Heart failure is a significant and growing problem in the United States, and is predicted to afflict 1 in 5 adults. It represents the most common Medicare diagnosis at hospital discharge and will account for approximately $37.2 billion in healthcare expenditures in 2009. Despite major advances in therapy over the past 2 decades, current treatment is often palliative and therapies are directed at symptom management and delay of disease progression. An improved understanding of the factors that modify prognosis and outcome would be beneficial in stratifying patient risk and developing novel therapeutic opportunities.

For any given myocardial insult, substantial variation is believed to exist in the susceptibility to developing heart failure, but the underlying factors responsible for this variation are only beginning to be understood. Interindividual differences in many components of the response to myocardial injury have been implicated, including local or remote myocardial remodeling. The impact of comorbid conditions, such as pulmonary hypertension (PH), is also believed to play a role in determining the course and prognosis of heart failure. The determinants and regulators of pulmonary vascular tone and the impact on heart failure are poorly characterized.

Increased pulmonary vascular tone and PH, together with consequent right ventricular dysfunction, are now known to be among the most significant modifiers of the natural history and prognosis of heart failure resulting from left ventricular disease. PH in heart failure is believed to result from congestion and chronic pulmonary venous hypertension. PH is associated with a negative impact on survival, and reversibility of PH in response to pharmacologic or mechanical interventions is a predictor of improved heart failure outcomes. PH in heart failure may begin as a passive process resulting from congestion and elevated filling pressures, and pulmonary venous hypertension. With chronic congestion, pulmonary vascular tone may be become irreversibly elevated. However, the fundamental mechanisms determining pulmonary vascular responses to heart failure and the development of PH remain incompletely understood.

Recently, advances have been made in understanding of the mechanisms underlying pulmonary arterial hypertension (PAH). In contrast to the substantial and growing burden of heart failure, primary PAH is a rare disease. Advances in dissecting the molecular pathogenesis of PAH have begun to illuminate some of the molecular pathways responsible for PH in its primary and secondary forms, and may help provide insights into the molecular and genetic factors regulating pulmonary vascular tone. Because pulmonary tone is a powerful determinant of outcomes in
heart failure, this understanding may provide insights into the factors that determine prognosis and disease course.

**CLASSIFICATION OF PULMONARY HYPERTENSION**

PH represents a diverse spectrum of disease. PH is usually associated with an underlying primary diagnoses, such as congenital heart disease, scleroderma/CREST, thromboembolic disease, chronic hypoxia, chronic obstructive pulmonary disease, and left heart failure. In the absence of an underlying cause, PAH is termed idiopathic or primary. Primary PAH is a rare disorder with an incidence of 1 to 2 cases per million in the United States, but may offer insights into the cause of more general diathesis toward aberrant pulmonary vascular responses. Between 10% and 30% of cases of primary PAH cluster in familial cohorts. These cases are autosomal dominant with low penetrance; only 10% to 20% of patients harboring a mutation exhibit the overt disease phenotype.

In 1998, the second World Symposium on Pulmonary Hypertension in Evian, France, represented the initial attempt to classify PH based on the underlying cause. The spectrum of pulmonary hypertensive diseases was divided into five clinical categories, which were grouped according to therapeutic treatment interventions: (1) PAH; (2) pulmonary venous hypertension; (3) PH associated with disorders of the respiratory system; (4) PH caused by thrombotic or embolic disease; and (5) PH caused by diseases affecting pulmonary vasculature. The third World Symposium on Pulmonary Arterial Hypertension in Vienna held in 2003 revised and extended the Evian classification scheme. As with the 1998 scheme, there were five categories but they were arranged somewhat differently: (1) PAH; (2) PH with left heart disease, (3) PH associated with lung diseases or hypoxemia, (4) PH caused by chronic thrombotic or embolic disease, and (5) miscellaneous. Important changes included the recognition of PH associated with left heart disease as a wholly distinct category (category 2).

