

Advances in

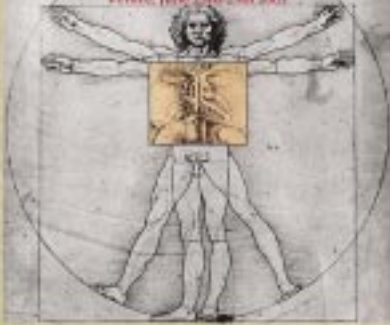
Pulmonary Hypertension

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Official Journal of the Pulmonary Hypertension Association

Featuring Highlights From
**3rd World Symposium on
Pulmonary Arterial Hypertension**
Venice, June 23rd - 25th, 2003

3rd World Symposium on
Pulmonary Arterial Hypertension
Venice, June 23rd-25th 2003



Pulmonary Hypertension Association

Editorial Mission

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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Cover Photo: Superimposed on a classical Venetian scene is the logo from the Third World Symposium on Pulmonary Hypertension, held June 23-25 in Venice. It is derived from Vitruvian Man, Study of Proportions, from Vitruvius's *De Architectura*, Leonardo da Vinci, 1492, Gallerie dell'Accademia, Venice. Photo of Venice © Photodisc.

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Presenting Highlights from Two Exceptional Meetings on Pulmonary Hypertension



Two exceptional meetings this year offered rare opportunities for clinicians involved with pulmonary arterial hypertension to evaluate the progress made in treating this disease. In each case, attendees not only reviewed the progress of recent clinical trials but also looked ahead toward what we can expect in the coming years.

Most of this issue is devoted to highlights from the Third World Symposium on Pulmonary Arterial Hypertension, held from June 23 to 25 in Venice, Italy. This group has been the prime mover in developing criteria for the classification and diagnosis of pulmonary hypertension, and the meeting this year once again demonstrated why the various task forces assembled contribute so much to our understanding of the pathophysiology of the disease and recent advances in diagnosis and treatment.

I want to express my appreciation for the contributions to this issue of *Advances in Pulmonary Hypertension* from members of the task force committees who provided summaries from their respective sessions and to Nazzareno Galiè, MD, for enabling us to put together this information. The reports from the physicians convey essential information and highlight key issues discussed. They will give you a sense of the excitement we all shared in Venice as we worked toward a consensus on many topics. As assessment and treatment strategies branch in many directions, it is critical for working groups like this to consolidate our knowledge base and seek a consensus that serves as the basis for new guidelines.

The other meeting of major importance was held earlier under the auspices of the National Institutes of Health, in Bethesda, Maryland. The report and interview with the meeting's chairman, John H. Newman, MD, ranges far and wide over a broad spectrum of topics that will put you on the cutting edge of developments in our field, including priorities for future research.

Victor Tapson, MD
Editor-in-Chief

Profiles in Pulmonary Hypertension

Cardiologist Nazzareno Galiè: A Guiding Light for Worldwide Consensus on Pulmonary Hypertension



Nazzareno Galiè, MD

If anyone is keeping track of the number of scientific publications on pulmonary arterial hypertension (PAH), pulmonary embolism, chronic heart failure, and heart transplantation authored or coauthored by Nazzareno Galiè, MD, the total has reached more than 280. But that impressive figure is only one measure of the stature of Dr Galiè as a world-class investigator in this field. Dr

Galiè's influence extends far beyond the borders of his native Italy where he is Head of the Pulmonary Hypertension Center at the University of Bologna.

Evidence of his influence on state-of-the art knowledge in PAH is apparent in this issue as he analyzed highlights

from the Third World Symposium on Pulmonary Hypertension held in Venice from June 23 to 25. As one of the organizers of this symposium, Dr Galiè helped bring together cardiologists and pulmonologists from leading research centers around the world to address topics of central importance to clinicians involved with the disease.

Aside from postdoctoral training in London and at the University of Arkansas, Dr Galiè has spent his entire career at the Institute of Cardiology, University of Bologna, where he is looked to as one of the guiding lights for European research in PAH. This is the program that kindled his interest in PAH soon after he wrote his doctoral thesis on the topic. As his interest in this field grew, he became more interested in PAH because it lacked a cure and other clinicians began sending more patients with PAH to Bologna for treatment. The University of Bologna's program earned a reputation as one of the centers of excellence for the treatment of PAH.

By the late 1990s, his center became one of the pivotal locations in Europe for investigations on new drugs being developed for PAH, including treprostinil, bosentan, beraprost, and iloprost. More recently, Dr Galiè's group has been involved in an international study on the effects of sildenafil in PAH, results of which are expected early in 2004. Working with colleagues in Europe and the United States, Dr Galiè has served on numerous committees to evaluate the effects of the new agents, and in particular he has led the first double-blind, placebo-controlled study on the effect of the endothelin receptor antagonist bosentan

(continued on page 21)

NIH Conference Charts Future Directions in Identifying Patients at Risk for Primary Pulmonary Hypertension

This report is based on information presented at a conference sponsored by the National Institutes of Health (NIH) earlier this year to identify trends in diagnosis and management of the disease.

As diagnostic and treatment approaches to pulmonary hypertension evolve over the next few years, clinicians may look back at an NIH conference held earlier this year as a watershed, a meeting where many of the new directions in care were charted.

The meeting, **Translational Research in Primary Pulmonary Hypertension**, was sponsored by the National Heart, Lung and Blood Institute and brought together leading experts to explore ways in which basic research may translate into clinical trials and related investigative work. Organized by Dorothy B. Gail, PhD, Director of Lung Biology and Disease in the Division of Lung Diseases at the NIH, the meeting provided a venue for reviewing new data and concepts, including recent findings in genetics and molecular medicine, as investigators discussed results from studies in transgenic mice and data about modulators for angiogenesis. One of the goals of the meeting was to provide the NIH with information on the kinds of research it may want to encourage, according to John H. Newman, MD, Professor of Medicine, Pulmonary Critical Care Division, Vanderbilt University School of Medicine, Nashville, Tennessee. The talks ranged across a broad spectrum of topics but generally relate to implications for the pathogenesis and treatment of primary pulmonary hypertension.

One of the areas covered involved potassium and calcium channel function, as delineated by Steven L. Archer, MD. "Information from various studies suggests that an alteration in channel function may be involved with determining whether potassium or calcium can enter or exit cells and whether they will contract. This issue is especially important for smooth muscle cells in the vascular bed, because if they contract, they cause vasoconstriction and raise pulmonary vascular resistance, and can exacerbate pulmonary hypertension," said Dr Newman.

The second group of talks was concerned with signal transduction, which is related to the manner in which circulating molecules activate cells. Serotonin was a chief consideration in this discussion, because it is a mediator that enters cells through a transporter, and once in cells, it activates certain pathways that may lead to new growth of vascular cells and production of collagen. This process may promote occlusion of vessels as seen in pulmonary hypertension. This is important because it is known that blood vessels in the lung become occluded through a process in which fibrosis results in blockage of the central channel.

One of the exciting areas covered at the conference included work being done on transgenic models of pulmonary hypertension. Mutations in the BMPR-2 gene are a hereditary cause primary familial hypertension. William C. Nichols, PhD, and David Rodman, MD, have used transgenic mice with this gene altered so that we have an animal model that can mimic situa-

tions of primary pulmonary hypertension. They presented information on these models and what directions research will take with these animal models. "The hope is that over the next couple of years we will be able to further characterize animal models of pulmonary hypertension, which will lead to a better understanding of how to treat the disease. Currently the transgenic model is still too early in development to have produced any striking leads, but our expectations are high," said Dr Newman

The discussion of genetic factors involved in pulmonary hypertension continued with presentations on genetic modifiers by Jane Morse, MD, and James A. Knowles, MD, PhD, who focused on the concept of genetic susceptibility to primary pulmonary hypertension. "We know from patients who are in families where the disease is highly prevalent that there is a mutation in a receptor, called BMPR-2," said Dr Newman. "Even if a person has a mutation, there is only about a 20% risk of getting the disease in his or her lifetime, so there must be other factors that increase the risk—either other mutations or just other genetic characteristics. For virtually every characteristic there are multiple genetic modifications, sometimes called polymorphisms. Nationally and internationally, the effort to identify the genetic makeup that may predispose to pulmonary hypertension is growing stronger. It will turn into a big project over the next 5 to 10 years as we examine the genome to determine the kinds of differences that leave some patients at greater risk. For example, why did some people who took fenphen develop pulmonary hypertension? What are the underlying susceptibilities to that?"

