Pulmonary Hypertension in China

Pulmonary Vascular Disease: The Global Perspective

Zhenguo Zhai, MD, PhD; Jun Wang, MD, PhD; Lan Zhao, MD, PhD; Jason X.-J. Yuan, MD, PhD; and Chen Wang, MD, PhD, FCCP

Significant progress has been made in understanding the pathogenesis of pulmonary hypertension (PH) and developing therapeutic approaches for PH in recent years. Most of the currently available data regarding the prevalence, diagnosis, treatment, and prognosis of PH are from American and European populations. Whether these data are also valid in the Chinese population is still controversial. China has a relatively large population of patients with PH for clinical and basic research. However, many medical centers and hospitals in China have limited experience with PH diagnosis and treatment. Given the potential higher prevalence of PH in China than in the United States and European countries, it is critical to develop suitable, effective, and novel therapeutic approaches for Chinese patients. Measures for the detection and prevention of PH need to be put in place urgently for the management of PH in China.

Abbreviations: CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PBC = primary biliary cirrhosis; PE = pulmonary embolism; PH = pulmonary hypertension; PPHN = persistent pulmonary hypertension of the newborn; PVRI = pulmonary vascular resistance index; SLE = systemic lupus erythematosus; TCM = traditional Chinese medicine

Pulmonary hypertension (PH) is a worldwide health problem recognized not only in the West but also in Asian-Pacific countries. Tremendous progress has been made in understanding the pathogenesis of PH and developing therapeutic approaches for PH in recent years. Updates and practice guidelines for PH are published more frequently than ever before. However, most of the currently available data regarding the prevalence, diagnosis, treatment, and prognosis of PH are largely from American and European populations. Limited data are validated in the Chinese population, so the issues regarding prevalence, and diagnostic and therapeutic approaches for PH need to be addressed in modern China. The objective of this article was to review and highlight the current status and future prospects for PH in China based on the current literature.

Brief History of PH Research in China

The research on PH in China can be traced back to the early 1970s. The National Collaboration Group of Pulmonary Heart Diseases, a major consortium organized by physicians and investigators in the field of cardiovascular disease and pulmonary vascular physiology, was established in 1973. The early research on pulmonary circulation in the 1970s was focused on pathogenic mechanisms, and the diagnosis and treatment
of COPD, PH associated with high altitude and hypoxia, and cor pulmonale. Several major research advancements were achieved during the next 20 years of extensive study on the prevention of and therapy for COPD and pulmonary heart disease in China, including findings that: (1) echocardiography and radioisotopes were useful for noninvasive estimation of pulmonary artery pressure and right-side heart function in patients with COPD; (2) traditional Chinese medicine (TCM) therapy combined with Western medicine was a better way to treat certain pathologic changes in the acute phase of cor pulmonale; (3) intensive care and mechanical ventilation improved hemodynamics and oxygen saturation in patients with COPD and cor pulmonale; and (4) pulmonary vasoconstriction, vascular remodeling, and inflammation played important roles in the development of PH.

Since the 1980s, research on PH has been established as one of the National Key Technology R&D Programs in China. Four Five-Year Plans have been implemented and made remarkable contributions to the innovation of research techniques and the improvement of clinical management of PH in China.

The main tasks of the seventh Five-Year Plan (1986-1990) of the National Key Technology R&D Programs included: (1) the development of noninvasive approaches for evaluation and quantification of pulmonary hemodynamics and right-sided heart function, as well as exercise tests for early diagnosis of PH; (2) a search for novel and effective TCM treatments to improve lung and heart functions in patients with PH; (3) the establishment of ICUs for patients with severe PH, pulmonary heart disease in COPD, and PH associated with chronic hypoxia and infection; (4) basic research on the pathogenic mechanisms of PH; and (5) clinical studies on the diagnosis and prevention of PH associated with pulmonary venoocclusive diseases.

