progression and patient's response to therapy⁵⁹ and is commonly used for this purpose clinically.

Summary

While right-heart catheterization is ultimately required, a constellation of noninvasive tests exist to aid the clinician in consolidating his or her diagnosis of PAH. These include the

electrocardiography, chest radiography, pulmonary function tests, nocturnal oximetry, blood serologies, computed tomography, Doppler echocardiography with and without "bubble" contrast, and cardiopulmonary exercise testing. While none of these taken in isolation are adequate to definitively establish the diagnosis, when assessed in combination these tests are most helpful in defining who should proceed to right-heart catheterization. All patients with unexplained PAH should undergo V/Q scanning to avoid missing surgically remediable CTEPH. While magnetic resonance imaging and contrast-enhanced computed tomographic angiography can be complimentary, pulmonary angiography remains the procedure of choice to define operability when CTEPH is uncovered.

References

1. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:14S-34S.
2. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med*. 1987;107:216-23.
3. Ahern GS, Tapson VF, Rebeiz A, et al. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. *Chest*. 2002;122:524-7.
4. Bossone E, Paciocco G, Iarussi D, et al. The prognostic role of the ECG in primary pulmonary hypertension. *Chest*. 2002;121:513-8.
5. Lupi E, Dumont C, Tejada VM, et al. A radiologic index of pulmonary hypertension. *Chest*. 1975;68:28-31.
6. Woodruff WW III, Hoeck BE, Chitwood WR Jr, et al. Radiographic findings in pulmonary hypertension from unresolved embolism. *AJR Am J Roentgenol*. 1985;144:681-6.
7. Murata I, Kihara H, Shinohara S, et al. Echocardiographic evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. *Jpn Circ J*. 1992;56:983-91.
8. Borgeson DD, Seward JB, Miller FA Jr, et al. Frequency Doppler measurable pulmonary artery pressures. *J Am Soc Echocardiogr*. 1996;9:832-7.
9. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med*. 2003;735-40.
10. McGoon MD, Fuster V, Freeman WK, et al. The heart and lungs: pulmonary hypertension. In: Guiliiani ER, Gersh BJ, Holmes DR, et al, eds. *Mosby Yearbook*. New York, NY: Mosby; 1996:1815-36.
11. Stephen B, Dalal P, Berger M, et al. Noninvasive estimation of pulmonary artery diastolic pressure in patients with tricuspid regurgitation by Doppler echocardiography. *Chest*. 1999;116:73-7.
12. Brecker SJ, Gibbs JS, Fox KM, et al. Comparison of Doppler derived haemodynamic variables and simultaneous high fidelity measurements in severe pulmonary hypertension. *Br Heart J*. 1994;72:384-9.
13. Denton CP, Cailles JB, Phillips GD, et al. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Br J Rheumatol*. 1997;36:239-43.
14. Kim WR, Krowka MJ, Plevak DJ, et al. Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transpl*. 2000;6:453-8.
15. Penning S, Robinson KD, Major CA, et al. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. *Am J Obstet Gynecol*. 2001;184:1568-70.
16. Bossone E, Avelar E, Bach DS, et al. Diagnostic value of resting tricuspid regurgitation velocity and right ventricular ejection flow parameters for the detection of exercise induced pulmonary arterial hypertension. *Int J Card Imaging*. 2000;16:429-36.
17. Gruenig E, Janssen B, Mereles D, et al. Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. *Circulation*. 2000;102:1145-50.

18. Rindermann M, Grunig E, von Hippel A, et al. Primary pulmonary hypertension maybe a heterogeneous disease with a second locus on chromosome 2q31. *J Am Coll Cardiol.* 2003;41:2237-44.
19. Naeije R, Torbicki A. More on the noninvasive diagnosis of pulmonary hypertension: Doppler echocardiography revisited. *Eur Respir J.* 1995;8:1445-9.
20. Koh ET, Lee P, Gladman DD, et al. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol.* 1996;35:989-93.
21. Rolla G, Colagrande P, Scappaticci E, et al. Exhaled nitric oxide in systemic sclerosis: relationships with lung involvement and pulmonary hypertension. *J Rheumatol.* 2000;27:1693-8.
22. Sacks DG, Okano Y, Steen VD, et al. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. *J Rheumatol.* 1996;23:639-42.
23. Steen VD, Ziegler GL, Rodnan GP, et al. Clinical and laboratory associations of anticentromere antibody in patients with progressive systemic sclerosis. *Arthritis Rheum.* 1984;27:125-31.
24. Okano Y, Steen VD, Medsger TA Jr. Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. *Arthritis Rheum.* 1992;35:95-100.
25. Mitri GM, Lucas M, Fertig N, et al. A comparison between anti-Th/To- and anticentromere antibody-positive systemic sclerosis patients with limited cutaneous involvement. *Arthritis Rheum.* 2003;48:203-9.
26. Ulanet DB, Wigley FM, Gelber AC, et al. Autoantibodies against B23, a nucleolar phosphoprotein, occur in scleroderma and are associated with pulmonary hypertension. *Arthritis Rheum.* 2003;49:85-92.
27. Stupi AM, Steen VD, Owens GR, et al. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum.* 1986;29:515-24.
28. Steen VD, Graham G, Conte C, et al. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum.* 1992;35:765-70.
29. Dawson JK, Goodson NC, Graham DR, et al. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology (Oxford).* 2000;39:1320-5.
30. Aoki A, Kenmochi H, Hagiwara E, et al. Pulmonary hypertension in a patient with primary Sjogren's syndrome, Hashimoto's disease, and primary biliary cirrhosis [in Japanese]. *Nihon Rinsho Meneki Gakkai Kaishi.* 2000;23:462-9.
31. Raeside DA, Chalmers G, Clelland J, et al. Pulmonary artery pressure variation in patients with connective tissue disease: 24 hour ambulatory pulmonary artery monitoring. *Thorax.* 1998;53:857-62.
32. Falcoa CA, Alves IC, Chahade WH, et al. Echocardiographic abnormalities and antiphospholipid antibodies in patients with systemic lupus erythematosus. *Arq Bras Cardiol.* 2002;79:285-91.
33. Asherson RA, Higgenbottam TW, Dinh Xuan AT, et al. Pulmonary hypertension in a lupus clinic: experience with twenty-four patients. *J Rheumatol.* 1990;17:1292-8.
34. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection: comparison with primary pulmonary hypertension. *Circulation.* 1994;89:2722-7.
35. Hadengue A, Benhayoun MK, Lebrec D, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology.* 1991;100:520-8.
36. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;350:2257-64.
37. Viner SM, Bagg BR, Auger WR, et al. The management of pulmonary hypertension secondary to chronic thromboembolic disease. *Prog Cardiovasc Dis.* 1994;37:79-82.
38. D'Alonzo GE, Bower JS, Dantzker DR. Differentiation of patients with primary and thromboembolic pulmonary hypertension. *Chest.* 1984;85:457-61.
39. Fishman AJ, Moser KM, Fedullo PF. Perfusion lung scans vs pulmonary angiography in evaluation of suspected primary pulmonary hypertension. *Chest.* 1983;84:679-83.
40. Ryan KL, Fedullo PF, Davis GB, et al. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. *Chest.* 1988;93:1180-5.
41. Steenhuis LH, Groen HJ, Koeter GH, et al. Diffusion capacity and haemodynamics in primary and chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2000;16:276-81.
42. Rafanan AL, Golish JA, Dinner DS, et al. Nocturnal hypoxemia is common in primary pulmonary hypertension. *Chest.* 2001;120:894-9.
43. Laffon E, Vallet C, Bernard V, et al. A computed method for non-invasive MRI assessment of pulmonary hypertension. *J Appl Physiol.* 2004;96:463-8.
44. Saba TS, Foster J, Cockburn M, et al. Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure. *Eur Respir J.* 2002;20:1519-24.
45. Bergin CJ, Hauschildt J, Rios G, et al. Accuracy of MR angiography compared with radionuclide scanning in identifying the cause of pulmonary arterial hypertension. *AJR Am J Roentgenol.* 1997;168:1549-55.
46. Hatabu H, Geffter WB, Axel L, et al. MR imaging with spatial modulation of magnetization in the evaluation of chronic central pulmonary thromboemboli. *Radiology.* 1994;190:791-6.
47. Boxt LM. MR imaging of pulmonary hypertension and right ventricular dysfunction. *Magn Reson Imaging Clin N Am.* 1996;4:307-25.
48. Frank H, Globits S, Glogar D, et al. Detection and quantification of pulmonary artery hypertension with MR imaging: results in 23 patients. *AJR Am J Roentgenol.* 1993;161:27-31.
49. Katz J, Whang J, Boxt LM, et al. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. *J Am Coll Cardiol.* 1993;21:1475-81.
50. Waxman AB. Pulmonary function test abnormalities in pulmonary vascular disease and chronic heart failure. *Clin Chest Med.* 2001;751-8.
51. Janicki J, Weber K, Likoff M, et al. Exercise testing to evaluate patients with pulmonary vascular disease. *Am Rev Respir Dis.* 1984;129:S93-5.
52. Sun XG, Hansen JE, Oudiz RJ, et al. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation.* 2001;104:429-35.
53. Yasunobu Y, Oudiz RJ, Sun XG, et al. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest.* 2005;127:1637-46.
54. Hansen JE, Sun XG, Yasunobu Y, et al. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary hypertension. *Chest.* 2004;126:816-24.
55. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension. Importance of cardiopulmonary exercise testing. *Circulation.* 2002;106:319-24.
56. Iwase T, Nagaya N, Ando M, et al. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. *Heart.* 2001;86:188-92.
57. Cahalin LP, Mathier MA, Semigran MJ, et al. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest.* 1996;110:325-32.
58. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2000;161:487-92.
59. Wax D, Garofano R, Barst RJ. Effects of long-term infusion of prostacyclin on exercise performance in patients with primary pulmonary hypertension. *Chest.* 1999;914-20.