Looking ahead to the most promising therapeutic strategies, presenters examined the relative merits of different approaches, particularly combinations of agents. "Everyone has been very excited about the advent of endothelin blockers and sildenafil," noted Dr Newman. "Now the question is, what kind of combinations should we use? Should we start oral drugs first and not use prostacyclin drugs until the oral therapy fails? Or will patients fare better if they undergo treatment with multiple drugs, such as we discovered with cancer therapy? In animal models, statins look very promising and they deserve clinical study because it is clear that they are useful in other vascular diseases. Sildenafil is also very exciting. In terms of feasible new approaches, the statins seem to be promising, but we are 2 to 3 years away from having specific drugs that may target other mechanisms such as serotonin or the mechanisms involving TGF-beta and potassium channels. These approaches are not quite ready but in the next 3 to 5 years we should have other new drugs with potential benefit."

Where does that leave prostacyclin, still considered the cornerstone of therapy? "Prostacyclin remains the gold standard and is the agent we would all like to see another drug supercede. The goal is to get people off of prostacyclin as primary therapy, both for cost and for safety reasons. That's where we want to be headed."

One of the ultimate goals is to initiate treatment in patients predisposed to pulmonary hypertension as early as possible. "Familial pulmonary hypertension affords a unique opportunity to identify people who have a mutation and who could be candidates for preventive therapy," added Dr Newman. The problem in managing the "sporadic" patients is that preventive treatment cannot be used. This is because disease is already advanced when the diagnosis is made. This is why the identification of patients at risk for familial disease is so exciting. "The cases that we may be able to prevent are those persons who have a mutation but don't have any disease. They are clinically completely normal. If the statins seem to work, we could potentially design a study that might involve administering statins, plus several other drugs, to patients who have the mutation but are clinically normal to determine whether we could prevent pulmonary hypertension from developing."

Despite the promise of genetic testing suggested by the NIH conference, Dr Newman said it remains a long way from being routinely applied in clinical practice. "The problem is that in the general population, primary pulmonary hypertension is too rare to test the whole population. The cost is prohibitive. It would not be cost-effective if only one person in a million gets the disease. Genetic testing will be done in families where we know that mutations exist and potentially in patients who already have the disease but are the only affected person in a family. The current problem is that the gene is so large, with so many mutation sites, that no laboratory has been able to develop a feasible test. What will emerge from genetic testing and preventive therapy is a clearer understanding of what causes primary pulmonary hypertension and where we can successfully direct therapy. This will be a wonderful development." ■

A Who's Who from the NIH Conference on Primary Pulmonary Hypertension

A conference earlier this year sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health drew experts from around the country and Canada to discuss new directions in research. This conference, *Transactional Research in Primary Pulmonary Hypertension*, was chaired by John H. Newman, MD, Chief, Medical Service, VA Medical Center, and Professor at Vanderbilt University School of Medicine, Nashville, Tennessee.

The conference, held in Bethesda, Maryland, also included: Cochairman, Barry L. Fanburg, MD, Professor of Medicine, Department of Medicine, Pulmonary and Critical Care Division, New England Medical Center, Boston, Massachusetts.

Participants included:

Steven L. Archer, MD

Professor of Medicine, Division of Cardiology, University of Alberta Hospital, Edmonton, Alberta, Canada

David Badesch, MD

Professor of Medicine, Department of Medicine, University of Colorado Science Center, Denver, Colorado

Robyn J. Barst, MD

Professor of Pediatrics, Division of Pediatric Cardiology, Columbia University College of Physicians and Surgeons, New York, New York

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James E. Loyd, MD

Professor of Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Michael D. McGoon, MD

Cardiologist, Department of Cardiology, Mayo Clinic, Rochester, Minnesota

Jane Morse, MD

Professor, Department of Medicine, Columbia University, New York, New York

William C. Nichols, PhD

Associate Professor, Division and Program in Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Marlene Rabinovitch, MD

Professor, Department of Pediatrics, Stanford University School of Medicine, Stanford, California

David Rodman, MD

Professor, Department of Medicine, University of Colorado Health Science Center, Denver, Colorado

Ivan Robbins, MD

Assistant Professor of Medicine, Director, Adult Allergy Pulmonary Hypertension Center, Vanderbilt University Medical Center, Nashville, Tennessee

Troy Stevens, PhD

Associate Professor, Department of Pharmacology, University of South Alabama College of Medicine, Mobile, Alabama

Rubin M. Tuder, MD

Associate Professor of Pathology and Medicine, Director of Pulmonary and Critical Care Medicine, Director, Division of Cardiopulmonary Pathology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland



Recapping Highlights from the Third World Symposium on Pulmonary Arterial Hypertension, Venice, Italy, June 23-25, 2003

As the broad range of topics suggests, the Third World Symposium on Pulmonary Arterial Hypertension (PAH) addressed many of the issues of overriding importance to clinicians involved with treatment of the disease. Held in Venice, Italy, from June 23 to 25, the symposium attracted key opinion leaders from Europe and the United States whose research has put them on the frontier of advances in PAH. The symposium assigned topics to various task forces that met and worked toward a consensus document for key issues, such as appropriate diagnostic algorithms, functional capacity tests, and the use

of echocardiography and other noninvasive tests.

The summaries presented in this issue highlight many of the trends observed by task force members in Venice and suggest future directions for research in PAH. The World Symposium on Pulmonary Arterial Hypertension has helped formulate definitions and classifications that contribute toward an improved understanding of the pathophysiology of PAH and have produced algorithms that help guide treatment strategies. A list of the task force members follows along with the topics assigned to them.

A Meeting of the Minds in Venice: A Roster of Attendees and Assignments

This listing of physicians indicates who attended the Third World Symposium on Pulmonary Hypertension and the Task Forces to which they were assigned as groups worked toward a consensus on selected topics. The Scientific Organizing Committee included three physicians in Europe and three in the United States. In Europe: Nazzareno Galiè, Bologna, Italy, Werner Seeger, Giessen, Germany, and Gérald Simonneau, Clamart, France. In the US, the committee included Robyn J. Barst, New York, New York, Stuart Rich, Chicago, Illinois, and Lewis J. Rubin, La Jolla, California.

Task Force on Pathology and Pathobiology

Committee: Chairman and Secretary: Marc Humbert, France

Chairs: Giuseppe Pietra, Switzerland; Marlene Rabinovitch, Stanford, California; Norbert F. Voelkel, Denver, Colorado.

Members: Stephen L. Archer, Edmonton, Canada; Frederique Capron, Paris, France; Brian Christman, Nashville, Tennessee; Friedrich Grimminger, Giessen, Germany; Sheila G. Haworth, London, UK; Phillipe Hérvé, Le Plessis Robinson, France; Irene Lang, Vienna, Austria; Ornella Leone, Bologna, Italy; Margaret R. MacLean, Glasgow, UK; Nick W. Morrell, Cambridge, UK; Lynne M. Reid, Boston, Massachusetts; Kurt Stenmark, Denver, Colorado; Susan Stewart, Cambridge, UK; Rubin Tuder, Baltimore, Maryland; and E. Kenneth Weir, Minneapolis, Minnesota.

Task Force on Genetics

Committee: Chairman and Secretary: Gregory Elliott, Salt Lake City, Utah; Chairs: John H. Newman, Nashville, Tennessee; and Richard C. Trembath, Leicester, UK.

Members: Serge Adnot, Cretail, France; Fabio Coccolo, Bologna, Italy; Oliver Eickelberg, Giessen, Germany; Ekkehard Gruenig, Heidelberg, Germany; James A. Knowles, New York, New York; James E. Loyd, Nashville, Tennessee; Jane H. Morse, New York, New York; William C. Nichols, Cincinnati, Ohio; John A. Phillips III, Nashville, Tennessee; Werner Seeger, Giessen, Germany; and Carlo Ventura, Sassari, Italy.

Task Force on Epidemiology, Nomenclature and Classification

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Members: Guido Domenighetti, Locarno, Switzerland; Nazzareno Galiè, Bologna, Italy; Simon Gibbs, London, UK; Miguel A. Gomez-Sanchez, Madrid, Spain; David Langleben, Montreal, Canada; Didier Lebrec, Clichy, France; Nick W. Morrell, Cambridge, UK; Robert Naeije, Brussels, Belgium; Stuart Rich, Chicago, Illinois; Lewis J. Rubin, La Jolla, California; Werner Seeger, Giessen, Germany; and Rudolf Speich, Zurich, Switzerland.

