Pulmonary Hypertension: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

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Abstract

Pulmonary vascular dysfunction (PVD) precedes the onset of clinical signs and symptoms of pulmonary arterial hypertension (PAH). PAH is defined by the elevation of pulmonary arterial pressure, which often progresses to right ventricular (RV) dysfunction and failure. PAH affects subjects of all ages, and is associated with diverse medical conditions, most of which are rare. Several factors pose immediate challenges to the development of strategies for primary prevention of PAH, including: (*1*) the idiopathic or primary form of the disease is extremely rare, limiting screening practicality; (*2*) methods for the detection of preclinical PVD are currently not established; (*3*) the understanding of determinants of pulmonary vascular growth, structure, and function in normal and PAH states is insufficient; (*4*) relatively small numbers of "at-risk" subjects are available for long-term studies to accurately assess disease development; and (*5*) preventative therapies for PVD are lacking. Despite these limitations, leveraging known at-risk patient populations for study, as well as growing progress across multiple disciplines, ranging from systems biology to advanced and more sensitive functional imaging modalities, may facilitate the opportunity to significantly improve primary prevention research and implementation over the next decade.

Keywords: pulmonary vascular disease; right ventricular failure

(Received in original form December 13, 2013; accepted in final form February 6, 2014)

Supported by National Institutes of Health grants IH K23 HL098743 (E.D.A.), P01HL103455 (M.T.G.), and R01 HL113988 (S.M.K.).

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Ann Am Thorac Soc Vol 11, Supplement 3, pp S178–S185, Apr 2014

DOI: 10.1513/AnnalsATS.201312-443LD
Internet address: www.atsjournals.org

Pulmonary vascular health refers to the normal structure and function of the lung macro- and microvasculature. Pulmonary vascular dysfunction (PVD) encompasses altered lung vascular development, growth, structure, or function, which long precedes the onset of measureable pulmonary arterial hypertension (PAH) that ultimately results in right ventricular (RV) dysfunction and failure. PAH is defined by the elevation of pulmonary arterial pressure; PVD may exist long before PAH is detected. In fact, due to the reserve of the pulmonary vascular bed, PAH is not present until extensive PVD exists (1, 2). However, no study exists to provide detailed assessment of cardiac structure and cardiopulmonary hemodynamics in subjects over time from true health to preclinical disease, to overt pulmonary hypertension (PH). Figure 1 provides one proposed generalization of these changes over time, although detailed studies are required to support or refute this visual representation. Current PAH therapies improve exercise capacity and time until clinical worsening, but are not curative, perhaps because they are applied too late in the disease course. It is unknown if early application of current or novel therapeutic agents would prevent PVD (or the progression of PVD to PAH).

The pursuit of preventative strategies of PVD and PH implies that we currently understand pulmonary vascular health, which is not the case. Changes in pulmonary vascular function and structure across the life course that reduce function are poorly understood, and this knowledge will be critical to prevent the development of PVD, and its progression to PH. In addition, elucidating "resiliency factors," which preserve pulmonary vascular health in the face of various endogenous and exogenous insults, could enlighten future prevention approaches. Finally, more sensitive, functional, and stress-induced imaging modalities are required to identify early vascular dysfunction in at-risk patient populations (i.e., those with mutations in bone morphogenetic protein receptor type 2 [*BMPR2*] gene before the development of overt PAH).