**THE CLINICAL DIAGNOSIS AND EVALUATION OF PULMONARY ARTERIAL HYPERTENSION**

The clinical presentation of PH can be nonspecific and difficult to differentiate from other cardiopulmonary diseases. Based on national registry data, the most frequently recorded symptoms were dyspnea (60% of patients), fatigue (19%), and presyncope or syncope (13%). Other symptoms may include chest pain, palpitations, or edema. The lack of specific findings can delay identification of a definitive diagnosis; the average interval between onset of symptoms and diagnosis was 2 years. Family history may offer little assistance given the relatively low prevalence and penetrance of identified mutations in PAH.

As pulmonary pressures rise and right heart failure ensues, the physical findings of PH become less subtle. Examination of the jugular pulsations can show elevated neck veins and prominent v waves. In the setting of more profound right ventricular dysfunction, hepatic enlargement, and pulsation, lower extremity edema and ascites may be found. Cardiac examination may also be notable for an right ventricular heave or lift. The classic auscultatory finding is of an accentuated pulmonic component of the second heart sound ($P_2$). Additionally, a systolic murmur of tricuspid regurgitation and a right-sided $S_3$ may also be heard. Other notable findings include Raynaud phenomenon in 10% of patients.

No definitive set of laboratory tests confirm the diagnosis of PH. Testing for HIV, hepatic enzymes, thyroid function, and rheumatologic markers of autoimmune and connective tissue diseases are helpful in identifying secondary causes of PH. Measurement of serum brain natriuretic peptide levels may be a useful correlate of hemodynamics.

Noninvasive testing can help raise PAH in the differential and in diagnosing PH. Although no pathognomonic EKG is available to diagnose PAH, common electrocardiographic findings include right atrial enlargement and prominent R wave voltages in the inferior leads, right-axis deviation, and right ventricular strain. The chest radiographic manifestations of PAH include pulmonary artery, right atrial, and ventricular enlargement. Ventilation/perfusion scans and CT angiography are useful in evaluating thromboembolic disease as the cause of dyspnea and pulmonary hypertension. Finally, transthoracic echocardiography can be used to confirm hypertrophy of the right-sided cardiac chambers and evaluate for structural defects, with the Doppler component of the echo serving as an important technique to evaluate right ventricular systolic pressure.

Although noninvasive methods such as echocardiography can suggest elevated right- sided pressures, the gold standard for diagnosing PH remains the finding of elevated pressures in the pulmonary artery and on the right side of the heart through right heart catheterization. The clinical threshold for PH is crossed when the mean pulmonary artery pressure exceeds 25 mm Hg at rest or 30 mm Hg during exercise.
PULMONARY ARTERIAL HYPERTENSION AND LEFT HEART FAILURE

Chronically elevated pulmonary venous pressures (reflected clinically as an elevation in pulmonary capillary wedge pressure [PCWP] on right heart catheterization) results from systolic and diastolic heart failure and mitral valvular disease and is the most common cause of PH.\textsuperscript{13,14} Conversely, PH represents a common finding in heart failure, and portends a poorer prognosis and worse outcomes.

The work of Butler and colleagues\textsuperscript{15} provides insight into the prevalence of PH in a cohort of patients who had advanced heart failure undergoing evaluation for heart transplantation. They studied 320 patients undergoing exercise testing with invasive hemodynamic monitoring for systolic heart failure. Overall, this was a relatively ill population that had a mean maximum oxygen consumption (VO\textsubscript{2}\textsubscript{max}) of 13 mL/kg per minute. Only 28% of their patients had a normal pulmonary vascular resistance (PVR) of less than 1.5 Woods units; the remaining 72% had elevated pulmonary vascular tone. Increased PVR negatively impacted peak exercise oxygen consumption per minute (VO\textsubscript{2}) and other indices of rest and exercise hemodynamics. No association was found between pulmonary vascular tone and ejection fraction, cause of the underlying cardiomyopathy, or functional status (according to New York Heart Association [NYHA] class). Similarly, Ghio and colleagues\textsuperscript{3} found PH in more than 60% of the patients they studied. Although abnormal pulmonary vascular tone and PH are common in patients who have systolic heart failure, clinical characteristics do not predict the likelihood of developing PH.