Task Force on Diagnosis and Assessment

Committee: Chairman and Secretary: Robyn J. Barst, New York, NY; Chairs: Michael D. McGoon, Rochester,

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UK; Gerald Simonneau, Clamart, France; Olivier Sitbon, Clamart, France; Gianni Tognoni, Milan, Italy; and Adam Torbicki, Warsaw, Poland.

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Task Force on Future Directions

Committee: Chairman and Secretary: Stuart Rich, Chicago, Illinois; Chairs: Robert Naeije, Brussels, Belgium; Andrew J. Peacock, Glasgow, UK.

Members: Brian Christman, Nashville, Tennessee; Gerry Coghlan, London, UK; Oliver Eickelberg, Giessen, Germany; Sean P. Gaine, Dublin, Ireland; Friedrich Grimminger, Giessen, Germany; Tim Higenbottam, Sheffield, UK; Stefan Janssens, Leuven, Belgium; John H. Newman, Nashville, Tennessee; Marlene Rabinovitch, Stanford, California; Richard C. Trembath, Leicester, UK; Norbert F. Voelkel, Denver, Colorado; and E. Kenneth Weir, Minneapolis, Minnesota.

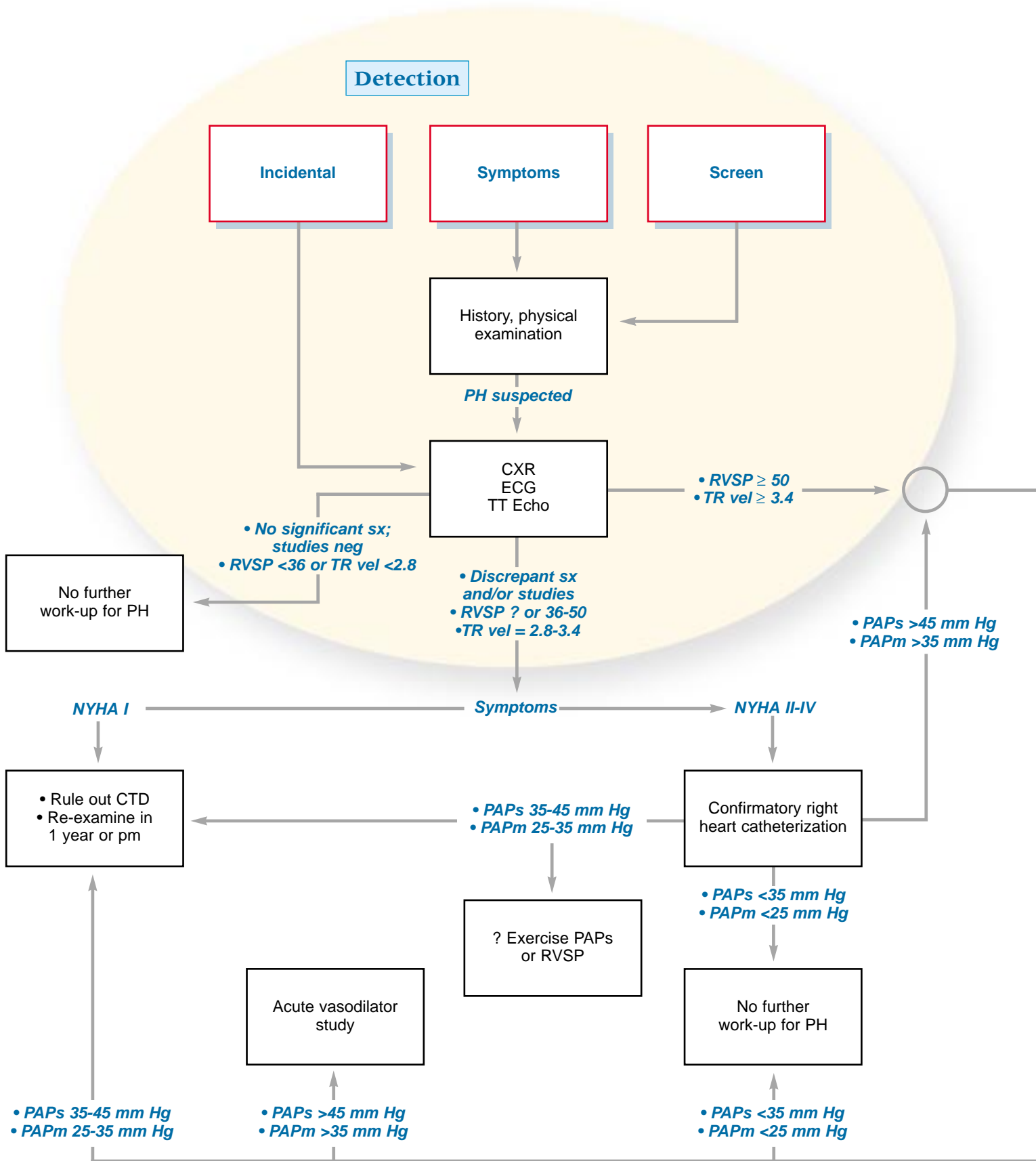
Previewing the Winter 2003 Issue of *Advances in Pulmonary Hypertension*

The Editors of *Advances in Pulmonary Hypertension* are pleased to present an entire issue focusing on Future Directions in Pulmonary Hypertension

Topics will include:

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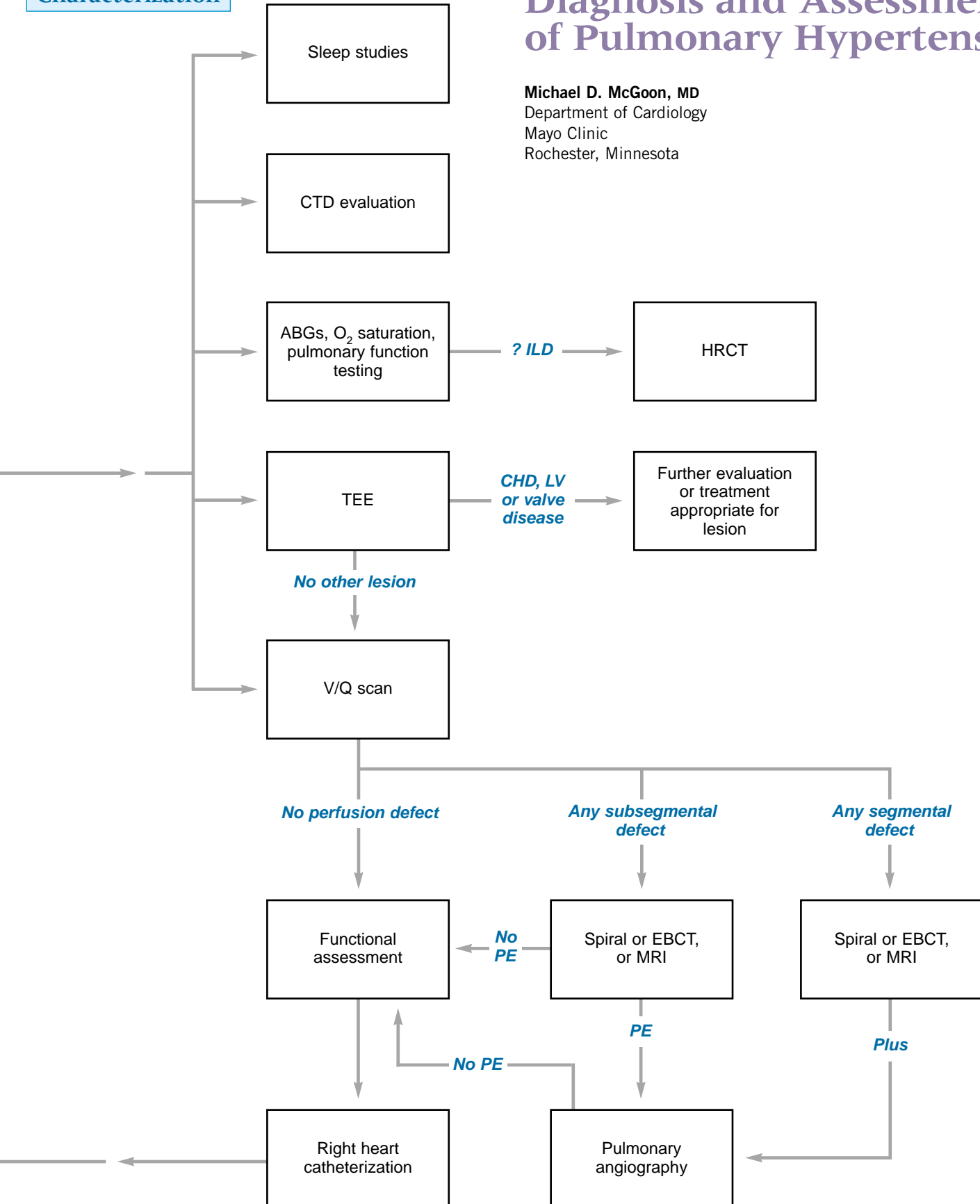