COPD is a major respiratory disorder in China as a result of the large population of smokers and the industrial air pollution in urban areas. Chronic bronchiolitis and peribronchiolitis, the late stage of bronchitis, are the major causes of lung tissue damage in patients with COPD and significantly contribute to complications (eg, PH and right ventricular hypertrophy) in these patients. Abnormalities in the extracellular matrix around pulmonary arteries due to bronchiolitis and peribronchiolitis decrease the pulmonary vascular compliance (or increase vascular stiffness), inhibit the recruitment and distension of small pulmonary arteries and arterioles, narrow the lumen of pulmonary arteries, and ultimately cause PH. Data also suggest that hypertrophy of the supraventricular crest is one of the diagnostic criteria of right ventricular hypertrophy due to PH.

During the eighth Five-Year Plan (1991-1995), studies focused on risk factors and preventive strategies in COPD and pulmonary heart disease, noninvasive mechanical ventilation in the prevention and management of pulmonary heart disease and respiratory failure, and drugs that can slow the progress of hypoxic PH. Special attention was paid in applying intensive care to prevent and treat pulmonary circulation disorders associated with mechanical ventilation and respiratory support. Furthermore, significant progress has been made in research on pathogenic mechanisms and drug development in COPD and hypoxic PH.

The impact of comprehensive prevention and treatment in COPD and cor pulmonale was reported by Cheng et al and Cheng. They concluded that active intervention was effective in reducing the occurrence of COPD and cor pulmonale among the population at high risk; however, COPD and cor pulmonale are both chronic diseases for which patience and continuous efforts are needed for prevention and treatment. Wang et al reported that the incidence of in situ thrombosis in small pulmonary arteries and arterioles during the exacerbation stage of chronic cor pulmonale was 90%, which provided a morphologic and theoretical basis for the clinical application of anticoagulants for cases of chronic cor pulmonale at the exacerbation stage.

Further research was developed on the pathogenic mechanism and drug development in COPD and hypoxic PH in the ninth Five-Year Plan (1996-2000). Owing to the study of standardized diagnosis and therapy for pulmonary embolism (PE), a substudy for the diagnosis and management of chronic thromboembolic pulmonary hypertension (CTEPH) was organized during the 10th Five-Year Plan (2000-2005). The number of patients diagnosed with CTEPH and pulmonary arterial hypertension (PAH) was increasing with better recognition of PE and other related pulmonary vascular disorders. There are currently more than five medical centers in China that can provide surgical treatment (eg, pulmonary endarterectomy, lung/heart transplantation) for patients with CTEPH and PAH.

**Epidemiologic Study of PH**

An epidemiologic study of human PH in China was reported by Cheng in 1992. The diagnosis was made by clinical and hemodynamic data in 59 patients, including 30 cases of idiopathic pulmonary arterial hypertension (IPAH), 26 cases of CTEPH, and three others. More than 73% of the patients with long-term treatment survived for >4 years (mean 4.2 years). The study was followed by one of the first long-term
1.3 billion, China is potentially a large source of patients with PH for clinical and basic research. Chinese physicians and scientists are eager to collaborate with colleagues in other countries to develop research projects and novel therapeutic approaches for PH. International recognition of the progress in basic and clinical studies on pathogenesis, diagnosis, treatment, and prognosis of PH in China is very important. Higher prevalence of PH from all causes has been reported recently in the United States and European populations, but PH may also be affecting millions of people in China. It is critical to develop effective and novel therapeutic approaches that are suitable and affordable for Chinese patients.

### Potential Cause and Pathogenesis

The initiation and progression of PH are related to an interaction among inherited and environmental risk factors (Table 1). Identifying the genetic and environmental risk factors in Chinese patients with PH is very important for developing new therapeutic approaches for the patients.