Cardiac Catheterization in Pulmonary Arterial Hypertension: An Updated Guide to Proper Use



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This article discusses several features of cardiac catheterization, specifically right-heart catheterization, as they relate to patients with pulmonary arterial hypertension (PAH).

Cardiac catheterization remains the gold standard and an essential component in the diagnosis and evaluation of PAH. While echocardiography can act as a very useful screening tool for the presence of pulmonary hypertension, it provides only an estimate of right ventricular systolic pressure. In an individual patient, this estimate may be quite close to the actual pulmonary arterial systolic pressure,^{1,2} or it may be a gross over- or underestimate. Thus, while pulmonary hypertension may be suspected on the basis of an echocardiogram, the patient should not be diagnosed as having pulmonary hypertension until it is confirmed by cardiac catheterization. This principle applies regardless of the cause of the pulmonary hypertension. Moreover, the information obtained from cardiac catheterization in combination with clinical findings can be used to monitor therapeutic and adverse effects of medical interventions. In addition to limitations in pressure estimates, the lack of ability of echocardiography to measure pulmonary capillary wedge (PCW) pressure (and thus left ventricular end diastolic pressure) bears important clinical significance, since it is essential to exclude pulmonary venous hypertension when making the diagnosis of PAH.

The standard definition of pulmonary hypertension is defined by most experts as a mean pulmonary arterial pressure of ≥ 25 mm Hg, with a concomitant pulmonary capillary wedge pressure of ≤ 15 mm Hg, and pulmonary vascular resistance of > 3 Wood units. These criteria are derived from the National Institutes of Health (NIH) registry of patients with primary pulmonary hypertension, now known as idiopathic pulmonary arterial hypertension (IPAH).³

Measurement of hemodynamics in patients with PAH via cardiac catheterization can also provide added prognostic value. For example, in patients with primary pulmonary hypertension whose mean right atrial pressure was less than 10 mm Hg, median survival was nearly 50 months without

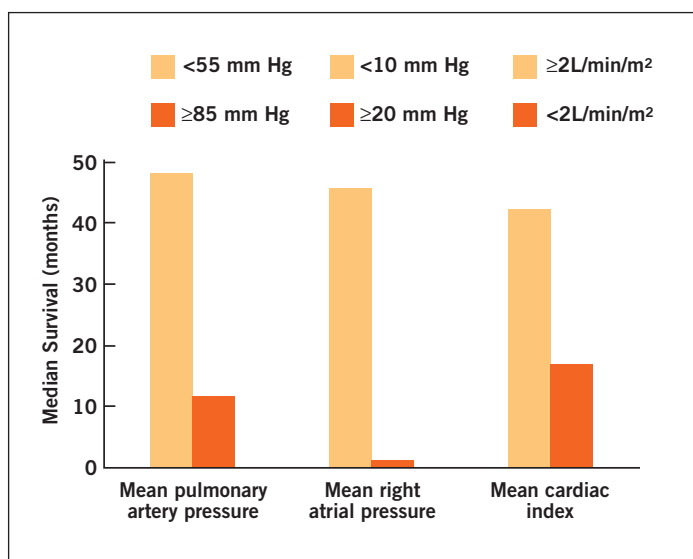


Figure 1. Survival and hemodynamics in idiopathic pulmonary arterial hypertension.

pulmonary vasodilator therapy, compared with less than 3 months in patients whose mean right atrial pressure was 20 mm Hg or greater (**Figure 1**).⁴

The Catheterization Procedure

The Catheter

The pulmonary artery (right heart) catheter is designed for use in the intensive care unit (ICU) or in the cardiac catheterization laboratory to measure right-heart and pulmonary arterial hemodynamics, to estimate left ventricular end diastolic pressure, and to measure cardiac output. The catheter is usually 120 cm long and has multiple lumens so that pressure recordings and infusions can be made from various locations in the heart and pulmonary arteries. In addition, a small plastic balloon that is located at the tip of the catheter can be inflated and used to “float” the catheter in the direction of blood flow in order to facilitate catheter advancement. This balloon is also used to occlude the pul-

monary artery in order to obtain estimates of left atrial pressure (see below). Finally, a thermistor (temperature indicator) is also located at the tip of the catheter; it is used to detect changes in blood temperature when performing thermodilution cardiac output measurements (see below).

When performing right-heart catheterization specifically for patients with PAH, the catheter used often has several modifications that are designed to facilitate the catheterization process. The catheter is stiffer than the standard right-heart catheter and contains a blind-end port, which allows passage of a guidewire for additional stiffness, if desired. This extra stiffness is often needed because advancing the catheter into the pulmonary artery can be technically difficult in the presence of a dilated right ventricle, elevated pulmonary arterial pressure, and tricuspid regurgitation.

Precautions

When planning cardiac catheterization for a patient with suspected PAH, it is important to understand the risks associated with the procedure and to have an emergency treatment plan in place should these risks occur. In addition, the desired measurements should be planned in advance, with careful consideration of the specific operational procedures that are to be done during the procedure.

Clinicians should be very familiar with how to interpret the measurements obtained at cardiac catheterization and be able to troubleshoot suspected inaccuracies. Anticipation of complications and unexpected findings is essential, so that immediate action can be taken. Finally, the clinician must continuously scrutinize the findings and question the measurements for both accuracy and clinical relevance.

Patients with PAH may present with relatively few physical signs of PAH, yet have significant cardiovascular abnormalities. These patients, with “compensated right-heart failure,” can easily decompensate when subjected to the stressors of cardiac catheterization. Despite these risks, however, cardiac catheterization is safe if appropriate precautions are carried out.

- **Staff experience.** The physician and nursing and technical staff must all be familiar with the diagnosis and management of PAH and with the catheterization laboratory equipment. The staff must be meticulous about flushing and leveling the pressure transducers and flushing the catheter to ensure that accurate measurements are recorded.
- **Patient sedation.** It is generally recommended that adult patients be kept awake during catheterization. However, it is important that anxiety, which may induce tachycardia and hemodynamic embarrassment, be controlled. Small doses of benzodiazepines are useful for controlling anxiety. Close attention to continuous pulse oximetry is required, however, as hypoxemia during catheterization is not uncommon.
- **Atrial and ventricular ectopy.** As the catheter is manipulated into positions in the right atrium and ventricle, ectopic electrical activity is common. Usually, atrial premature beats and ventricular ectopic beats are brief and self-limited. Sustained activity including atrial and ventricular tachycardia may occur, however. Immediate repositioning or removal of the catheter is required in these instances, and antiarrhythmic therapy should always be available should the arrhythmia persist.

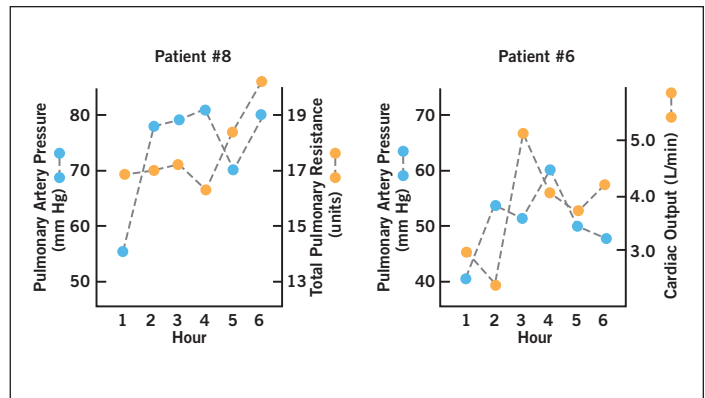


Figure 2. Spontaneous variation in pulmonary arterial hemodynamics over time in two representative patients.

- **Reliability of measurements.** Cardiac catheterization measurements should be made preferably when the patient is supine, with anxiety minimized (see above), and at steady state. Spontaneous variation in hemodynamics over time is a known shortcoming of cardiac catheterization (**Figure 2**)⁵ and thus great care should be taken to ensure that all measurements are taken in close proximity of each other. In general, waiting at least 15 minutes after catheter insertion is advisable. Hemodynamic measurements should then be obtained as close together as possible.