Clinical Algorithm

Diagnosis and Assessment of Pulmonary Hypertension

Michael D. McGoon, MD
Department of Cardiology
Mayo Clinic
Rochester, Minnesota

Characterization





November is Pulmonary Hypertension Awareness Month

This year's theme is **Pulmonary Hypertension: The Other High Blood Pressure**. The more people are aware of the seriousness of this illness, the more support they will offer. In addition, with increased awareness among the general public and medical professionals, more people will be diagnosed early.

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- Register to attend the PHA Scientific Session and Annual Meeting in June 2004. Visit www.phassociation.org/Conference



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See Summary/Please see package insert for full prescribing information.

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

WARNING: Potential liver injury. TRACLEER causes at least 2-fold (upper limit of normal) SUN 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 5 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Therefore, aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER should generally be avoided in patients with elevated aminotransferase (> 3 x UN) 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 fatigue or fatigue or increase in bilirubin > 2 x UN), 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 the 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 use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in women receiving TRACLEER (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained.

Because of potential liver injury and as 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 1 866 381 346. Adverse events can also be reported directly on this website.

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

CONTRAINDICATIONS: TRACLEER is contraindicated in pregnancy, with concomitant use of cyclosporins, with co-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 embryonic 1 knockout mice and in animals treated with other endothelin receptor antagonists indicate 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 signs the prescription that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 3 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Following urine or serum pregnancy tests should be obtained monthly in women of childbearing potential using TRACLEER. The patient must be advised that there is a 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 the fetus.

WARNINGS: Potential liver injury. Bosentan in ALT or AST by more than 2 x UN were observed in 11% of bosentan-treated patients (N = 88) compared to 2% of placebo-treated subjects (N = 200). The combination of hepatocellular injury (increases in aminotransferases of > 3 x UN) and increases in total bilirubin (> 2 x UN) 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, or typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may resolve 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 fatigue or fatigue) or increase in bilirubin > 2 x UN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Precautions: 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 aminotransferase (> 2 x UN) because monitoring liver injury in these patients may be more difficult.

PRECAUTIONS: Hematology. Change: 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 (range to end of treatment). Most absolute decreases in hemoglobin concentration were detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 8-12 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 85% of bosentan-treated patients compared to 79% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhagic or hemolytic. If a marked decrease in hemoglobin concentration is checked after 1 and 3 months, and every 2 months thereafter, if a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

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 these female patients (input from a gynecologist or similar expert or adequate contraceptive should be sought as needed).

Drug Interactions: CYP Isoenzymes. Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inhibitor of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER is co-administered. Contraceptive Specific Interaction Studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraceptives when TRACLEER is co-administered. Women should not rely on hormonal contraceptives alone when taking TRACLEER. Cyclosporin A During the first year of concomitant administration through concentrations of bosentan were increased by about 20-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporin A. The concomitant administration of bosentan and cyclosporin A is contraindicated. Sitruvite: An increased risk of elevated liver aminotransferase was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of TRACLEER and glyburide is contraindicated, and 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 increased 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 5-hydroxy acid metabolite, by approximately 20%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other drugs that have significant metabolism by CYP3A4 such as losartan and atorvastatin. The possibility of reduced drug efficacy should be considered. Patient using CYP3A4 metabolized drugs should have cholesterol levels monitored after TRACLEER is initiated to see whether the drugs show steady adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 14 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 28 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 (dosage up, and of the clinical studies), and the need to change the warfarin dose during the trial due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Diphenhydramine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with diphenhydramine 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., in a mg/m² basis. In the same study, doses greater than about 20 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 9 times the MRHD. Impairment of Fertility/Endocrine Function: Many endothelin receptor antagonists have profound effects on the physiology and function of the testes in animals. These drugs have been shown to reduce sperm of the seminiferous tubules if the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Therefore, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear reversible. In fertility studies in which male and female rats were treated with bosentan at oral doses up to 30 times the MRHD on a mg/m² basis, no effects on sperm count, sperm quality, 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 at 10 to 12 times the MRHD for about 18 weeks. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects, Category X

PRECAUTIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Concomitantly drugs are used 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 discontinuation due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent in bosentan (N= 870 patients) than in placebo (N= 240 patients). In this database the only cause of discontinuation > 1%, and occurring more often in 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 oral doses ranging from 125 mg to 3000 mg and 268 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 8 months, for the adverse drug reactions that occurred in > 2% of bosentan-treated patients the only ones that occurred more frequently in bosentan than in placebo (≥ 2% difference) were headache (10% vs. 5%), fatigue (7% vs. 2%), abnormal hepatic function (5% vs. 2%), leg cramps (3% vs. 1%), and anemia (3% vs. 1%).

INDICATIONS: Bosentan has been given as a single dose of up to 3000 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 comparative interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporin A, though plasma concentrations of bosentan increased 20-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. All 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 has not been reported in patients receiving active or placebo support.

INDICATIONS AND ADMINISTRATION: TRACLEER treatment should be initiated at a dose of 62.5 mg b.i.d. for 1 week and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit but increased the risk of liver injury. Tablets 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 UN	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 UN	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 UN	Treatment should be stopped and reintroduction of TRACLEER should not be considered. There is no experience with re-introduction of TRACLEER in these circumstances.

TRACLEER is re-introduced it should be at the starting dose, aminotransferase levels could be checked within 1 day and thereafter according to the recommendations above. If low aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue) or increase in bilirubin > 2 x UN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Use in Women of Childbearing Potential: TRACLEER treatment should only be initiated in women of childbearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely only upon hormonal contraceptives, including oral, injectable or implantable contraceptives, but use a progesterone or similar agent. An adequate contraceptive should be sought if needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential using TRACLEER. Dosage Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is oral 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 adjustment in elderly patients over the greater frequency of decreased 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 should 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 Pediatric: 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 17 years of age the recommended initial and maintenance dose 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, it would be prudent to consider a gradual dose reduction (0.5 mg b.i.d. for 3 to 4 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, oval, bisectate, orange/red tablets, embossed with identification marking "125" NDC 60215-10-06. 125 mg film-coated, oval, bisectate, orange-white tablets, embossed with identification marking "125" NDC 60215-100-06. Bottle containing 60 tablets.

U.S. 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).

References

1 Zimmerman HJ. Hepatotoxicity - The adverse effects of drug and other chemicals on the liver. Second ed. Philadelphia: Lippincott, 1985.

Manufactured by: Actelion Inc.
Mossburn, Ontario, CANADA
Marketed by: Actelion Pharmaceuticals US, Inc.
South San Francisco, CA

Information for previous page: 1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals, Inc. 2004.

Task Force on Diagnosis and Assessment: Identifying the Most Useful Tools

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A diagnostic algorithm that is accepted among experienced centers (Pull-Out, next page) can guide the evaluation of pulmonary hypertension. Like all guidelines, the algorithm may be modified according to specific clinical circumstances. Most patients are diagnosed as the result of an evaluation of symptoms, while others are diagnosed during screening of asymptomatic populations at risk. Symptomatic patients should be managed with an aggressive therapeutic strategy to reduce symptoms, improve hemodynamics, and prolong survival. Asymptomatic or incidentally discovered subjects should be managed with conservative treatment (depending on the severity of the hemodynamic abnormality), identification of reversible underlying causes, and close monitoring for progression.