Primary prevention concerns efforts undertaken to prevent a disease from

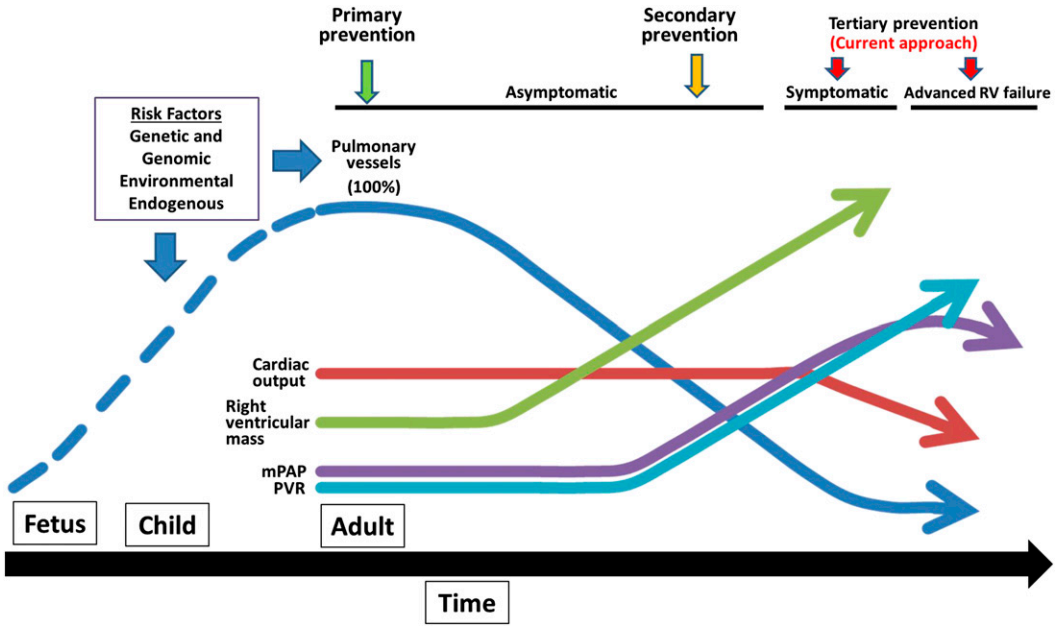

Figure 1. Due to the tremendous reserve of the pulmonary vasculature, resting pulmonary arterial hypertension (PAH) and symptoms occur long after the initial inciting events trigger pulmonary vascular dysfunction (PVD). Multiple known risk factors exist that can prompt the loss of normal pulmonary vessel function *in utero* and beyond. Risk factors are variable, including: (*1*) genetic (e.g., bone morphogenetic protein receptor type 2 [*BMPR2*] gene mutations and sickle cell lung disease); (*2*) environmental (e.g., dietary stimulants); and (*3*) endogenous (e.g., premature lung disease and portal hypertension). Resting pulmonary hypertension (PH) only occurs after an enormous proportion of the pulmonary vascular bed is lost, causing a rise in mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR). By the time a diagnosis of PH is made, PVD is far advanced. Ultimately, advanced right ventricular (RV) failure will occur. Primary prevention efforts must focus upon the detection and prevention of PVD, before the onset of PH.

occurring; although the prevention of the condition of PVD would be ideal, for the purposes of this document we focus upon the primary prevention of PH, which occurs in the setting of pre-existent PVD. The primary prevention of PH will require scientific progress in understanding the normal pulmonary circulation, molecular and signaling mechanisms initiating PVD, and improved detection of subclinical PVD before PH ensues. Additional goals for PH care, although not the rigorous focus of this National Heart, Lung, and Blood Institute Workshop product, include the secondary prevention of PH (defined as PH that is present, but not yet detected), and tertiary prevention of PH (in the circumstance in which PH has been detected, tertiary prevention would aim to limit PH disease progression and associated complications).

