Advances in
# Pulmonary Hypertension
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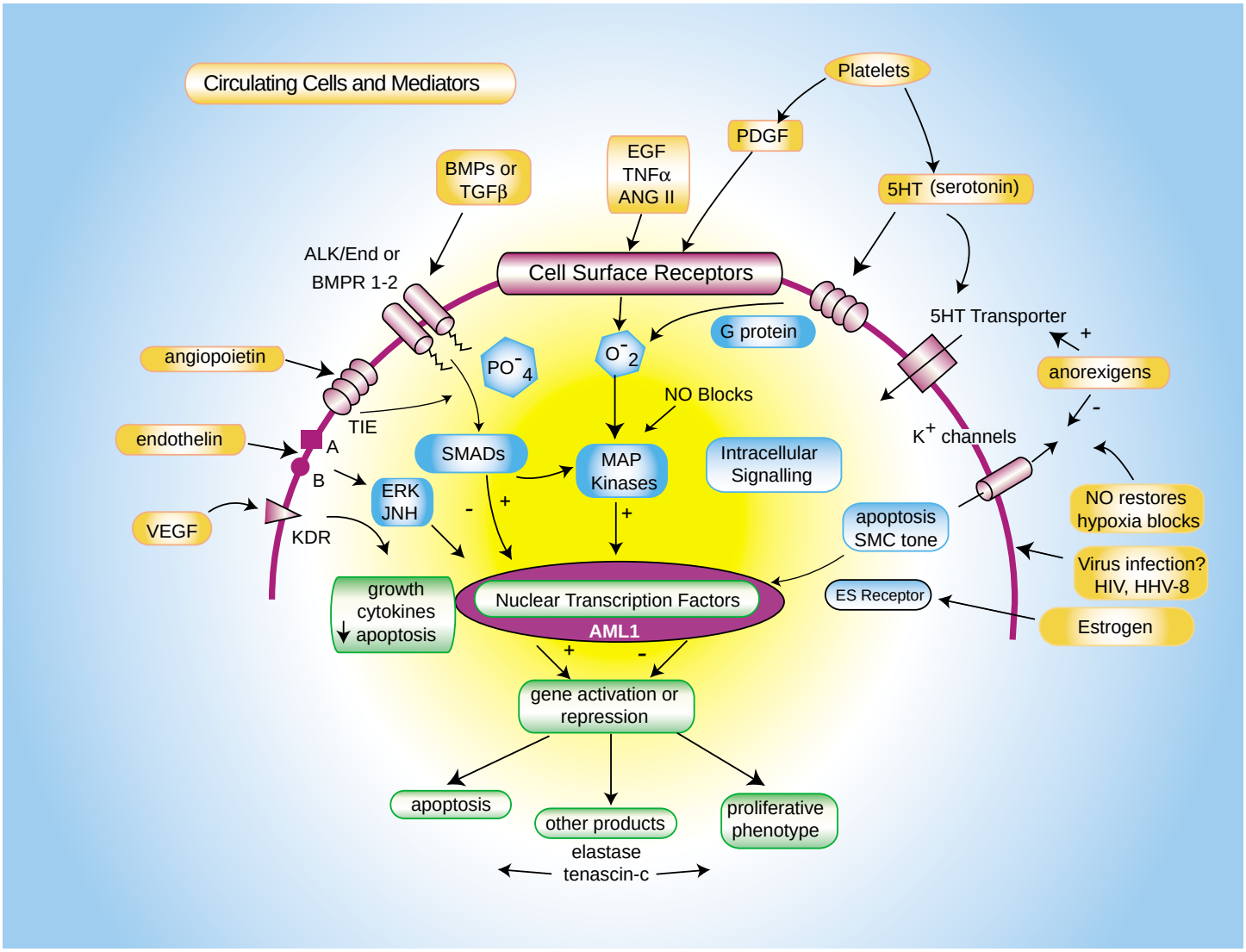
# Mechanisms of PH: the Next Therapeutic Targets

**Highlights from the Scientific Sessions of the 6th PHA International Conference**

*PLUS:*

## Medical Treatment Options and Advances in Portopulmonary Hypertension




See description on page 2.

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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.

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Cover image: Drawing depicts possible mechanisms operating at the cellular level to influence pathophysiology of pulmonary hypertension. Note cell surface receptors, triggers, and related factors that may be involved.
(Courtesy of John H. Newman, MD)

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*Editor's Memo*

# PHA Scientific Sessions Break New Ground, Providing Timely, Focused Venue for Current Research

This issue of *Advances in Pulmonary Hypertension* is the next best thing to being there—attending the first Scientific Sessions of the Pulmonary Hypertension Association, held from June 24 to 26 in Miami, in conjunction with PHA's 6th International Conference. The reports from presenters will give you a sense of the excitement attendees shared in being a part of this effort to break new ground by establishing a PH focus for results of current research. Until this meeting was held, physicians seeking such information had to look toward multiple meetings where research findings were presented, including large cardiology and pulmonology conferences, sporadic symposia, and a number of smaller conferences. Few, if any, of these meetings were dedicated to PH research per se.

Because few physicians are able to attend all of these meetings pertaining to PH, the 2004 PHA Scientific Sessions were intended as the first of a series of conferences consolidating PH-related information and allowing professionals to network with others sharing a similar interest. The sessions also focused on another objective—presenting viewpoints of those working primarily in fields outside of PH, such as cancer and genetics. The coverage in this issue provides a representative sample of new directions in PH research from those who presented this information during the Scientific Sessions.

A total of 47 abstracts were presented, 5 orally and the rest as posters. These abstracts covered the gamut of PH research, including clinical drug studies, patient demographics, hemodynamic monitoring, treatment strategies, and basic studies of the molecular processes and cell biology of PH. The Scientific Sessions proved to be a valuable addition to the well-established International PHA Conference. The financial support provided by the National Heart, Lung, and Blood Institute, the Centers for Disease Control and Prevention, the Office of Rare Diseases, and healthcare sponsors assured a forum for the productive exchange of information. Looking ahead, the next Scientific Sessions will be held in Minneapolis in 2006; you may want to make early note of a meeting that should not be missed.

Michael McGoon, MD
Guest Editor

## Juggling Roles of Patient Advocate and Director of a Leading Research Center, Robyn Barst Meets the Challenge

**Robyn J. Barst, MD**

Great clinicians often distinguish themselves by fulfilling several demanding roles at the same time, by not only establishing their reputation as preeminent caregivers but also leading their colleagues toward excellence in other ways—for instance, in patient advocacy and establishment of referral centers. A case in point is Robyn J. Barst, MD.

There is her role as a pioneer in the early studies of epoprostenol in pulmonary hypertension, a time when she battled for a patient's right to receive the best available treatment, persuading the FDA to allow investigators to use epoprostenol. Then there is the role Dr Barst played—and continues to enlarge upon—as Director of the Pulmonary Hypertension Center at New York Presbyterian Hospital, a center currently serving at least 800 patients of all ages. Regardless of which role occupies her at the moment—and they frequently overlap—she has been in the forefront of virtually every significant advance in the treatment of pulmonary hypertension and will oversee future research developments as Chair of the Scientific Leadership Council of the Pulmonary Hypertension Association.

A pediatric cardiologist by training, Dr Barst has been Director of the New York Presbyterian Pulmonary Hypertension Center since 1987. The center's prodigious growth over the last two decades has largely been because of her organizational efforts, her commitment to building a first-rate facility, and her fund-raising skills in obtaining the requisite support for its programs. Yet all of it began on a personal level with Dr Barst's relationship with each patient, including the first patient she saw with primary pulmonary hypertension, a 16-year-old girl who died on the eve of receiving a lung transplant. "I was devastated the next day and started reading about the condition, realizing that there was no treatment for it. I went into pedi-

***(continued on page 16)***

# Exploring the Role of BMPR2 as Key Genetic Marker in Pulmonary Vascular Disease

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## Introduction

The genetics of pulmonary arterial hypertension is a rapidly growing investigative area that has witnessed significant advances in the past few years. A heritable form of pulmonary hypertension, familial primary pulmonary hypertension, was first recognized in 1948.[1] In the general population the incidence of primary pulmonary hypertension ranges from 1 to 2 cases per million, and its pattern of inheritance is autosomal dominant with incomplete penetrance.

Genetic linkage analysis of individuals with familial primary pulmonary hypertension first identified an allele on chromosome 2q31-32 (later refined to 2q33).[2] In 2000 this locus was recognized as containing the gene for bone morphogenetic protein receptor 2 (BMPR2).[3] Since that original observation, heterozygous mutations in BMPR2 have been found to account for approximately 50% of familial primary pulmonary hypertension, and may also account for approximately 25% of the so-called sporadic form of the disease.

## BMPR2 Mutations in Pulmonary Hypertension

BMPR2 is a ubiquitously expressed receptor member of the transforming growth factor-beta (TGF-beta) receptor family. These receptors mediate cellular responses to TGF-beta superfamily members, including TGF-beta, activins, inhibins, and the bone morphogenetic proteins (BMPs). BMPs manifest pleiotropic activities in various cell types, including regulation of cell growth, apoptosis, and differentiation, as well as tissue patterning and organogenesis in the developing embryo. TGF-beta receptors comprise two classes of serine/threonine kinase receptors, types I and II, and BMPR2 is a member of the type II class. Upon ligand binding, type II receptors phosphorylate type I receptors, which, in turn, phosphorylate a restricted set of intracellular signal-transducing molecules, the Smads, to regulate cell function. BMPR2-dependent signaling modulates proliferative responses of pulmonary vascular smooth muscle cells; in particular, BMP2 and BMP7 inhibit vascular smooth muscle cell proliferation. Thus, the current working hypothesis holds that mutations in BMPR2 lead to proliferation of pulmonary vascular smooth muscle cells, promoting an increase in pulmonary vascular resistance and pulmonary hypertension.[4]

To date, 46 different germline mutations in the BMPR2 gene have been identified in familial and sporadic primary pulmonary hypertension. These mutations span the majority of the open reading frame of the BMPR2 gene. Missense, nonssense, and frameshift mutations have been identified, as have partial deletions. The majority of these mutations (approximately 60%) cause premature truncation of the transcript through nonssense-mediated accelerated mRNA decay. Theoretically, BMPR2 mutations could lead to simple haploid insufficiency, haploid insufficiency with a secondary somatic mutational or regulatory event affecting a second allele, or a dominant negative effect. Functional studies suggest that truncations and point mutations in the kinase domain of BMPR2 exert dominant-negative effects on receptor function.[5-7] A recent report of pulmonary hypertension developing in a mouse model in which a dominant negative BMPR2 transgene is expressed is entirely consistent with this hypothesis.[8]

## Other Pathogenic Factors

While the genetic associations studies and functional genetic analyses strongly support BMPR2 as a key genetic determinant of primary pulmonary hypertension, other genetic factors undoubtedly play a role in the pathobiology of the disease and its phenotypic expression.[9] The incomplete penetrance of the disease and its genetic anticipation in families bearing mutations suggest that other genetic factors and/or environmental exposures contribute to disease pathogenesis. Carrying a mutation in BMPR2 does not ensure that one will invariably develop the disease: other factors, or Ahits@ appear to be required that are determined by other genes or environmental factors.

### 5-Lipoxygenase

Our own work in this area stems from our interest in another gene product that is upregulated in established pulmonary hypertension, 5-lipoxygenase (5LO). This enzyme catalyzes two consecutive reactions that convert arachidonic acid to leukotriene $A_4$, a central precursor for the synthesis of leukotriene $B_4$ and other downstream leukotrienes (collectively called cysteinyl leukotrienes) that mediate inflammatory responses in the vasculature and in the lung. Increased expression of 5LO has been demonstrated in the lung tissue of patients with primary pulmonary hypertension, within infiltrating perivascular alveolar macrophages and in small pulmonary artery endothelial cells.[10] Owing to the vasoconstrictor and cell proliferative effects of this inflammatory mediator, 5LO has been considered a potentiator of pulmonary hypertension. In a rat model of monocrotaline-

induced pulmonary hypertension, we found that the 5LO gene, administered in an adenoviral vector by inhalation, potentiated the pulmonary hypertension induced by the alkaloid. Furthermore, we showed that a 5LO inhibitor prevented the potentiation of the pulmonary hypertension evoked by overexpression of 5LO, as well as, interestingly, preventing the development of pulmonary hypertension in the rats treated with moncrotaline alone.[11] These results indicate the essential role that 5LO plays in the pathogenesis of this form of inflammation-dependent pulmonary hypertension.