A high level of suspicion is of paramount importance for the diagnosis of pulmonary hypertension regardless of underlying cause. Once suspect, a methodical workup using commonly employed diagnostic interventions allows confirmation of the presence of pulmonary hypertension and elucidation of its etiology. Clarification of etiology is necessary to ensure that the proper therapeutic interventions are implemented.

In patients with a suspicion of, or risk of, pulmonary arterial hypertension (PAH), the physical examination should be performed to assist in directing further evaluation to more specific and efficient assessment for defining the presence, severity and substrate of PAH. In addition, an ECG should be performed to screen for a spectrum of cardiac and arrhythmic problems. Although an ECG lacks sufficient sensitivity to serve as an effective screening tool for PAH, it does contribute some prognostic information in patients with known idiopathic PAH. A chest X-ray should also be obtained to reveal features supportive of a diagnosis of PAH and lead to diagnoses of underlying diseases.

Doppler echocardiography should be performed as an appropriate and useful screening tool to detect clinically significant degrees of elevated pulmonary pressure, although in some patients it may be imprecise in determining actual pressures (compared with invasive evaluation). In patients with high-risk substrates, eg, systemic sclerosis, family history of idiopathic PAH, known genetic predisposition, Doppler echocardiography should be performed periodically, ie, every 1 to 3 years, to screen for possible development of clinically significant degrees of elevated pulmonary pressure. Doppler echocardiography should also be obtained in patients with suspected or documented pulmonary hypertension to look for left ventricular systolic and diastolic dysfunction, left-sided chamber enlargement, or valvular heart disease, any of which may cause or contribute to pulmonary hypertension and may be treatable. A contrast study during Doppler echocardiography is also useful to look for evidence of intracardiac shunting.



Screening for connective tissue disease and HIV infection by serologic testing (along with appropriate history and physical examination) should also be performed in patients with suspected or documented pulmonary hypertension. A ventilation-perfusion lung scan should be performed to rule out chronic thromboembolic pulmonary hypertension; a negative scan effectively excludes a diagnosis of chronic thromboembolic pulmonary hypertension. Contrast-enhanced computed chest tomography or magnetic resonance imaging can provide useful morphologic information, but should not be relied upon to unequivocally exclude chronic thromboembolic pulmonary hypertension. In patients with a V/Q scan suggestive of chronic thromboembolic pulmonary hypertension, pulmonary angiography is required for accurate diagnosis and best anatomic definition. Contrast enhanced computed chest tomography or magnetic resonance imaging can be obtained to provide complementary morphologic, functional and prognostic information.

Pulmonary function testing and arterial blood gas measurements should be performed to evaluate potentially contributory ventilatory factors and diffusion abnormalities. In patients with systemic sclerosis, pulmonary function testing should be performed periodically, ie, every 6 to 12 months, to detect deteriorating DLCO as a sign of progressive pulmonary vasculopathy.

Lung biopsy is not recommended because of the risk in patients with suspected or documented pulmonary hypertension, except under circumstances in which a specific question can be answered only by tissue examination. Finally, right heart catheterization is required in patients with suspected pulmonary hypertension to establish the diagnosis of pulmonary hypertension and document pulmonary hemodynamics. Furthermore, prior to initiation of medical therapy, assessment of vasodilating capacity (during the right heart catheterization) is required to determine the appropriate therapy for an individual patient.

Techniques that have recently been evaluated to predict disease severity include: assessment of right ventricular function, using Doppler echocardiographic semi-quantitative indices, functional class, exercise testing, ie, exercise endurance assessed by a 6-minute walk test and exercise tolerance assessed with cardiopulmonary exercise testing, and demographic and hemodynamic parameters. Neurohormone levels, such as BNP and ANP, have recently been demonstrated to correlate with survival, and norepinephrine and endothelin-1 levels also appear to be useful parameters of disease severity. In addition, uric acid levels have been reported to correlate with the severity of PAH.

Some of these modalities may provide prognostic information that is similar to that derived from invasive tests and may be more useful and convenient in assessing treatment efficacy

over time. These newer tools may also enhance predictive accuracy when used in combination with the “standard” testing modalities. Many of these variables have been shown to correlate with one another; thus, which parameters will prove to be the most useful in assessing disease severity requires further investigation. Importantly, all of the above studies evaluated idiopathic PAH patients but not patients with PAH related to connective tissue disease, congenital heart disease, anorexigen, HIV infection, or portal hypertension. Thus, these parameters must be applied cautiously to PAH patients in whom comorbid factors may contribute significantly to overall outcome, eg, in general, patients with PAH related to connective tissue disease have a worse prognosis than idiopathic PAH

patients, whereas patients with PAH related to congenital heart disease have a much more slowly progressive course than do patients with idiopathic PAH.

In conclusion, PAH is diagnosed by following a careful series of investigations that include tests that are regarded as essential in making the diagnosis, as well as additional tests that may help clarify the category of pulmonary hypertension present. Disease severity can be evaluated by several modalities that are complementary and that together are useful in helping to choose therapy and evaluate the response to therapy. Close follow-up at a center specializing in pulmonary hypertension is recommended, with careful monitoring at frequent intervals of the course of the disease. ■

Overview of Genetics as presented at the PAH Symposium in Venice

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Medical scientists have achieved three major goals proposed by the 1998 Evian task force on the genetics of pulmonary hypertension. First, mutations in the gene that codes for bone morphogenetic protein receptor 2 (BMPR2) are linked to familial primary pulmonary hypertension. BMPR2 mutations are detectable in approximately half of the families affected by primary pulmonary hypertension. The gene that codes for BMPR2 is large (13 exons) and already more than 26 mutations are described. Second, many patients with apparently sporadic primary pulmonary hypertension have mutations of the gene that codes for BMPR2. This observation, combined with observations of common ancestors among patients with apparently sporadic primary pulmonary hypertension, indicates that an inherited basis underlies many cases of primary pulmonary hypertension. However, the relatively low penetrance of these mutations (only 15% to 20% of persons carrying a BMPR2 mutation develop clinically evident disease in their lifetime) makes identification of familial disease difficult. Third, BMPR2 mutations are rare in other classifications of pulmonary arterial hypertension, eg, pulmonary arterial hypertension associated with CREST, HIV infection, or fenfluramine exposure. Rare cases of pulmonary arterial hypertension with BMPR2 mutations and fenfluramine exposure raise the possibility of disease triggered by genetic predisposition and an environmental trigger.

The exact pathogenesis of familial primary pulmonary hypertension remains elusive in spite of the identification of BMPR2 mutations. The identification of abnormalities in other TGF beta receptors [ALK-1; TGF beta R2, and BMPR1A (ALK3)] suggests that dysfunctional TGF beta receptors are important in the pathogenesis of familial primary pulmonary hypertension. Indeed, TGFβ represents a classic pleiotropic mediator to the vascular system by modifying growth, differentiation, and death of vascular cells. Nevertheless, other genes and/or environmental factors must also be important in order to explain the reduced penetrance of BMPR2 mutations. Genes



that control nitric oxide synthesis, serotonin transport, or prostacyclin may prove important to the expression of disease. Animal models (eg, mice) allow study of genetic alterations of BMPR2 as well as other pathways, eg, serotonin. Inactivation of BMPR2 in mice leads to pre- and perinatal mortality because of abnormal mesoderm formation, illustrating the potential of BMPR2 mutations to cause vascular disease. To date, scientists have not been able to reproduce primary pulmonary hypertension in mouse models, but this remains an important goal for future research.

The discovery of mutations in the gene that codes for BMPR2 makes genetic testing and counseling possible. In the future such tests may corroborate diagnostic impressions and provide estimates of an individual's risk to develop primary pulmonary hypertension. The use of such tests requires an understanding of the meaning of the test results, as well as the risks and benefits of this knowledge to those who are tested and to other family members. Before and after the tests, education and counseling will be necessary, especially because the penetrance of known BMPR2 mutations is low and because the results may prove psychologically (eg, depression, anxiety) or socially (eg, employment barriers and effects on insurability) harmful.

For these reasons genetic testing for BMPR2 mutations will require adherence to basic rules. Informed consent is essential when a test can be linked to an individual. The consent should be voluntary, without coercion or intimidation; and patients should be assured that their care is unaffected by decisions to forego genetic tests. In addition confidentiality of results must be assured.

