A Paradigm Shift Is Needed in the Field of Pulmonary Arterial Hypertension for Its Entrance Into the Precision Medicine Era

Vikram Gurtu, Evangelos D. Michelakis

Pulmonary arterial hypertension (PAH) is a complex disease leading to right ventricular (RV) failure and death, because of a proliferative vascular remodeling that obstructs the lumen of resistance pulmonary arteries (PA). Despite tremendous investments from the scientific community and industry over the past 20 years, the disease remains deadly. Currently approved therapies act mainly as vasodilators that cannot reverse the disease or improve survival, while they are offered at a prohibitive cost for many patients. Is the field in crisis?

PAH Field Is in Crisis and a Paradigm Shift Is Needed

Kuhn1 described scientific crisis as a state where there is loss of confidence in the current paradigm while alternative, more attractive theories emerge and social pressures push toward a new outlook and proposed that these conditions promote a paradigm shift. The PAH community is losing confidence in the current paradigm, ie, the use of vasodilators as therapy for PAH, a disease in which vasoconstriction plays only a minor role. Yet, more drugs from the same families (endothelin receptor antagonists, activators of the NO/cGMP axis, or prostacyclin analogues) continue to be developed, tested, and approved. Although these drugs may also affect apoptotic and proliferation mechanisms, their primary mode of action is vasodilation. The proproliferative and antiapoptotic environment within the PA wall can be explained by a myriad of molecular abnormalities discovered in preclinical research, many of which show translational promise as targets for novel therapies.1 But none has been approved, and only a small fraction enters clinical trials.1

Translation to early-phase trials is a challenging stage in drug development, and many bottlenecks have been identified.1 Instead of intensifying efforts to develop novel drugs that target the foundation of PAH’s pathology, the development of vasodilators remains attractive for industry. Although vasoconstriction is not an important factor for most PAH patients, it contributes to a small degree to all of them. On the contrary, molecularly driven therapies may not universally apply to all because phenotypic diversity is increasingly being recognized in PAH, limiting candidate consumers and reducing profit. But patients may respond better and suffer less toxicities (ie, precision medicine). This phenotypic diversity continues to be ignored by the current PAH classification system, which continues to promote one-fits-all drug development, as discussed below.

Although RV function is now recognized as the most important prognostic factor in PAH, it is ignored by most drug development efforts in PAH and there is little progress identifying the molecular basis of RV failure.4 Potential direct effects of PAH therapies on RV myocardium4 are not considered clinically or in research.

Social pressures are emerging as patients are frustrated by the lack of significant progress and the fact that they often cannot afford these drugs, which can at least limit symptoms. Although the government, National Institutes of Health, and Food and Drug Administration (FDA) are convinced that precision medicine will dominate medical research and practice the PAH field is far from it.5

The loss of confidence in the current paradigm, the appearance of alternative, potentially better theories/approaches compatible with precision medicine, and the emerging social pressures, fulfill the criteria for a scientific crisis. Here, we propose a change in our approach to PAH toward a paradigm shift (Figure).

PAH Needs a Molecularly Driven Reclassification and a Change in Our Research and Clinical Approach

The current characterization of PAH is based on superficial features like histology and hemodynamics. The first attempt for pulmonary hypertension classification was pioneered by the late Alfred Fishman in 1998 (Evian World Health Organization [WHO] Symposium on Pulmonary Hypertension).6 He recognized that clinicians needed help navigating through the complexities of many diseases associated with pulmonary hypertension. The term PAH was soon coined (Class I Pulmonary Hypertension) and in addition to idiopathic PAH included several conditions that have a similar histological and hemodynamic profile (eg, PAH associated with collagen vascular disease, congenital heart disease, HIV infection, and anorexigen use) Two years later the FDA assessed bosentan’s effects in mostly idiopathic PAH patients, but approved it for all of Class I for unclear reasons. Since then, all approvals for PAH therapies included the whole class. The same classification persisted in subsequent WHO symposia with minor changes.

PAH’s histology (eg, small PA muscularization, intimal-media adventitial hypertrophy, and plexogenic lesions7) is a result of the PA’s proproliferative/antiapoptotic environment.
But the diverse molecular pathways that lead to the same end-result are lost by WHO classifications, which are driven by a diagnosis of exclusion, using common tests to prove that a PAH patient simply does not belong to the other, easier to define classes, like left ventricular (Class II), chronic lung (Class III), or thromboembolic disease (Class IV).