State of the Science in PAH

Progressive Vascular Changes from Normal Lung Health to PVD and PAH

The development of PVD that precedes and leads to the progression of PAH is a complicated interplay of a large number of risk factors. Although precise mechanisms are variable and remain poorly understood, a number of major risk categories are known, such as: genetic and genomic risks (e.g., heritable mutations in the *BMPR2* gene, sickle cell disease [SCD]); environmental risks (e.g., chronic hypoxia, appetite suppressant drugs, methamphetamine abuse); and endogenous risks (e.g., premature lung disease, portal hypertension, systemic sclerosis [SSc]) (Figure 1). An imbalance between risk and resiliency factors likely gradually impairs the capacity of the pulmonary vasculature (functioning at "100%" without structural abnormalities) to keep adverse processes (e.g., nitric oxide deficiency, oxidative stress, altered cellular apoptosis) "in check." Exposure to adverse stimuli can occur even during the antenatal or early postnatal periods, impacting the trajectory of pulmonary vascular development. Gradual decline in pulmonary vascular function and progression of structural changes due to PVD likely occur over a protracted period, and can be asymptomatic during the early stages. Resting PAH only occurs after an enormous proportion (roughly 50–70%) of the pulmonary vascular bed is lost and pulmonary vascular resistance and pulmonary artery pressure rises, so that when a diagnosis of PAH is made, by definition, the PVD is far advanced. RV morphology may serve as a barometer of pulmonary vascular health (much like left ventricular mass does for systemic vascular disease). Early increases in RV afterload (such as with exercise, stress, or obstructed sleep) could result in RV hypertrophy, with the eventual progression to RV failure. Our techniques to suggest or diagnose PAH (echocardiography, right heart catheterization) are unlikely to be useful metrics for gauging pulmonary vascular health or early PVD. The potential for successful primary prevention strategies in PAH is supported by available high-risk groups (e.g., families with germline mutations in the *BMPR2* gene), an advanced understanding of mechanisms of vascular disease, and the availability of many approved classes of drugs that target these pathways (e.g., endothelin receptor

antagonists, phosphodiesterase-5 inhibitors [PDE5i], soluble guanylate cyclase modulators, or prostacyclin analogs). On the other hand, such an approach is challenged by a lack of advanced functional diagnostic or imaging approaches to detect early PVD, before PAH develops. The latter is identified as a major scientific opportunity that could catalyze advances for the field.

Opportunity: Leverage High-Risk Populations for Prevention Research

Compounding the difficulties in interrogating pulmonary vascular health and PVD, the rarity of idiopathic PAH presents additional challenges to prevention strategies. However, cohorts of subjects at enriched risk of PAH offer the opportunity to optimize prevention research.

Heritable PAH due to BMPR2 gene mutations. Heritable PAH (HPAH) is a subtype of PAH associated with rare genetic variants (mutations). Heterogeneous germline mutations in the *BMPR2* gene have been found in the majority of familial (>75% tested) as well as approximately 20% of idiopathic PAH cases (3). Patients with PAH with an identifiable germline mutation in *BMPR2* have HPAH by definition (4). *BMPR2* mutation carriers can be diagnosed with PAH at any age; however, only 26% of *BMPR2* mutation carriers develop disease (reduced penetrance) (5). *BMPR2* mutation carriers without PVD or PAH would be an ideal population in which to perform clinical trials testing novel screening modalities and preventative therapies, with the understanding that such trials would require extensive follow-up time to determine the efficacy of this approach at preventing PVD and PAH.

Although subjects with heritable risk provide a potentially high-yield cohort, some limitations specific to HPAH do exist. For example, because HPAH is a rare disease (with prevalence estimates in the population roughly five subjects per million), few PH research or clinical centers follow a large cohort of patients and at-risk kin (although several centers in North America and Europe do have large research cohorts). In addition, the reduced penetrance, combined with overall rarity of HPAH, results in a very small number of subjects who will ever convert from healthy mutation carrier status to HPAH patient—roughly one out of every two females versus only roughly one in seven males who carry *BMPR2* mutations will develop detectable HPAH in their lifetime (5, 6). Thus, large numbers of at-risk research subjects must be followed for decades, not years. In addition, a formal diagnosis of PAH requires cardiac catheterization; however, this invasive study is difficult to justify in healthy *BMPR2* mutation carriers unless a preventive intervention can be provided, making echocardiogram the current screening tool of choice (3, 4).

PAH associated with prematurity and/or abnormal lung development. Pediatric PVD and PAH may be triggered by prenatal and early postnatal factors (such as premature birth), and are linked to lung growth and development. Between birth and adulthood, the alveolar and capillary surface areas expand nearly 20-fold, and the capillary volume by 35-fold, primarily by sprouting angiogenesis from pre-existing vessels and intussusceptive growth. Disruption of this process by premature birth and its postnatal consequences significantly increase the risk of PVD.