#### Genetic Factors

Recently, a few published studies regarding the molecular and genetic basis of PH in China advanced our understanding in this aspect. The VIP gene variant g.8129T→C may be one of the genetic factors in the pathogenesis of IPAH. The BMPR2 promoter mutation −142G→A may be associated with familial PAH. Jing et al reported that the missense mutation of R491W in the BMPR2 gene was associated with familial PAH in the Han Chinese. Fu et al reported a three-generation pedigree of familial PAH and 10 new patients with IPAH. They found that Glu forms an ion pair with Arg at position 491 in BMPR2, thereby helping stabilize the large lobe. Substitution of Arg at position 491 is the most frequently observed missense mutation in familial PAH. Further, Sun et al reported that the G894T polymorphism of the eNOS gene is associated with PH of COPD in the Chinese population. The T allele may be involved in the cause of PH with COPD by reducing nitric oxide release from the endothelium.

#### CTDs and Autoimmune Diseases

PAH maybe a complication of CTDs such as systemic sclerosis. This form of PAH, referred to as associated PAH, is indistinguishable from IPAH. A comprehensive survey of patients with rheumatic diseases in China reveals that rheumatic complaints are also common in China. The prevalence of rheumatic diseases in the Chinese population is becoming similar to that of the Western countries. Xing et al reported that in 290 patients with CTD, 31 (10.4%) patients (28 girls and 3 boys), aged 7 to 18 years (average, 12.5 years), were found to have PAH. Ji et al investigated the clinical features and prognosis of PAH in 2,189 patients with CTD and found that 82 patients had PAH (3.7%). Their results showed that PAH often occurred at the fourth year after initial CTD manifestations but occurred earlier in patients.

---

**Table 1—Prevalence Data on Pulmonary Hypertension for Different Conditions From Studies in China**

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Area</th>
<th>Conditions</th>
<th>Diagnostic Method</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li and Tam 1999</td>
<td>Hong Kong</td>
<td>SLE</td>
<td>Echocardiogram and postmortem</td>
<td>18/419 (4.3)</td>
</tr>
<tr>
<td>Shen et al 1999</td>
<td>Shanghai</td>
<td>SLE</td>
<td>Echocardiogram and clinical examination</td>
<td>9/84 (11)</td>
</tr>
<tr>
<td>Shen et al 2005</td>
<td>Beijing</td>
<td>SLE</td>
<td>Clinical and echocardiogram</td>
<td>49/320 (15.3)</td>
</tr>
<tr>
<td>Siu et al 2007</td>
<td>Hong Kong</td>
<td>Hyperthyroidism</td>
<td>Echocardiogram</td>
<td>35/75 (47)</td>
</tr>
<tr>
<td>Xing et al 2008</td>
<td>Beijing</td>
<td>CTD</td>
<td>Echocardiogram</td>
<td>31/299 (10.4)</td>
</tr>
<tr>
<td>Ye et al 2008</td>
<td>Beijing</td>
<td>Sjogren syndrome</td>
<td>Clinical and echocardiogram</td>
<td>51/396 (12.9)</td>
</tr>
<tr>
<td>Shen et al 2009</td>
<td>Beijing</td>
<td>PBC</td>
<td>Echocardiogram</td>
<td>21/175 (11.8)</td>
</tr>
<tr>
<td>Hua et al 2009</td>
<td>Shanghai</td>
<td>Portal hypertension</td>
<td>Echocardiogram</td>
<td>4/105 (3.8)</td>
</tr>
</tbody>
</table>

CTD = connective tissue diseases; PBC = primary biliary cirrhosis; SLE = systemic lupus erythematosus.
with systemic lupus erythematosus (SLE) or mixed CTD. Luo et al\textsuperscript{34} reported that the prevalence of PAH was 4.9% in a cohort of patients with SLE. Positive correlations were found between the occurrence of PAH and Raynaud phenomenon, fingertip vasculitis, anti-U1RNP antibody positivity, antiphospholipid antibody positivity, pericardial effusion, and interstitial pneumonia. Ye et al\textsuperscript{35} reported that PAH was found in 12.9% of 396 patients with Sjögren syndrome. The γ-globulin level was significantly higher in the PH group than that in the non-PH group. The estimation of the real prevalence of PAH in CTD remains open for discussion because of the lack of consistent epidemiologic data in the Chinese population.

