Pulmonary, Sleep, and Critical Care Updates

Update on Pulmonary Vascular Diseases 2010

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Significant discoveries in the biology of pulmonary hypertension and thromboembolic disease were published in 2010. Continuing in the *Journal's* tradition (1, 2), a summary of many of these publications is provided in this update. The reader is also referred to the National Heart, Lung, and Blood Institute (NHLBI) Strategic Plan report (3) and the primary manuscripts summarized in this review for detailed information.

UPDATE ON SURVIVAL WITH PULMONARY HYPERTENSION: REGISTRIES

The French Registry reported on survival of 674 adult patients with pulmonary arterial hypertension (PAH) (121 incident and 553 prevalent cases) (4). In the overall cohort of 674 patients, 1-, 2-, and 3-year survival rates were 87, 76, and 67%, respectively. In prevalent idiopathic, familial, and anorexigen-associated PAH, survival rates were higher than in incident patients. Multivariable analysis suggested that survival could be estimated by means of a risk-prediction equation using sex, 6-minute walk distance, and cardiac output at diagnosis. One of the major insights from this study is that despite the many advances in therapy since the National Institutes of Health (NIH) Registry (5), current-day survival has improved just modestly. Importantly, survival data in PAH cohorts are significantly biased by the inclusion of patients with prevalent disease, who have a better prognosis than patients with incident disease (6).

Outcomes from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), a 54-center collaborative U.S. effort, were also reported last year. Survival at 1 and 3 years from the time of PAH diagnosis in 2,716 patients was 87.7 and 72.1%, respectively. Similar to the French Registry, sex, functional class, and 6-minute walk distance were predictive of outcome. Additional prognostic variables included origin of PAH, age, pulmonary vascular resistance, right atrial pressure, renal insufficiency, resting systolic blood pressure and heart rate, brain natriuretic peptide, presence of a pericardial effusion, and diffusing capacity of the lung. A prognostic equation using all of these factors was generated that allowed risk stratification for 1-year survival (7), and can be used with data available at any point in time in the disease course (8).

In an attempt to reappraise the NIH risk stratification equation, Thenappan and colleagues reported on the contemporary survival in PAH in 576 patients referred during 1991–2007 to a single center (9). The observed 1-, 3-, and 5-year survival rates in the total cohort were 86, 69, and 61%, respectively. A new equation was proposed, but will require prospective validation (9).

UPDATE ON RIGHT HEART DISEASE IN PULMONARY ARTERIAL HYPERTENSION

Withdrawal of nonselective β -blockers in patients with portopulmonary hypertension improved cardiac output and the distance walked in 6 minutes (10). However, the association of sympathetic activation with worse outcome in PAH, the adverse effects of such activation on the left ventricle, and the survival benefit of β -blockade in congestive heart failure have led some to question the conventional wisdom in right heart failure.

Ciarka and colleagues reported that an increase in sympathetic nervous system activity is an important prognostic factor indicating an adverse outcome for pulmonary arterial hypertension (11). Thirty-two patients with PAH were included in their study and underwent a measurement of the sympathetic nervous system and clinical assessment of disease progression over a median of 21 months. The 17 patients who had clinical deterioration had increased sympathetic activation, higher heart rate, lower walk distance, and worse New York Heart Association (NYHA) functional class than those individuals who did not deteriorate. Multivariate analysis showed that sympathetic nervous system activation is an independent predictor of clinical deterioration in pulmonary arterial hypertension (11). In support of these findings, work in an experimental angioproliferative pulmonary hypertension model in rats showed that adrenergic receptor blockade reverses right heart remodeling and improves right ventricle function (12). At present, however, β -adrenergic receptor blockers are not recommended in humans with PAH; safety and efficacy studies must be assessed in well-designed clinical trials (13).