Bronchopulmonary dysplasia (BPD) leads to PAH in nearly 25% of infants born at less than 28 weeks gestation (7). Preclinical studies suggest that strategies to preserve endothelial function may not only prevent the development of PAH, but also decrease lung airspace growth abnormalities. More data are needed to best identify which preterm infants are at highest risk for PAH and BPD, to help design prevention studies.

Preterm birth is also associated with alterations in RV structure and reduced function in young adults, supporting the potential importance of perinatal events and developmental biology on RV performance (8). Furthermore, it has been hypothesized that adult PAH may have its origins during the perinatal period (9), and a common progenitor of heart and lung imply that early events may impact on the cardiopulmonary unit (10). As airway size and function in early infancy dictate lung function in adulthood, vascular structure and function in infancy could affect adult PVD, although this is speculative and needs further evaluation using animal models and human studies, such as those that employ serial diffusing capacity measures or lung magnetic resonance imaging (MRI) with hyperpolarized gas (11, 12). This implies that the early identification of such risk factors early in childhood may be critical to developing successful strategies to prevent progressive PVD and, ultimately, PAH.

PAH associated with connective tissue disease. PAH has an incidence of about 10 to 12% in SSc, and appears to show some benefit in response to all types of PAH-specific therapies, making PAH-SSc possibly amenable to a prevention strategy (13). Although recent evidence demonstrates that PAH screening programs in SSc are able to identify patients with PAH (potentially resulting in lead and length time bias), randomized clinical trials of prevention have not been performed. This is an ideal population for the testing of innovative imaging and diagnostic modalities and prevention at the stage of early PVD, rather than PAH. In addition, the numbers of at-risk potential research subjects is high—with a U.S. population prevalence of approximately 250 to 300 per million, there are approximately 90,000 people in the United States right now with a 10 to 12% lifetime risk of PAH associated with SSc (14).

A large cohort of patients with evidence for PVD (based on functional, stress-induced, or novel molecular imaging approaches to vascular evaluation) that has not yet progressed to PAH could be enrolled in a randomized clinical trial of known or novel PAH-specific drug therapy. Examples of novel detection methods for PVD might include severe exercise stress–mediated increases in pulmonary pressures, altered pulmonary vascular endothelial function measures, pulmonary vascular biopsy-proven early abnormalities in smooth muscle or endothelial function and cellular proliferation, or abnormal vascular MRI or positron emission tomography (PET)–computed tomography (CT) measures using new molecular probes. Treatment studies in these populations would need to be large and of relatively long duration to evaluate both the incidence of PAH and the impact on subsequent function and survival. Such a study would be predicated on the unproven assumption that effective treatments for clinical PAH (e.g., endothelin receptor antagonists, PDE5 inhibitors, soluble guanylate cyclase modulators, or prostacyclin analogs) would also be effective primary or secondary prevention interventions. Even if effective, such a prevention strategy in large groups of patients (most of which are not destined to develop PAH) would be very expensive, so that the cost:benefit ratio would need to be favorable before recommending

large-scale implementation. The PAH field has a unique strength in the availability of more than 10 U.S. Food and Drug Administration–approved drugs, with many going off patent soon.

PH associated with hemolytic disease. PH, diagnosed by right heart catheterization, occurs in approximately 10% of patients with SCD, and is associated with an increased risk of death (15–17). PH associated with chronic hemolytic anemia, including SCD, is now classified as group 5 PH (unclear/multifactorial mechanism) (4). There are an estimated 30 million individuals worldwide with SCD (18), and approximately 100,000 in the United States, making for a substantial burden of PAH. SCD is an excellent target for primary prevention of PAH, because SCD: (*1*) provides a large population of at-risk individuals; (*2*) is diagnosed at birth or in early childhood, and patients are closely followed over long periods of time; and (*3*) may be amenable to SCD-specific (e.g., hydroxyurea or transfusions) and PH-specific preventative regimens (e.g., nitric oxide pathway or endothelin receptor–modifying therapies) to prevent PVD and PH.