In work presented at this meeting from our group by Y. Song, we more recently showed that adenoviral-mediated overexpression of 5LO in the lungs of mice with heterozygous deficiency of BMPR2 (-/+), kindly provided by H. Beppu (Massachusetts General Hospital), led to the development of pulmonary hypertension in these mice. The increases in pulmonary arterial pressures we measured were transient and coincident with transgene expression. Measurement of vasoactive mediators that may either be stimulated by 5LO overexpression or coincident with it, including cysteinyl leukotrienes, prostaglandin $E_2$, and prostacyclin metabolites showed no difference between groups of mice. Interestingly, however, thromboxane $B_2$ levels were considerably higher in the 5LO-expressing BMPR2(-/+) mice compared with wildtype mice (120,000 $\pm$ 11,000 vs 60,000 $\pm$ 5,500 pg/mg urinary creatinine on day 7 following administration of the 5LO-containing adenovirus, $P < .05$). This prostanoid is the stable metabolite of thromboxane $A_2$, which has vasoconstrictor, proliferative, and prothrombotic effects; its synthesis has been found to be increased in individuals with pulmonary hypertension by Christman and colleagues in 1992.[12]

### Thromboxane $A_2$

Thromboxane $A_2$ is synthesized by thromboxane synthase, which is found in inflamed lung tissue; its expression appears to be regulated by the GATA transcription factor, which is induced by BMPs. GATA-1, in turn, induces the expression of NF-E2, which is the key transcription factor regulating expression of thromboxane synthase.[13] Current work focuses on the molecular regulatory events that may account for the interrelationships among BMPs signaling through BMPR2, GATA, thromboxane synthase, and thromboxane $A_2$ and their potential links in the pathogenesis of primary pulmonary hypertension.

As a platelet activator, thromboxane $A_2$ can stimulate the release of serotonin from platelets. Recent work on the serotonin transporter and the serotonin 2B receptor suggests another potential link among these pathways. The L-allelic variant of the serotonin transporter, which is associated with increased expression of the transporter and increased pulmonary vascular smooth muscle cell proliferation, is more prevalent among pulmonary hypertensives than controls.[13] Furthermore, a study by Launay and colleagues[14] showed that hypoxia-induced pulmonary hypertension in mice is associated with an increase in the expression of the 5HT2B serotonin receptor, which promotes serotonin-dependent adverse vascular remodeling. This group also showed that the main metabolite of dexfenfluramine, nor-dexfenfluramine, promotes vascular smooth muscle cell growth via this receptor, thus potentially linking anorexigenic pulmonary hypertension to genetically determined signaling pathways in pulmonary vascular smooth muscle cells.

## Conclusion

These intriguing yet not fully substantiated links among gene products suggest that the determinants of the pulmonary hypertensive phenotype are complex. Future studies of these complex interactions among genetic and environmental determinants of pulmonary hypertension should continue to shed light on the pathogenesis of this disorder.

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# Why Potassium Channel Dysfunction May Be 'Missing Link' in Pathophysiology of PAH

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Potassium ($K^+$) channel dysregulation in pulmonary artery smooth muscle cells (PASMCs) is important in understanding the etiology of pulmonary arterial hypertension (PAH), which is characterized by abnormalities in the vascular biology of the pulmonary circulation at all levels from lumen to adventitia (**Figure 1**).[1] The challenge for any proposed mechanism for PAH is to account for the entire spectrum of the syndrome. The number of abnormalities in PAH suggests a "multiple hit" etiology. A permissive "primary" abnormality, such as a mutation of the gene for the serotonin transporter or the bone morphogenetic protein receptor 2 (BMPR2) gene or a Kv channel deficiency, may be inadequate to provoke PAH unless accompanied by one or more exogenous stimuli (eg, ingestion of dexfenfluramine), a situation analogous to atherosclerosis or cancer. A gene chip-based comparison of gene expression in lungs from patients with PAH versus controls found upregulation of genes that favor proliferation (ie, oncogenes like v-myc, jun D proto-oncogene, etc) and suppress apoptosis (eg, apoptosis inhibitory genes).[2] In support of the theory that Kv channels are important to PAH,[3,4] Kv channel gene expression was also suppressed in PAH.[2] It is encouraging that the $K^+$ channel hypothesis (**Figure 2**), derived by conventional means in humans and rats, is supported by a nonbiased genomic screening approach. Since PAH is rarely detected in an early or asymptomatic phase, there are no natural history data to indicate the relationship between the onset of pulmonary hypertension and the decrease in Kv channel expression and function.

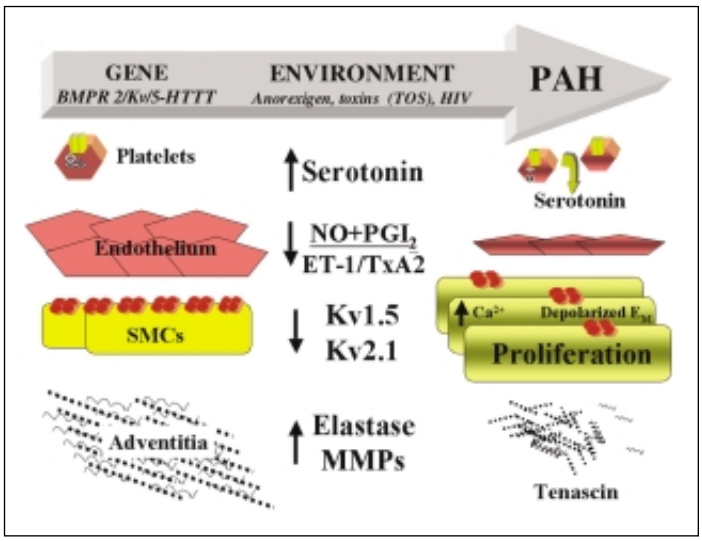


**Figure 1. The pathobiology of pulmonary arterial hypertension (PAH). In a manner similar to the pathogenesis of cancer, environmental stimuli (which include anorexigens, toxins, or viral infections) act upon a permissive genotype (which includes abnormalities in the bone morphogenetic protein axis, Kv channels, or serotonin transporters) and trigger the development of PAH. Abnormalities in PAH cover the whole spectrum of vascular biology: platelets, endothelium, smooth muscle cells, and the adventitia are abnormal, although in a specific individual one or more might predominate. *TOS: toxic oil syndrome; PGI2: prostaglandin I2; ET-1: endothelin 1; TxA2: thromboxane A2; HTTT: 5-hydroxytryptamine transporter; MMPs: matrix metalloproteinases; Em: membrane potential; SMCs: vascular smooth muscle cells.* (Modified from Archer et al[1] with permission.)**

## Overview of K+ Channels in Vascular Biology

$K^+$ channels are transmembrane spanning proteins that contain a pore with great selectivity for $K^+$.[5] There are three major classes $K^+$ channels: Kv channels (including $Ca^{2+}$-sensitive channels, $K_{Ca}$), the inward rectifier channels (Kir), and a family with a tandem, 2-pore motif (TASK). Kv channels are tonically active in vascular smooth muscle cells, allowing a basal efflux of $K^+$ down the ion's concentration gradient. It is this efflux of $K^+$ that, in balance with the intra- and extracellular $K^+$ concentrations (145 and 5 mM, respectively), largely establishes the resting membrane potential of the PASMC (**Figure 3**). Healthy PASMCs from resistance arteries have a membrane potential of ~ -60 mV. Inhibition of certain $K^+$ channels (only those that are open at resting membrane potential) results in accumulation of positively charged $K^+$ ions within the cell, depolarizing the membrane potential to more positive levels. This activates the voltage-gated, L-type calcium channel. Calcium then enters the cell through this selective conduit, flowing down a 10,000/1 concentration gradient. The increase in $Ca^{2+}$ activates the

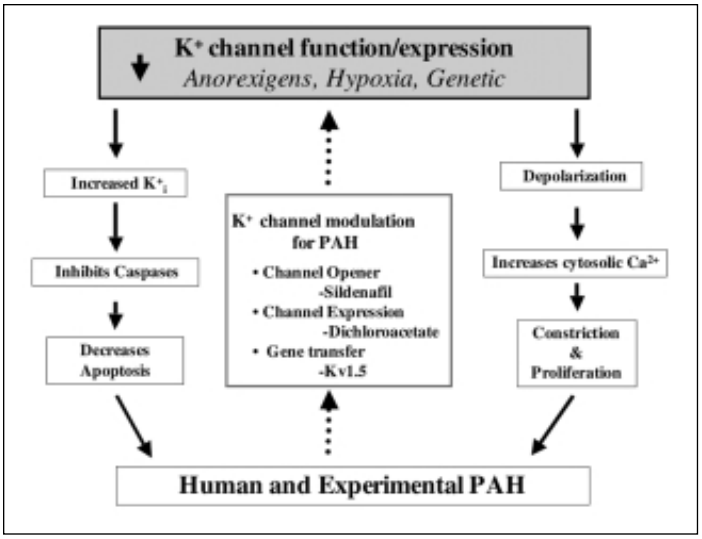


**Figure 2. $K^+$ channels are important therapeutic targets in pulmonary arterial hypertension (PAH). Since $K^+$ channels are involved in apoptosis, proliferation and vascular tone, they are critical in the development of PAH. Drugs that open (sildenafil), upregulate (dichloroacetate) or restore the expression of $K^+$ channels (Kv 1.5 channel gene transfer), alone or in combination, are promising candidate therapies for human PAH.**

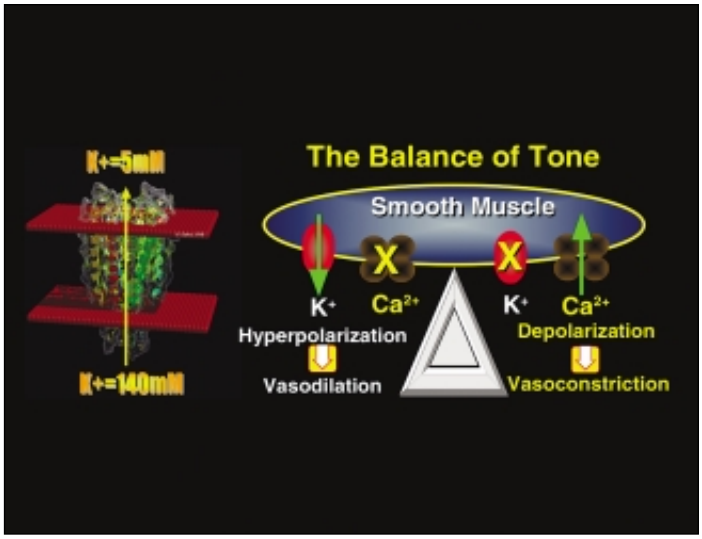


**Figure 3. $K^+$ channels affect the balance of tone. *Left:* Computer-generated representation of a Kv channel as seen by crystallography, developed by Professor Hérve Darbon, Marseilles, France. (Reproduced with permission from Archer et al.[5]) *Right:* Circulating or endothelial-derived factors can act on the smooth muscle cell and open or close $K^+$ channels. Since $K^+$ channels control the cell membrane potential, they regulate the opening or closure of the voltage-dependent L-type $Ca^{++}$ channels, and thus the influx of calcium and vascular tone. Whether a smooth muscle cell relaxes or contracts depends on the balance between $K^+$ channel openers (vasodilators) and $K^+$ channel inhibitors (vasoconstrictors).**

PASMC's contractile apparatus, leading to vasoconstriction. If depolarization is long-term, the cell enters a proliferative phase and, interestingly, expression of the specific Kv channels occurs (**Figure 4**). The loss of channels, particularly Kv1.5, is not restricted to PASMCs and was first described in pituitary cells.[6]

The Kv1.x channel family is particularly relevant for PAH. This family of channels is selectively inhibited by correolide.[7] It is noteworthy that correolide, like hypoxia, selectively constricts "resistance" pulmonary arteries, having little effect on large, proximal pulmonary arteries.[7] The Kv1.x family of channels includes several $O_2$ sensitive channels found in PASMCs, most notably Kv1.5 and Kv1.2, and it appears the constrictor effects of correolide mostly relate to inhibition of Kv1.5.