The discovery of a counterregulatory vasodilatory system to the renin-angiotensin system, composed of the heptapeptide Ang-(1–7), a metabolite derived from angiotensin I by the action of angiotensin-converting enzyme-2 (ACE2), and Mas, the Ang-(1–7) receptor, provided the rationale for a study. A lentiviral Ang-(1–7) fusion gene or ACE2 cDNA was intratracheally administered into the lungs of male Sprague Dawley rats followed by bleomycin to induce pulmonary fibrosis or monocrotaline to induce pulmonary hypertension. In both models, rats developed elevated right ventricular systolic pressure, right ventricular hypertrophy, and pulmonary vascular remodeling, all of which were attenuated by Ang-(1–7) overexpression. Blockade of the Mas receptor abolished the beneficial effects of Ang-(1–7). These observations suggest a cardiopulmonary protective role for the ACE2/Ang-(1–7)/Mas axis in the treatment of pulmonary hypertension, especially pulmonary hypertension associated with pulmonary fibrosis (14).

Saouti and colleagues determined power generated by the right heart and the proportion accounting for oscillatory power. Interestingly, although pulmonary vascular resistance and compliance change significantly in pulmonary arterial hypertension, the oscillatory power remains 23% of total power overall. This implies that a considerable amount of power is not used for forward flow, making the right ventricle less efficient with respect to its arterial load. These findings highlight a need to develop

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treatment strategies to reduce the workload and optimize right ventricular power output in pulmonary vascular diseases (15).

The French Registry provided the first prospective study analyzing data from 46 consecutive patients requiring intensive care unit admission for severe acute right ventricular failure. The 3-month mortality was high at 41%. There was no difference in terms of demographics, clinical data, and hemodynamic measurements, but systemic arterial pressure was significantly lower in the subgroup of patients whose clinical course was fatal. The plasma brain natriuretic peptide, C-reactive protein, and serum sodium and creatinine at admission correlated with survival. Demonstration of an infection during the intensive care unit stay was also associated with a worse prognosis (16).

UPDATE ON PHENOTYPES OF PULMONARY HYPERTENSION

Pulmonary hypertension is a heterogeneous disorder and thus precise phenotypic definition has eluded the medical and research communities for years. Defining pulmonary hypertension phenotypes is important for several reasons: it can provide new insights about the etiology of disease, help to predict prognosis, and hopefully identify phenotypes that are more likely to respond to a particular treatment or management strategy.

One insight into phenotypes came from baseline characteristics in the REVEAL Registry, which demonstrated that patients included in the registry are older and more often female than in previous descriptions. Importantly, patients with a pulmonary capillary wedge pressure (PCWP) of 16 to 18 mm Hg had a distinct phenotype different in a number of important respects from those meeting the traditional hemodynamic definition of PAH (PCWP < 15 mm Hg) (17); they were older, more obese, had a shorter walk distance, and were more likely to have systemic hypertension, sleep apnea, renal insufficiency, and diabetes than adult patients meeting the traditional definition (17).

A well-recognized PH phenotype is scleroderma-related pulmonary hypertension, which carries a poorer prognosis compared with most other forms of PAH, but for reasons that remain unexplained. In a single-center study of 76 consecutive patients, predictors of mortality in scleroderma-related pulmonary arterial hypertension were identified, including stroke volume index, pulmonary arterial capacitance, and estimated glomerular filtration (18). In a related prospective study, patients with scleroderma-related pulmonary hypertension had significantly higher brain natriuretic peptide levels than patients with idiopathic pulmonary hypertension, despite less severe hemodynamic profiles (19). Analysis of patients with connective tissue disease-associated pulmonary hypertension in the REVEAL Registry identified similar characteristics. Patients with connective tissue disease-associated PAH ($n = 641$) had better hemodynamics but 1-year survival and freedom from hospitalization were lower compared with patients with idiopathic disease ($n = 1,251$) (20). Taken together, these studies emphasize the importance of a more focused approach to the pathogenesis of scleroderma-related pulmonary hypertension and the need to develop reliable tools to adequately assess functional impairment and monitor therapy in this phenotype (18, 21).