Since the FDA’s decision in 2000, Class I patients with potentially different molecular phenotypes are presumed to benefit from the same therapy. This was welcome by the industry, which faced the challenge of proving effectiveness using approaches developed for more common diseases. This required trial enrollment of large patient numbers to reach statistical significance for endpoints like 6-minute walk or hemodynamics. Many drugs were approved because they all targeted a common (but minimally important) denominator (vasoconstriction) among otherwise diverse patients. The high cost of trials led to high prices of marketed drugs, which failed to reverse the disease or improve survival, because they did not attack the foundation of PAH’s pathology.

The cancer field has entered the field of personalized, target-driven trial design. But in cancer the molecular phenotype can be personalized because tumor biopsies are easily available. This is impossible in PAH where lung biopsies are avoided because of high risk of the procedure. The field must creatively use noninvasive methods to identify molecular targets. In addition, molecular targets identified in animals may not be the same in patients where the molecular milieu is also dynamic, at least in early versus late stages of the disease. Creative noninvasive biomarkers correlating to such targets need to be developed in parallel with companion drugs, an approach encouraged by the FDA. No such examples are currently available for PAH.

**Define the Molecular Phenotypes of Human PAH in Preclinical and Clinical Research**

We must change our approach to animal research, studying models later in the development of the disease and perhaps already treated with currently approved vasodilators, because this will mimic patients enrolled in future trials. Translation-driven approaches need to be followed, studying multiple models of young and old animals in long-term studies focusing on toxicity and efficacy, with strict quality control criteria similar to those followed in clinical research (prespecified endpoints and sample sizes, registration of trials, independent data monitoring, etc). Noninvasive biomarkers relevant to PAH pathology need to be developed along with potential therapies.

The most critical emphasis needs to be on human tissues studies. In a rare disease like PAH, centralizing efforts with biobanks linked to clinical registries is essential. Stacher et al showed the feasibility of systematically studying human PAH and non-PAH lung tissues in a standardized manner. The importance of using standardized protocols in extracting, handling, and studying human tissues cannot be overemphasized. Of similar importance is the National Heart, Lung, and Blood Institute–driven initiative of pulmonary vascular disease phenomics. Its goal is to systematically characterize ≈1500 patients using genomics, transcriptomics, proteomics, and metabolomics to describe the PAH phenotype, providing an invaluable source for drug and biomarker discovery. Studying live human PAH lungs at the organ level can be facilitated by the emerging ex vivo lung perfusion models, currently used to optimize the function of borderline donor lungs at transplantation. Even more important is studying PAH specimens at earlier stages than transplantation. The ability to biopsy PAs could revolute precision PAH medicine, and novel intravascular biopsy catheters have shown promise in pigs. Concerns over safety will require bold initiatives, but one should not forget similar concerns for myocardial biopsies at earlier stages of that procedure. Less invasive methods are also being developed to collect circulating blood-outgrowth endothelial cells or PA endothelial cells directly through right heart catheterization. Induced pluripotent stem cells derived from PAH patients skin fibroblasts and differentiated into endothelial cells is another important development.
Reclassify Class I PAH, Based on Molecularly Driven Subgroups

The list of molecular abnormalities described in PAH is long, but could be shortened if more strict quality criteria are followed in animal work and correlation with human molecular targets is a requirement before a molecular pathway is considered important. Nevertheless, it may still be impractically long for meaningful classification of human molecular phenotypes. This can be addressed by grouping molecular abnormalities based on mechanistic studies. For example, several described PAH molecular abnormalities (eg, NFAT [nuclear factor of activated t cells], STAT3 [signal transducer and activator of transcription 3], HIF [hypoxia inducible factor] activation, epigenetic signatures, and Kv channel downregulation) may simply be downstream from a primary mitochondrial suppression (the metabolic theory of PAH), or primary inflammatory abnormalities (the inflammatory theory of PAH). This means that potential PAH subgroups could be those that are mostly characterized by a metabolic phenotype, inflammatory phenotype, etc. Genetically driven subgroups can also be defined by the known mutations in PAH (eg, BMPR2 [bone morphogenetic protein receptor type II], Cav-1 [caveolin-1], and ALK1 [activin receptor-like kinase type-1]).

Design Precision Medicine Trials Through Networks Partnering With Industry and Regulatory Authorities

Precision medicine trial designs need smaller sample sizes and novel statistical approaches and trial designs. Still, it will be only through clinical networks that adequate numbers of patients can be recruited for trials prioritized within the network. Adoptive trial designs can be utilized more, and parallel tracks within a trial can test >1 drug/biomarker at a time. For example, if a biomarker (eg, lung glucose uptake via positron emission tomography) identifies a patient as a candidate for a molecularly driven subgroups could also be defined by the known mutations in PAH (eg, BMPR2 [bone morphogenetic protein receptor type II], Cav-1 [caveolin-1], and ALK1 [activin receptor-like kinase type-1]).