## Lessons from the Mechanism of Hypoxic Pulmonary Vasoconstriction

Hypoxia initiates hypoxic pulmonary vasoconstriction (HPV), at least in part, by inhibition of Kv channels in the PASMC.[8] $O_2$-sensitive $K^+$ channels are involved in $O_2$ sensing in virtually all mammalian $O_2$-sensitive tissues, including the mechanism of HPV in the pulmonary circulation. The resulting depolarization activates the voltage-gated, L-type $Ca^{2+}$ channel. The importance of these two voltage gated channels to the pulmonary circulation is clear. $K^+$ channel blockers cause vasoconstriction; $K^+$ channel openers cause pulmonary vasodilatation. Moreover, inhibiting the L-type $Ca^{2+}$ channel using drugs such as nifedipine, which are also useful therapy for PAH,[3] largely inhibits HPV.[9] The Kv channels and the L-type $Ca^{2+}$ channel are functionally coupled through membrane potential, which is established by the $K^+$ channels.[10] As will be discussed subsequently, Kv1.5 is particularly important in the PASMC in both HPV and PAH.

Homo- or heterotetramers composed of Kv1.2, Kv1.5, Kv2.1, Kv3.1b, and Kv2.1/Kv9.3 channels have been proposed as potential "$O_2$-sensitive" channels mediating HPV.[11,12] It appears that some of these same channels are downregulated in pulmonary hypertension. In humans with PAH, PASMCs are depolarized and calcium overloaded, as a consequence of decreased expression of certain Kv channels, most notably Kv1.5.[13] In rats, chronic hypoxia-induced pulmonary hypertension recapitulates many of the hallmarks of human pulmonary hypertension, including increased pulmonary vascular resistance (PVR), medial hypertrophy of small pulmonary arteries, and right ventricular hypertrophy.[14] Interestingly, acute HPV is selectively suppressed in rodents with chronic hypoxia-induced pulmonary hypertension, even though constriction to other stimuli is enhanced.[15] This is associated with a functional deficiency of a select group of PASMC $K^+$ channels (Kv1.5 and Kv2.1).[16] This Kv expression is downregulated early, probably before pulmonary hypertension occurs.[16] Indeed, chronic hypoxia reduces Kv1.5 expression in cell culture models, suggesting that it is the channel deficiency that drives the pulmonary hypertension, rather than the reverse.[13,17] In chronic hypoxia-induced pulmonary hypertension PASMCs are depolarized, much as has been described in studies of human PAH.[13,17]

As would be predicted if the $K^+$ channel hypothesis were correct, increasing the expression of Kv channels ameliorates established chronic hypoxia-induced pulmonary hypertension. Increasing $K^+$ current can be accomplished by increasing expression of Kv channels by stimulating endogenous channel production (**Figure 4**), activating existing

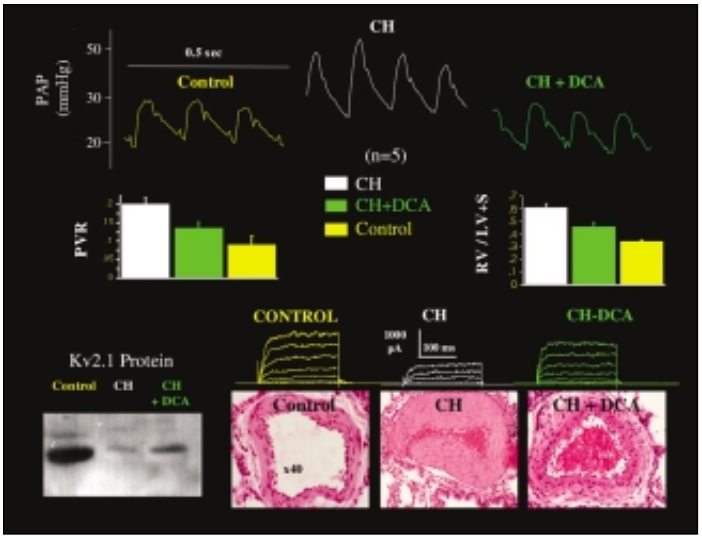


**Figure 4. Dichloroacetate (DCA) reverses chronic hypoxia-induced pulmonary hypertension. *Top:* High-fidelity pulmonary artery trace in the three rat groups studied. DCA in drinking water reverses rise in pulmonary artery pressure caused by chronic hypoxia. *Middle:* Mean data show that DCA treatment reverses the increase in pulmonary vascular resistance and right ventricular hypertrophy. *Bottom:* Immunoblotting data on isolated pulmonary arteries shows that treatment with DCA partially reverses the downregulation of Kv2.1. Representative trace of $K^+$ currents in freshly isolated pulmonary artery smooth muscle cell shows that suppression of the $K^+$ current seen in chronic hypoxia rats is reversed by DCA treatment. Histology (H-E stain) of medium-size pulmonary arteries shows that DCA reverses the medial hypertrophy caused by chronic hypoxia. (Modified from Michelakis et al[14] with permission.)**

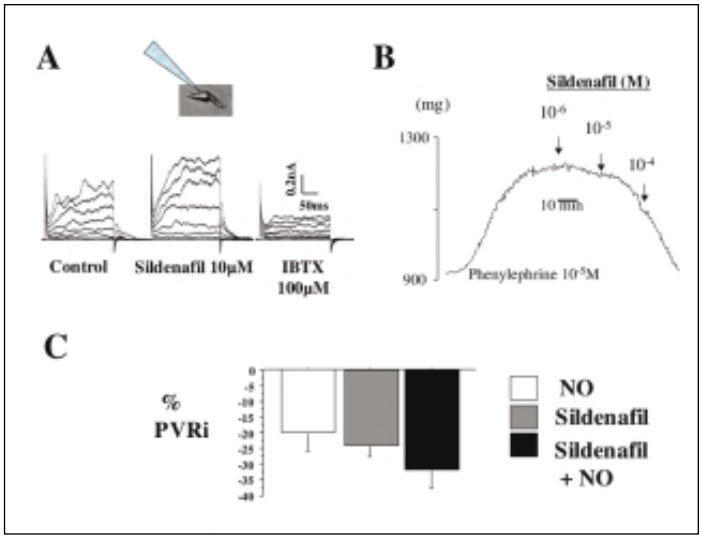


**Figure 5. Sildenafil acutely increases pulmonary artery smooth muscle cell (PASMC) $K^+$ current and dilates the human pulmonary circulation. *A:* Sildenafil acutely increases the outward $K^+$ current in PAMSCs from a lung transplant donor. This current is mostly inhibited by iberiotoxin (IBTx), suggesting that is conducted by large conductance calcium-activated $K^+$ channels ($BK_{Ca}$). *B:* Sildenafil causes acute vasodilatation in a dose-dependent manner (left) in a human pulmonary artery preconstricted with phenylephrine (PE). *C:* Percent change in pulmonary vascular resistance index (PVRi) in response to inhaled nitric oxide (80 ppm), sildenafil (75 mg), or their combination in humans with PAH. Sildenafil is as effective as nitric oxide in decreasing PVRi, and their combination has additive effects (mean±SEM). (Modified from Michelakis et al[20] and Michelakis et al[21] with permission.)**

channels (**Figures 5** and **6**), or increasing channel expression via gene transfer (**Figure 7**). Sildenafil elevates cyclic guanosine monophosphate (c-GMP) in PASMCs, at least in part, by opening PASMC $BK_{Ca}$ channels via a protein kinase G-dependent mechanism.[18,19] This hyperpolarizes and relaxes the pulmonary artery (**Figure 5**). In humans with PAH, acutely sildenafil is as effective and selective a pulmonary vasodilator as inhaled nitric oxide,[20] likely because of the relative enrichment of the pulmonary arteries in phosphodiesterase 5. Long-term administration of sildenafil (50 mg tid) improves the 6-minute walk by more than 100 m in functional class II-II patients (**Figure 6**).[21]

Dichloroacetate (an inhibitor of the mitochondrial enzyme, pyruvate dehydrogenase kinase, reverses established chronic hypoxia-induced pulmonary hypertension by both increasing the opening and upregulating the expression of Kv2.1 and Kv1.5 channels (**Figure 4**).[14] Dichloroacetate's mechanism of action remains unclear, but might include metabolic actions that occur at higher doses (dichloroacetate is an inhibitor of pyruvate dehydrogenase kinase that increases the pyruvate/lactate ratio) and more rapid kinase-dependent mechanisms that occur at lower doses. Dichloroacetate causes rapid activation of Kv channels by a tyrosine kinase-dependent mechanism. Dichloroacetate is a very attractive drug to be tested in the treatment of primary pulmonary hypertension since it has little effect on $K^+$ channels in nonhypertensive PASMCs. Moreover, it has been tried in humans with coronary disease and heart failure, with a very good safety profile. Dichloroacetate is also beneficial in monocrotaline models (our unpublished data).

If Kv channels are crucial to the pathogenesis of PAH, restoration of channels directly, via gene therapy, should also be beneficial. This has been tested in the chronic hypoxia-induced pulmonary hypertension model using serotype 5 adenovirus (Ad5) as the vector to deliver human pulmonary artery-Kv1.5 to the pulmonary circulation.[15] Rodents exposed to chronic hypoxia selectively lose HPV, which appears to relate to the loss of Kv1.5 and Kv2.1 expression in PASMCs. Kv1.5 expression and function were restored by adenoviral gene therapy (**Figure 7**). Lightly anesthetized rats with established chronic hypoxia-induced pulmonary hypertension were nebulized with 100 μL of sterile saline, Ad5-GFP, or Ad5-GFP-Kv1.5 using an intratracheal microspray device. Transgene expression was evident 2 days after nebulization, and persisted for more than 14 days, gradually disappearing by 1 month. PVR was lower in the gene therapy group, largely because of increased CO.

This group also displayed partial regression of right ventricular hypertrophy and medial hypertrophy of small pulmonary arteries, but had no significant fall in pulmonary artery pressure. The decreased PASMC $K^+$ current density in chronic hypoxia-induced pulmonary hypertension was reversed by Kv1.5 gene therapy and there was a corresponding restoration of HPV in rats that received Kv1.5 gene therapy (**Figure 7**). Thus, restoration of a single Kv channel

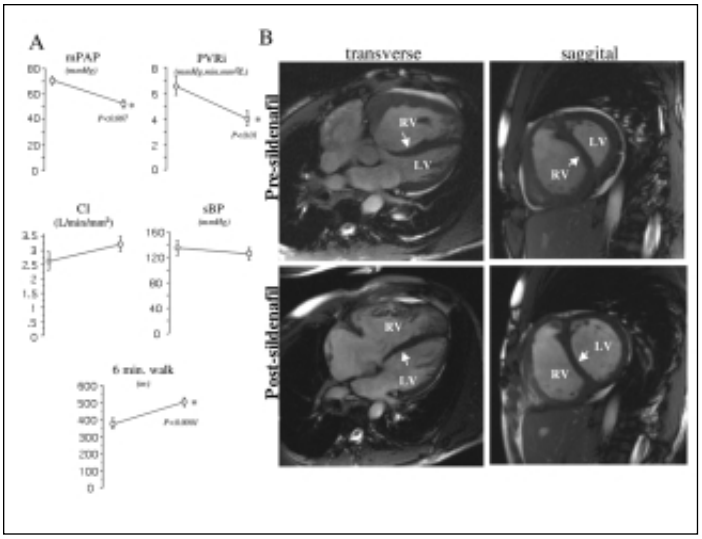


**Figure 6. Long-term treatment with sildenafil improves hemodynamics and functional capacity in patients with pulmonary hypertension. *A: CI: cardiac index; sBP: systolic blood pressure; mPAP: mean pulmonary artery pressure (mean±SEM). B:* Magnetic resonance imaging angiography shows reversal of the pathological septal shift after sildenafil treatment. *RV: left ventricle; LV: left ventricle.* (Modified from Michelakis et al[21]with permission.)**