Genetic tests for mutations associated with primary pulmonary hypertension are not available in the United States. The BMPR2 gene is large, making tests expensive unless the test is directed at a known mutation. For these reasons the task force concluded that genetic testing needs development and is not ready for widespread implementation. ■

Pathophysiology of Pulmonary Hypertension: Recognizing Triggers of the Disease

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It is unclear whether the various types of PAH share a common pathogenic mechanism. Although our understanding of the pathobiological changes underlying PAH has progressed rapidly over the past few years, it is still impossible to classify patients on a pathogenic basis and to define therapeutic approach accordingly. Three factors are considered to cause the increased pulmonary vascular resistance in PAH: vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis in situ. The latter two are easily evident with light microscopy, whereas vasoconstriction is best demonstrated by vasodilator testing. Most specialists now agree that pulmonary vascular proliferation and remodeling, and not vasoconstriction, is the hallmark of PAH pathogenesis.



Bone morphogenetic protein receptor 2 and related molecules

The recent identification of a pulmonary hypertension gene (bone morphogenetic protein receptor 2, *BMPR2*, a member of the transforming growth factor beta superfamily) provides the opportunity to develop a deeper understanding from a molecular biology perspective. Heterogeneous germline mutations in *BMPR2* occur in approximately 60%, 25%, and 10% of patients with familial, sporadic, and fenfluramine derivatives-associated PAH, respectively. In addition, germline mutations in the gene coding activin-like receptor kinase 1, another member of the transforming growth factor beta superfamily, have been identified in patients with hereditary hemorrhagic telangiectasia. These patients develop severe plexiform pulmonary (or idiopathic) hypertension, which is symptomatically indistinguishable from PPH. The relevance of the transforming growth factor beta superfamily in the etiology of PAH is further supported by a recent report of endoglin germline mutation in a patient who had hereditary hemorrhagic telangiectasia and dexfenfluramine-associated PAH. These observations support the hypothesis that mutations in the transforming growth factor beta superfamily may be a trigger for pulmonary vascular remodeling.

The transforming growth factor beta superfamily is diverse, comprising transforming growth factor beta isoforms, the bone morphogenetic proteins, activins, and growth and differentiation factors. A possible mechanism whereby such a mutation could trigger remodeling is emerging from studies on *BMPR2*. *BMPR2* mediates its actions by binding ligand in conjunction with a type I receptor to form a heterodimer complex on the cell surface and subsequently propagate an intracellular signal via Smad molecules. As *BMPR2* is involved in cell proliferation and apoptosis, the occurrence of a mutation in this protein could

result in abnormal signaling in pulmonary artery smooth muscle cells, leading to loss of antiproliferative or apoptotic mechanisms. This theory is supported by the demonstration of dysregulated growth inhibition of pulmonary artery smooth muscle cells from patients with PPH exposed to bone morphogenetic proteins and transforming growth factor beta. In fact, additional findings suggest that all forms of pulmonary hypertension may be linked to defects in the signaling pathways involved in angiogenesis, such as angiotensin-1 and bone morphogenetic protein receptors. The possible involvement of the transforming growth factor beta superfamily in the pathophysiology of PAH may have identified a novel target for therapeutic intervention.

Modifier genes and environmental factors

As PAH develops in only 10% to 20% of individuals with *BMPR2* mutations, the contribution of other factors for the development of PAH is undeniable. The “multiple hit” hypothesis has been proposed whereby the combination of a number of factors may precipitate the disease. In such a scenario, a susceptible individual with a *BMPR2* mutation would require additional insults such as exposure to anorectic drug before manifesting PAH. Another theory is that of the role of modifier genes in the pathogenesis of PAH. As recently detailed by Runo and Loyd in their *Lancet* review, genes and gene products putatively implicated in the pathogenesis of PAH include prostacyclin synthase, nitric oxide synthase, serotonin transporter, serine elastases, matrix metalloproteinases, voltage-gated potassium channels, angiotensin-converting enzyme, vascular endothelial growth factor, carbamoyl phosphate synthase, plasminogen activator inhibitor type 1, and endothelins.

Endothelial dysfunction

Recent advances in the understanding of the molecular mechanisms involved in PAH suggest that endothelial dysfunction could correspond to downstream manifestations of the disease rather than a central pathogenic mechanism. There is now considerable evidence that endothelial dysfunction leading to exaggerated vasoconstriction, and impaired vasodilatation plays a key role in PAH. Interestingly, chronically impaired production of vasodilators such as nitric oxide and prostacyclin along with prolonged overexpression of vasoconstrictors such as endothelin-1 not only affect vascular tone, but also promote vascular remodeling and therefore represent a logical pharmacological target. ■

Report From the Task Force on Medical Treatments

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The recent clinical trials with novel compounds have produced a tremendous increase of both knowledge and therapeutic options in patients with pulmonary arterial hypertension (PAH). The analysis of placebo-treated groups in the various trials has allowed a better understanding of the natural history of PAH on conventional treatment. In fact, signs of functional and hemodynamic deterioration are detectable as early as after 3 months in previously stable patients. The new trials have similar designs, duration, and end points but relevant differences including the baseline NYHA functional class and the etiology profiles need to be taken into account in the comparative evaluation of these studies. Each new compound presents side effects that are unpredictable in the individual patient and require an appropriate attention upon treatment initiation and maintenance. The lack of effect on mortality can be explained by the study protocols that were not designed for assessing this end point and by the overall low mortality of the study populations as compared with the historical controls. Extension, open label studies will help us to understand whether the favorable effects and safety profiles observed in the randomized phases are maintained over the long term. Unfortunately, in these cases, the effects on mortality can be assessed only by comparison with historical controls.

The discussion in the Task Force on Medical Treatments of the 3rd WSPAH has been focused on the attempt to derive an evidence-based treatment strategy that includes all available treatments already approved or tested. The treatment strategy is targeted to patients in NYHA functional class III and IV, which is the patient population predominantly enrolled in clinical trials. For NYHA functional class I and II patients the most appropriate strategy is yet to be determined.

The traditional approach to treat patients with oral anticoagulant drugs and diuretics if needed has been confirmed even if controlled studies are lacking. The vasoreactivity test is also mandatory to identify the minority of patients with a favorable acute response (approximately 20%). In this group, a chronic treatment with high doses of Ca⁺⁺-channel blockers is justified but clinical, functional, and hemodynamic improvements need to be confirmed after 3 to 6 months with formal noninvasive and invasive investigations. In patient nonresponders to acute vasoreactivity tests or responders with no favorable effect of chronic Ca⁺⁺-channel blocker treatment who are in NYHA functional class III treatment with an endothelin receptor antagonist (ERA) or with a prostanoid is indicated. Up to now the only commercially available and approved ERA is the oral dual antagonist bosentan that has been successfully tested in two



controlled clinical trials. The ET_A selective ERA sitaxentan has been tested in an uncontrolled and a controlled trial and a second study is ongoing, while the ET_A selective ERA ambrisentan has been tested in an uncontrolled trial and controlled studies should be implemented soon. Among prostanoids, treprostinil, administered subcutaneously has been approved in the USA; it was tested in two controlled clinical trials and only in one was the primary end point fulfilled. Iloprost, administered by aerosol, has been approved in Europe, and it has been tested successfully in one controlled trial. Beraprost is administered orally and is approved in Japan; it was tested in two controlled clinical trials and only in one was the primary end point fulfilled. The first class of drug and the specific compound to be initiated are related to different factors including the approval state, the preferred mode of administration, the side effect profile, and the specific experience of the centers. The orally active phosphodiesterase V inhibitor sildenafil has not yet been approved for the treatment of PAH patients even though multiple uncontrolled favorable experiences have been published. The role of this drug can be better understood after the evaluation of the controlled clinical study that is currently ongoing. In patients with NYHA functional class III the continuous intravenous administration of epoprostenol should be considered (two controlled clinical trials with favorable results) because the best effects on survival are observed in this functional class.

Continuous intravenous administration of epoprostenol is the treatment of choice in patients in NYHA functional class IV, and it is approved in the United States and in Europe. In these cases also bosentan and treprostinil have an official approval by the FDA but given the small number of patients included in the clinical trials the experts consider these treatments as a second choice. Iloprost administered intravenously is approved in New Zealand, even though no controlled trials are available.

Continuous intravenous administration of epoprostenol may be indicated also in NYHA class III patients who have no favorable response with ERAs or to other prostanoids.