Screening studies have shown that asymptomatic PVD is a large problem in SCD. For example, 20–30% of patients with SCD have an elevated pulmonary artery systolic pressure by Doppler echocardiogram (tricuspid regurgitant jet velocity $\geq$ 2.5 m/s) (19–22). This finding indicates an increased risk of death for patients with SCD, despite no known clinical PH (19–21). Methods to detect and intervene in patients with and without PVD, but no PH (and other hemolytic anemias), may represent an ideal platform for prevention studies of PVD and PH.

Portopulmonary hypertension associated with portal hypertension. PAH may develop among those with hepatic disease and portal hypertension, termed portopulmonary hypertension. Approximately 6% of candidates evaluated for liver transplantation have portopulmonary hypertension, whereas the overall prevalence of portopulmonary hypertension among those with cirrhosis and/or portal hypertension is lower (ranging from 1 to 3%) (23, 24). There are several factors that appear to increase the risk of portopulmonary hypertension in patients with portal hypertension, including female sex and the presence of autoimmune hepatitis, making these populations potentially further enriched for the disease of interest and potentially amenable to prevention (25).

Methods to Assess Pulmonary Vascular Health and Dysfunction

Current Methods

There are no data that show that early diagnosis of PAH improves long-term outcomes, much less that primary or secondary prevention to prevent PVD or PAH is effective. The lack of effective methods and related strategies to assess the early onset and impact of PVD is a key knowledge gap that needs to be addressed to make progress in this area.

Novel Methods to Detect PVD before PAH Is Present

Early detection strategies must safely identify PVD before it has progressed sufficiently to cause PAH and clinical symptoms. Although various approaches have been used in clinically apparent PAH, there are no established metrics for subclinical PVD. Thus, novel approaches are needed.

Novel structural and functional imaging techniques. Traditionally, pulmonary perfusion has been assessed using conventional pulmonary angiography (invasive catheterization), lung perfusion scintigraphy (ionizing radiation), or dynamic CT (ionizing radiation). However, methods to noninvasively image with or without ionizing radiation are rapidly advancing. For example, contrast-enhanced MRI of the lungs may provide a technique for accurately evaluating pulmonary perfusion and hemodynamics, detecting asymptomatic structural changes of PVD (26–30). Furthermore, the addition of phase–contrast flow measurements could facilitate reasonably accurate estimates of pulmonary artery velocities and pulmonary arterial pressure; however, detectable structural changes likely lag behind changes in pulmonary vascular function (31, 32). CT measures have shown vascular changes in smokers, suggesting that this may be another useful technique for detection of subclinical PVD (33).

Functional and metabolic assessments of the lungs and RV may offer the dimension missing in traditional imaging methods. Molecular imaging agents have been developed in the cancer field for evaluation of matrix deposition, metabolism, and cellular proliferation, which are all excellent targets for PVD as well. For example, 18F-fluoro-2-deoxy-d-glucose (FDG) can serve as a tracer to measure exogenous glucose uptake; investigators have used this to estimate cardiomyocyte viability and pulmonary vascular function using PET (34). Early studies suggest that FDG uptake by the RV reflects the severity of pulmonary vascular resistance in PAH, and RV FDG uptake may be a sensitive marker of poor prognosis and responsiveness to therapy in PAH (35, 36). Intriguingly, fasting FDG-PET may detect changes in right heart metabolic and structural function in patients with PAH over time, and associate with changes in echocardiographic parameters (37). Although speculative at this time, it is conceivable that FDG-PET (or similar metabolic imaging approaches) could provide a mechanism to identify early subclinical PVD, which predates PAH; such a modality could serve as a preclinical risk marker for primary prevention efforts. However, further studies are needed in the PAH population first, and ultimately in at-risk subjects.