Siu et al\textsuperscript{21} reported that the prevalence of PAH is related to hyperthyroidism and the associated hemodynamic changes and outcome. Serial echocardiographic examinations in 75 patients with hyperthyroidism were carried out to assess the hemodynamic changes. All the patients had normal left ventricle systolic function, and 35 (47%) had PAH. There was no significant difference in the clinical characteristics of patients with hyperthyroidism with or without PH. Most importantly, hyperthyroidism-related PH was largely asymptomatic and reversible after restoration to a euthyroid state.

**CHDs**

Severe PH is a common complication of patients with CHD, particularly in those with relevant systemic-to-pulmonary shunts. The prevalence of PH associated with congenital systemic-to-pulmonary shunts in Europe and North America has been estimated to range between 1.6 and 12.5 cases per million adults, with most of this population affected by Eisenmenger syndrome. Some reports detected the cause of PH in patients with Eisenmenger syndrome.\textsuperscript{35,36} The prevalence of CHD in stillbirths and live births was 168.8 per 1,000 and 6.7 per 1,000, respectively,\textsuperscript{37} which is considerably higher than the World Health Organization estimation for the region (3.8%). There were 38,160,000 moderate-to-severe COPD cases reported by the Regional COPD Working Group.\textsuperscript{50} The prevalence of COPD was estimated at 8.2% (men, 12.4%; women, 5.1%) in subjects who are older than 40 years of age, according to the most recent studies.\textsuperscript{38} The related PH prevalence in COPD and hypoxemic conditions remain unknown. A recent retrospective study of 998 patients with COPD who underwent right-sided heart catheterization indicated that only 1% had severe PH (mean positive airway disregulation; the patients with portal hypertension and PH have a poor prognosis.

PAH is a rare but well-established complication in subjects who are HIV-positive. The prevalence of PAH associated with HIV was reported to be approximately 0.5% in Western countries.\textsuperscript{40,41} Although the official statistics suggest a low rate of HIV/AIDS prevalence in China, the condition is now widely recognized as bad enough to engage necessary approaches to prevent it from becoming worse.\textsuperscript{42,43} In 2007, it was estimated that there were approximately 700,000 individuals infected with HIV in China, among whom 85,000 had AIDS.\textsuperscript{43} The prevalence of HIV infection as a whole is about 0.05% in China;\textsuperscript{42,44} the precise prevalence of PAH in subjects who are HIV-positive, however, remains to be determined.

Schistosomiasis (bilharziasis) is the third-leading endemic parasitic disease in the world. Pulmonary vascular remodeling may be involved in causing PH and right-sided heart failure in patients with schistosomiasis. Recent studies have reported that PAH occurred in 7.5% to 25% of patients with schistosomiasis in South America.\textsuperscript{44,45} Significant progress has occurred over the past 50 years in the control of *Schistosoma japonica* in China; however, the available data suggest that schistosomiasis has reemerged in recent years.\textsuperscript{46,47}

**Persistent PH in the Newborn**

Persistent pulmonary hypertension of the newborn (PPHN) is a failure of normal postnatal adaptation that occurs at birth in the pulmonary circulation. In a study of 27 newborn infants with persistent hypoxemia in the first 3 days after birth, Su et al\textsuperscript{48,49} reported that 19 infants (70.4%) had PH based on hemodynamic assessment using echocardiography. This study also indicated that PPHN is common in newborn infants with persistent hypoxemia and suggested using echocardiography for screening PPHN to strategize therapeutic plans for this group of newborn infants.