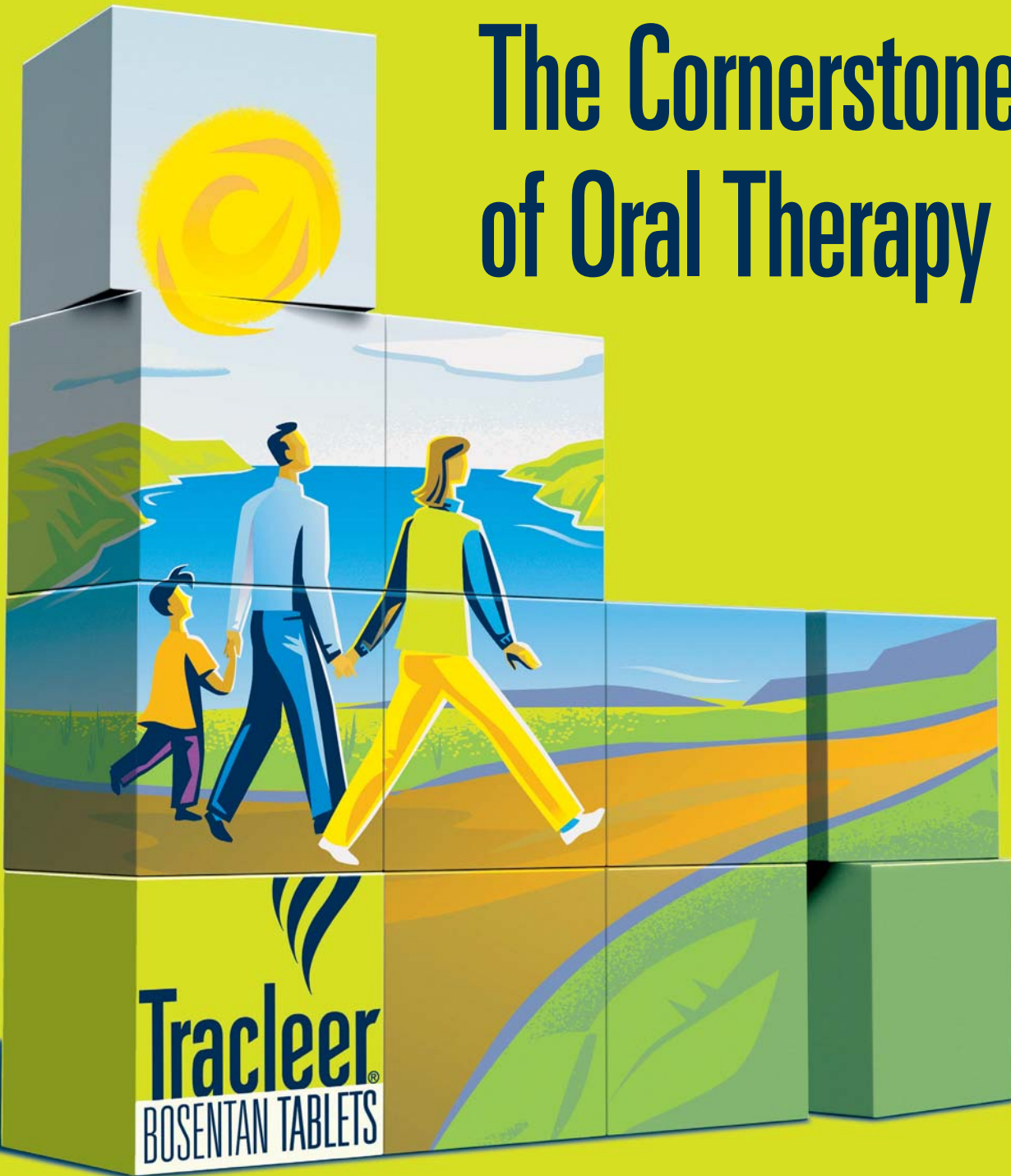
Choice of Venous Access Sites

Commonly, the right internal jugular vein is used for insertion of a venous sheath through which the pulmonary artery catheter is passed. For patients in whom it is difficult to advance the catheter into the pulmonary artery because of high pulmonary arterial pressures, the right internal jugular approach may be superior to approaches via the inferior vena cava. This is because the former approach allows the catheter to form a natural curve on the floor of the dilated right ventricle and point upward into the main pulmonary artery, making it easier to advance into the more distal pulmonary arteries. Other sites can be advantageous, depending on the situation (**Table 1**). Formerly, for a patient’s initial

For Patients with Pulmonary Arterial
Hypertension WHO Class III or IV



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Please see the following brief summary of prescribing information.

In Pulmonary Arterial Hypertension WHO Class III or IV

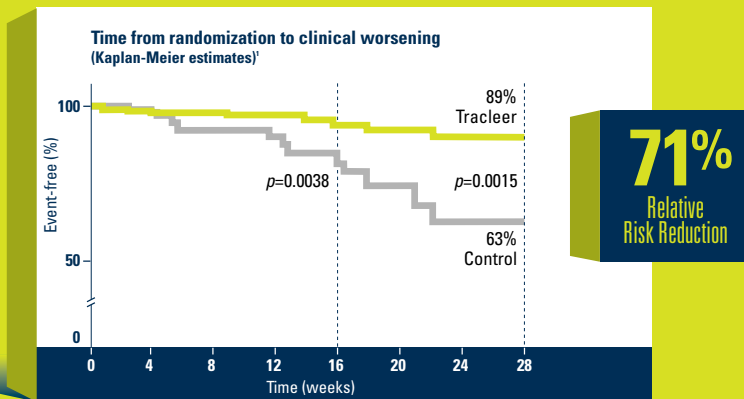


Start with Tracleer

The oral endothelin receptor antagonist backed by long-term data

- Improves exercise ability
- Improves hemodynamics (CI, PAP, PVR, RAP)

Reduces risk of clinical worsening



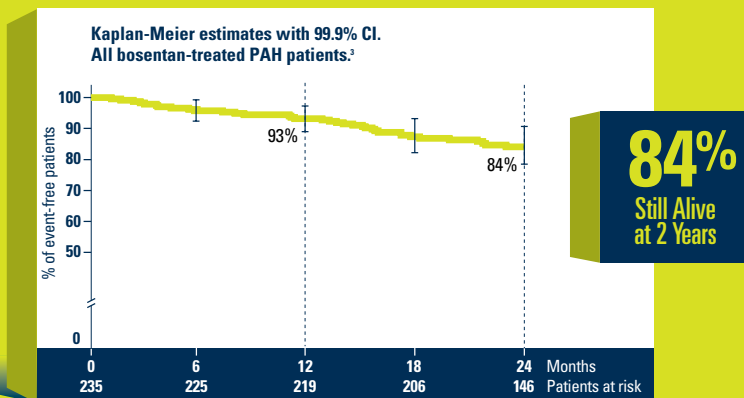
BREATHE-1 All patients (n=144 in the Tracleer group and n=69 in the control group) participated in the first 16 weeks. A subset of this population (n=35 in the Tracleer group and n=13 in the control group) continued for up to 28 weeks.

Tracleer significantly reduced risk of clinical worsening by 71% relative to control at week 28.¹

- Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy¹
- A statistically significant difference was apparent as early as week 16¹
- Treatment effect was notable because both the Tracleer groups and the control groups could have received background therapy, which excluded IV epoprostenol but may have included²:
 - Vasodilators
 - Calcium channel blockers
 - ACE inhibitors
 - Digoxin
 - Diuretics
 - Anticoagulants

Stay with Tracleer

Long-term data for patients treated with Tracleer



In the 2 Tracleer pivotal trials and their open-label extensions (n=235), 93% and 84% of patients were still alive at 1 year and 2 years, respectively, after the start of treatment with Tracleer.²

- Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival²
- These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43 of the 235 patients²
- Patients in the Tracleer trials may have also been receiving vasodilators (calcium channel blockers or ACE inhibitors), digoxin, anticoagulants, and/or diuretics²

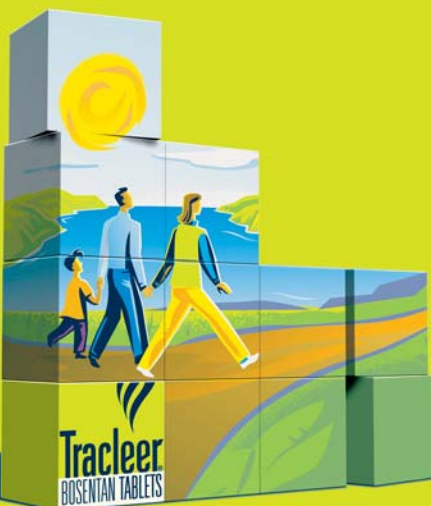
Liver and pregnancy warnings

- Requires attention to two significant concerns
 - Potential for serious liver injury: Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter
 - High potential for major birth defects: Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained
- Contraindicated for use with cyclosporine A and glyburide

For additional information about Tracleer or to report any adverse events, please call T.A.P. at 1-866-228-3546.

To learn more: Call 1-866-228-3546 or visit www.TRACLEER.com

The Cornerstone of Oral Therapy



Please see brief summary of prescribing information and full reference list on following page.

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62.5 mg and 125 mg film-coated tablets

Brief Summary: Please see package insert for full prescribing information.

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential Liver Injury. TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy. TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions). Therefore, effective contraception through additional forms of contraception must be practiced. Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through the TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

INDICATIONS AND USAGE: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: TRACLEER® is contraindicated in pregnancy, with concomitant use of cyclosporine A, with administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER® in pregnant women. TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER® should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

WARNINGS: Potential Liver Injury: Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with TRACLEER®. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. *Pre-existing Liver Impairment:* TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult.

PRECAUTIONS: Hematologic Changes: Treatment with TRACLEER® caused a dose-related decrease in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dl (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4-12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values of < 11 g/dl) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg b.i.d., marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients. A decrease in hemoglobin concentration by at least 1 g/dl was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of cases, the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 88% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment. *Fluid Retention:* In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with TRACLEER®. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting TRACLEER®. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

Information for Patients: Patients are advised to consult the TRACLEER® Medication Guide on the safe use of TRACLEER®. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions: Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER® is co-administered. Contraceptives: Co-administration of bosentan and the oral hormonal contraceptive Ortho-Novum® produced decreases of norethindrone and ethinyl estradiol levels by as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when TRACLEER® is co-administered. Women should practice additional methods of contraception and not rely on hormonal contraception alone when taking TRACLEER®. Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A (see CONTRAINDICATIONS). Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together. Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide (see CONTRAINDICATIONS). Alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered. Ketoconazole: Co-administration of bosentan 125 mg b.i.d. and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4, eg, lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Digoxin, Nimodipine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine, and losartan has no effect on plasma levels of bosentan.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d. on a mg/m² basis. In the same study, doses greater than about 32 times the MRHD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses about 16 times the MRHD. Impairment of Fertility/Testicular Function: Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible. In fertility studies in which male and female rats were treated with bosentan at oral doses of up to 50 times the MRHD on a mg/m² basis, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MRHD for two years but not at doses as high as about 50 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to about 75 times the MRHD or in dogs treated up to 12 months at doses up to about 50 times the MRHD. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects: Category X

SPECIAL POPULATIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking TRACLEER® is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER® in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

ADVERSE REACTIONS: Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (≥ 2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%). Additional adverse reactions that occurred in > 3% of bosentan-treated pulmonary arterial hypertension patients were: nasopharyngitis (11% vs. 8%), hypotension (7% vs. 4%), palpitations (5% vs. 1%), dyspepsia (4% vs. 0%), edema (4% vs. 3%), fatigue (4% vs. 1%), and pruritus (4% vs. 0%). Post-marketing experience: hypersensitivity, rash.