Advanced echocardiography with and without functional challenges. Novel echocardiographic measures could use assessments of RV morphology and function that may precede resting PAH. Real-time three-dimensional echocardiography, for example, may provide quantitation of RV end-diastolic volume and other focused assessments of the RV. Likewise, two-dimensional speckle-tracking image analysis can assess myocardial deformation to inform about the extent of RV remodeling and strain; this may prove particularly useful in detecting subclinical PVD (which presumably predates PH) in the setting of subjects who are at risk of PH due to a coexistent condition, such as scleroderma (38).

Hemodynamic coupling of the lung circulation with the RV is a key component of cardiopulmonary status (ventricular–vascular coupling). The metrics of RV efficiency and ventricular–vascular coupling in the subject with asymptomatic PVD before PAH detection could serve as end points for clinical prevention trials (39).

Physical provocation may elicit functional abnormalities suggestive of PVD in the absence of symptomatic PAH. For example, hypoxic and pharmacologic

challenges may provide additional approaches to safely assess asymptomatic at-risk subjects. Likewise, cardiopulmonary exercise testing has recently been applied to the evaluation of RV function and PAH, as demonstrated for the diagnosis of PAH among patients with SSc (40). In fact, several recent studies in the SSc population have suggested that pulmonary vascular resistance and pulmonary artery pressure elevations are associated with decreased exercise capacity and even the presence of PVD before detectable PH, and that PH-specific therapy may be an appropriate consideration (14, 41–43). Pharmaceutical interventions with infusions of acetylcholine, L-NMMA, and angiotensin II may provide evidence for early endothelial dysfunction and redox dysfunction. Although patients with established PAH appear to manifest characteristic patterns of abnormal responses to exercise, the same may be true of those with preclinical disease.

Biometric health monitoring to detect reductions in fitness. The expansion of mobile smart technologies that facilitate small size and portability has supported the emergence of a large array of biometric health monitoring systems. These systems have the capacity to collect data using a wide variety of sensors and monitoring devices. Although, for decades, sensors have existed to record parameters of sleep and activity, portable devices can now record objective, long-term data regarding a patient's daily activity level and movements in multiple dimensions. For example, current technology now affords the capacity to incorporate monitoring systems into one's daily life without additional devices, such as the use of a smartphone accelerometer and associated applications. Use of geographic positioning system tracking can facilitate advanced measurement of individual mobility, both rate and distance, compared with population and environmental information to control for variations in weather and social dynamics. The incorporation of novel technologies to advance our understanding of subject activity and biometric health measures may uncover subtle reductions in fitness due to PVD long before symptomatic PAH is detectable, as has been shown in patients with PAH (44). As with other methods proposed to detect PVD before the presence of PAH, the highest yield approach to such studies would be to start with subjects enriched for PH risk, such as those with scleroderma.

Additional novel approaches to assess lung vascular structure and function. Although advances in functional noninvasive assessments are critical, there is also a need for novel invasive assessments that can be safely applied to asymptomatic at-risk subjects. For example, RV endomyocardial biopsy can be safely performed and provides tissue for morphometric and other assessments. In addition, rapid advances in transbronchial biopsy approaches provide the opportunity to safely acquire a limited amount of primary lung tissue for histologic assessment, and may soon be entering clinical trials to assess subjects at risk. Beyond the issue of PVD screening, this may provide important contributions to the understanding of the structure of the pulmonary vasculature among healthy subjects at various ages to add to a currently small body of data that suggest that roughly 20% of healthy older subjects have asymptomatic histologic changes of their pulmonary vasculature consistent with PVD (45).

Although a single assessment method would be optimal, the phenotyping of lung health and PVD will likely require a collection of metrics. As shown in Table 1, a given subject's current phenotype will determine which metrics are appropriate to apply to each individual. For example, not all invasive assessments will be appropriate for the evaluation of an asymptomatic subject, although this may vary according to risk.