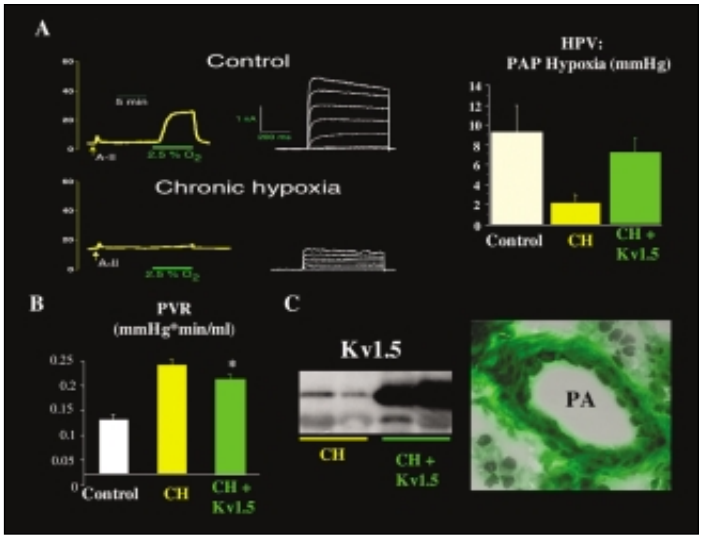


**Figure 7: Restoration of Kv1.5 expression with gene therapy reverses blunting of hypoxic pulmonary vasoconstriction (HPV) and decreases pulmonary artery pressure in chronic hypoxia-induced pulmonary hypertension (CH-PHT). *A:* Representative traces and mean data from isolated perfused lungs showing that HPV is attenuated by chronic hypoxia and is restored in Kv1.5 gene therapy in rats. The blunted HPV is associated with a suppression of $K^+$ current. *AII: angiotensin II. B:* Measurement of pulmonary arterial pressure and cardiac output in anesthetized close-chest rats showed that human pulmonary artery Kv1.5 gene therapy reduced pulmonary vascular resistance in the CH-PHT model. *C:* Representative immunoblot (each lane is one lung; two noninfected and two infected rats) showing that Ad5-Kv1.5 increases Kv1.5 expression. *D:* Demonstration of effective gene transfer to a medium sized pulmonary artery. Green fluorescence indicates that both the green fluorescent protein reporter and Kv1.5 transgenes were expressed throughout the vessel wall. (Modified from Pozeg et al[15] with permission.)**

to resistance pulmonary arteries restored HPV and reduced PVR, despite ongoing exposure to hypoxia.

## Kv1.5 and Pulmonary Arterial Hypertension

Kv1.5 is an appealing candidate for involvement in PAH not only because to is central to the control of membrane potential in the PASMC[7] and involved in HPV,[11,22] but also because loss of Kv1.5 expression appears to be important to the pathogenesis of various forms of pulmonary hypertension, including chronic hypoxia-induced pulmonary hypertension. In addition, anorexigens (eg, dexfenfluramine) that cause pulmonary vasoconstriction[23] and have led to outbreaks of PAH, inhibit $K^+$ current in PASMCs by directly blocking Kv1.5 and Kv2.1. Finally, targeted deletion of Kv1.5 in mice reduces HPV and eliminates the hypoxia and 4-AP-sensitive component of the $K^+$ current.[22] Kv1.5 is an interesting therapeutic target because its expression is dynamically regulated, both at the level of transcription and post-translationally. The rapid pathophysiological changes in Kv1.5 expression in chronic hypoxia-induced pulmonary hypertension may reflect decreasing Kv1.5 gene transcription, destabilization of Kv1.5 mRNA or accelerating turnover of Kv1.5 protein. The fact that the CMV-promoted Kv1.5 transgene product was not suppressed by chronic hypoxia suggests that downregulation of the endogenous rat Kv1.5 occurs at the transcriptional level, as this would not be expected to alter episomal Kv1.5 expression. Chronic hypoxia-induced pulmonary hypertension may activate KRE (Kv1.5 repressor element), a dinucleotide repetitive DNA sequence forming a cell-specific silencer that inhibits transcription of the Kv1.5 gene.[24,25] Other regulators of gene expression may also be important. The fact that Kv1.5 expression can be rapidly suppressed offers hope that it might also be rapidly restored to a therapeutic end.

## Channel Diversity in the Pulmonary Circulation

$K^+$ channels manifest a diversity in expression and function that could explain the pulmonary circulation-specificity of the vascular disease in PAH. Use of patch-clamp techniques to directly record $K^+$ currents from freshly dispersed PASMCs, isolated from various segments of the pulmonary circulation, reveals a differential distribution of ionic currents along the length of the pulmonary artery tree. Relevant to PAH, there is enrichment of the Kv channels involved in PAH, most notably Kv1.5,[7] in the resistance arteries that largely determine PVR. In addition to longitudinal differences in whole-cell $K^+$ current are electrophysiologically distinct cell populations, coexisting side by side, within an arterial segment.[26] The smooth muscle cells of conduit pulmonary arteries are large and predominantly express $BK_{Ca}$ current; conversely, the resistance arteries are enriched in smaller smooth muscle cells with a high density of 4-AP-sensitive Kv current. Consistent with this finding, small pulmonary arteries vigorously contract in response to inhibition of Kv1.x channels by correolide but do not respond to pharmacological block of $BK_{Ca}$ channels, indicating that Kv1.x channels are the primary determinants of resting membrane potential. $K^+$ channel diversity can result from one or more of the following mechanisms:

**Heterogeneous distribution of α-subunits.** The concept that a particular segment of the pulmonary vascular bed

uniquely expresses HPV or develops pulmonary hypertension because of heterogeneous expression or loss of a single α-subunit is appealing, but has not been demonstrated.

**Heterotetramer formation.** The "mix and match" of various α- or γ-subunits in a tissue-specific manner could yield functionally discrete channels that are unique to the pulmonary circulation. This concept awaits formal testing.

**Alternate splicing variants of genes for α- and ß-subunits.**[27] This is an appealing mechanism by which PAH could be focused on the pulmonary circulation, but testing this requires sophisticated sequencing of the relevant channel in the tissue of interest, since results from immunoblotting are likely not to distinguish among splice variants unless a unique epitope is identified and targeted.

**Association with ß-subunits.** Kvβ-subunits (Kvβ 1-4, each with splice variants) are small cytosolic proteins (~30 KDa) that associate intimately with the channels. The β-subunits create heterogeneity by modifying the gating and cell-surface expression of Kv channels.[28]

**Transcriptional regulation of $K^+$ gene expression.** Some $K^+$ channels, such as Kv1.5, have very rapid rates of turnover, which can account for diversity in expression in pathological situations, such as in response to hypoxia. The Kv1.5 gene has cyclic adenosine monophosphate and glucocorticoid response elements. Local variation in promoters and silencers, such as KRE, CREB, and KCRF may be important, particularly in light of the short half-life of Kv channel mRNA and protein (~8 hours for Kv1.5).[6]

**Environmental regulation.** The regional fine-tuning of ionic expression is also regulated by the phosphorylation of these channels by various protein kinases, notably protein kinase A, G, and C. Phosphorylation can activate (as when nitric oxide activates protein kinase G, which phosphorylates and activates $BK_{Ca}$ channels) or inhibit channels (as occurs with endothelin and serotonin, resulting in protein kinase C-mediated $K^+$ channel inhibition). The local kinase environment may create tissue heterogeneity independent of variation in the α, β, or γ-subunits expression.

Thus, Kv channels have a remarkable propensity for heterogeneity, and the PASMCs appear to take full advantage of this to generate diverse populations of Kv channels.

## Genetics of Primary Pulmonary Hypertension

The established biological consequences of activating the BMPR2 pathway include cell differentiation, growth inhibition, and stimulation of collagen synthesis. BMP 2, 4, and 7 suppress PASMC proliferation in cells from normal subjects and patients with secondary PAH, but not in PASMCs from PAH patients.[29] In normal PASMCs, BMP 2 or 7 markedly increase the percentage of cells undergoing apoptosis and cause phosphorylation of Smad1.[30] The 5' sites of the Kv1.5 gene may be regulated by Smad activation. Since PAH is associated with reduced expression of the same channel that is crucial to HPV, Kv1.5, we speculate that there is a link between the pathways that is relevant to both.

## Environmental Stimuli: Diet Drugs, Toxic Oil, HIV

Both with aminorex and dexfenfluramine outbreaks only a small proportion of the patients exposed to anorexigen developed PAH, suggesting a requirement for one or more predisposing conditions. What are predisposing conditions for anorexigen-induced PAH?

First, many of the anorexigens are in fact also serotonin transporter substrates[31] and thus get translocated into pulmonary vascular cells where, depending on the degree of retention, their intrinsic toxicity is amplified. Second, endothelial dysfunction, acquired or genetic, is almost certainly a predisposing factor. There is also a potential link between the anorexigens, PASMC Kv channels, and the endothelium. Kv channel inhibition and membrane depolarization partially account for the pulmonary and systemic vasoconstriction that dexfenfluramine and aminorex induce.[23,32] Recent studies show that Kv1.5 and Kv2.1 are directly inhibited by the anorexigens, even when the channels are studied in expression systems. In addition to their effects on smooth muscle cells, anorexigens also promote vasoconstriction by enhancing $Ca^{++}$ release from the sarcoplasmic reticulum.[33] The anorexigens also block Kv channels in platelet progenitor cells, megakaryocytes.[4] Kv channel inhibition in platelets leads to serotonin release. Furthermore, fenfluramine reduces Kv1.5 mRNA levels by 50% in PASMCs from normotensive patients,[34] suggesting inhibited gene transcription and expression of Kv channels play an important role in anorexigen-associated PAH.

Thus anorexigens are in reality Kv channel blockers that cause their intended effects (appetite suppression and alteration of serotonin levels) and their unintended effects (altered platelet function and increased vascular tone) through their control of membrane potential and cytosolic $Ca^{++}$ levels. Are $K^+$ channel abnormalities also found in HIV-associated PPH? Interestingly, expression of Kv1.3, an important molecular target for immunosuppressive agents in T lymphocytes, is inhibited, via a PKC-dependent mechanism, in HIV-PPH,[35] suggesting a link between cellular electrophysiology, immunity, and PAH.[36]

## The Link

There is a potential unifying link between the $K^+$ channel hypothesis and the many other abnormalities observed in the platelets, endothelium, serotonin handling, and vascular tone in PAH (**Figure 1**). That link may be the common role of $K^+$ channels in controlling membrane potential and thus intracellular concentrations of $Ca^{2+}$ and $K^+$ in platelets, smooth muscle cells, and possibly endothelial cells (**Figure 3**). By regulating cytosolic $Ca^{2+}$, $K^+$ channels can control vascular tone and cell proliferation (**Figure 2**). By regulating cytosolic $K^+$, $K^+$ channels modulate apoptosis and thus influences vascular remodeling. The loss or inhibition of Kv channels that occurs in PPH may also account for the observed decrease in platelet serotonin stores and the rise in plasma serotonin levels. The elevated serotonin, in the presence of endothelial dysfunction, would act as a vasoconstrictor and reinforce pulmonary hypertension, particularly in the setting of PASMC membrane depolarization and elevated cytosolic $Ca^{2+}$. Recently it has been recognized that inhibition of $K^+$ channels reduces and activation of $K^+$ channels increases programmed cell death. By blocking the tonic egress of $K^+$, Kv channel inhibition elevates intracellular $K^+$.