A more recently recognized PH phenotype is that associated with insulin resistance and the metabolic syndrome (22, 23). In a study by Heresi and colleagues, high-density lipoprotein-cholesterol (HDL-C) levels were significantly depressed in pulmonary arterial hypertension and were associated with worse clinical outcomes; levels less than 35 mg/dl discriminated survivors from nonsurvivors with a sensitivity of 100% and specificity of 60%. HDL-C remained a significant predictor of survival after adjusting for cardiovascular risk factors, C-reactive protein, indices of insulin resistance, and severity of PAH. Whether

modifying HDL-C will result in improvement in PAH outcomes, however, will require clinical trials (24).

Another more recently recognized PH phenotype is that of pulmonary hypertension in the setting of combined pulmonary fibrosis and emphysema. In a report of 40 patients with pulmonary hypertension in the setting of pulmonary fibrosis and emphysema, the mean pulmonary artery pressure was about 40 mm Hg, cardiac index 2.5 L/minute/m², and pulmonary vascular resistance 521 dyn/second/cm⁵, yet 1-year survival was 60%. This confirms the clinical impression that these patients have a dismal prognosis despite modest impairment of lung physiological and hemodynamic functions (25).

UPDATE ON GENETICS AND STEM CELLS IN PAH

Using new genome-wide technologies to analyze pulmonary artery endothelial cells and smooth muscle cells from PAH lungs, Aldred and colleagues showed that more than half of cases harbor somatic chromosome deletions that may contribute to the unchecked proliferative nature of the cells (26). Mosaic chromosomal abnormalities were detected in pulmonary artery endothelial cell cultures derived from patient-explanted lungs. Fluorescence *in situ* hybridization confirmed the presence of abnormalities *in vivo*. This study indicates that in addition to germline mutations of the bone morphogenetic protein pathway, acquired genomic rearrangements occur frequently across idiopathic, heritable, and associated forms of PAH, which may constitute a “second-hit” cancer-like mechanism in pathogenesis.

Patients with a bone morphogenetic protein receptor type 2 (BMPR2) mutation present earlier than noncarriers and have more severe pulmonary hypertension at diagnosis (27). Mutations in the activin A receptor type II-like kinase-1 (ACVRL1, also known as ALK1) can lead to heritable pulmonary hypertension but the clinical characteristics were unclear. Girerd and colleagues reviewed clinical, functional, and hemodynamic characteristics of 32 patients carrying an ACVRL1 mutation in comparison with patients with a BMPR2 mutation and idiopathic cases without identified mutation. The investigators identified that ACVRL1 mutation carriers are also characterized by a younger age at diagnosis and have a worse prognosis compared with other patients with pulmonary hypertension (28).

Since Geraci and colleagues first reported on genome-wide RNA expression, using lung tissue specimens from six subjects with PAH and six normal control subjects (29), there has been an evolution in microarray technology, bioinformatics analytic tools, and availability of lung tissue specimens. Using genome-wide microarray analysis, Rajkumar and colleagues generated RNA expression profiles from lung tissue of 18 patients, 8 with pulmonary hypertension secondary to idiopathic pulmonary fibrosis, in comparison with 13 healthy subjects. They identified distinct signatures in idiopathic pulmonary arterial hypertension (IPAH) and the secondary pulmonary hypertension, implying distinct pathophysiological mechanisms (30). The samples differed in expression of genes that regulate actin-based motility, protein ubiquitination, transforming growth factor- β , nitric oxide, platelet-derived growth factor signaling, estrogen receptor, and bone morphogenetic protein receptor type II expression (30).

UPDATE ON NEW MECHANISMS IN PH

Although several studies have shown that circulating microparticles are elevated during pulmonary arterial hypertension, the origin and the role played by microparticles in the regulation of endothelial function are not known. Tual-Chalot, and colleagues demonstrated that circulating microparticles from hypoxic rats can induce endothelial dysfunction via inhibition of

nitric oxide production and an augmentation of oxidative stress. These data provide evidence that hypoxia-induced circulating microparticles can cause endothelial dysfunction and hence contribute to the pathobiology of pulmonary hypertension (31).