**COPD and High-Altitude Diseases**

The overall prevalence of COPD is 6.5% in the Chinese population, according to previous studies,\textsuperscript{50-52} which is considerably higher than the World Health Organization estimation for the region (3.8%). There were 38,160,000 moderate-to-severe COPD cases reported by the Regional COPD Working Group.\textsuperscript{50} The prevalence of COPD was 8.2% (men, 12.4%; women, 5.1%) in subjects who are older than 40 years of age, according to the most recent studies.\textsuperscript{38} The related PH prevalence in COPD and hypoxemic conditions remain unknown. A recent retrospective study of 998 patients with COPD who underwent right-sided heart catheterization indicated that only 1% had severe PH (mean positive airway...
reason for the increased prevalence of PE in China is the improvement of imaging techniques used for diagnosis of DVT and PE. The high-risk group includes patients who have had an acute stroke and who received orthopedic surgery. The prevalence of DVT in 488 people who had an acute stroke was 21.7% to 40%, and the prevalence of DVT in 1,606 people who had orthopedic surgery was 21.2% to 24.4%. A database of 516 PE cases, including clinical characteristics, laboratory indicators and natural history of PE, was established. The characteristics of patients were investigated using ultrasonography, CT scans, and MRI, and standardized therapeutic regimens suitable for PE were determined. Through a series of research activities, this project has helped to correct the wrong perception that PE is a rare disease in China, establish a PE diagnosis and treatment system suitable for the Chinese, lower the PE mortality rate from 25% to 9%, and identify more patients with CTEPH. Despite its rising prevalence, PE is a preventable disease overall. Control of risk factors, such as lifestyle change, and effective prophylaxis will be beneficial in reducing this trend.

Diagnosis and Treatment of PH

Because of a lack of evidence regarding diagnosis and treatment strategies for patients with PH in China, a series of clinical trials have been designed recently to determine whether medications (eg, inhaled iloprost, sildenafil) that are strongly recommended to treat PAH in the United States and some European countries are valid for Chinese patients with PAH.

Evaluation of Diagnostic Techniques

The correlation between Doppler echocardiography and right-sided heart catheterization in PH has been evaluated in early studies. Wang et al\(^\text{61}\) reported that, in the early stage of COPD-related cor pulmonale, the pulmonary artery pressure (PAP) might be normal, but the pulmonary vascular resistance is elevated. The authors studied the pulmonary hemodynamics in 62 cases of chronic cor pulmonale due to COPD. They found that 24 of 62 cases did not meet the diagnostic criteria even after exercise, despite clinical evidence of cor pulmonale. However, in all cases, the pulmonary vascular resistance index (PVRI) was significantly elevated after exercise. These observations imply that (1) it is inappropriate to set diagnostic criteria based solely on PAP to define pathologically increased right ventricular overload; (2) the measurement of the PVRI allows identification of patients who develop latent PH; and (3) the PVRI is a more sensitive parameter of right ventricular overload than PAP, especially when referring to the results of exercise tests.
In another study, echocardiography and right-sided heart catheterization were compared with evaluation of the pulmonary blood flow and PAP changes. The pulmonary blood flow pattern was analyzed by the pulsed Doppler flowmeter. The pulmonary artery acceleration time showed a significant inverse correlation with the mean and systolic PAP.

**Current Treatment of PH**

There still exists great challenge in China in terms of the treatment of PH. The effects of calcium channel blockers (eg, nifedipine, diprophylline, tetrandrine), leukotriene receptor antagonists (eg, zafirlukast), and endothelin receptor blockers (eg, bosentan) have been evaluated for PH associated with COPD and PAH.

TCM is widely accepted among the Chinese population and also has become increasingly popular throughout the world to treat different physical conditions, including PAH. Qian-Hu has been used for the treatment of respiratory diseases and PH. Ginsenosides have antihypertensive effect via releasing nitric oxide and decreasing intracellular free Ca2+ in vascular smooth muscle cells and cardiomyocytes. Qin et al reported that total ginsenosides are effective in protecting against monocrotaline-induced right ventricular hypertrophy, possibly through their vasodilative effect on pulmonary arteries and antiproliferative effect on pulmonary vascular smooth muscle cells. The role of endothelial progenitor cells in PAH treatment has been reported by Wang et al and Zhu et al. The study showed that intravenous infusion of autologous endothelial progenitor cells seemed to be feasible, safe, and effective, and can significantly improve exercise capacity, New York Heart Association functional class, and pulmonary hemodynamics in children with IPAH.