For Patients with Pulmonary Arterial Hypertension WHO Class III or IV

# Tracleer— The Cornerstone of Oral Therapy

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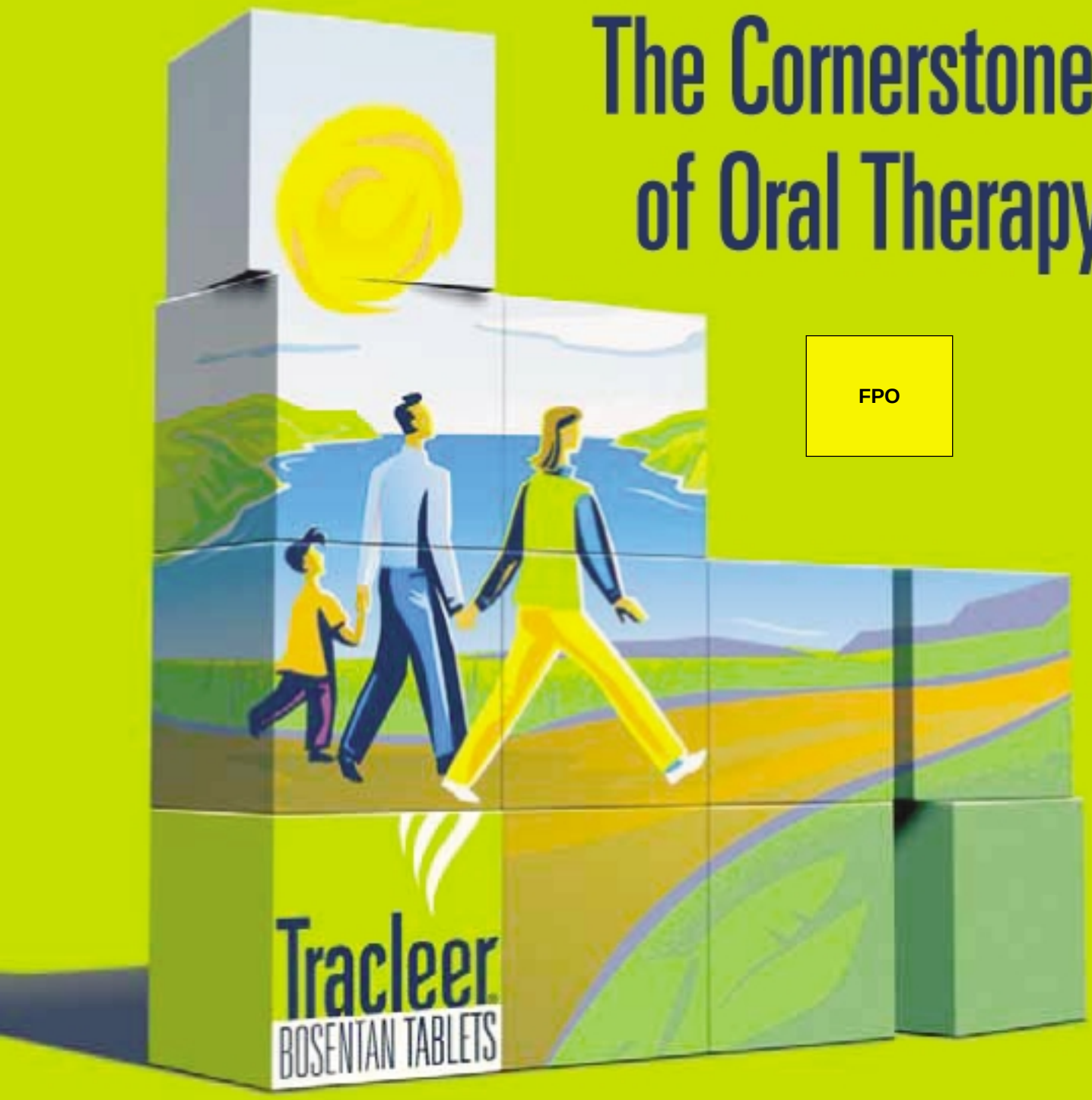



*Please see the following brief summary of prescribing information.*

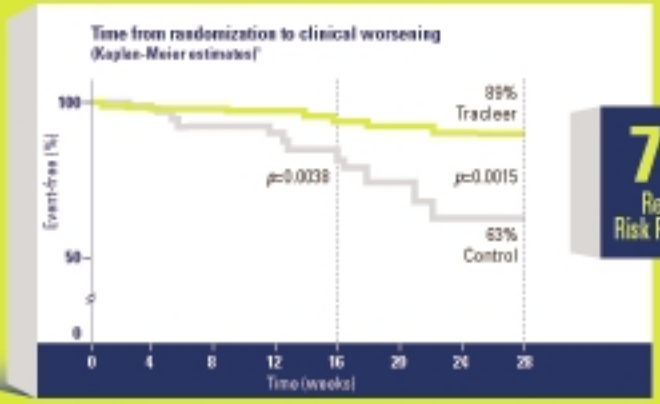
## In Pulmonary Arterial Hypertension WHO Class III or IV

# 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




**71%**
**Relative Risk Reduction**

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 end-point of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy[1]
- A statistically significant difference was apparent as early as week 16[1]
- Treatment effect was notable because control groups received placebo plus current therapy, which excluded IV epoprostenol but could include[1]:
  - —Vasodilators
    - –Calcium channel blockers
    - –ACE inhibitors
  - —Digoxin
  - —Diuretics
  - —Anticoagulants

# Stay with Tracleer

**Long-term data for patients treated with Tracleer**

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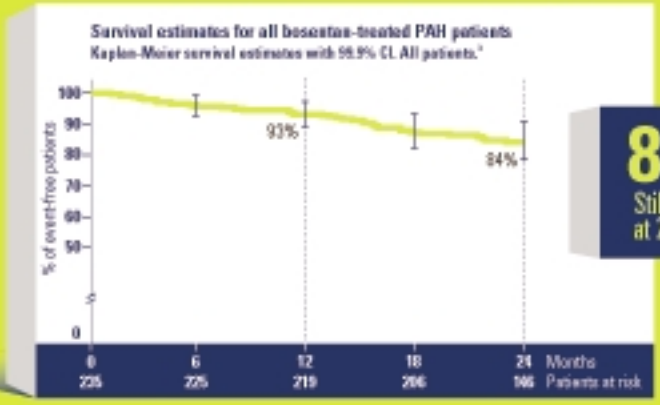


**84%**
**Still Alive at 2 Years**

### 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 survival[2]
- These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43 of the 235 patients[2]
- Patients in the Tracleer trials may have also been receiving vasodilators (calcium channel blockers or ACE inhibitors), digoxin, anticoagulants, and/or diuretics[1]

### 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

**Tracleer may be prescribed only through the Tracleer Access Program (T.A.P.) by calling 1-866-228-3546.**

## The Cornerstone of Oral Therapy

Tracleer BOSENTAN TABLETS

**www.TRACLEER.com**

ACTELION

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

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# Tracleer® BOSENTAN TABLETS

# 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 8 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 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). 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 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 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 = 698) compared to 2% of placebo-treated patients (N = 399). The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 2 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 51% of bosentan-treated patients as compared to 25% of placebo-treated patients. In 80% of cases, the decrease occurred during the first 8 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 75% 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/or new or worsening 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:* 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 contraception when TRACLEER® is co-administered. Women should 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 DOSAGE AND ADMINISTRATION). 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 CYP3A 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 6-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, e.g. 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, Nifedipine and Losartan:* Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nifedipine, 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 11 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 33 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 reduce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 18 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 58 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 58 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 58 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) on 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%, 51/165 patients) than on placebo (3%, 2/60 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 (≥ 3% difference) were headache (18% 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%).

**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=335) shows that 90% 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 43/335 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. Doses above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased 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 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 reintroduction 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 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 dosing 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 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, 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 66215-101-08: Bottle containing 60 tablets. 125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125" NDC 66215-102-08: Bottle containing 60 tablets.

Rx only

**STORAGE:** Store at 39°F – 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].

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Because intracellular $K^+$ tonically inhibits caspases, the inhibition or lack of Kv channels, as occurs in PAH and experimental pulmonary hypertension, contributes to a resistance to apoptosis.[37,38] Whether primary or secondary, the loss of $K^+$ channels, the increased endothelin levels, and the increased serotonin levels all eventually result in increased intracellular $Ca^{++}$ levels in PASMCs. In turn, this results in vasoconstriction and activation of genes that lead to cell proliferation. Normally, the BMPR2 , via the Smad pathway, exhibits a negative tonic control of gene transcription, promoting apoptosis rather than proliferation. The "loss of function" mutations in the BMPR2, in addition to one or more other abnormalities, create an imbalance that favors vasoconstriction and proliferation. It is uncertain how this $K^+$ channel hypothesis relates to the matrix metalloproteinase and prothrombotic theories. Once initiated, PPH may be sustained and exacerbated by elastase and matrix metalloproteinase-induced matrix remodeling and a prothrombotic diathesis. Taking a lesson from recent advances in dilated cardiomyopathy, one is mindful of the possibility that PPH may result from a variety of molecular mechanisms.[39]

## Conclusion

PAH is a model disease in vascular biology. Its pathogenesis involves complex interactions among a predisposing genome, a permissive phenotype, and environmental stimuli, and it involves all the elements of the vasculature. An understanding of the pathways that are disordered leading to PPH suggests a number of attractive candidate targets for gene therapy, including Kv1.5, Kv2.1, and BMPR2.

## Acknowledgment

Drs Michelakis and Archer are supported by the Canada Foundation for Innovation, the Alberta Heart and Stroke Foundation, the Alberta Heritage Foundation for Medical Research, and the Canadian Institutes for Health Research. Dr. Archer is supported by NIH-RO1-HL071115. Drs Archer and Michelakis hold a patent (2001057 US Prov) for $K^+$ channel replacement therapy for vascular diseases, including pulmonary arterial hypertension.

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## Profiles

***(continued from page 3)***

atrics because I've always believed that if you make a difference with children you are making a very long-term difference. They told me at that time that I would never see another case of primary pulmonary hypertension because it was so rare."

### Pioneer in the Epoprostenol Experience

During several years of basic research on the pulmonary circulation, including two fellowships, one in pulmonary medicine and one in cardiology, at Columbia University's College of Physicians and Surgeons, Dr Barst returned to her interest in pulmonary hypertension and learned of the investigative work being done with epoprostenol for acute vasodilator testing in pulmonary hypertension. At that time it was not being allowed for use in children; however, Dr Barst obtained permission from the FDA to begin using it in children, initially only at the dosages used in adult patients, 2 to 12 ng/kg/min. She subsequently persuaded the FDA to allow higher dosages in children and in 1986 she published the first paper on its use in a pediatric setting, a report involving only 9 patients.

Through the support of Burroughs Wellcome, research began with the long-term use of epoprostenol, enrolling 25 patients in the first long-term intravenous study. "Prior to using chronic intravenous epoprostenol, at least 40% of our patients were dying while awaiting transplantation. We did our first study with epoprostenol over 8 weeks and at the end of that time we were convinced that the drug was lifesaving." The FDA remained skeptical, however, and wanted more evidence of the drug's safety and efficacy in a large, randomized trial.

Enrolling 81 patients, Dr Barst and her colleagues reported that 8 of 40 patients receiving conventional therapy died while none of the 41 patients receiving epoprostenol died. "We had 4 patients at our center who were not randomized to epoprostenol and I had to watch those 4 patients die because they were not on active drug. It was one of the worst things I had to deal with as a physician—wanting to give the best clinical care I could yet also wanting to be aggressive about clinical drug development. I'm convinced that when we went to the FDA the drug would not have been approved if it had not been for the survival benefit."

From epoprostenol, Dr Barst has moved on to more recent trials evaluating the use of treprostinil, bosentan, sitaxsentan, ambrisentan, and iloprost. "One thing we've tried to do at our center, and what makes our center somewhat different, is that we treat patients of all ages from newborns to patients in their 80s, thereby giving us the opportunity to explore the disease process in patients of all ages.

"We also are involved in as many clinical development programs as is feasible, thereby giving us firsthand experience with how patients respond to one drug versus another." As she looks back on the clinical trial experience, Dr Barst has seen significant progress made since the time when clinicians routinely told patients with a diagnosis of pulmonary hypertension to "put your affairs in order." Today, she says, "we can guarantee that we can make patients feel better and live longer." With a new generation of studies on the horizon, Dr Barst, as Chair of the Pulmonary Hypertension Association's Scientific Leadership Council, looks forward to more advances in treatment as she and her colleagues evaluate new strategies involving a more complex and broader spectrum of therapy.

# Medical Treatment Options/Advances in Portopulmonary Hypertension: How the Spectrum Is Expanding

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***[Editor's Note: This article is Part 2 of coverage that began in the last issue on pulmonary hypertension in the setting of liver disease. Whereas the first articles discussed pathophysiology and liver transplantation, this article reviews medical treatment and related options.]***

## Introduction

Portopulmonary hypertension is defined as the presence of an elevated pulmonary artery pressure (PAP; resting mean PAP >25 mm Hg or exercise PAP >30 mm Hg), with a normal pulmonary capillary wedge pressure in the presence of portal hypertension.[1] Portopulmonary hypertension is a recognized complication of end-stage liver disease that carries a high risk for orthotopic liver transplantation mortality.[2-4] The prevalence of significant pulmonary arterial hypertension in cirrhotic patients ranges from 2% to 20%, across studies that utilized different screening techniques (ie, Doppler echocardiography versus right heart catheterization).[5-7] A recent prospective analysis of Doppler echocardiographic measurements and pulmonary hemodynamics in cirrhotic patients awaiting transplant revealed a 6% incidence of portopulmonary hypertension.[8] The actual prevalence may be greater in the cirrhotic population because patients are asymptomatic early in the disease. Six-month mortality in patients with portopulmonary hypertension is estimated to be 50%,[9] emphasizing the need for appropriate medical therapy, especially for the transplantation candidate with portopulmonary hypertension.