Dahal and colleagues investigated the effects of three clinically approved epidermal growth factor receptor (EGFR) antagonists in experimental pulmonary hypertension induced by monocrotaline in rats and by chronic hypoxia in mice. The EGFR inhibitors gefitinib and erlotinib reduced right ventricular systolic pressure and right ventricular hypertrophy in the rat monocrotaline (but not the mouse hypoxia) model. The partial therapeutic efficacy of the EGFR antagonists in animal models of pulmonary hypertension and the absence of significant alteration in EGFR expression in the lungs of patients with idiopathic pulmonary hypertension suggest that EGFRs may not be an optimal strategy for the treatment (32).

Schistosomiasis is likely the most common cause of pulmonary hypertension worldwide, but little is known about its pathobiology (33). Crosby and colleagues induced *Schistosoma mansoni* infection in mice (34). The infected animals developed pulmonary vascular remodeling, including the appearance of plexiform-like lesions, accompanied by perivascular inflammation. Lung egg burden correlated with right ventricular index, although significant cardiac hypertrophy was lacking. This model may be useful in future studies because of pathologic similarities with human pulmonary hypertension (35). In this context, inflammation appears to play a role in vascular remodeling associated with idiopathic pulmonary hypertension (36). Hecker and colleagues demonstrated that dysregulation of the IL-13 receptor in IPAH, and in animal models of pulmonary hypertension, may underlie the smooth muscle hypertrophy associated with vascular remodeling (37). The IL-13 decoy receptor, IL-13R α 2, was up-regulated relative to that of the functional IL-13 signaling receptors IL-4R and IL-13R α 1, in patients with idiopathic pulmonary hypertension and in animal models. IL-13 via signal transducers and activators of transcription (STAT3 and STAT6) suppressed proliferation of pulmonary artery smooth muscle and endothelin-1 production by pulmonary artery smooth muscle. The ectopic expression of IL-13R α 2 resulted in loss of growth control, whereas small interfering RNA knockdown of IL-13R α 2 had the opposite effects (37).

Prostacyclin analogs, used to treat pulmonary arterial hypertension, are assumed to work through prostacyclin (IP) receptors linked to cyclic AMP generation. However, in a study by Falcetti and colleagues, down-regulation of the IP receptor, related to chronic treatment with prostacyclin, did not affect the ability of prostacyclin to inhibit pulmonary smooth muscle cell proliferation. In fact, antiproliferative effects of prostacyclin analogs were preserved in pulmonary hypertension despite IP receptor down-regulation and abnormal coupling. Peroxisome proliferator-activated receptor- γ (PPAR γ) may represent a novel pathway by which prostacyclin analogs can inhibit smooth muscle proliferation (38). These findings suggest that a combination of prostacyclin analogs and PPAR γ agonists may be effective to counteract the abnormal vascular remodeling in PAH. Although further clinical studies are clearly needed, this research emphasizes the importance of the study of these interrelated signaling pathways in identifying novel or at least synergistic targets that can improve the treatment of patients with PAH.

Thrombosis and thrombotic arteriopathy are common pathological findings in pulmonary arterial hypertension. Maki and colleagues reported that thrombin potentiates pulmonary vasoconstriction via a canonical mechanism dependent on intracellular calcium and myosin light chain phosphorylation, as well as through a noncanonical mechanism mediated by reactive oxygen species. Rho-kinase contributes to both canonical and noncanonical contractile mechanisms downstream of thrombin (39). Fibrin isolated from patients with chronic thromboembolic pulmonary

hypertension is resistant to lysis. Miniati and colleagues found that fibrin resistance to lysis is not limited to thromboembolic pulmonary hypertension but also occurs in idiopathic and some forms of acquired pulmonary hypertension. Fibrinogen was purified from 96 subjects (17 with thromboembolic pulmonary hypertension, 14 with pulmonary arterial hypertension, 39 with prior pulmonary emboli, and 26 healthy control subjects) and exposed to thrombin to obtain fibrin clots. Fibrin band intensity was significantly different among the four groups, revealing that fibrin resistance to lysis generally occurs in pulmonary hypertension (40). Because pulmonary hypertension is frequently associated with thrombotic pulmonary arteriopathy, alterations in the contractile effects of thrombin may contribute to hypertensive pathophysiology.

