Circulation Research Compendium

Pulmonary Arterial Hypertension

Editor: Evangelos Michelakis
With more than 25 centuries of efforts to resolve its mysteries, the pulmonary circulation continues to inspire and humble researchers, frustrate clinicians, and scare patients with pulmonary arterial hypertension (PAH). Its mysteries lie in lost manuscripts written in the 12th-century Syria; within the pages of one of the rarest books in history written in 1531 by an author burned alive with his books, condemned by the Inquisition; within a publication from a young urologist self-experimenting 30 years before he received the Nobel prize...What kind of disease is this one that in the age of planning missions to Mars, no medical therapy can save its victims? It is certainly a disease that deserves our respect. The objective of this compendium is to present the state of the art in PAH, but mostly emphasize its future, discussing several evolving theories on its pathogenesis. Its objective is also to comprehensively summarize our current clinical approach to the disease, with patients in mind. In addition to researchers, clinicians, health professionals, students, and residents, its target audience includes patients: the patients who suffer, desperate for answers, and the patients who, one way or another, not only participate in but also fund our research through their taxes and donations. In the age of instant and easy information dissemination, many patients are already quite informed when they visit a specialist. How do we describe the cutting-edge developments in this complex disease to the informed patient? It is not easy, but most would agree that only the expert who really understands his/her subject is able to describe it in lay terms and pass its main messages.

Humbled by the complexity of PAH and its challenges, we need to focus on what drives all of us fighting this disease. In addition to our patients, it is scientific curiosity: PAH is a model of vascular disease, involving multiple cell types and organs, and trying to solve its mysteries is a fascinating endeavor. A brief travel in time will provide powerful evidence on the magnitude of the effort the scientific community has put on this problem. This does not intend to be a comprehensive historical overview; it only aims to reveal some fascinating aspects of the history of the pulmonary circulation researchers and describe their passion. Then, the articles of the compendium will be briefly discussed through the questions that an actual typical patient asks.

Twenty-Five Centuries of Struggle

Hippocrates (460–377), Aristotle (384–322), Erasistratus (304–250), and Galen (192–200) were all attempting to reveal the structure and function of the circulation. They described and named all the major vessels as we know them today. Galen...
described the two parallel circulations (arterial and venous) but said that they communicate through invisible pores in the cardiac septum. The first mechanistic description of the pulmonary circulation comes from Ibn Nafis, a respected Syrian physician, born in 1213 in Damascus. He worked and published his ideas in Egypt, but his contribution to lung anatomy and physiology was not realized until 1924. That year, a physician studying the history of Arab Medicine discovered an article called Commentary on the Anatomy of Canon of Avicenna in the Prussian State Library in Berlin (Figure 1). Here, Ibn Nafis described for the first time and in detail how the blood comes to the left ventricle not through the septum, but from the right ventricle (RV) through the pulmonary artery, lungs, and the pulmonary vein. He also first described the presence and function of the coronary circulation.

But it was not until 1553 that a Spanish physician, Michael Servetus, published a book in which he provided the most accurate and complete description of the pulmonary circulation at the time. He specifically wrote that it is air mixed with blood that is sent from the lungs to the heart through the pulmonary vein, concluding that the mixture (the spirit as it was known since Aristotle) is made in the lungs. He said that bright color is given to the sanguine spirit by the lungs, not by the heart, as believed until that time by all, including Ibn Nafis. Although Servetus had previously published several medical books, his description of the pulmonary circulation was included within his last book, Christianismi Restitutio, a theology book in which he proposed a reform of Christianity toward a more tolerant and inclusive direction (Figure 1). He published the book knowing very well what was to follow. The Inquisition considered the work heresy and condemned him, burning all known copies of the book later in that year. Shortly thereafter and under continuous attack by John Calvin, he was sentenced to burn alive along with what was believed to be the only remaining copy of his book in Geneva. Calvin persisted in his efforts after Servetus’s horrific death to make sure that no copy of the book survived. Three copies of the book did however survive and can still be found in the Bibliothèque nationale de France, the Austrian National Library, and the University Library in Edinburgh. Eventually, all the pieces were put together by William Harvey in his complete description of the circulation in 1628. William Osler was inspired by Michael Servetus and gave several lectures on his life and his book, while he tried for many years to obtain a copy of his books himself.