Medical treatment of portopulmonary hypertension has typically been empirical and similar to that described for pulmonary arterial hypertension (**Table 1**). The numbers of reported portopulmonary hypertension patients treated with medical therapy are small, and long-term studies or consensus guidelines are lacking. This article focuses on the published data for the current medical management of portopulmonary hypertension as well as possible future treatments.

## General Considerations For Treatment

Prior to the institution of pharmacologic therapy, the patient with portopulmonary hypertension should undergo a complete hemodynamic evaluation to determine the severity of pulmonary hypertension and right ventricular dysfunction. Exercise capacity and New York Heart Association (NYHA) functional class should also be documented prior to any therapeutic intervention. The clinician will also need to consider the potential orthotopic liver transplantation eligibility of each patient and the specific long-term treatment goals. Other factors of importance in this unique patient population would include, but not be limited to specific adverse effects of drug therapy (eg, thrombocytopenia); the potential for altered drug metabolism; drug-specific hepatic toxicity; the route of administration and technical considerations for drug administration; patients' ability to use the prescribed drug correctly (presence or absence of encephalopathy); and any pertinent logistic considerations (eg, family support).

**Table 1. Current and Potential Medical Treatment Options for Portopulmonary Hypertension.**

| |
|---|
| Intravenous prostacyclin (epoprostenol) |
| Prostacyclin analogs (treprostinil, iloprost) |
| Inhaled nitric oxide |
| Phosphodiesterase inhibitors (sildenafil) |
| Endothelin antagonists (bosentan, sitaxsentan, ambrisentan) |
| L-arginine |
| ? Combination therapy |

## Therapeutic Options

### Prostacyclin

Epoprostenol (prostacyclin) is a potent vasodilator produced by the endothelial and smooth-muscle cells of the vasculature. Prostacyclin also possesses antiproliferative and antiplatelet aggregating effects. The improvement in survival of

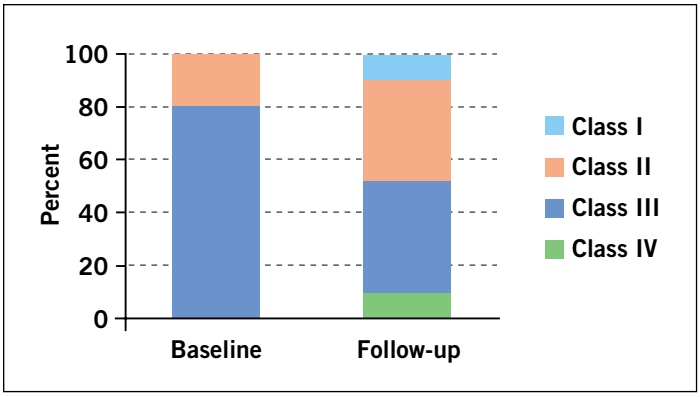


**Figure 1. New York Heart Association functional classification for portopulmonary hypertension patients treated with treprostinil (n = 21).**

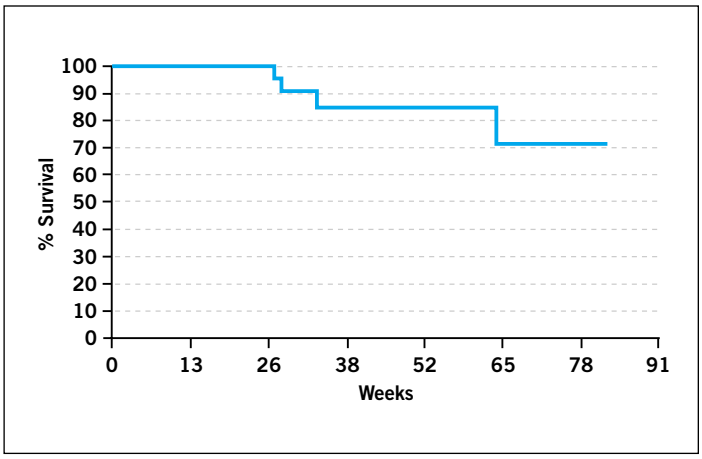


**Figure 2. Kaplan-Meier survival estimates for portopulmonary hypertension patients treated with treprostinil.**

pulmonary arterial hypertension patients treated with intravenous epoprostenol as compared to historical controls is well documented.[10,11] Intravenous epoprostenol also has proven efficacy in the treatment of portopulmonary hypertension and has been used as a therapeutic bridge to orthotopic liver transplantation.[12-15] Kuo et al[13] observed a decrease in mean PAP and pulmonary vascular resistance (PVR) as well as an increase in cardiac output in 4 patients with portopulmonary hypertension treated for 6 to 14 months with intravenous epoprostenol (10 to 28 ng/kg/min). McLaughlin et al[15] studied 7 patients with portopulmonary hypertension following an average of 12.7 months of treatment with continuous epoprostenol infusion. In this subgroup of pulmonary arterial hypertension patients, right-heart catheterization demonstrated a 33% decrease in mean PAP and a 68% decrease in PVR. Krowka et al[14] confirmed the hemodynamic benefits of both acute and long-term intravenous epoprostenol in a study of 15 patients with moderate to severe portopulmonary hypertension (mean PAP 35 mm Hg).

Intravenous epoprostenol serves an important role in the perioperative period to decrease PVR in portopulmonary hypertension patients undergoing orthotopic liver transplantation. Published case reports have documented the efficacy of epoprostenol both prior to transplantation and in the treatment of portopulmonary hypertension that has progressed after transplantation.[16,17]

Commonly observed side effects of epoprostenol include flushing, headache, jaw pain, leg pain, diarrhea, and nausea. These adverse events are generally mild and dose-related. More serious complications are related to the delivery system for epoprostenol administration. Because of its short half-life (1 to 2 minutes) and chemical instability, epoprostenol must be administered via a central venous catheter and a portable infusion pump. This route of delivery exposes patients receiving long-term treatment to potential catheter-related complications such as sepsis and venous thromboembolism.

The inhaled route has been described in a single case report as a potential alternative delivery method for epoprostenol in the acute therapy of portopulmonary hypertension.[18] After 10 minutes of inhaled delivery, mean PAP decreased by 26%; cardiac output increased by 22%, and PVR decreased by 42%.

### Prostacyclin Analogs

***Treprostinil.*** This stable prostacyclin analog administered as a continuous subcutaneous infusion has documented clinical efficacy in pulmonary arterial hypertension.[19,20] Potential advantages of subcutaneous treprostinil administration compared with intravenous epoprostenol include lack of an indwelling catheter and stability of the medication at room temperature. The reduced infection risk with subcutaneous administration is significant in the potentially unstable post-orthotopic liver transplantation patient.

We recently reported the results of long-term subcutaneous treprostinil infusion in the treatment of portopulmonary hypertension.[21] Thirty-seven portopulmonary hypertension patients (20 women, 17 men) received treprostinil for an average of 8.1 months. The dose of treprostinil increased over time with a mean maximum dose of 16.5 ± 12.6 ng/kg/min. Mean PVR index decreased by 18% compared to baseline. Prior to treprostinil treatment, 29 patients (78%) were classified as NYHA functional class III and 8 patients (22%) were classified as functional class II. Twenty-one patients had an assessment of functional class at both baseline and follow-up. Functional class at final assessment was improved or unchanged in 19 of 21 patients ($P = .031$; **Figure 1**). Lifetime cumulative survival rates are shown in **Figure 2**. At 19 months the Kaplan-Meier survival estimate was 71%. This improvement in mortality, compared with historical control data, will need to be confirmed with long-term follow-up.

The most common drug-attributable adverse events were related to the infusion site and included site pain and reaction and bruising. Other common adverse events included diarrhea, headache, vasodilatation, and nausea. Importantly, there were no significant changes in platelet count, total bilirubin, alkaline phosphatase, AST, ALT, PT or PTT.

***Iloprost.***—Inhaled iloprost, delivered via a hand-held nebulizer, is currently approved for pulmonary arterial hypertension treatment in Europe. A randomized trial of this stable prostacyclin analog in 203 patients with NYHA func-

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tional class III or IV disease demonstrated clinical efficacy compared with placebo.[22] Secondary etiologies of pulmonary arterial hypertension in this trial did not include portopulmonary hypertension, so the efficacy of this agent for this particular patient subgroup is currently unknown. Inhaled iloprost has the disadvantage of a short duration of action and requires six to nine daily inhalations.

### Inhaled Nitric Oxide

Nitric oxide is a potent, endogenous, endothelium-derived vasodilator that directly relaxes vascular smooth muscle by increasing cyclic guanosine monophosphate (cGMP). Inhaled nitric oxide, a pulmonary vasodilator, reduces PAP in some patients with primary pulmonary hypertension. The effect of this compound in patients with portopulmonary hypertension is controversial. In one series 5 of 6 patients responded to nitric oxide inhalation with decreases in PAP and PVR of greater than 10%; cardiac output did not significantly change.[23] These findings have not been consistently reproduced in other patient series and may be due to the increased levels of endogenous nitric oxide observed in patients with advanced liver disease.[24,25] The ability to predict hemodynamic responsiveness to inhaled nitric oxide would be clinically useful for the potential treatment of portopulmonary hypertension. It should be noted that this treatment requires a continuous inhalation device.

### Phosphodiesterase Inhibitors

Phosphodiesterase (PDE) inhibitors have been suggested as potentially effective therapies for pulmonary arterial hypertension, but no PDE inhibitors are currently approved for this indication. PDE inhibitors presumably improve the hemodynamic abnormalities of pulmonary arterial hypertension by enhancement of endogenous nitric oxide effects (via inhibition of cGMP breakdown). Sildenafil, a PDE type-5 inhibitor, has been shown in uncontrolled, open-label studies to improve functional status and pulmonary hemodynamics.[26,27] The European Commission recently granted orphan drug status to sildenafil citrate for possible use as a treatment of pulmonary arterial hypertension. This agent has not been studied for portopulmonary hypertension but may prove beneficial and should be evaluated in a placebo-controlled, randomized clinical trial. Dosage adjustments may be necessary in the cirrhotic patient as sildenafil undergoes extensive hepatic metabolism.

### Endothelin Receptor Antagonists

Increased concentrations of endothelin-1 (ET-1), a potent vasoconstrictor, are found in the plasma and lung tissue of patients with pulmonary hypertension secondary to congenital heart disease and also in patients with liver disease. The involvement of ET-1 as a modulator of increased PVR in pulmonary arterial hypertension patients has led to the development of endothelin receptor antagonists as potential therapeutic agents. Bosentan is an orally active, nonpeptide, competitive antagonist of both ET-A and ET-B (endothelin type A and B) receptors, with a slightly higher affinity for the ET-A receptor. Bosentan is the only approved oral medication for the treatment of pulmonary arterial hypertension in the United States. The orally active selective ET-A receptor antagonist, sitaxsentan, is currently in clinical trials. The potential for hepatic toxicity with therapeutic doses of these agents precludes their use in the treatment of portopulmonary hypertension. Bosentan resulted in a threefold increase in aminotransferase enzymes in 11% of patients treated in the clinical development program.[28] Similar hepatotoxic findings have also been reported with sitaxsentan.[29] Another orally active selective ET-A receptor antagonist, ambrisentan, is currently entering phase 3 clinical trials. The potential for liver toxicity with this agent is currently unknown.

### L-arginine

L-arginine is a substrate for the production of nitric oxide by the enzyme nitric oxide synthase. Oral supplementation of L-arginine could possibly lead to an increase in endogenous nitric oxide production and subsequent pulmonary vascular dilation. Modest decreases in PVR and improved exercise capacity were noted in 10 patients with pulmonary arterial hypertension following 1 week of oral L-arginine supplementation.[30] Additional studies will be necessary to confirm the potential role of L-arginine supplementation in the management of pulmonary arterial hypertension and portopulmonary hypertension. As with nitric oxide administration, increased levels of endogenous nitric oxide in patients with liver disease may blunt the therapeutic response observed with L-arginine.