More recently, heart failure with preserved ejection fraction (HFpEF), which accounts for nearly half of heart failure cases in the United States, has received considerable attention. PH also seems to be a common hemodynamic finding in this group. In a population of patients who had HFpEF in Olmstead County, Minnesota, pulmonary artery systolic pressure (PASP) and PCWP were estimated from echocardiography and compared with a control population who had no heart failure.\textsuperscript{16} Although PH (defined here as PASP>35 mm Hg) was diagnosed in 8% of the control group, 83% of the HFpEF group had elevated pulmonary artery pressures. The median value in the hypertensive control group who had no heart failure was 28 mm Hg, whereas it was 48 mm Hg the HFpEF group.

Similar to systolic heart failure, PASP correlated with pulmonary venous pressures as determined by PCWP in HFpEF. PH also seems to impact survival when present in HFpEF, as the presence of PH was significantly associated with increased mortality. Hence, PH is both a prevalent comorbidity and poor prognostic finding in heart failure with either preserved or impaired left ventricular systolic function.

PH and abnormal pulmonary vascular tone may impact heart failure through affecting right ventricular function. The importance of right ventricular performance in predicting functional capacity and survival in heart failure was established by Di Salvo and colleagues.\textsuperscript{17} who studied exercise capacity in patients who had advanced heart failure. Specifically, although left ventricular ejection fraction (LVEF) predicts prognosis in heart failure, the investigators found no association between LVEF and exercise capacity as determined by peak oxygen consumption. However, exercise capacity correlated with right ventricular ejection fraction (RVEF). Furthermore, better RVEF was a significant predictor of survival in the advanced heart failure population. Ghio and colleagues\textsuperscript{3} examined the relationship between pulmonary artery pressures and right ventricular performance. Their analysis showed a significant inverse relationship between RVEF and pulmonary artery pressures, although they noted several clinically relevant exceptions to this finding (eg, normal pulmonary artery pressures with right ventricular dysfunction and PH with preserved RVEF). The combination of PH and heart failure is associated with an especially poor prognosis in the setting of concomitant right ventricular dysfunction. The authors speculate that the loss of right ventricular performance may represent a late finding in the setting of increased right ventricular afterload and PH, and that compromised RVEF may be a surrogate marker for the chronicity of heart failure. However, the determinants of right ventricular compromise in the setting of heart failure and PH remain unknown.

Recent studies support the notion that selective right ventricular afterload reduction using strategies to decrease PVR and treat PH may be beneficial in heart failure. Inhaled nitric oxide, a pulmonary specific vasodilator, has been shown to effectively decrease PVR in patients who have heart failure without lowering systemic vascular resistance or causing significant hypotension.\textsuperscript{18} Koelling and colleagues\textsuperscript{19} studied the impact of inhaled nitric oxide on exercise capacity in patients who had severe heart failure. In patients who had elevated pulmonary artery pressures, exercise capacity increased by 22% with treatment. Selective pulmonary vasodilation and right
ventricular afterload reduction did not improve peak VO₂ in patients who had no PH. Thus, inhaled nitric oxide ameliorates exercise capacity only in patients who have PH.

Although administration of inhaled nitric oxide is not practical chronically, other strategies to augment its effects and preferentially reduce PVR have been attempted in heart failure. Specifically, pharmacologic agents such as sildenafil and tadalafil potentiate the endogenously produced nitric oxide through inhibiting type 5 phosphodiesterase (PDE5), resulting in intracellular accumulation of cGMP. Acutely, a single dose of sildenafil has been shown to decrease PVR and pulmonary artery pressures preferentially, compared with the systemic circulation, both at rest and with exercise in patients who have NYHA class III heart failure and PH.20