Long-term Treatment: The long-term follow-up of the patients who were treated with TRACLEER® in the two pivotal studies and their open-label extensions (N=235) shows that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment with TRACLEER®. These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43/235 patients. Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival.

Special Considerations: Patients with Congestive Heart Failure (CHF): Based on the results of a pair of studies with 1613 subjects, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

OVERDOSAGE: Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed. There is no specific experience of overdosage with bosentan beyond the doses described above. Massive overdosage may result in pronounced hypotension requiring active cardiovascular support.

DOSAGE AND ADMINISTRATION: TRACLEER® treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Tablets above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Doses should be administered morning and evening with or without food.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and < 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of TRACLEER® should not be considered. There is no experience with re-introduction of TRACLEER® in these circumstances.

If TRACLEER® is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. Use in Women of Child-bearing Potential: TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable, transdermal or implantable contraceptives. Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. Dosage Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosage adjustment. Dosage Adjustment in Geriatric Patients: Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. Dosage Adjustment in Hepatically Impaired Patients: The influence of liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER® is biliary, liver impairment would be expected to increase exposure to bosentan. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. Dosage Adjustment in Children: Safety and efficacy in pediatric patients have not been established. Dosage Adjustment in Patients with Low Body Weight: In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance doses is 62.5 mg b.i.d. Discontinuation of Treatment: There is limited experience with abrupt discontinuation of TRACLEER®. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg b.i.d. for 3 to 7 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62.5" NDC 66215-101-06; Bottle containing 60 tablets. 125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125" NDC 66215-102-06; Bottle containing 60 tablets.

Rx only.

STORAGE: Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature.]

Reference: 1. Zimmerman HJ. *Hepatotoxicity - The adverse effects of drugs and other chemicals on the liver.* Second ed. Philadelphia: Lippincott, 1999.

References for previous page: 1. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903. 2. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. 2003. 3. Data on file, Actelion Pharmaceuticals.

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Manufactured by:
Patheon Inc.
Mississauga, Ontario, CANADA

Marketed by:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA



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Table 1. Common Venous Access Sites.

Site	Advantages	Disadvantages	Complications
Right internal jugular vein	Facilitates pulmonary artery access; proximity to heart; may not need fluoroscopy	Cutaneous access can be difficult	Hematoma, pneumothorax, tracheal obstruction
Left subclavian vein	Facilitates pulmonary artery access; proximity to heart	Vascular control of bleeding difficult	Pneumothorax, hemothorax
Femoral veins	Easiest to cannulate; easiest for vascular control of bleeding	Most problematic for pulmonary artery access; small risk of infection; limits patient mobility; fluoroscopy required	Hematoma

catheterization, use of the femoral veins for catheterization was preferred, because it allowed the greatest flexibility with which the clinician could perform the most thorough evaluation. This was especially important for excluding left heart pathology when direct measurement of left ventricular end diastolic pressure was necessary. The advent of left-sided cardiac catheterization via the radial artery approach has, in patients with adequate radial arterial flow, eliminated the absolute necessity for a femoral approach, and the combination of the right internal jugular venous approach to the right heart and the radial artery approach to the left heart has become a viable and convenient alternative for the patient and clinician.

Measurements to Record

Standard right-heart catheterization measurements (**Figure 3**) include:

- right atrial pressure (RAP)
- right ventricular pressure (RVP)
- pulmonary arterial pressure (PAP)
- pulmonary capillary wedge pressure (PCWP)
- systemic arterial pressure (BP) and heart rate
- cardiac output (CO)
- pulmonary arterial vasoreactivity
- pulmonary arterial (PA) (“mixed venous”) saturation
- superior vena cava (SVC) saturation*
- inferior vena cava (IVC) saturation*
- right atrial (RA) saturation*
- right ventricular (RV) saturation*

*When indicated.

Normal pressure waveforms are shown in **Figure 3**. Pulmonary capillary wedge (PCW) pressure measurements are made when the balloon of the catheter is inflated after the catheter has been properly advanced into the pulmonary artery. The inflated balloon prevents the measurement of any pressure proximal to the balloon, and thus measurements recorded from the tip of the catheter reflect only left atrial pressure, which is commonly used as a surrogate for left ventricular end diastolic pressure.

The PCW pressure tracing should display three wave-

forms: The *a* wave represents contraction of the left atrium. The *c* wave is due to a rapid rise in the left ventricular pressure in early systole, causing the mitral valve to bulge backward into the left atrium, so that the atrial pressure increases momentarily. The *v* wave is produced when blood enters the left atrium during late systole, the time at which most filling of the left atrium occurs.

It is essential that, in spontaneously breathing (ie, not on ventilatory support) subjects, the pressures be measured at end-expiration, since that is the only instant in the respiratory cycle that intrapleural pressure has the least effect on pressure measurements. Most cardiac catheterization laboratories and critical care areas employ monitors that can provide an estimate of mean pressures. However, this “mean” is actually derived from all waveforms throughout the respiratory cycle, and is therefore a physiologically incorrect estimate of the true mean pressure. In patients with PAH, actual waveform tracings should be printed out, only the end-expiratory waveforms considered, and the mean calculated as:

$$\text{Mean pressure} = \text{diastolic pressure} + (\text{pulse pressure}/3), \text{ where pulse pressure} = \text{systolic pressure} - \text{diastolic pressure}.$$

Figure 3B shows a tracing of pulmonary artery pressure where the respiratory variation is evident. The recorder in the catheterization lab provides a mean pressure (solid black line) that is significantly lower than the true end-expiratory mean pressure (dashed red line). The same holds true for pressure tracings at any right-heart site, including wedge pressure, right atrial pressure, and right ventricular pressure.

Hemodynamic calculations. The following formulas are used to calculate standard hemodynamic parameters derived from the above measurements:

$$\text{Mean* systemic arterial pressure (mBP)} = \text{diastolic BP} + (\text{systolic-diastolic BP})/3$$

$$\text{Mean* pulmonary arterial pressure (mPAP)} = \text{diastolic PAP} + (\text{systolic-diastolic PAP})/3$$

$$\text{Pulmonary vascular resistance (PVR)} = \frac{\text{mPAP} - \text{mean PCW pressure}}{\text{Cardiac output (CO)}}$$

$$\text{Pulmonary vascular resistance index (PVRI)} = \frac{\text{PVR}}{\text{Body surface area (BSA)}}$$

$$\text{Systemic vascular resistance (SVR)} = \frac{\text{mBP} - \text{RAP}}{\text{CO}}$$

$$\text{Systemic vascular resistance index (SVRI)} = \frac{\text{SVR}}{\text{BSA}}$$

*Mean values may be more readily obtained by taking readings from bedside electronic monitoring equipment, which obviates the need for adjusting arithmetic means for extreme heart rates.

Cardiac output measurements. There are two standard methods for determining cardiac output. Both methods measure pulmonary blood flow, which in the absence of an intracardiac shunt is equal to systemic blood flow.

The thermodilution method for determining cardiac output uses the indicator dilution principle, where the indicator is cold saline infused as a bolus injection into the proximal port of the right-heart catheter. The thermistor at the distal end of the catheter then measures the appearance and disappearance of indicator over time, and a cardiac output is then calculated. This method can be inaccurate at very high or very low cardiac outputs, and can underestimate cardiac output when significant valve regurgitation is present.

When using this technique, the clinician must ensure that the proximal right atrial port for injection is actually in the right atrium, since the port can be in the right ventricle when the catheter is wedged.

The Fick method for determining cardiac output is based on the principle that consumption of a substance (oxygen in this case) must equal blood flow to the organ multiplied by the difference between the arterial and venous concentrations of the substance. For this method, the formula for cardiac output is as follows:

$$\text{CO} = \frac{\text{oxygen consumption per minute (VO}_2\text{)}}{\text{(arterial oxygen content} - \text{venous oxygen content)}}$$

where oxygen content is calculated as: $1.34 \times [\text{Hb}] \times \text{oxygen saturation}/100$.

In this case, the oxygen consumption can either be estimated or directly measured using standard techniques.⁶ Arterial oxygen saturation is usually determined by arterial blood gas analysis, while venous oxygen saturation is determined by mixed venous (pulmonary arterial) blood gas analysis.

Note: In order to measure systemic arterial oxygen saturation for determining cardiac output using the Fick method, caution should be exercised when relying on pulse oximetry, since both overestimation and underestimation can lead to significant errors in cardiac output calculations.⁷⁻⁹ Additionally, pulse oximetry may not be reliable in patients with Raynaud's phenomenon, a common finding in patients with PAH.