## Conclusions and Implications for Clinical Practice

The therapeutic agents available for the treatment of portopulmonary hypertension have been primarily used in the treatment of pulmonary arterial hypertension. Not all of the available pulmonary arterial hypertension treatments have been systematically evaluated in portopulmonary hypertension patients. Clinical experience is most extensive with intravenous epoprostenol for this patient population. Epoprostenol improves the hemodynamics of portopulmonary hypertension and can be used as a bridge to orthotopic liver transplantation. Recent data would suggest that continuous subcutaneous treprostinil infusion has a beneficial effect on portopulmonary hypertension patient functional class and overall mortality. Inhaled iloprost has not been adequately studied in this population and inhaled nitric oxide has pulmonary selectivity, but the data in portopulmonary hypertension patients have been conflicting. Bosentan, an orally active endothelin receptor antagonist, has demonstrated efficacy in pulmonary arterial hypertension but should be avoided in patients with portopulmonary hypertension because of its potential for liver toxicity. Because of altered hepatic metabolism in cirrhotic patients, therapeutic agents with extrahepatic mechanisms of excretion and without specific hepatic toxicity are preferred in the treatment of portopulmonary hypertension. Potentially useful agents for future study include phosphodiesterase inhibitors, "nonhepatotoxic" endothelin receptor antagonists, and L-arginine. Studies of combination therapy in pulmonary arterial hypertension, utilizing agents with differing mechanisms of action, are anxiously awaited and may also have application in portopulmonary hypertension.

Pulmonary Hypertension Association

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- Visit the Awareness section of PHA's store to order and distribute free materials from the Pulmonary Hypertension Association (www.phassociation.org/Store)
- Display an awareness month poster in your office and/or hospital
- Order copies of the new *Pulmonary Hypertension: A Patient's Survival Guide (3rd ed.)* for yourself and your patients (www.phassociation.org/Learn/Survival-Guide)
- Refer patients to a local support group (www.phassociation.org/Support_Groups)
- Review Consensus Statements approved by PHA's Scientific Leadership Council (www.phassociation.org/Learn/Consensus-Statements/)
- Order a free copy of the new ACCP Practice Guidelines for PH (www.phassociation.org/Medical/accp.htm)
- Build your own PH education by joining PH Doctor (www.phassociation.org/Help/doctors.htm)

**For more information and additional ideas, order a complete Awareness Month Action Kit, available now! Visit the PHA Web site at www.phassociation.org/Awareness or contact Carla Samuels at carla@phassociation.org or 301-565-3004 x109.**

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# Recapping Highlights from Pulmonary Hypertension Association Scientific Sessions and Identifying Key Issues Driving Translational Research

Michael McGoon, MD

Victor F. Tapson, MD

Richard N. Channick, MD

Vallerie V. McLaughlin, MD

Ronald J. Oudiz, MD

Ivan M. Robbins, MD

*This discussion was moderated by Michael McGoon, MD, Professor of Medicine and Consultant in the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota. Participants included members of the Editorial Advisory Board of Advances in Pulmonary Hypertension: Victor F. Tapson, MD, Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina, and Editor-in-Chief of the journal; Richard N. Channick, MD, Associate Professor of Medicine, Pulmonary and Critical Care Division, University of California, San Diego Medical Center, San Diego, California; Vallerie V. McLaughlin, MD, Associate Professor of Medicine, Director, Pulmonary Hypertension Program, University of Michigan Health System, Ann Arbor, Michigan; Ronald J. Oudiz, MD, Associate Professor of Medicine, UCLA School of Medicine, and Director, Liu Center for Pulmonary Hypertension, Division of Cardiology, Harbor-UCLA Medical Center, Torrance, California; and Ivan M. Robbins, MD, Director, Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee.*

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**Dr McGoon:** Judging from what's been discussed at the recent Pulmonary Hypertension Association Conference, what would each of you consider to be the main themes emerging in the field of pulmonary vascular pathobiology?

**Dr Tapson:** Genetics will be crucial. There is a genetic basis for the disease and we will likely learn much more about the genetic basis for response or lack of response to different therapies. The development of, for example, specific molecular probes is allowing the characterization of growth factor genes, and markers of cell growth. Gene expression profiles will enable the distinction of different forms of pulmonary arterial hypertension.

**Dr Oudiz:** Mike, what I got from the scientific presentations this year was a renewed excitement about the progress made in understanding pulmonary vascular pathology. The multiple mechanisms involved in propagating the disease process are coming into better focus, and this is exciting because it puts us that much closer to finding ways to stop it or at least slow it down.

**Dr Robbins:** I think that a major theme is a shift away from vasoconstriction as the primary abnormality in pulmonary vascular disease to abnormal proliferation as a much more important process. As such, therapy is starting to target inhibition and regression of proliferation as opposed to mere vasodilation. In addition to the emphasis on the proliferative aspect of pulmonary vascular disease, emerging therapy is targeting specific pathobiological pathways and mediators that have been shown to be dysregulated in pulmonary vascular disease, such as the nitric oxide synthesis or endothelin. The serotonin pathway, particularly abnormalities in the serotonin transporter, seems to have come full circle. That is, serotonin was evaluated as a potential mediator 20 years ago and is now being reevaluated both as a primary cause of disease and as a modifier, affecting expression of BMPR2. In addition to abnormal pathways, additional genetic factors besides BMPR2, affecting disease expression, are starting to be evaluated. It seems that mutations in BMPR2 are unlikely to explain the development of disease in patients other than those with IPAH. Analysis of common polymorphisms in a variety of vascular mediators and pathways may provide significant information of disease expression.

**Dr Channick:** I agree. The area of growth and proliferation and what drives these processes may be fundamental for devising novel therapies in the future.

**Dr McGoon:** Are any or all of these concepts ready to be translated into clinical research, or are they already? For example, when the current crop of medications was under investigation, we talked about them as vasodilators, and their efficacy was thought likely to be a function of their vasodilator potency. We still do vasodilator studies in trying to guide therapy. Now there's a sense that some of these drugs' effects derive from other mecha-

nisms. Should we be more aggressive in identifying, testing, and using drugs that are less vasodilatory and more something else?

**Dr Channick:** Definitely. Examining true "antiproliferative" or even antithrombotic agents may yield exciting results. In fact, we may be able to take lessons from novel treatments used in coronary artery disease.

**Dr Oudiz:** I agree that we should focus more on the mechanisms that our guest lecturers spoke about. What I worry about is, as you say, that many of the cardiovascular drugs we use today seem to work by mechanisms not apparent when they were first developed, not only Flolan but statins and beta blockers, etc. So how can we be sure that, going forward, we're focusing on the correct targets and mechanisms? Hopefully, researchers like the ones who spoke are better equipped today to stand up to this challenge.

**Dr Tapson:** It is clear that vasodilation is not the answer. Very abnormal vessels need to be remodeled. We need to impact on angioproliferation and combat cancerlike lumen-obliterating cells. We need a more multifaceted approach.

**Dr McLaughlin:** I agree that vasodilatation alone is not the answer, and that chronic remodeling plays a role also. One other area that I would like to see us start investigating is right ventricular function—how the disease affects the right ventricle and how we might treat the right ventricular dysfunction.

**Dr Robbins:** Yes, as mentioned already, the importance of the proliferative aspect of pulmonary vascular disease is being increasingly recognized. Medications such as bosentan, although possessing some vasodilatory properties, are likely to work much more through inhibition of fibrosis and inflammation. Even epoprostenol, long used as a vasodilator, is becoming recognized as being much more. It is likely that its long-term beneficial effects result from inhibition of platelet aggregation and smooth muscle growth as well as direct inotropic effects. It is still important to find the rare acute vasodilators (using the new classification of acute vasodilator effect, that is, decreasing the mean pulmonary arterial pressure to less than 40 mm Hg and maintaining a normal cardiac output) because these patients can safely and effectively be treated with inexpensive medications. These responders likely represent a subgroup of patients with a different disease, one that is predominantly vasoconstrictive as opposed to proliferative. One wonders if other antihypertensives, for example ACE inhibitors, which have never been evaluated in more than a handful of PAH patients, would work as well if not better in this group. I think what may be of great benefit in guiding therapy will be genotypes or haplotypes of common polymorphisms. For example, some patients may have endothelin polymorphisms that predispose to increased synthesis and would be expected to respond to endothelin receptor antagonists or patients with increased serotonin transporter activity may benefit from serotonin reuptake inhibitors. Identifying genotypes and haplotypes to predict clinical disease is at least one major way to guide therapy. Finally, investigators have just begun to think about known antiproliferative and antiangiogenic agents such as thalidomide which deserve more consideration

**"Medications such as bosentan, although possessing some vasodilatory properties, are likely to work much more through inhibition of fibrosis and inflammation. Even epoprostenol, long used as a vasodilator, is becoming recognized as being much more."**

**Dr McGoon:** If it's true that we need to look at new avenues of treatment, then from a practical perspective, how will we design future clinical research? Controlled prospective studies of specific drugs, registries of experience using empiric drugs or combinations, unique pilot studies of novel drugs like immunosuppressives or angiogenesis inhibitors? Who should do these studies? Where should funding come from?

**Dr Oudiz:** This is a big barrier to seeing novel research move forward. The government is not likely to provide sufficient funds for such research, and the pharmaceutical companies may not be interested if it does not affect their bottom line. Not only that, but the choice of what end points to measure for these newer treatments, even if we can find funding, is becoming even more difficult.

**Dr Robbins:** As we are all aware, it is becoming increasingly difficult to conduct studies of investigational agents in PAH. Although industry can supply funding for studies, such interests are focused, and there is little, if any, funding for purely scientific questions. The NIH can supply some funding for scientific questions but this is limited. Establishment of a network of centers, such as has been done in ARDS with the ARDSNet, to conduct studies that are industry sponsored with substudies funded by the NIH may be one solution. In addition, placebo-controlled studies, at least in the United States, are no longer possible. I think there will be a growing emphasis on combination over solo therapy. Less mainstream therapies will have to be evaluated in small pilot studies, which may mean some therapies that are potentially helpful will be overlooked. One possible solution to this is to perform parallel design studies in which subgroups of patients receive an additional medication.

**Dr Tapson:** Although we would prefer to, we will not be able to rely on large, multicenter, prospective, randomized clinical trials as much as we have in the past. With new agents and limited funding resources and patient supply, we may have to build on basic science hypotheses with open-label, nonrandomized trials and registries, and more carefully choose our large evidence-based studies. I believe this kind of preplanning and pilot protocols will be even more vital. A more solid genetic understanding may aid in more meaningful clinical trial design. Competition between protocols is already upon us. With the advent of new oral therapies, treatment may (unfortunately) become less centralized and we may find ourselves expanding our PH centers to include smaller, less experienced centers. This may impact on our

clinical trial capabilities unless it is done in a supervised, organized manner. Funding will be difficult.

**Dr McLaughlin:** I agree with Vic. Clinical trials in PAH have become increasingly difficult to enroll as more therapies become FDA approved. Ethically, it has become more difficult to conduct placebo-controlled trials, at least in de novo patients. I suspect that combination therapy trials will become more commonplace. Although good for the patients, the commercial availability of more and more drugs may make both funding and enrollment more challenging.

**Dr Channick:** Given the number of possible targets and agents that might act on the pulmonary vasculature and the limited number of patients, clinical trials will become increasingly more difficult. It is likely that future studies will be "add-on" in nature. I believe the NIH needs to play a greater role in funding studies, especially examining drugs currently approved for other uses (eg, statins).

**Dr McGoon:** How should clinicians respond to ideas or early favorable research? Take statins or sildenafil—should clinicians begin using them liberally or wait for further data?

**Dr Oudiz:** This is a personal practice choice. Some clinicians like to be aggressive and others like to wait to see the data. For them, it is a good thing that the aggressive bunch do their thing, because this is sometimes, at least in part, how the data are generated. Overall, I think we should remain fairly conservative and not jump the gun.

**Dr Robbins:** Although it is tempting to use medications based on anecdotal results or positive outcomes in small, uncontrolled studies, we all can cite numerous medications that looked good initially but proved to be ineffective or harmful when studied in a randomized fashion. Since large randomized studies will not be practical for all potential therapies, the idea of cautious use, initially under very controlled circumstances, in conjunction with a database registry has a lot of appeal. Of course it is crucial to ask the right questions and keep the database focused on specific, answerable questions.