Moreover, the improvement in hemodynamics and measured peak oxygen consumption seems to be durable and generalizable to other indices of functional capacity. Lewis and colleagues21 studied patients who had systolic heart failure and PH undergoing optimal medical therapy and randomized them to chronic treatment with either sildenafil or placebo. After 12-weeks of treatment, patients receiving sildenafil had significantly improved exercise time, VO₂max, 6-minute walk distance, and heart failure symptom scores. These findings have been substantiated in other trials of PDE5 inhibition in heart failure.22,23 Therefore, decreasing pulmonary vascular tone and treating PH in heart failure with PDE5 inhibition seems to offer beneficial effects in terms of hemodynamics, symptoms of heart failure, and functional capacity. None of these studies has been sufficiently powered nor performed for sufficient duration to assess whether PDE5 inhibition might also impact survival in heart failure.

Although studies of sildenafil-induced right ventricular afterload reduction may provide enthusiasm for therapeutic strategies to treat PH and heart failure, earlier trials using the pulmonary vasodilators epoprostenol and endothelin antagonists in heart failure did not achieve positive primary end points,24–27 suggesting that the functional benefits of inhaled nitric oxide and PDE5 inhibition may not result purely from the hemodynamic effects of these agents. Instead, activation of nitric oxide and cGMP signaling may have direct myocardial effects that at least may partly explain some of the beneficial effects of these agents.28 A more detailed understanding of the basic biology of PH may help define the advantages and pitfalls and help in the development of novel treatment approaches.

**THE BIOLOGY OF PULMONARY HYPERTENSION**

Primary PAH is a rare disorder with an incidence of 1 to 2 cases per million in the United States.6 However, it may offer insights into the cause of more general diathesis toward aberrant pulmonary vascular responses in the secondary PH encountered in heart failure. Familial PH is an autosomal dominant disease with low penetrance; only 10% to 20% of patients harboring a mutation exhibit the overt disease phenotype.7

The diathesis to PH seems to vary based on environmental and genetic factors. Acquired disorders and exposures serve as triggers for PH, including appetite suppressants (derivatives of fenfluramine and other anorexigens), toxins, and infection (eg, HIV29). However, only few individuals exposed to environmental triggers eventually develop PH, suggesting that the acquired exposure may trigger a genetic susceptibility. Gender clearly exerts an influence on the diathesis to PH; women are diagnosed two to five times more often than men.

Although several diverse causes of PH exist, shared pathologic findings are identified in lungs of affected patients, including (1) thickening of the walls of small pulmonary arteries with concomitant neointima formation and smooth muscle cell (SMC) proliferation in large and small pulmonary arteries, (2) the presence of plexiform endothelial cell lesions characterized by capillary-like channels near pulmonary arterioles (200–400 mM in diameter), and (3) the presence of thrombosis in situ. Tuder and colleagues30,31 reported that these plexiform lesions are characterized by proliferating endothelial cells30 and the abundant expression of angiogenesis-related molecules.31 The same laboratory has also reported that endothelial cells in plexiform lesions of patients who have primary PH are monoclonal, but are not in those who have secondary PH.32 Similarly, because patients who had PH associated with anorexigen use had monoclonal populations of endothelial cells in plexiform lesions, Tuder and colleagues33 suggested that anorexigens may serve as an environmental cofactor that precipitates PAH in susceptible individuals.

**The Role of BMP/BMPR2 Signaling in Disease Pathogenesis**

The existence of familial forms of PH has offered a unique opportunity to define the cause of at least one form of pulmonary vascular disease. Using unbiased genetic approaches mutations in the bone morphogenetic protein (BMP) type 2 receptor (BMPR2) gene have been identified as
the cause of approximately one third of familial PH. BMPR2 mutations characterized to date suggest that haploinsufficiency may be the primary mechanism of action in a proportion of these cases, but detailed studies in tractable animal models will be required to establish this formally. BMPR2 mutations also may have more pleiotropic cardiovascular effects than previously believed. In a detailed re-examination of families with PAH, Newman and colleagues established that several families that were previously believed to be distinct were in fact distantly related and that several family members also harbored congenital cardiac abnormalities or developed cardiomyopathy. Therefore, in addition to their role in PH, heritable abnormalities in BMPR2 may also be associated with congenital heart disease and cardiomyopathy.