Shunt measurements. An abnormally high pulmonary arterial saturation suggests a right-to-left shunt due to con-

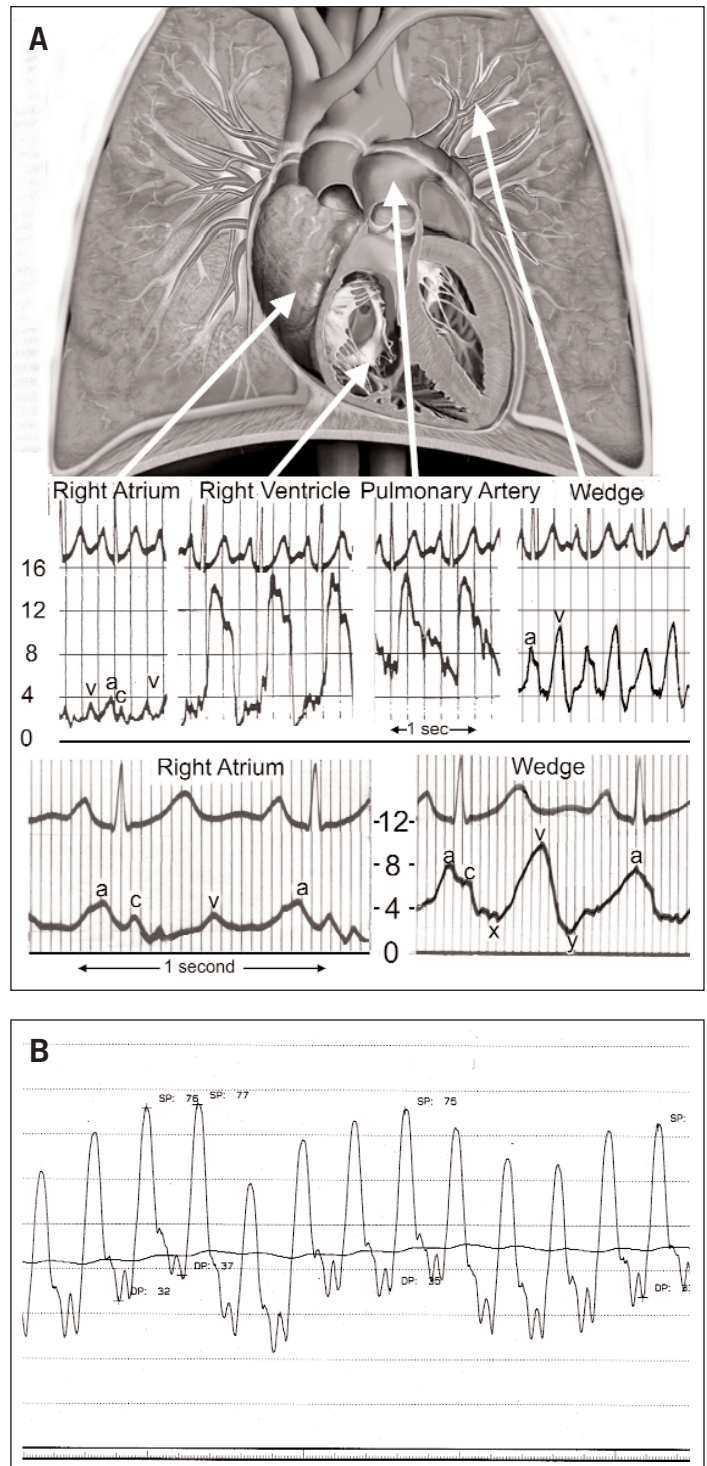


Figure 3. A, upper panel: Recordings of individual hemodynamic measurements during right-heart catheterization in a normal patient, and corresponding anatomic locations. **Lower panel:** Expanded recordings of right atrial pressure and pulmonary capillary wedge pressure (Wedge). In the Wedge recording, the presence of a waves and v waves is supportive evidence of reliable balloon occlusion measurement and accurate estimation of left atrial pressure. (Images courtesy of Blaufuss Multimedia Laboratories, San Francisco, CA.) **B:** Tracing of pulmonary artery pressure with evident respiratory variation. The mean pressure (solid black line) provided by the recorder is significantly lower than the true end-expiratory mean pressure (dashed red line).

genital heart disease and requires further evaluation and testing to identify and quantitate the shunt. Quantitation of left-to-right and/or right-to-left shunting is an integral part of right-heart catheterization.¹⁰ However, these calculations are beyond the scope of this article.

Left-heart catheterization. Left-heart catheterization is not absolutely required in all patients with suspected PAH, although many PAH specialists prefer to perform left-heart catheterization in all patients with suspected PAH as part of their initial (diagnostic) evaluation, to assure that the all-exclusive workup of PAH is complete.

Left-heart catheterization should be considered a mandatory part of the evaluation of pulmonary hypertension in the following instances:

- validation of abnormal pulmonary capillary wedge pressure/evaluation of left ventricular diastolic dysfunction
- suspected left-sided valvular lesion (mitral, aortic)
- suspected coronary artery disease

Special Considerations

Exercise

Special consideration is required when obtaining right-heart hemodynamics during exercise. Unfortunately, there is no consensus on the modality of exercise, nor the exercise protocol recommended for exercise right-heart catheterization. Many clinicians employ arm exercise, placing weights such as 1L saline bags in each arm and having the patient perform over-the-head arm abduction until fatigue ensues. Others use a cycle ergometer, which provides a more controlled workload, but may pose risks for patients when catheterized via the femoral vein approach.

The minimum exercise load and target end point during exercise during catheterization has not been established. In addition, factors such as wider swings in intrathoracic pressure during rapid breathing with exercise, and the patient's inability to maintain peak exercise during the entire hemodynamic registration, may render interpretation of the exercise procedure difficult. These issues are beyond the scope of this article.

Vasodilator Testing

Measurement of pulmonary vasoreactivity has an extremely important role in the diagnosis and management of patients with PAH,¹¹ and it is prognostic^{12,13} although recent studies suggest that it be performed only in selected subgroups of PAH.¹⁴

The presence of pulmonary vasoreactivity predicts the response to long-term calcium channel blocker (CCB) therapy.^{14,15} Patients who lack pulmonary vasoreactivity respond poorly to long-term CCB use and must be treated with specific pulmonary vasodilators. Patients with significant pulmonary vasoreactivity, by contrast, have been shown to respond well to CCB therapy. Moreover, cardiac catheterization is extremely useful in these patients, with graded dosing during catheterization helping to aid in choosing the appropriate effective dose of CCB.¹⁶ Finally, pulmonary vasoreactivity has been shown to correlate with survival in patients with idiopathic PAH (Figure 4).¹⁷

A recent comprehensive retrospective review of the experience in Clamart, France, suggests that while 10% of

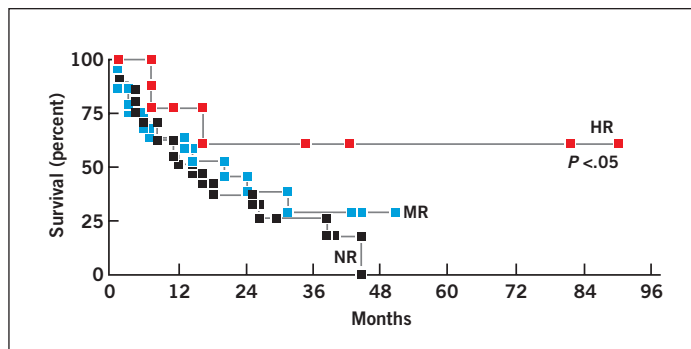


Figure 4. Pulmonary vasoreactivity and prognosis in idiopathic pulmonary arterial hypertension. HR = highly responding, MR = moderately responding, NR = nonresponding.

patients with idiopathic and anorexigen-induced PAH have a good long-term response to calcium blockers that can be predicted by acute vasodilator testing, none of the other forms of PAH (related to connective tissue disease, congenital heart disease, or others) have good long-term responses.¹⁴ Thus, acute vasodilator testing should be reserved for patients with idiopathic or anorexigen-related PAH only. Moreover, based on the experience from France, the criteria for a true vasodilator response have changed (see section 3 below).

Caution should be exercised when considering vasodilator testing and the use of a CCB for patients with PAH. Specifically, while about 25% of patients without significant heart failure symptoms exhibit pulmonary vasoreactivity,¹⁸ patients with New York Heart Association (NYHA) functional class III or IV symptoms exhibit pulmonary vasoreactivity at considerably lower rates. Furthermore, patients with overt signs and symptoms of right-heart failure do not tolerate the high doses of a CCB required to produce hemodynamic benefit. The use of a CCB in these patients carries significant risk of worsening right ventricular failure and death.

This illustrates the complexities associated with vasodilator testing and the importance of understanding how to use CCB therapy. These agents should not be prescribed empirically for patients with PAH and should be reserved for patients with pulmonary vascular vasoreactivity who do not have signs of right ventricular failure (see below).

Vasodilator Testing: How Is It Done?

The basics of pulmonary vasodilator testing in PAH include:

1. Administration of appropriate pulmonary vasodilator.

The most commonly used pulmonary vasodilators for acute vasodilator testing are intravenous epoprostenol or adenosine and inhaled nitric oxide. These agents have been used by many PAH experts, and there is substantial documentation of their utility in PAH.

Initially, very low doses of the pulmonary vasodilator should be administered (Table 2). If at any time during up-titration of the vasodilator the systolic pressure falls below 85 mm Hg or the patient complains of dyspnea or dizziness, the vasodilator should be discontinued, and the patient watched carefully until hemodynamics return to baseline.

Hemodynamic measurements should be repeated every 10 to 15 minutes as the dose of the vasodilator is increased.



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Table 2. Common Pulmonary Vasodilator Agents and Their Dosages.