**Dr Tapson:** I believe that registries and open-labeled pilot studies may assume increasing importance in determining the clearest phase 3 approaches.

**Dr McLaughlin:** I agree with that. However, we should always strive to rely on well-designed, placebo-controlled trials. Sometimes we rely on registries and open-label pilot studies when we don't have well-designed, placebo-controlled trials, and that's OK. What I don't think is OK is giving a patient a new "hot" drug, without good data to back it up, in lieu of a drug that has been critically studied in phase 3 trials.

**Dr Channick:** I feel that it's important that clinicians avoid off-label use of drugs unless there is either a contraindication to the approved drugs or failure of therapy. For instance, the only time I prescribe sildenafil outside a clinical trial is in patients who cannot receive bosentan or as add-on therapy in patients in whom bosentan is failing. I agree, though, it is important to collect these off-label data, possibly by means of a large registry.

**Dr McGoon:** In view of all the developments in less than a decade, as high volume PH practitioners with referral-based practices, do you feel the general medical community has made progress in the understanding of PH, diagnosing it, and referring it? Where should PH best be treated, at least initially, now that therapeutic alternatives have broadened? With the primary physician, the secondary specialist (cardiologist or pulmonologist), or the tertiary subspecialist referral PH clinic? And why?

**Dr Tapson:** In spite of tremendous advances, there is still a clear sense in the community that PAH is untreatable. It remains a rare disease in smaller cardiology and pulmonary practices. We are still seeing late referrals of very ill patients and interestingly these include both late-stage untreated patients and late-stage patients receiving some oral therapy without a practical knowledge of when or how to proceed when therapy fails. Many cardiologists and pulmonologists understand that the appropriate time to refer is at diagnosis. It is difficult for the best of clinicians to have a good working knowledge of the disease when they don't follow 100 patients on intravenous prostacyclin. Family practitioners cannot possibly deal with this disease and should not be expected to. The range of diseases and problems that they face is extraordinary.

**Dr Robbins:** I think there has been progress in the awareness and diagnosis of PH during this time, especially with regard to patients at risk for the development of PH, namely patients with scleroderma, liver disease, or HIV infection. There has been a big emphasis on PH at numerous national meetings. However, I think there is still a long way to go in the general understanding of the differential diagnosis of PH, and in particular, the fact that pulmonary venous hypertension is a frequent cause of not only moderate but severe PH. Obviously I am biased, but I feel that initial treatment of PH should be at a tertiary specialty center. These centers have access to all advanced therapies and the support personnel to manage them. These are not available even in big cardiology or pulmonary practices. In addition, with a variety of medications now available to treat PAH, the experience offered by a specialty center is, in my opinion, very important. We are seeing patients mismanaged in the community. They are misdiagnosed, left on oral therapy for too long a time, or not even evaluated with a proper diagnostic right heart catheterization. Once therapy is initiated, I think it is very important to work closely with local pulmonologists or cardiologists.

**Dr McLaughlin:** Multiple efforts, on the part of both professional organizations (eg, the ACCP Evidence-Based Guidelines) and the private sector (eg, pharmaceutical-company sponsored symposia and meetings) have assisted in educating the community about PAH over the years. I think

this has had both positive and negative impact. In a positive sense, more physicians are aware of the disease, and I am seeing some patients earlier in the course of the disease than I did 5 years ago. However, in the negative sense, I am seeing patients treated in the community without being properly evaluated and followed, and by the time I see them, their disease is very advanced. I think it makes sense to have a pulmonary hypertension specialist involved in the care of most patients.

**Dr Channick:** There has been a large effort to educate physicians about PH, much of it highly successful. There is no question that recognition of PH has increased. However, with increased recognition comes the risk of inappropriate diagnostic approach and treatment. The availability of highly effective oral therapy (bosentan) has created an opportunity for both early treatment and misuse. It is now the role of the expert to clearly define which patients should be treated with which agent, how patients should be followed, and when patients should be referred to a PH center. My general opinion is that it is appropriate for nonexperts to start oral therapy, provided the standard work-up is performed, including right heart catheterization. If a patient is getting worse while receiving oral therapy, it is appropriate to refer to a center for consideration of parenteral therapy, or enrollment in a clinical trial. For example, we (and others) are examining inhaled prostacyclins as add-on therapy in patients already receiving bosentan.

**Dr Oudiz:** Until PAH becomes common enough, like heart failure, and until medical schools start devoting bigger blocks of time to teaching pulmonary vascular disease management, I am a firm believer that PAH is something that should be left, at least in the initial few months of diagnosis and treatment, to PH specialty referral centers. Given the rarity and complexity of the disease, patients are much better served if they are cared for by people who understand the nuances of diagnosing and treating PAH.

**Dr McGoon:** Speaking of patient demographics, when I read the pertinent PH literature I get the impression that there is a nice neat population of classic PAH patients with symptoms who should be treated with certain medications or procedures. What about atypical (but common) patients, such as those with quite mild resting PH with disproportionate symptoms? Or patients with exercise PH? Or elderly patients with significant PH but also multiple contributing factors, such as diastolic dysfunction, some obstructive airways disease, sleep disturbance, obesity, systemic hypertension, a past history of PE, etc? Are these a part of your practice? How do they tend to be handled?

**Dr Oudiz:** They are a significant part of our practice, but a surprisingly smaller part than I would expect, given the frequency with which these entities are seen. We rely a lot on exercise testing in these patients, since it helps us sort out the relative contribution and significance of a confounding disease process. Unfortunately, there is no predefined algorithm for atypical PAH patients, all the more reason that these patients should be referred to specialty centers.

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**Dr Tapson:** What's most obvious to me is that patients with PAH are not simply straightforward PPH patients or straightforward patients with COPD and secondary PH. There are patients with COPD and an FEV1 of 50% of predicted with systemic PA pressures who should be treated like PAH patients. There are individuals with mild and often meaningless sleep apnea with mild nocturnal hypoxemia but who have very "vasoconstrictive" vessels for some genetic reason. There are scleroderma patients with severe PAH and severe pulmonary fibrosis or with severe parenchymal sarcoidosis who clearly respond to Flolan, even though they don't appear to have pulmonary arterial hypertension. They do have it. Diastolic dysfunction means a left ventricular abnormality, but with severe PH, should Flolan or bosentan be administered? Perhaps so, but there are no good data.

**Dr McLaughlin:** Yes, I agree. The percentage of my practice that falls into that nice neat PPH diagnosis has been shrinking over the years. Although I see some patients with PH related to the pulmonary diseases that Vic has outlined, I see many more with components of diastolic dysfunction and valvular heart disease. We have come to refer to it as "multifactorial" pulmonary hypertension. It is an area that is desperately in need of further investigation.

**Dr Channick:** There is no question that many of the patients we see are of the "other" types, especially diastolic dysfunction in older patients. I think this changing demographic is a manifestation of increased recognition of PH in general. In our center, we follow these patients. I think it is useful to see these patients, address appropriate therapy, and analyze response or lack thereof to standard PH therapies.

**Dr Robbins:** These atypical patients are a huge part of our practice and present a big management challenge. I think some of the hardest patients in terms of deciding what to do are those with systolic pulmonary artery pressures in the 40 to 50s range, normal or near normal RV function on echo, but with significant symptoms. In other cases, it is often difficult to decide what the primary problem is. Sometimes we try an endothelin receptor antagonist or PDE5 inhibitor in borderline cases, ie, significant PH with a mildly elevated left ventricular end-diastolic pressure or in a patient with sarcoidosis and significant parenchymal lung disease but severe PH. Clearly, the longer I do this, the less certain and neat the diagnoses become for most patients. There are very few "pure" PAH patients, particularly once you consider subgroups other than idiopathic or familial PAH.

**Dr McGoon:** One theme that comes up more is whether

treatment should be started earlier now that we have treatments that are at least partially beneficial in advanced symptomatic PH. No matter what underlying mechanisms of disease are identified by researchers and what drugs are under development, there's a sense that by the time we start treatment, the cat is out of the bag. So what goes into a recommendation one way or the other in terms of methods of screening, defining a point of hemodynamic abnormality, or a constellation of risk markers that would warrant consideration of early treatment, evidence of efficacy, etc?

**Dr Channick:** This is truly the $64,000 question. Unfortunately, to study early intervention of any kind, you typically need large numbers of patients followed over long periods. PAH is simply not that common, especially compared to coronary artery disease or congestive heart failure. Hence, we may be forced to empirically treat patients based on biological plausibility, results in more advanced stages of disease, and risk factors.

**Dr McLaughlin:** One of the problems with drug development is that you have the best chance of detecting a treatment difference in the more ill group. Showing statistically different difference in less ill groups requires more patients and longer studies, which are expensive. With the advent of oral therapy, I think we are all inclined to start treatment earlier than we were with intravenous therapy. A trial with the endothelin receptor antagonist, bosentan, in functional class 2 patients will soon be under way. This study will also include an exercise hemodynamic subset, which will be very interesting.

**Dr Tapson:** This is an ideal setting for genetic screening. If I had PAH, I would unequivocally want early therapy and would certainly be minimally concerned about the prospect of developing abnormal LFTs in a carefully monitored setting.

**Dr Robbins:** Before considering early treatment, we have to be able to diagnose PAH earlier. As we are all aware, most patients are initially diagnosed with advanced disease. We just reviewed our current practice and only about 5% or 6% were not severely advanced enough to warrant specific PAH treatment (ERA, PDE5 inhibitor, or prostaglandin therapy). I don't have any good ideas about how to pick out this disease earlier. It's a rare disorder and symptoms mimic those of other more common diseases. Currently, I don't see a role for genetic screening, but in the future, if we are able to define genotypes and haplotypes that predict disease progression or response to therapy, it will have a big role.

**Dr Oudiz:** This is one of the hottest topics up for discussion these days in PAH. I believe that because of our long history with Flolan treatment, where it was easy to say that Flolan was just too toxic for early PH patients, we are afraid of using less toxic medications, such as ERAs and sildenafil, when really they might be worth the risk. The problem, as you mention, is then how do we prove that early intervention is of benefit? In Scotland and in Venice, this was discussed extensively, and many ideas were circulated, but there was no definite consensus on what future end points should actually be used. I suspect that investigators will continue to explore their personal favorites and that some of these end point modalities will make it into larger clinical trials. This may be the only way that we can actually validate a newer end point.

**Dr McGoon:** The PHA is opening up membership to all interested physicians (the PH Doctor initiative). How should the PHA, and in particular PH Doctor, be involved in the future of managing and investigating PH?

**Dr Robbins:** I don't know how feasible this is, but I think the PHA, with guidance from the SLC (Scientific Leadership Council), should attempt to work with industry to help direct future research. The number of PAH patients is limited and prioritization of potential treatments is needed. In addition, through PHA-administered grants, something akin to an RFA might be set up to focus investigators on specific topics or areas. Providing grant opportunities, not only for young investigators but for midlevel and even senior investigators with a track record of research in PH is another way to promote high quality research involving PH. With regard to managing patients, if there is some way to designate centers of excellence that would be listed on the PHA Web site, I think this could improve care. Another way to improve care might be clinical sessions for physicians—reviewing evaluation and management of PH—at the PHA.

**Dr Tapson:** Education is key. The PHA has done a wonderful job in getting this difficult disease some well-deserved attention. The disease often affects young persons in the prime of their lives. Media attention, patient and physician education, and support for continued research will be instrumental. And don't forget nursing. I believe the PH nurses have been the mortar that has held the bricks together. We not only need funding for research, we need it for clinical nursing support. It is becoming increasingly financially difficult to run a PH center. It would be impossible for small practices to handle large numbers of patients. Education and referral to large PH centers are key.

**Dr Channick:** Increasing the involvement in nonexpert specialists may be very important in increasing our database. As mentioned, community physicians are already treating patients, so developing a network or registry will become more plausible if these physicians are invested in the PH community.

**Dr Oudiz:** PH Doctor will certainly help further the campaign to educate the medical and scientific community worldwide. Bringing these issues to a wider audience will introduce that much more scientific input into future diagnostic and therapeutic modalities. It should facilitate further discussion of what we've been talking about here; namely, the issues surrounding the screening of candidate therapeutic mechanisms, earlier intervention, and finding additional clinical end points to measure the effects of these interventions. Hopefully, an even more concerted effort at creating and maintaining a sound patient database might result.

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