A proteomic analysis of human lung tissues from patients with PAH compared the relative abundance of more than 300 proteins in lungs from patients with advanced pulmonary hypertension and healthy donors (41). The levels of 25 proteins varied between the 2 groups. The major classes of proteins that were increased in pulmonary hypertension were involved in cell growth, proliferation, and cell metabolism. Among the findings were greater expression of chloride intracellular channel-4, a multifunctional protein involved in angiogenesis. It is a target for several of the signaling pathways implicated in pulmonary arterial hypertension, such as transforming growth factor- β , vascular endothelial growth factor, and bone morphogenetic protein. Immunohistochemistry identified chloride intracellular channel-4 within endothelial cells in occlusive and plexiform vascular lesions in diseased lungs. This study demonstrates the potential of proteomics to provide an unbiased analysis of the protein changes underlying pulmonary arterial hypertension to better understand the disease to inform new treatments and biomarkers (41).

UPDATE ON PULMONARY EMBOLISM

Patients who survive acute thromboembolic episodes face an increased risk for several serious clinical complications, including recurrent venous thrombosis, pulmonary hypertension, cancer, arterial cardiovascular events, and death caused by comorbid conditions. The combined risk for these adverse events is not known. A study by Klok and colleagues indicates that the fraction of patients without adverse events at 1 year after pulmonary embolism was about 70%, and decreased to less than 60% after 2 years and further was less than 50% after 4 years for the overall population. This unexpectedly high risk of adverse events underlines the need for individualized, better risk stratification and screening for patients after acute pulmonary embolism to improve outcomes (42).

In the prospective multicenter Prognostic Factors for Pulmonary Embolism (PREP) study, brain natriuretic peptide and echocardiography were useful determinants of the short-term outcome for patients, together with clinical findings. Patients ($n = 570$) were stratified according to the initial risk of adverse outcome, using clinical, echocardiographic, and biochemical variables. Altered mental state, shock on admission, cancer, and higher brain natriuretic protein level and right-to-left ventricle diameter ratio were associated with adverse events. A predictive model made it possible to develop a bedside prognostic score that may prove useful for selecting patients for outpatient treatment and identifying patients requiring more careful follow-up at the hospital or for whom additional treatment may be necessary (43).

Although associated with adverse outcomes in heart failure, pneumonia, and pulmonary hypertension, the prognostic value of hyponatremia in patients with acute pulmonary embolism is unknown. In a study of 13,728 patients with a primary diagnosis of pulmonary emboli, serum sodium levels greater than 135,

between 130 and 135, and less than 130 mmol/L had a cumulative 30-day mortality of 8, 13.6, and 28.5%, and a readmission rate of 11.8, 15.6, and 19.3%, respectively. These findings indicate that hyponatremia is an independent predictor of short-term mortality and hospital readmission (44). These provocative data suggest that sodium levels might be used for prognostication and warrant further investigation as a therapeutic approach (45).

A study by Jimenez and colleagues validates the use of lower extremity venous compression ultrasonography for prognostication and risk stratification of patients with acute symptomatic pulmonary embolism (46). Of 707 patients diagnosed with pulmonary emboli, 51% had concomitant deep vein thrombosis and had increased mortality compared with those without concomitant deep vein thrombosis. In an external validation cohort of 4,476 patients with acute pulmonary emboli enrolled in the Spanish International Multicenter Computerized Registry of Patients with Venous Thromboembolism (RIETE) (47), concomitant deep vein thrombosis remained a significant predictor of all-cause and pulmonary-specific mortality. Thus, in patients with a first episode of acute symptomatic pulmonary emboli, the presence of concomitant deep vein thrombosis is an independent predictor of death in the ensuing 3 months after diagnosis (46).

Pulmonary embolism that obstructs a segmental or larger pulmonary artery increases alveolar dead space, which leads to decreased exhaled CO_2 . The diagnostic accuracy of a purely breath-based test that simultaneously measures the exhaled CO_2/O_2 ratio, as a noninvasive method to assess increased alveolar dead space with segmental or larger emboli, was evaluated. The investigators found that normal end-tidal CO_2/O_2 (etCO_2/O_2) or a normal D-dimer level was associated with a low rate of segmental or larger pulmonary embolism on computerized tomography multidetector-row pulmonary angiography. Thus, a strategy that combines testing of D-dimer plus etCO_2 may have clinically important advantages as a screening step (48).