	Epoprostenol	Adenosine	Nitric oxide
Route of administration	Intravenous infusion	Intravenous infusion	Inhaled
Systemic effect	Moderate decrease in systemic vascular resistance	Moderate decrease in systemic vascular resistance	No change in systemic vascular resistance
Use(s)	Short/long-term	Short term only	Short/long-term
Dose range	2-10 ng/kg/min	50-500 ng/kg/min	10 ppm

The dosing should continue until any one of the following criteria is met:

- drop in systolic pressure by 30% or greater than 85 mm Hg systolic
- increase in heart rate by 40% or greater than 100 bpm
- fall in heart rate to less than 65 bpm with symptomatic hypotension
- intolerable side effects develop, such as headache, lightheadedness, or nausea.
- target response achieved (see below)
- maximum dose of vasodilator agent given

2. *Recording the change in hemodynamics.* Focus on changes in mean pulmonary arterial pressure, PCWP, and cardiac output allows the quantitation of change in pulmonary vascular resistance (see above), however close attention must be given to systemic blood pressure, heart rate, and oxygen saturation as well, to ensure patient safety during up-titration of the pulmonary vasodilator.

3. *Interpreting the change in hemodynamics.* Formerly, PAH experts regarded a positive pulmonary vasodilator response as one in which the mean pulmonary arterial pressure falls by at least 22%, and others use a fall in pulmonary vascular resistance of at least 26% to label a positive response. However, the recent evidence from the cohort of patients in Clamart, France suggests that those criteria are inadequate. Currently, the criteria for an acute response are a decrease in mean pulmonary arterial pressure of at least 10 mm Hg with the mean pulmonary arterial pressure decreasing to 40 mm Hg or less, accompanied by a normal or high cardiac output. Only patients that satisfy these criteria should receive long-term oral calcium channel blockade therapy. Data exist that correlate a robust vasodilator response with improved prognosis compared with patients without such a response.

Congenital Heart Disease

A large number of alternative etiologies of pulmonary hypertension should be entertained when evaluating a patient with suspected PAH. Of particular importance is the patient with congenital heart disease. Because congenital heart disease can be easily overlooked or missed, cardiac catheterization may be the only study to uncover its existence. Thus,

when planning catheterization for PAH patients, careful consideration should be given to the measurements that are to be obtained at the time of catheterization. In particular, when the patient develops hypoxemia with exercise, the clinician should take extra care not to miss an intracardiac shunt, which may be due to an atrial septal defect, especially of the sinus venosus type, which may be missed at echocardiography, or may be due to the presence of anomalous pulmonary veins. Standard measurements for patients with suspected intracardiac shunts should always include blood sampling at various sites to determine oxygen saturation at all levels (SVC, IVC, RA, RV, and PA; see Measurements to Record, above).

Pitfalls of Measurements

Incorrect Recordings of Pulmonary Capillary Wedge (PCW) Pressure

A common pitfall when measuring pulmonary capillary wedge pressure in patients with PAH involves incorrect interpretation. This occurs when the right-heart balloon flotation catheter is not in proper position, yielding an inaccurate pressure tracing (**Figure 5**). The most common cause of this error is the recording of a dampened pulmonary arterial pressure rather than a true occlusion pressure. This error results in a falsely elevated pressure measurement, often misleading the clinician into believing that the patient has pulmonary venous hypertension rather than PAH.

The authors frequently employ two techniques for avoiding this measurement error: 1) Partially inflating the balloon and gentle forward advancement of the catheter, in order to better seat and seal the catheter against the walls of the pulmonary artery branch. 2) Validating an abnormally elevated measurement by gently withdrawing a blood sample from the distal port of the right-heart catheter during balloon inflation and pulmonary capillary wedge pressure recording, to ensure that the saturation of the sample matches systemic arterial (left atrial) saturation, ie, if the catheter is correctly placed in the wedge position, the oxygen saturation of the blood distal to the catheter should be very high (see text, **Figure 5**).

Another problem with capillary wedge pressure measurements is overinflation or excessive advancement of the balloon, which results in “over-wedging.” Prolonged over-wedg-

ing will yield a falsely high pulmonary capillary wedge pressure and may result in pulmonary infarction. If an accurate pulmonary capillary wedge pressure cannot be obtained during right-heart catheterization, it is prudent to consider direct measurement of left ventricular end diastolic pressure via left-heart catheterization.

Summary

Cardiac catheterization is mandatory for definitive diagnosis in all patients suspected of PAH. It is the only reliable method for this purpose. It can be used for determining vasodilator responsiveness of the pulmonary vasculature in appropriate patients, and it is part of a standard diagnostic workup for patients with suspected congenital heart disease. It is also mandatory for the evaluation of patients with nonidiopathic PAH since it is especially important to be certain that the diagnosis is accurate, as many of these patients have concomitant left heart and lung disease that could confound the diagnosis.

References

1. Homma A, Anzueto A, Peters JI, et al. Pulmonary artery systolic pressures estimated by echocardiogram vs cardiac catheterization in patients awaiting lung transplantation. *J Heart Lung Transplant.* 2001; 20: 833-9.
2. Shapiro SM, Oudiz RJ, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol.* 1997;30: 343-9.
3. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med.* 1987;107:216-23.
4. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115:343-9.
5. Rich S, D'Alonzo GE, Dantzker DR, Levy PS. Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. *Am J Cardiol.* 1985;55:159-63.
6. Mueller HS, Chatterjee K, Davis KB, et al. ACC expert consensus document. Present use of bedside right heart catheterization in patients with cardiac disease. *J Am Coll Cardiol.* 1998;32:840-64.
7. Benson JP, Venkatesh B, Patla V. Misleading information from pulse oximetry and the usefulness of continuous blood gas monitoring in a post cardiac surgery patient. *Intensive Care Med.* 1995;21:437-9.
8. Vicenzi MN, Gombotz H, Krenn H, Dorn C, Rehak P. Transesophageal versus surface pulse oximetry in intensive care unit patients. *Crit Care Med.* 2000;28:2268-70.
9. Van de Louw A, Cracco C, Cerf C, et al. Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Med.* 2001;27:1606-13.
10. Wood P. *Diseases of the Heart and Circulation.* 3d ed. Philadelphia, Pa: Lippincott; 1968.

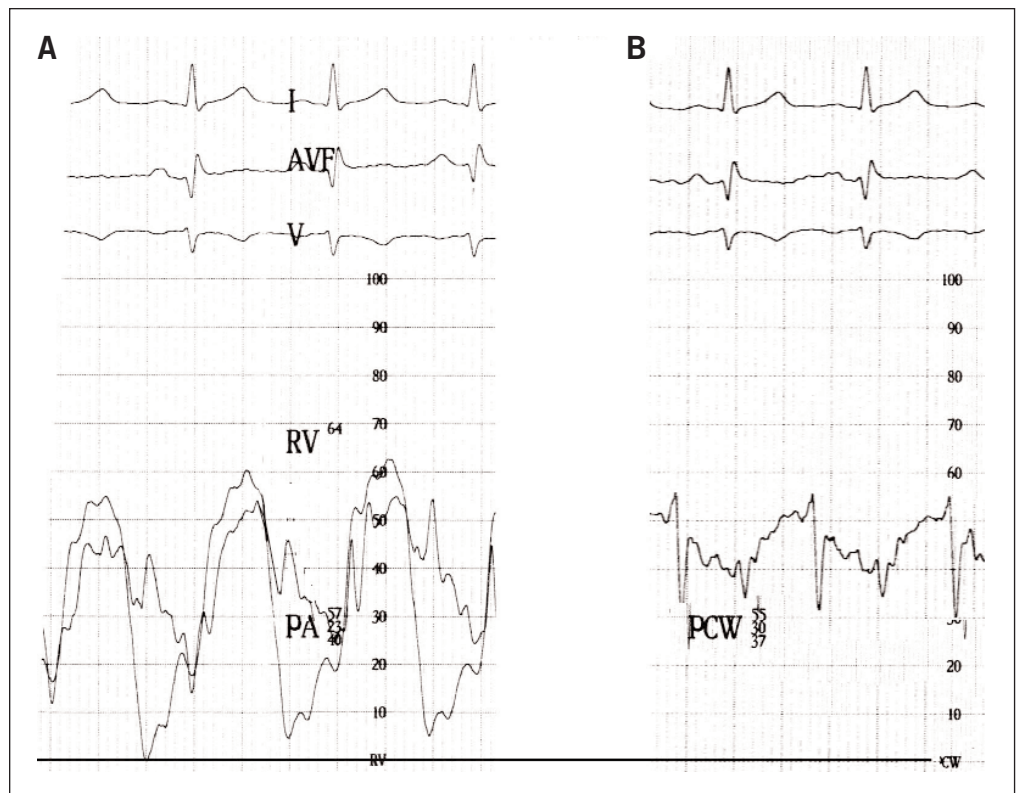


Figure 5. A: Balloon flotation catheter recordings of pulmonary arterial (PA) and right ventricular (RV) pressure in a patient with pulmonary hypertension. B: Recording of the same PA pressure after inflation of balloon, mistakenly labeled as pulmonary capillary wedge (PCW) pressure. Note dashed vertical lines depicting peak PA and purported PCW pressure tracings, which occur at the same time in the cardiac cycle. Also note lack of a and v waves in the purported PCW recording. Measurement of arterial saturation from blood withdrawn from the distal catheter port demonstrated a saturation of 74%, with a simultaneous arterial sample measured at 99%. If this had been an actual PCW recording, oxygen saturation from the distal catheter port would also have been 99%. Also, since the v waves in a true PCW recording are transmitted waves, the peaks in v waves would have occurred later than the peak in the PA pressure wave. (I, AVF, V = electrocardiogram leads.) (Images courtesy of Blaufuss Multimedia Laboratories, San Francisco, CA.)

11. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation.* 1987;76:135-41.
12. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation.* 2002;106:1477-82.
13. Kawut SM, Horn EM, Berekashvili KK, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. *Am J Cardiol.* 2005;95:199-203.
14. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation.* 2005;111:3105-11.
15. Schrader B, Inbar S, Kaufman L, et al. Comparison of the effects of adenosine and nifedipine in pulmonary hypertension. *J Am Coll Cardiol.* 1992;19:1060.
16. Rich S, Kaufmann E. High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. *J Am Coll Cardiol.* 1991;18:1323-7.
17. Raffy O, Azarian R, Brenot F, et al. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. *Circulation.* 1996;93:484-8.
18. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet.* 1998;352:719-25.

Integrating Current Strategies for Continuing Assessment of Pulmonary Arterial Hypertension



Vallerie V. McLaughlin, MD



Richard N. Channick, MD



Ivan M. Robbins, MD



Victor F. Tapson, MD

In this discussion four experts shared insights on what might be considered the “gestalt” of diagnosing and monitoring pulmonary arterial hypertension. They ranged over a broad spectrum of issues that included thromboembolic pulmonary hypertension, exercise testing, hemodynamics, imaging studies, and response to therapy. The discussion was moderated by Vallerie V. McLaughlin, MD, Associate Professor of Medicine, Director, Pulmonary Hypertension Program, University of Michigan Health System, Ann Arbor, Michigan. The participants included Richard N. Channick, Associate Professor of Medicine, Pulmonary and Critical Care Division, University of California, San Diego Medical Center, San Diego, California; Ivan M. Robbins, MD, Director, Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee; and Victor F. Tapson, MD, Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina.

Dr McLaughlin: We welcome everyone and thanks for joining us. Today’s Roundtable is going to elaborate on the issues regarding diagnosis that were raised in the three articles in this issue of the *Journal* and also focus on the continuing assessment of patients with pulmonary hypertension. One important aspect of the diagnostic algorithm includes the evaluation for thromboembolic disease. The guidelines clearly state that the ventilation perfusion scan is the test of choice for this. However, we commonly see patients with some amount of interstitial lung disease, for example, in the setting of scleroderma, in whom the V/Q scan can be problematic. Rich, how do you evaluate thromboembolic disease in patients in whom the ventilation perfusion scan might be problematic because of underlying lung disease?

Dr Channick: We still are big fans of V/Q scans here at UCSD. Our experience has been that we don’t see small, matched defects in patients who have operable thromboembolic pulmonary hypertension but typically we’re talking about large, seg-

mental or greater or multiple defects. Even in the setting of underlying lung disease the V/Q scans in those cases can be very useful. CT angiography does have a role in some of these patients to confirm the diagnosis and also to look for other abnormalities in the mediastinum. We’re concerned about patients who have false-negative CT angiograms in the setting of chronic thromboemboli, and we have some clear examples of that, so we would never eliminate a patient from surgery based on a negative CT angiogram.

Dr McLaughlin: But say you have a patient with scleroderma with mild pulmonary fibrosis and quite severe pulmonary hypertension that you really think is PAH associated with scleroderma. The lung scan is interpreted as intermediate probability. What do you do at that point?

Dr Channick: There are many kinds of “intermediate probability” scans. That’s such a broad term. Any matched defects are going to be intermediate probability, but if you’re experienced in looking at V/Q scans, you will get a lot more information by looking at the scan and so if we see several large perfusion defects even if there may be a small ventilation abnormality in an area with fibrosis, that appearance will certainly be suspicious enough for us to probably proceed with pulmonary angiography. Because, again, even if you do a CT angiogram and it looks “unremarkable,” you should give the patient the benefit of the doubt and proceed with a definitive study before deciding he or she is not going to be a candidate for surgery.

Dr McLaughlin: Vic, how do you handle those patients?

Dr Tapson: I completely agree with Rich. There are a couple of key things that people who do not practice at PH centers may not realize. You really cannot rule out chronic thromboembolic pulmonary hypertension with a spiral CT scan. You may see clues. Mosaic perfusion is a great clue; it is not

diagnostic. The key about V/Q scans is that in certain patients sometimes even a so-called high probability V/Q scan can throw you off. Certain centers will realize that if a patient has interstitial lung disease and sarcoidosis and has a high probability scan, sometimes that's not thromboembolic disease. That's where a PA angiogram can be very helpful. We have had at least 5 or 6 cases like that. CT and V/Q can complement each other, but I always hate to say someone does not have chronic thromboembolic pulmonary hypertension on a CT scan.

Dr McLaughlin: Ivan, anything to add?

Dr Robbins: It's hard to argue with these two experts. All I would say is that we have been using a 64-slice CT scanner recently. The interventional radiology people here are even advocating a CT angiogram over a pulmonary angiogram in some patients. The images are phenomenal. Now I know there are not studies comparing it with an angiogram. What they like about it is that you get a view of the thickness of the vessel wall, whereas with a pulmonary angiogram you just get the inside of a vessel. You get some very nice pictures of the irregularities of the vessel wall with CT angiography.

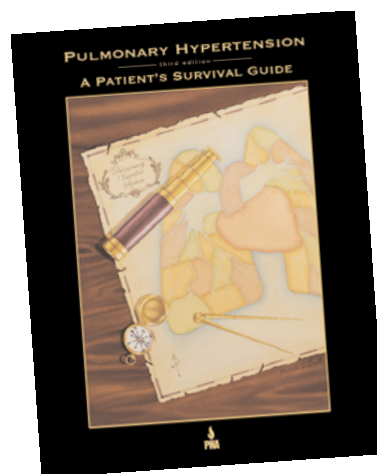
Dr Tapson: That's a good point. I agree with Ivan. CT has come a long way. With 64-slice scanners it's hard to know exactly what its sensitivity is, but clearly it's a fast, easier study, there's less concern about breath hold, and patients can get a better quality study.

Dr McLaughlin: Do you think MRI will ever replace the CT scan or pulmonary angiography in the diagnosis of chronic thromboembolic pulmonary hypertension?

Dr Channick: Certainly the images can be impressive and there is the potential in the future to replace conventional angiography. I would not use it as a screening test but some of the images on MR angiography approach conventional pulmonary angiography. I don't think it's quite there yet, but if I see an MR angiogram that shows clear-cut findings of chronic thromboembolic disease and let's say you already have hemodynamics from a cath, then we'll proceed with surgery based on that study.

Dr McLaughlin: Let's move on to echo. There are some pitfalls to echo, including overestimation and underestimation of PA pressures. And there's much more to echo than the PA pressures. Any pearls you want to share as you interpret echo results?

Dr Robbins: I agree that I do not look at it for the pressure at all. To me, it's a good test to look at the RV function, RV size, and RV hypertrophy, and to exclude valvular disease. Patients and even other physicians ask what the pressure is. They'll quote you the pressure but it is so dependent on the TR jet, so I just like to look at the RV function. Having said that, I'm sure everyone has had the experience of a complete disconnect between what the echo shows the RV function to



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be and how your patients are doing. I think it's a good screening tool. I don't know what the perfect screening tool is. It's becoming more apparent that resting hemodynamics don't tell us the whole story either.

Dr Tapson: Ivan makes a good point about echo and that is number one, estimated RV systolic pressure is not always terribly accurate. When patients ask us what their pressures are we try to get away from that. As they get worse, their pressures may actually go down some. As they get better, they may go up a little bit. Even if it was accurate, you need to be careful interpreting that. RV function is the key issue with echo.

Dr McLaughlin: Those are some of the issues I wanted to bring out. For example, if a patient is at risk, such as a scleroderma patient who has a normal estimated PA pressure, but when you look at the echo the right ventricle is big and the septum is flattened, that leads me to believe the patient has pulmonary hypertension no matter what the echo estimate is. That patient should still have a further evaluation, including the heart cath. And the other way around, too. Sometimes the echos can overestimate pressures. They can misinterpret the tricuspid closure sound as the TR jet. If someone has a pressure estimated to be 70 and the right ventricle is nice and small with normal function and the septum moves normally, I question that pulmonary artery pressure. So, as Ivan said, we're looking at more than just the PA pressure on echo, we're looking at the size and function of the right ventricle too. But Ivan, you made another point that is really interesting. We measure the hemodynamics at rest and, most commonly, patients complain of symptoms with exercise. Many practices are starting to incorporate exercise echo or exercise cath in their protocols. What are your thoughts on exercise hemodynamics and how do you make treatment decisions based on them?

Dr Channick: I have quite a bit of experience in that, but the answer to your questions is I don't really know, even though we do exercise hemodynamics on virtually every patient who has normal or near normal pulmonary artery pressures and find abnormal increases in pressure not uncommonly—at least half the time we do these tests. All these patients are symptomatic. What we don't really know is clinical significance. A fair number of these patients don't in fact have pulmonary arterial hypertension but have left ventricular diastolic dysfunction. Even in the patients we diagnose as having PAH just with exercise, we don't have a really good sense of whether it is important to treat those patients or, if we do treat, what medication to use. We have followed many of these patients now for several years with yearly exercise tests and, for the most part, the disease remains stable. In other words, we continue to see the abnormal exercise response. Patients still have some symptoms. They have not gotten better or worse. We haven't done a systematic look at

treatment effect on this phenomenon, but many of these patients are not getting any active treatment and remain basically the same for now up to 7 years for some of these patients we have followed.