Combination therapy (eg, ERA plus prostanoids) has to be considered in any case of no improvement or deterioration with the first treatment even if data on this specific strategy are few and uncontrolled. Appropriate protocols for timing and dosing to limit possible side effects of the combination have still to be implemented.

In case of failure and/or unavailability of medical treatments, balloon atrial septostomy and/or lung transplantation are indicated. These procedures should be performed in experienced centers. ■



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Acute Vasodilator Testing in PAH

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Vasoconstriction of pulmonary arteries is recognized as an important component of the pathogenesis of pulmonary arterial hypertension (PAH). Pure vasodilators alleviate vasoconstriction with little effect on the fibrotic and proliferative changes that frequently predominate over vasoconstriction in PAH. Uncontrolled studies have suggested that long-term administration of calcium-channel blockers (CCBs) prolongs survival in the rare subset of responsive patients (representing around 10% of patients referred to pulmonary vascular centers), compared with unresponsive patients. Therefore, the question of the overall efficacy of administering CCBs is still of concern, as well as the way of safely identifying the patients who may benefit from long-term oral treatment. Unfortunately, any clinical or hemodynamic parameter can predict acute and chronic responses to CCBs in patients with PAH. It is generally accepted that patients who may benefit from long-term use of CCBs can be identified by an acute vasodilator challenge performed during right heart catheterization in specialized pulmonary vascular units.

The magnitude of acute vasodilator response that predicts a favorable outcome with long-term CCB therapy remains poorly defined. Until recently, a reduction of both mean artery pulmonary pressure (mPAP) and of pulmonary vascular resistance (PVR) by at least 20% was used as the criterion for the initiation of oral CCB therapy. A drop in mPAP by more than 10 mm Hg without decrease in cardiac output could be the minimum acceptable response. A decrease in PVR of 50% relative to baseline value and an mPAP lower than 30 mm Hg could indicate better clinical outcome. However, these definitions do not discriminate between patients with a sustained benefit from CCBs (defined as being in NYHA functional class I or II with near-normal hemodynamics after at least one year follow-up) and those whose condition will fail to improve. In our experience, only 7% of patients referred to a specialized pulmonary vascular center with idiopathic PAH will have a sustained benefit from treatment with CCBs. During acute vasodilator challenge, these rare patients markedly improve their pulmonary hemodynamics, achieving an mPAP less than 40 mm Hg, and



associated with a normal or high cardiac output. We therefore consider that a positive response to acute vasodilator challenge is defined by a substantial reduction in mPAP (decrease exceeding 10 mm Hg to reach an mPAP lower than 40 mm Hg) with a normal or high cardiac output. The occurrence of severe life-threatening

hemodynamic compromise during acute vasodilator challenge with CCBs is an obvious risk, even when conventional doses of CCBs are used. Therefore, there is a need for a safe, potent, and short-acting vasodilator having limited side effects during acute testing to accurately identify patients who may benefit from long-term CCB therapy. In the therapeutic approach of patients with PAH, numerous vasodilator agents have been used on a short-term basis to evaluate the capacity of the pulmonary vascular bed to vasodilate. Among them, prostacyclin, adenosine, and nitric oxide are the most widely used drugs. Recent data suggest that inhaled iloprost may be more effective than nitric oxide to decrease PVR. However, no information is available regarding acute response to iloprost as a predicting factor to long-term efficacy of CCB therapy.

With emerging potent oral and inhaled drugs combining vasodilatory and antiproliferative properties, the issue of invasive testing for pulmonary vasoreactivity in selecting treatment may lose its importance. It should be easy to prescribe oral therapies such as an endothelin receptor antagonist (bosentan), a prostacyclin analogue (beraprost), or a phosphodiesterase inhibitor (sildenafil) to all PAH patients whatever their functional class (except for class IV) and acute pulmonary vasoreactivity. Although it is reasonable to think that patients who respond to intravenous prostacyclin, adenosine, or inhaled nitric oxide are able to respond to such oral therapies, no study has evaluated the acute and chronic response to these drugs in vasoreactive patients. In addition, the cost of these therapies could be a limitation to their prescription in some PAH patients.

In conclusion, the drugs of choice for testing vasoreactivity are short-acting agents, intravenous prostacyclin, adenosine, or inhaled nitric oxide. Long-term treatment with oral CCBs will be considered only in responders to one of these three drugs. ■

Transplantation and Thromboendarterectomy for Severe Pulmonary Hypertension: Report from the Transplant and Interventions Task Force

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Recent advances in medical and interventional approaches to the management of patients with pulmonary arterial hypertension (PAH) have had a marked effect on the policy toward referring such patients for transplantation and there has been a reduction of 50% in numbers of patients with primary pulmonary hypertension (PPH) undergoing transplantation over the last decade.¹ In practice patients are being referred at a later stage, often in decompensated right heart failure. Such patients present a major challenge to both peri- and postoperative management, with some centers identifying the need for elective ECMO support or at least prolonged ventilatory support. The prognosis of patients presenting with WHO class III and IV symptoms has been improved by both prostaglandin and endothelial antagonist therapy.²⁻⁶ But not all patients show a significant response, so the concept of assessing a patient with advanced disease, listing when appropriate and de-listing if there was a significant response to medical therapy such that the patient improved to WHO class II on symptoms, was supported. The literature supports that transplant centers currently show wide variation in their approach to indications for and timing of lists. It is clear that close communication between PAH centers and transplantation centers is very appropriate.

The results of transplantation for patients with severe pulmonary hypertension (PH) as documented in the International Society for Heart and Lung Transplantation registry data are significantly less good than for patients with respiratory failure due to other causes. It was concluded that transplantation for patients with PH might be best limited to specialist transplant centers with specific interests and skills in treating such patients, rather than being offered by a transplant center, and that such an approach might best fulfill the needs of our patients. It was recognized that the problem of donor lung shortage had led to the need to use marginal lungs from older donors, and that this practice was a particular risk for patients with pulmonary vascular disease.

No true consensus was established with regard to the operation of choice for patients with PH. There was a broad body of literature supporting single lung, bilateral lung, and heart-lung procedures for these patients.⁷⁻¹⁰ It was accepted that patients with Eisenmenger syndrome associated with complex congenital heart disease could not be repaired during an isolated lung transplantation procedure and required heart-lung transplantation. There was a trend to supporting the concept of transplanting two lungs rather than one in patients with advanced disease with established right heart failure. However, it was accepted that specialist centers would carry out whichever type



of operation they felt was most appropriate for an individual case. It was also accepted that individual differences would occur given differences in thoracic organ allocation and availability.

The recent UNOS guidelines relating to organ allocation to patients with PH in the United States were discussed and it was felt that the proposed walking distance of 160 feet as an arbiter of clinical need and benefit regarding transplantation was too low and incompatible with satisfactory outcomes.

It was recognized that the development in molecular biology offered unrivaled opportunity to help understand underlying mechanisms leading to PPH and associated conditions and that lungs removed at transplantation offered an important resource for research. It was proposed that attempts should be made to ensure that all lungs removed at surgery should be stored in tissue banks and made available to the many individual laboratories worldwide to foster basic research in this area. It was regrettable that lungs from patients transplanted for PH were not systematically being stored. Finally, brief guidelines regarding referral and listing are summarized below.

- WHO class III patients with 6-minute walk distance >332 meters: Treat medically and refer for transplant if no clinical improvement over 3 months.¹¹
- WHO class IV patients with 6-minute walk distance <352 meters: Assess and list immediately for transplantation, treat medically, and de-list if improvement over 3 months to class II. Deteriorating patients may be considered for septostomy as a bridge to transplantation.
- Hemodynamic markers of adverse outcome are right atrial pressure >15 mm Hg, cardiac index <2 L/min/m², and mixed venous oxygen saturation of ≤63%.

Thromboendarterectomy

There was a clear consensus that patients with PH due to chronic thromboembolic disease should be assessed for thromboendarterectomy and it was proposed that the name of this operation should be changed to pulmonary endarterectomy.¹²⁻¹⁴ This suggestion was made because by the time of surgery no true thrombus remained. It was recognized that more experienced centers worldwide were carrying out successful surgery in patients with severe distal disease as well as proximal disease, a technically more challenging procedure.¹⁵ Discussion concerned the presence of vasculopathy similar to that seen in PPH in the vessels of patients with chronic thromboembolic hypertension unaffected by previous thrombi. Mechanisms leading to

this vasculopathy are not understood at present but it did provide a rationale for consideration of medical therapy with prostaglandins and endothelial antagonists in some patients prior to definitive surgery.¹⁶ The worldwide results of thromboendarterectomy are good, and prognosis and health-related quality of life in such patients are much improved by this operation.¹⁴ ■

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(continued from page 3)

on the echocardiographic and Doppler parameters in PAH patients.