Table 1. Potential methods to assess pulmonary vascular health and dysfunction in different clinical conditions related to pulmonary vascular dysfunction and pulmonary arterial hypertension*

1. Genetic testing for specific gene mutations known to associate with PAH
2. Genomic studies
3. Biologic markers
4. Systems biology approaches incorporating genetic, genomic, and biologic data
5. Noninvasive measurement approaches
   a. Biometric health monitoring
   b. Echocardiographic methods
   c. CPET
   d. MRI
   e. PET
   f. CT
   g. Metabolic imaging approaches (e.g., FDG-PET)
6. Invasive measurement approaches†
   a. Right heart catheterization
   b. Pulmonary angiography by catheterization
   c. Lung biopsy by transbronchial or alternative approach
   d. Right ventricular biopsy

Definition of abbreviations: CPET = cardiopulmonary exercise testing; CT = computed tomography; FDG = 2-deoxy-2-[18F]fluoro-d-glucose; MRI = magnetic resonance imaging; PAH = pulmonary arterial hypertension; PET = positron emission tomography.
*Example conditions include: (*1*) general population of subjects with no pulmonary vascular dysfunction (PVD) risk factors; (*2*) asymptomatic subjects with PVD risk factors; and (*3*) subjects diagnosed with PAH
†Invasive techniques, which may not be appropriate to apply as screening tools for the general population of subjects with no PVD risk factors.

Possible Approaches and Recommended Priorities for Primary Prevention Research

There is clearly a need for research focused upon primary prevention of PVD. While multiple different proposals may exist, below we demonstrate one method to prioritize potential approaches (Table2).

Immediate Research Priorities (1–5 Years)

Human studies. First, novel tools (as well as the novel application of existing tools) must be developed for the detection and monitoring of pulmonary vascular health and PVD. Improved noninvasive functional and imaging assessments of PVD, pulmonary hemodynamics, cellular and endothelial function, and ventricular–vascular coupling are needed.

Second, we must identify disease-specific groups that are at high risk for developing PVD to facilitate clinical trials of prevention strategies, as such trials will be impossible in the general population with an overall low risk of disease.

Third, once identified, high-risk cohorts will require detailed endotyping to elucidate subtypes defined by distinct pathophysiological mechanisms and natural history studies across the life course; those studies must be linked with biospecimen repositories to support systems biology studies. Of note, many medical centers and research programs are currently collecting and banking biospecimens from a wide range of subjects linked to rich phenotypic

Table 2. Recommendations for research priorities for the primary prevention of pulmonary arterial hypertension

Immediate research priorities (1–5 yr)
1. Develop novel tools (and optimize existing ones) for the detection and monitoring of PVD.
2. Leverage current, and develop new, high-risk research cohorts.
3. Detailed phenotyping and natural history studies linked to biospecimen repositories.
4. Collaboration within at-risk research cohorts across disease type (e.g., SSc)
5. Plan and initiate cohort studies for long-term studies.
6. Broad approach to biospecimen type should be planned for in advance.
7. Leverage existing large research cohorts with unused lung and heart data and specimens.

Intermediate and long-term research priorities (5–10 yr)
1. Bioinformatic advances to synergize robust and varied data.
2. Novel collaborative infrastructures across high-risk research cohorts.
3. Novel methods to assess the fetal determinants of pediatric and adult pulmonary vasculature.
4. Longitudinal assessments of the prenatal, postnatal, pediatric and adult pulmonary vasculature in settings of health and disease.
5. Pharmacologic intervention trials to assess current and novel therapeutics to prevent PAH.

Definition of abbreviations: PAH = pulmonary arterial hypertension; PVD = pulmonary vascular dysfunction; SSc = systemic sclerosis.

information—these resources should be optimized for the study of PVD.

Fourth, to optimize yield in human studies, PVD prevention studies should be linked with prevention studies for other diseases in which the cohorts may be the same. Examples include patients with SSc at risk of both PVD and interstitial lung disease, or preterm infants who are at particularly high risk for BPD and PAH.

Fifth, all human studies will require a long duration of follow up to facilitate longitudinal evaluations with recurrent assessments under the assumption that cross-sectional studies will be of limited utility—cohort studies should incorporate plans for long-term follow up. As with phenotypic data, collection of biospecimens should be broad ranging.