Transforming growth factor β (TGF-β) family signal transduction has been implicated in other genetically mediated causes of PH in a separate but related condition called hereditary hemorrhagic telangiectasia (HHT). HHT is caused by mutations in ACVRL1/ALK1, a type I TGF-β receptor, and endoglin, a TGF superfamily ligand. These same pathways have been implicated in secondary forms of PH. Expression of BMPR2 is diminished in patients who have PH; BMPR2 transcript is downregulated in the endothelium of patients who have PH who do not harbor a mutation in the gene. Acquired forms of PH have also been associated with attenuation of the BMPR2 coreceptor ALK3/BMPR1α, which may be mediated through angiopoietin-1.

**BMPR2 Signal Transduction**

BMPs belong to a large family of proteins related to TGF-β. Proteins in this family have effects on various cell types, depending on the cell environment and developmental stage. The TGF-β family of peptides can modulate the function of vascular cells (endothelial cells and SMCs), including proliferation, migration, apoptosis, and secretion of extracellular cell matrix. BMPs are known to inhibit vascular SMC proliferation, stimulate vascular SMC migration, and inhibit neointima formation in balloon-injured rat carotid arteries. BMP-β family members bind to two different types of cell-surface receptors, referred to as type I and type II, both of which have intracellular serine-threonine kinase domains. On ligand binding, type II receptors complex with type I receptors, leading to type I receptor phosphorylation and activation. The activated type I receptors subsequently phosphorylate receptor-regulated Smad proteins (R-Smads) that interact with common-mediator Smads (Co-Smads), leading to modulation of gene transcription (Smad-dependent signaling). TGF-β and BMPs have also been shown to activate mitogen-activated protein kinases, including ERK, SAPK/JNK, and p38 (Smad-independent signaling). As with all type 2 BMP receptors, BMPR2 consists of a ligand-binding (extracellular) domain, a transmembrane domain, a serine/threonine kinase domain, and a C-terminal cytoplasmic tail (a shorter splice variant was also found in humans).

All mammals, despite the large number of BMP ligands, have a limited repertoire of type I and II BMP receptors. Multiple combinations of type I and II receptors create ligand-binding preference for specific ligands, but also afford receptor redundancy within the same class of receptors. BMP binding activates a subset of R-Smads (Smad1, Smad5, and Smad8) that, together with the coreceptor ALK1 (Smad4) and other transcription factors, leads to BMP-responsive gene transcription. BMP (and TGF-β) signaling can be modulated by inhibitory Smads (I-Smads: Smad6 and Smad7), which compete with R-Smads for activated type I receptors and whose expression can be induced by TGF-β or BMPs in a negative feedback loop.

Abundant evidence has shown that TGF-β/BMP signaling is required for the normal development in several vertebrate model organisms, including chicken, mouse, frog, and zebrafish, in general and within the cardiovascular system specifically. BMPs can induce the expression of cardiac transcription factors such as Nkx2.5, GATA4, and TBX2 and -3. Various cardiac phenotypes have been reported in mice carrying targeted deletions of the genes encoding members of the TGF-β/BMP family, including BMP2, -4, -5/7, -6/7, -10, and TGF-β2. Investigations in Xenopus indicate that BMP signaling is required for late manifestation of cardiac development but not for early markers of cardiac specification. Less is known about the contribution of specific receptors for BMP ligands and the roles played in cardiovascular development.

**Signaling Defects Observed with BMPR2 Mutations**

Signal transduction through BMPR2 is initiated by ligand binding to a receptor and activation of Smad-dependent and -independent intracellular signaling events. Although a relatively restricted set of type I and II receptors are known, heterodimerization enables potential combinatorial interactions between subunits. Hence, rather than interrupting BMP signaling altogether, nullification of one type II receptor may instead shift the...
balance of signaling through other receptor subtypes.