Academically, he earned appointments as Associate Professor of Cardiology on the Medical Faculty at the University of Bologna and Professor at the Postgraduate Medical Schools of Pulmonary Diseases and of Cardiology at the same University. He has served as past chairman of the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology, and he is also a member of the Scientific Council of this Society.

Much of his time in recent years has been consumed with organizing the sessions of the World Symposium on Pulmonary Hypertension, including the Evian conference in 1998 when he served on the Task Force on Medical Treatment. The excitement generated by this year's Third World Symposium on Pulmonary Arterial Hypertension in Venice—which produced a consensus

on many key issues affecting diagnosis and treatment—will continue as new options in therapy are explored and delineated in the reports emerging from this meeting. Many of the consensus statements will serve as the basis for revising the guidelines for treating PAH.

Looking ahead to these developments, Dr Galiè predicted many advances in basic science and therapy during the next 5 to 10 years. "We need to identify the precise link between the mutation of the gene responsible for familial idiopathic PAH. We have the disease on one side and the mutation on the other—what lies between is still unknown, yet critical to understanding the disease. New treatments have been focused on correcting the changes in different pathways, including the endothelin pathway, the prostacyclin pathway, the nitric oxide pathway, and in the future perhaps the serotonin pathway. In addition the appropriate strategy for the combination of these therapies represents an important challenge for the coming years." ■



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Seeking a Consensus on PH: Challenges Left by the Venice Symposium



Victor F. Tapson, MD



Nazzareno Galiè, MD

The Venice Symposium was a unique assemblage of physicians and scientists representing a variety of disciplines ranging from pulmonary medicine to cardiology, rheumatology, pathology, genetics, molecular biology, and surgery, all with a common interest in pulmonary vascular disease. The state-of-the-art overviews provided not only a perspective of where we are and how we got there, but also glimpses into the future of new and exciting directions in basic and translational research. The opportunity for basic investigators, clinical researchers, and representatives from industry to interact and explore new avenues to pursue will undoubtedly lead to fruitful collaborations and innovative approaches to the understanding, and ultimately the cure, of hypertensive pulmonary vascular disease. It is remarkable that, despite the attendance by several hundred individuals, a consensus on major issues was reached, including the adoption of a revised nomenclature. - Lewis Rubin, MD, University of California at San Diego.

Commentary on the Venice Meeting, featuring an interview of Nazzareno Galiè, MD, one of the organizers of the Third World Symposium on Pulmonary Hypertension. Victor Tapson, MD, is Editor-in-Chief of *Advances in Pulmonary Hypertension*.

Dr Tapson: Nazzareno, would you give us an overview of this meeting and how you would compare it with other sessions?

Dr Galiè: This meeting was a challenge because we tried to combine the concepts of the Evian meeting based on task force discussions with more conventional scientific presentations in front of a larger audience. It was a challenge because the plenary presentations to a wide audience were really prepared

during the task force meeting. This was difficult because the time allowed was not infinite and we forced competitive scientists with different ideas to reach a consensus on “hot” topics and to have this consensus written and definite before the plenary presentation. The real success was this: we forced and we obtained this consensus between the task force members because during the plenary presentation only attending people asked additional questions. There was not additional discussion among the task force members. This means that the consensus was reached.

Dr Tapson: Did you think there were any big surprises or controversies with the meeting that were difficult to resolve?

Dr Galiè: I don't think so. There were challenges because in some task forces—for example, genetics, we put together people who were “scientifically” competing among themselves for the last 3 or 4 years. This has been important because they had consensus to collaborate, to define some common research strategies for the future. This was another success. Another surprise was the consensus we reached on the treatment algorithm. I thought it would have been very difficult to get a consensus between people in Europe and the United States because the approved drugs and experiences are somewhat different. Nevertheless, we reached a good compromise in the treatment algorithm.

Dr Tapson: Despite initial differences, it's impressive to make those agreements when practices can be quite different. There are certain obvious things like the use of inhaled prostacyclin, iloprost in some countries. Were there any international differences that were really significant in terms of diagnosis and treatment?

Dr Galiè: The main difference is that in the United

States subcutaneous prostacyclin (treprostinil) is approved whereas this is not approved in Europe. And in contrast, iloprost is already approved in Europe. It was adopted as “off-label” use in some German-speaking countries. Now we have the official approval of the EMEA (European Agency for Evaluation of Medicinal Products) that will become fully operative in a few months. In the United States you have the availability of subcutaneous treprostinil that we have utilized only in patients enrolled in clinical trials. The lack of availability of treprostinil in the clinical setting limits our experience with the use of this drug. This is the main difference. Otherwise, epoprostenol is approved in most European countries, as is bosentan.

Dr Tapson: Did you get a sense from the task force on pathology and pathobiology that there is any one disease mechanism that people seem to agree is the most important or that there is any trend in priorities of the most important mechanism?

Dr Galiè: No, we didn’t find a particular mechanism that can be considered more important than any other. We have the problem related to the endothelial dysfunction, to all the changes in the NO, prostacyclin, or endothelin pathways. We have the serotonin hypothesis. This is coming back because of the genetics. Serotonin transport can explain some differences in the development of pulmonary hypertension in subgroups such as those with HIV or people with portal pulmonary hypertension. I think also the TGF-beta pathway has been studied a lot because of the mutations found on that type of receptor. But I haven’t found a pathway that has been more explored than any other.

Dr Tapson: So the concept of combination therapy is still going to be important in the future?

Dr Galiè: Yes, this is the rationale for the combination therapy. It is linked to the multiple changes in the different pathways. The concept of combination therapies is quite complex because you combine drugs but you also can combine side effects. We cannot forget that all the drugs we are using in pulmonary hypertension are also systemic vasodilators. So you combine many systemic vasodilators and this combination may be detrimental for blood pressure. In any case, this is a problem that can be addressed by an appropriate dosing and timing strategy.

Dr Tapson: Along the lines of treatment, one of the tough topics for me has been the timing of transplantation. Do you think we came to any more consensus?

Dr Galiè: This is another challenge that is linked to the length

of the waiting list. If we could rely on a definite mean time for the waiting list (for example 6 months) we could wait until the patient’s condition has deteriorated to the level at which the expected survival is approximately 6 months. But this is not the case. You know that the waiting list is usually longer than 12 months and up to 18 to 24 months. This is why it is difficult to include in a treatment algorithm the lung transplantation intervention. How can you decide to put a patient on a waiting list 18 to 24 months before the transplantation? Anything can happen in 18 to 24 months. Despite this, the long-term experience with Flolan published recently by Vallerie McLaughlin (Chicago) and by Olivier Sitbon (Paris) showed that the people who have not shown an adequate hemodynamic or exercise capacity improvement after 3 to 4 months of therapy need to be listed for lung transplantation. For example, if the patient cannot walk more than 350 meters, he or she should be considered for listing for lung transplantation because this is a negative prognostic factor. This is probably what we will implement in the future. Maximized medical treatment, including combination therapy. If you cannot obtain a good hemodynamic profile and an exercise capacity above a defined level, they are likely candidates who should be listed.

Dr Tapson: Let’s backtrack for a second. In terms of genetics, do you have a sense of who should be tested for BMPR-2 mutations? Do you test families or do you have a sense of what we should do?

Dr Galiè: I don’t think we have a consensus about this. It’s still a matter of research. Genetics is still a research tool, not something you can use in clinical practice. Even if you identify a mutation in family members who do not have pulmonary hypertension, you do not know if they will ever develop pulmonary hypertension. And in any case, if you tested such patients who are otherwise healthy and you reported to them that they have the mutation you can completely change their lives. For scientific and ethical reasons, we believe that genetic testing does not currently play a role in clinical practice for pulmonary hypertension.

Dr Tapson: That seems to be the consensus of most. It sounds like most people think we should be careful about how we’re using genetic testing at this point. It was a fantastic meeting. What does the future hold?

Dr Galiè: We look forward to the proceedings being published. We will not have another meeting for some time. It’s like the Olympics. We need to wait maybe another 4 years. ■



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