**Clinical and Translational Research Centers on PH**

Several groups have gradually established their expertise in the PH field. There are several clinical referral centers located in Beijing (eg, Fuwai Hospital, Anzhen Hospital, Chaoyang Hospital, Peking Union Medical College Hospital) and Shanghai (eg, Zhongshan Hospital, Shanghai Pulmonary Hospital) that have established standard protocols and possess well-equipped facilities for the clinical management and treatment of patients with PAH, PE, and other pulmonary vascular diseases. In other large cities, such as Nanjing, Hangzhou, Xi’an, Xining, and Wuhan, clinics and research facilities have also been established recently for basic research and clinical management of PH, including PAH, associated PAH, hypoxia-induced PH, and high-altitude PH. Furthermore, an increasing number of investigators in China have begun to publish their original research findings in national and international journals (Fig 2), including some in world’s most prestigious journals in the field of pulmonary circulation and cardiopulmonary diseases.

Two projects from the 11th Five-Year Plan (2006-2010) related to pulmonary vascular diseases are ongoing. One is to improve the diagnosis and treatment of PE and CTEPH; the other is to improve the diagnosis and therapy for PH. In the PE project, a registry and follow-up study of PE and CTEPH, clinical trials on new anticoagulants, and a study of thrombolytic therapy for submassive PE have been initiated. In the second project, a registry study of PAH and multicenter trials for the evaluation of atorvastatin, simvastatin, sildenafil, and iloprost on PAH in the Chinese population are in progress. With the development of these projects, the awareness and knowledge about pulmonary vascular diseases and the management of these diseases in China will be significantly improved.

In terms of the basic and translational research of PH, as pivotal signals, the effects of the ion channel and 

\[ \text{Ca}^{2+} \] 

in human pulmonary artery smooth muscle cell proliferation have been investigated in PAH and CTEPH models by many investigators. The regulatory effect of endogenous hydrogen sulfide on pulmonary vascular structure has been studied by Du et al and Li et al. Iptakalim inhibited endothelin-1-induced proliferation of human pulmonary artery smooth muscle cells through activation of the adenosine triphosphate-sensitive K+ channel has been determined by Wang et al and Xie et al. Their findings provided further evidence that iptakalim may serve as another candidate drug to treat PH.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22086/) Exponential rise in the number of articles related to pulmonary hypertension published in CBM-Disc (solid circles) and PubMed (open squares) between 1978 and 2008. CBM-Disc = China Biologic Medicine on Disc or China BioMedical Literature database.
Chinese clinicians and investigators have made significant progress in the clinical management of PH and PE, and actively participate in international associations and societies devoted to the research, treatment, and prevention of pulmonary vascular diseases. The China Academic Group for Pulmonary Embolism and Pulmonary Vascular Diseases was established in 2001 as a regional scientific body and set up the guidelines for treatment and prevention of pulmonary vascular diseases. More and more, Chinese physicians and researchers are invited to attend and present their clinical and research observations at international scientific conferences. Chinese experts in the field have also organized multiple events, including clinical forums, scientific symposia, and teleconferences, to enhance communication and collaboration with worldwide experts and universities and hospitals, aimed at improving the health care of patients in China with PH and PE.

Despite the advances and progress made recently for the treatment and prevention of PH in China, the prevalence of PH is increasing, which is a major concern for Chinese doctors and researchers. In a country the size of as China, in which one-sixth of the world’s population lives, it is important and urgent to use the limited resources to develop more infrastructure and train more pulmonary specialists for the diagnosis, treatment, and prevention of pulmonary vascular diseases. It is also critical for Chinese doctors and researchers to learn more from international experts in the field and bring in more advanced knowledge, novel therapeutic regimens, necessary research equipment, and efficient clinical management, which can be used for patient care and clinical and basic research on the pathogenic and therapeutic mechanisms of PH in Chinese hospitals and research institutes. We hope, with the effort of domestic doctors and researchers and help from international experts, that the clinical management of PH and research on its cause in China will be significantly improved in the near future.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

REFERENCES