Yu and colleagues\textsuperscript{50} investigated the impact of the loss of BMPR2 in pulmonary artery SMCs in vitro. Using cre-lox ex vivo inactivation and siRNA inactivation, they showed that, although some BMP ligands seemed to have attenuated intracellular signaling by way of the classic SMAD-1/5/8 pathway, others (specifically BMP6 and BMP7) exhibited augmented signaling through alternate use of the ActR-2a receptor. This finding suggests that the molecular defect in PH may result in augmented rather than attenuated BMP signaling. However, whether Smad activity is increased or decreased in vivo with PH is unclear.

**ANIMAL MODELING OF PULMONARY HYPERTENSION WITH BMPR2**

Transgenic mouse models have been used to dissect how BMPR2 contributes to development. Knockout of both BMPR2 alleles showed that it is required for early development and led to complete involution and loss by embryonic day 9.5. Histologic analysis of homozygous embryos showed lack of mesoderm formation.\textsuperscript{51} Mice heterozygous deficient for BMPR2, although grossly normal, exhibit increased mean PAH and PVR compared with their wild-type littermates. Quantitative histologic analysis shows that heterozygous mice have increased wall thickness in muscularized pulmonary arteries (<100 µm in diameter) and an increased number of alveolar–capillary units compared with wild-type mice.\textsuperscript{52} These histologic findings parallel several pathologic findings in patients who had PH. Furthermore, under conditions of inflammatory stress, heterozygous mice are more likely to develop increased right-sided pressures and increased pulmonary vascular remodeling, consistent with the observation that environmental factors can exacerbate a genetic diathesis to PH.\textsuperscript{53} Finally, transgenic mice with expression of a dominant-negative BMPR2 in SMCs only have histologic findings of intimal proliferation and increased mural thickness in pulmonary arterioles.\textsuperscript{54} The alveolar/capillary ratio was unchanged and abnormalities were not observed in the smallest vessels.

Thus, BMPR2 is absolutely required in mammalian development. Germline heterozygous deficiency (ie, in all tissues) phenocopies many aspects of PH. Familial PH results from germline transmission to all cells rather than mosaic loss in one cell type, and observational in situ data suggest that PH is associated with greater loss of transcript in vascular endothelial cells rather than other cell types. Tissue specific interruption in the SMC of transgenic mice leads only to partial recapitulation of the observed pathologic deficits in PH.\textsuperscript{54} Conditional deletion in other tissues with murine transgenics is an active area of investigation and anticipated to provide new insights into the ways BMP signaling is involved in the vascular abnormalities underlying PH.

These studies highlight the emerging understanding that the pathophysiologic abnormalities of PH may have their origin during ontogeny. Animal models such as transgenic mice and other vertebrate developmental systems should provide a suitable platform for discovering the molecular and cellular alterations that produce the structural and functional defects in primary and acquired forms of PH, as is seen in heart failure. The detailed exploration of these experimental systems will provide the opportunity to integrate the basic discoveries with the clinical observations and trial data reviewed earlier and inform strategies to treat the spectrum of pulmonary hypertensive diseases.

**SUMMARY**

When PH and right ventricular dysfunction accompany heart failure, the impact on functional capacity and prognosis are ominous. Newer clinical strategies to preferentially lower pulmonary pressures and pulmonary vascular tone improve functional performance and symptoms of heart failure by targeting the nitric oxide signal transduction pathways, as with PDE5 inhibition. Additional studies are needed to delineate if these therapies will impact long-term patient outcomes and elucidate the specific mechanisms whereby these treatments are effective. Furthermore, the recent finding that mutations in BMPR2 cause familial forms of PAH and that BMPR2 expression is decreased in secondary forms of PH strongly implicate BMP signaling in the underlying pathophysiology of PH. Translation of emerging basic science insights in the vascular biology of PH and BMP signaling will provide novel therapeutic strategies for the spectrum of pulmonary hypertensive diseases.

**REFERENCES**