UPDATE ON CLINICAL TRIALS

Despite currently available treatments, pulmonary arterial hypertension remains a progressive and frequently fatal condition. Platelet-derived growth factor (PDGF) and its receptor (PDGFR) have been implicated in the pathobiology of pulmonary hypertension (49), and are potential new targets for the treatment of this disease. Imatinib, a tyrosine kinase inhibitor of PDGFR α and β kinases, and c-KIT was tested in a double-blind, placebo-controlled trial in 59 patients (50). The primary end points were safety, tolerability, and change from baseline in 6-minute walking distance. Compared with placebo, there was no significant change in 6-minute walk distance; however, there was a significant decrease in pulmonary vascular resistance and an increase in cardiac output with imatinib.

Post hoc analyses showed that patients with high ($>1,000$ dyn) pulmonary vascular resistance may respond better than patients with lower pulmonary vascular resistance (50). A phase 3 study is currently underway to assess the efficacy and safety of imatinib in pulmonary hypertension.

The Simvastatin Pulmonary Hypertension Trial (SiPHT) Study Group reported their findings this year (51). Simvastatin reduced right ventricle mass and N-terminal pro-B-type natriuretic peptide levels over the course of 6 months in patients with pulmonary hypertension as compared with patients receiving placebo, but this was not sustained over 12 months (51).

Blanco and colleagues demonstrated that in patients with COPD-associated pulmonary hypertension, sildenafil improves pulmonary hemodynamics at rest and during exercise, but also entails the risk of worsening arterial oxygenation due to the inhibition of hypoxic pulmonary vasoconstriction, especially at rest (52).

Thus, as concluded in an editorial in a previous issue of the *Journal*, there are currently no data to support treatment of COPD with therapies indicated for the management of pulmonary arterial hypertension, and additional clinical trials are needed in this area (53).

The therapeutic potential of riociguat, a novel soluble guanylate cyclase stimulator, was assessed in adults with pulmonary hypertension in a 12-week, multicenter, open-label, uncontrolled phase II study. Riociguat was generally well tolerated. Median 6-minute walking distance increased and pulmonary vascular resistance was reduced from baseline. The preliminary data suggest that riociguat has a favorable safety profile. A multinational, randomized, controlled, double-blinded phase III study is currently underway (54, 55).

In a study that assessed the efficacy and safety of inhaled treprostinil in pulmonary hypertension, 235 patients receiving either bosentan or sildenafil were randomized to inhaled treprostinil or placebo. The study demonstrated that inhaled treprostinil was safe and well tolerated and had modest efficacy (56). Quality of life measures and brain natriuretic factor and 6-minute walk distance improved on active therapy (56).

In a placebo-controlled trial of intravenous therapy, treatment-naïve patients were randomized to intravenous treprostinil, a prostacyclin analog, for 12 weeks, or placebo. Treprostinil increased walk distance by a placebo-corrected median of 83 m, reduced Borg score by a median of 2 units, and improved NYHA class by a median of 1. Treatment with treprostinil was also associated with decreased angiopoietin-2 levels (57). The significance of this study comes from the fact that, because of the availability of several effective therapies for PAH, conducting placebo-controlled trials has become more difficult to justify in treatment-naïve patients and is the subject of significant ethical controversies.

CONCLUSIONS

We have summarized the year in pulmonary vascular disease published in the *American Journal of Respiratory and Critical Care Medicine* and selected significant papers from the rest of the literature in 2010. Our review addressed a wide range of topics including new survival data from several registries, update on the right heart, description of new and old PH phenotypes, insights into genetics and pathobiological mechanisms, pulmonary embolism, and findings from clinical trials. This retrospective look at a highly impactful year for pulmonary vascular disease in the *Journal* provides hope for many new directions for PH research in the future.

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