Finally, given the paucity of data concerning the normal changes that occur to the pulmonary vasculature over time, existing large research cohorts (including both healthy participants and those with noncardiopulmonary diseases) with available lung and heart phenotyping should be explored to improve understanding of the causal pathways of normal lung vascular development, growth, and maintenance from childhood into all stages of adulthood. Coincident with required advances for the study of asymptomatic PVD is a more comprehensive understanding of the healthy pulmonary vasculature, ventricular–vascular coupling, and the RV itself.

Additional approaches. Further advances in the molecular and systems biology are needed to support novel therapeutic options based upon advanced pathophysiologic understanding. This will require the use of human biospecimens linked with detailed phenotypic data, but also improved *in vivo* and *in vitro* work on the underlying pathobiology and progression of PVD. In addition, novel informatics strategies to examine existing data resources, and incorporate new metrics, are necessary.

Intermediate and Long-Term Research Priorities (5–10 Years)

Bioinformatic methods and infrastructure. As high-risk cohorts are established (and existing cohorts leveraged) and followed over time, the capacity to optimize novel screening strategies will be increasingly critical. Thus, the ability to synergize multiple types of information into a unified model of disease risk assessment over time will be critical bioinformatically. This includes, but is not limited to, systems biology approaches. Collaboration across the different at-risk research cohorts should be made facile by novel infrastructure and collaborative arrangements, under the hypothesis that novel advances for one PVD at-risk group may be applicable to other research cohorts.

Understanding changes to the pulmonary vasculature in healthy and at-risk individuals over time. The concept that all "healthy" subjects are born with the same number of normally functioning pulmonary vessels, and that the vessels may regress in function or structure equally over time, is simplistic. We must develop novel methods to assess the fetal determinants of pediatric and adult pulmonary vasculature. Similarly, lung vascular structure and growth in prenatal, immediate postnatal, child, and adult subjects must be evaluated comprehensively over time to determine the critical modulators of maturation and aging. Understanding this will facilitate the incorporation of risk factors and resiliency factors into the equations, to assess for response to insults over time in the diseased pulmonary vasculature.

Interventions. Ultimately, the goal is the prevention of PVD and PAH by identifying healthy subjects at risk for PVD (or with early PVD) to prevent PH and improve functional status and survival. There are approved, safe agents that can improve PAH outcomes among patients with disease. Although some require parenteral infusion, many are taken orally (e.g., PDE-5 inhibitors and endothelin receptor antagonists) or by inhalation. Administration of vasodilator therapies may prevent disease or disease progression in those with established disease and those healthy but at risk; however, this is unknown. In addition, some "vasodilator" therapies can also alter lung vascular growth and structure in experimental models. Thus, an intermediate goal is the application of current pharmacologic agents, in isolation and in combination, to subjects at risk of PVD and thus PAH. Immediate steps needed to achieve this goal include, but are not limited to: (*1*) detailed animal model prevention studies using all currently available pharmacologic agents, recognizing the lack of a perfect animal model system; (*2*) meticulously phenotyped cohorts of at-risk subjects with comprehensive biospecimen acquisition ready for the implementation of prevention trials; (*3*) comprehensive review of safety data from human subjects pertinent to each pharmacologic agent, including all pharmaceutical company trial data; and (*4*) improvement of noninvasive methods to detect PVD before PAH detection. Long-term, novel pharmacologic approaches are needed to safely prevent disease and improve survival, which is the ultimate goal. In both cases, large, randomized, controlled trials of pharmacologic agents applied to well phenotyped at-risk subjects will be needed. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgments: The authors thank Drs. Carol Blaisdell, Patricia Noel, Tim Moore, Serpil Erzrum, and William Busse for their assistance with the development of this article. The authors also thank each participant in the National Institutes of Health Primary Prevention of Chronic Lung Disease Workshop, which stimulated consideration of many important ideas and concepts contained in this article.

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