Dr Robbins: That's one of the biggest problems with doing that. We don't do that at all because there is no good standard as to what is a normal hemodynamic response to exercise.

Dr McLaughlin: There are a couple of things. The first is the point Rich made about diastolic dysfunction. That is something you are not going to be able to tell on an echocardiogram because if you do an exercise echo and your PA pressures go up, there's really no good way to tell if it's because your left heart pressures went up too. Rich, were you referring to exercise echo or exercise cath that you had the most experience with?

I think we are raising the treatment standards, we're raising the bar. We are much less likely to accept the same now as we were a year or two ago because we have other options and we understand the prognostic value of certain treatment goals. My plea would be for us to try to figure this out in a controlled fashion.

Dr Channick: Exercise cath was what I was referring to. With regard to exercise echos, I would say my overall sense is that they tend to overestimate the actual pressures

Dr McLaughlin: Rich, when you do an exercise cath do you find you can reliably measure the wedge pressure while patients are exercising and while their respiratory rate is so high?

Dr Channick: In some cases you can't. I think it's variable. In some patients you see a lot of artifact and then stop exercise and measure immediate postexercise wedge pressure. And in some of these patients who I believe have

diastolic dysfunction you can see an elevated wedge pressure that very quickly returns to normal following cessation of exercise. You can look at end-expiratory wedge pressure even when they're breathing fairly hard.

Dr Robbins: But again I come back to the point that we don't know what the normal response is, necessarily, and I think it's very variable between people. A study was done in Leadville, Colorado, which is at about 3000 meters, where the high school students were studied. The researchers catheterized all of them and found that the champion skier had a mean PA pressure of greater than 100 mm Hg with exercise. So, I don't know what the normal response is. That may be why a lot of patients followed by Rich are fine, because that's just their normal response to activity.

Dr Tapson: I wish there were an easy way to do this because it's a point well taken that resting hemodynamics may not tell the whole story. We have not had good luck with exercise tests—exercise echo or exercise imaging.

Dr McLaughlin: As you all know, exercise hemodynamics will be performed in a subgroup of patients enrolled in the EARLY trial and perhaps we might glean a little bit of information from that. Let's move on to vasoreactivity testing at

the time of the right heart catheterization. The paper from the French group was recently published in *Circulation* that shows this is a very small portion of patients with IPAH who respond to vasodilators at the time of cath and ultimately do well long term with calcium channel blockers. They have also presented data at meetings suggesting that virtually none of the patients with any other type of associated pulmonary arterial hypertension respond in this fashion. Of course at many academic centers we still do vasodilator testing on everyone just because it's part of the evaluation, but in reality it probably does not affect patients with scleroderma or portal hypertension or congenital heart disease all that much. Do you all still do acute vasodilator testing on all of the patients you evaluate for pulmonary arterial hypertension?

Dr Tapson: I would say we still do unless the patient is very sick, for example, class IV patients, those with a low cardiac index. We're not going to use calcium channel blockers in those patients. I will say that we do test some other patients. Although I don't know why, we find a really good responder, about 1 in 3 or 1 in 5 in whom we use calcium channel blockers. We can't get them up to 720 mg of diltiazem a day. We're going to end up treating them with endothelial antagonists anyway or perhaps some other drug, so I think while it's nice to collect the data, it's not nearly as useful as we gather data with new drugs. On the other hand, maybe we will learn something with new drugs, maybe we will find out patients respond to vasodilators and ultimately do better with some new drug we try. But I think it's decreasingly useful.

Dr Robbins: We still tend to do it on everyone except, as Vic says, those who are severely compromised. There's no way they are getting calcium channel blockers. But I think it is useful, and as Vic touched on, it may be helpful, and we don't have enough data on this now, in predicting response to therapy or guiding your medication. The other thing I would point out is that even though we do a vasodilator study in the scleroderma population and have had some patients who have exhibited a fairly profound vasodilatory response with inhaled nitric oxide, these patients do not do well and they feel worse and do worse when you try to treat them with calcium channel blockers.

Dr McLaughlin: As an academic center we tend to use nitric oxide in nearly every patient at the time of the first cath and I think it's very rare that you ever see anyone respond according to the strict definition. Perhaps some day we'll sit down and analyze the prognosis with different medications based on the response to a vasodilator. I'm a little more conservative in the patients who have elevated left heart pressures. We see a lot of left heart disease, so if I see a wedge pressure of 20 mm Hg, I tend not to give a vasodilator in the cath lab for two reasons. First, we're not looking for long-term calcium channel blocker responsiveness in patients

with this diagnosis, and second, there is certainly the risk of putting them in pulmonary edema in the cath lab with nitric oxide. Let's move on to how we follow patients. We have good guidelines for diagnosis, although there are little aspects that each of us tweak here and there. But we all follow patients in a different way and this is becoming increasingly important as we have more therapeutic options from different classes to offer patients. In general, consider your average functional class III PAH patients whom you treat with, for example, an oral agent initially. How do you follow those patients, how often do you see them, what tests do you do, and what makes you decide that they are not responding or inadequately responding to a therapy and that it is time to switch or add something?

Dr Tapson: As a general rule we follow most of our PH patients every 3 months. We have less severely ill patients whom we see less often. Like many big PH centers we have patients from far away, from Florida, from Maryland, so we try to take that into account. But 3 months is the general rule. At every 3 months we do a 6-minute walk test, an echo at 6 months, and we don't have any specific time when we repeat a right-heart catheterization. We always do a right-heart catheterization at the onset and we don't necessarily repeat it at a year or two, but we do it as clinical status and therapy dictate. We do other tests now, brain natriuretic peptide (BNP) levels every 3 months in all of our patients. I wouldn't use that alone, although in some patients we have found that BNP level correlates very well with worsening of the echo and worsening of clinical status and the walk test. It may be that in certain patients that might reduce the need for

more invasive testing or more expensive testing. We don't do a formal Borg test or dyspnea evaluation. We always report the functional class of each patient. To be old fashioned, one of the most important things we do is talk to the patient. Usually in talking to the patient we know after 5 minutes whether they are better or worse. Your clinical studies usually confirm that. We always examine the patient and it never ceases to amaze me that in a new patient you might hear findings classic for PH, a booming second heart sound that has not been detected before. It's important for medical students and trainees to understand that there are some very simple classic, dramatic findings in some patients by physical exam in PH.

Dr McLaughlin: Ivan?

Dr Robbins: In general with oral therapy we see patients back, during the first year, every 3 months. As they get better we stretch it out a little if they're stable, anywhere from 4 to 6 months. Some patients will wait at home while they're getting worse and not let you know, even with fairly frequent follow-up. But most patients will, hopefully, tell you. We in general do a repeat cath at about one year after starting a new therapy. If there's deterioration and we're thinking of

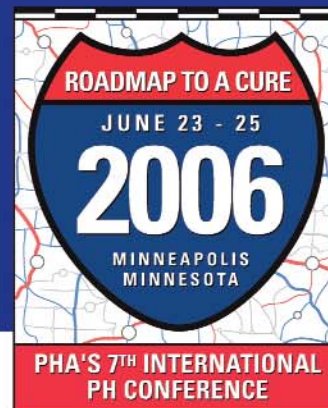
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another therapy, we usually do another right-heart cath. Obviously, if they are in severe right-heart failure, we would not delay getting patients epoprostenol or other therapy waiting for a repeat cath. We are following BNP levels now. We probably don't have the database that Vic has, but we've seen some patients who were in severe heart failure, and their BNP levels were not terribly high. They weren't normal but they weren't as high as those of some other patients. We've found that it's pretty variable. That may reflect how we do the test here. I'm not sure.

Dr Channick: The way I look at it very simply is that you want to determine whether a patient is better, worse, or the same. Given the fact that we have multiple other therapeutic options, it is important to make that determination. If a patient is clearly improved, and I agree that there is not any single predictor of what we mean by improvement—function, walk distance, hemodynamics—I think you have to look at all of those things in composite without any clear guidance for specific levels of the parameters. If a patient is clearly improved at 3 to 4 months, I would not change therapy. If a patient is worse, and you could also debate what we mean by worse—worsening function or walk test at 3 to 4 months or even increasing BNP—we like to do a cath to confirm worsening, and then obviously we would add another therapy. A sizable number of patients fall into the third group: they are about the same. In other words, they're functionally about the same, their walk distance is about the same. Those are the patients we will really learn from because now that we have other therapies, either experimental or approved, that we can add on, we are gaining experience in this combined approach.

Dr McLaughlin: I think we are all saying the same thing in a slightly different way. Those stable patients, not the critically ill patients whom we give parenteral therapy immediately, but those stable patients in whom we might start oral therapy, we tend to see them every 3 to 4 months. The patients will tell you how they are doing, whether we call it functional class or whether we talk to the patient for 5 minutes. We will have a pretty good idea of how the patient is doing. The other testing helps add to our database when we make decisions on those patients and we, too, do the 6-minute walk test regularly at visits every 3 to 4 months and get a BNP. You put all those together when you try to make decisions for the patient. We tend to do a right-heart cath after patients have been receiving a therapy for about a year and that time may shrink now that we're thinking about other additive therapies. I think we are raising the treatment standards, we're raising the bar. We are much less likely to accept the same now as we were a year or two ago because we have other options and we understand the prognostic value of certain treatment goals. My plea would be for us to try to figure this out in a controlled fashion. Many of us are starting to add other therapies because we are trying to do the best thing for our patients, and I wonder if we're ever going to know unless we do a controlled trial. I think the next wave of clinical trials in pulmonary hypertension is going to be the combination trials, and I am hopeful that these patients Rich described will be entered into combination trials so we can answer this question in an evidence-based fashion.

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