RV Function Needs to Be a Primary End Point in PAH Trials and a Therapeutic Target

RV failure is recognized as the most important negative prognostic factor in PAH, independent of pulmonary vascular resistance (PVR). Despite this recognition, RV-specific therapies remain nonexistent. The following assumptions are detrimental to the field:

1. The RV will normalize after PVR improves. This may be true if the PVR is normalized (lung transplantation) or if the impact on the RV was hyperacute (pulmonary embolism). It is unlikely that a dilated and fibrotic RV will improve with modest PVR reductions. This is complicated further by the fact that PA-targeting therapies can directly (positively or negatively) affect the RV myocardium, but this is ignored in preclinical and clinical studies. The response of the RV to afterload resembles that of the LV. This is unlikely because both chambers have different embryology and biology. RV-specific targeting drugs should be developed and tested in parallel with PA-targeting therapies. In some cases, it may be possible that the same drug may have beneficial effects in both tissues. For example, the metabolic modulator dichloroacetate may reverse PA remodeling while directly increasing RV inotropy because mitochondrial remodeling is important for both PA and RV remodeling in PAH. The same may be true for anti-inflammatory therapies.

2. Most preclinical studies that directly target the RV, use regression of RV hypertrophy as their goal. But RV hypertrophy is a compensatory mechanism and a potential pharmacologically driven regression could be catastrophic under high RV afterload. When the RV compensates well, patients can survive with less symptoms, despite extremely high PA pressures, as in congenital heart diseases. The transition from compensation to decompensation varies from patient to patient despite similar PA pressures, suggesting mechanisms intrinsic to RV myocardium. It is these mechanisms that must be targeted. Some reports described mechanisms for transition to decompensation, but have to be confirmed by others and extended further.

The following suggestions may help the field:

1. Elucidate the mechanism(s) of RV decompensation in animals and human tissues. Higher utilization of RV biopsies will be essential. Our goal should be to maintain compensatory RV hypertrophy and prevent or even reverse, decompensation. Biomarkers predicting this transition will be important.

2. Establish anatomic, functional, and molecular criteria (through biopsies or functional/molecular imaging) for compensating versus decompensating RV, so that this RV state can be included in PAH classification or criteria for clinical trial enrollment.

3. The effects of candidate PAH therapies need to be tested directly on RV myocardium in preclinical studies, using models that separate the effects on pulmonary vasculature (eg, working heart or PA banding models). This needs to also be assessed clinically and indices of RV function need to be as important as PA pressure or PVR in early-phase mechanistic studies in patients.

PAH Should Be Approached as a Systemic Disease

The dogma that the primarily (and perhaps only) affected tissue in PAH is the lung microvasculature is being challenged. When searching for novel PAH therapies, we had previously tried to identify targets that are uniquely present in diseased PAs, yet absent in other tissues. An alternative possibility is that while many tissues are primarily affected, the PAs are the most sensitive and the first to show molecular and structural signs of disease. Instead of trying to explain extrapulmonary abnormalities as secondary to lung pathology and its systemic effects (eg, circulating lung-derived factors), we should consider that extrapulmonary abnormalities may advance independently of PAs. Several lines of evidence support this concept. Silencing genes that regulate mitochondrial function (eg, Sirt3 [sirtuin 3] and Ucp2 [uncoupling protein 2]) in the whole body cause spontaneous PAH without signs of systemic disease in the short-term and in young animals, which later on develop skeletal muscle abnormalities and insulin resistance. Recently described links...
between PAH, skeletal muscle dysfunction, or insulin resistance are easier to explain using this logic. This suggests that 1. Registries and biobanks should include not only lungs but also RV and skeletal muscle tissues/biopsies, blood, immune cells, etc. 2. Our approach to PAH drug discovery should widen, considering drugs approved for other indications, such as metformin, or novel anti-inflammatory therapies. PAH may not then appear as a stand-alone rare disease but perhaps a part of a group of more common diseases, for example mitochondrial diseases and inflammatory diseases, expanding the interested PAH groups (scientists, industry, and public).

Although the field is not ready to change practices and enter the precision medicine era, we have discussed several issues that if addressed may facilitate this in the near future. Such efforts have already started with the Pulmonary Hypertension Academic Research Consortium (including systematic discussions and meetings among all stakeholders: scientists, clinicians, National Institutes of Health, and FDA) and other similar efforts (including patient groups) may need to be developed. Such consortia may replace the international classifications and biobanks should include not only lungs but also RV and skeletal muscle tissues/biopsies, blood, immune cells, etc.

Disclosures

None.

References


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