Leap forward a few centuries, in 1929, we find a young resident in Eberswalde Hospital, Werner Forssmann (1904–1979), who is fascinated with the heart and the pulmonary circulation. Despite the lack of support from his colleagues and the objections from his superiors, he secretly plans a self-experiment: he advances a ureteral catheter through his antecubital vein for ≈35 cm. He then takes an x-ray film and finds the tip of the catheter to be at the clavicle level. He then sits in front of the x-ray machine and through a mirror he advances the tip of the catheter further to the level of the right atrium (Figure 2). He published this work with the x-ray proof in a short article, describing for the first time heart catheterization in a living human. Disappointed by the lack of support for his research plans, he entered a career in Urology. He did not know that Drs Cournand and Richards at the Bellevue hospital in New York saw his article and went on to publish their seminal work on the hemodynamics of the pulmonary circulation and the technique of right heart catheterization.

Many years later, in 1956, a retired physician by then, Werner Forssmann received a call from the Nobel committee, informing him that he was awarded the Nobel prize in Physiology/Medicine along with Drs Courmand and Richards.

It was then a matter of time…. Few years later, a Courmand and Richards trainee, Dr Dresdale, published the first comprehensive description of what he called primary pulmonary
hypertension. Although pathology findings that described pulmonary arterial sclerosis (likely idiopathic pulmonary arterial hypertension) had been published in 1891 by von Romberg, Dresdale et al described the new syndrome with clinical, hemodynamic, imaging, and pathology data and remarkable accuracy, essentially as we know it today (Figure 2).

Scientists continued to work on the mysteries of the pulmonary circulation including hypoxic pulmonary vasoconstriction (HPV), a fundamental property of the pulmonary arteries of all mammals. Although the pulmonary arteries constrict to hypoxia, all systemic arteries dilate. Hypoxic pulmonary vasoconstriction has also fascinated scientists and provides clues about the pathology of PAH. As the most fundamental difference to the systemic vessels, it provides many important clues on how to perhaps selectively target the pulmonary arteries while sparing the systemic arteries, a great challenge of PAH therapeutics. But research in the physiology of the pulmonary circulation, hypoxic pulmonary vasoconstriction or PAH remained primarily driven by a few centers, such as the Cardiovascular and Pulmonary Laboratory at the University of Colorado, Denver. The CVP laboratory trained a large number of researchers, many of whom are now leaders in the field. Despite the fascinating fundamental physiology research in animal models, there was silence in the literature when it came to PAH therapies.

**Figure 2.** Top: The x-ray film shows the tip of the ureteral catheter advanced into the right atrium through the left antecubital vein, as described by Forssmann in 1929. This was the first catheterization of the heart in a living human. **Bottom:** A comprehensive description of a patient with idiopathic pulmonary arterial hypertension, as described by David Dresdale in 1951. This is the second of the 3 cases presented in detail in his article: “MR,” a 35-year-old woman presented with exertional dyspnea and chest pain. The classic hemodynamic measurements of the patient at catheterization are shown: there is an increase in mean pulmonary artery pressure (normal <25 mm Hg), an increase in right atrial pressure and resting heart rate and a decrease in cardiac output. The chest x-ray film (left) shows cardiomegaly, the heart at autopsy (middle) shows enlargement of the right atrium and right ventricle and the lung pathology (right) shows a classic lesion with intimal and medial hypertrophy of a small pulmonary artery. PA indicates pulmonary artery. Data taken with permission from Dresdale et al.

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<tr>
<th>PA pressure mmHg</th>
<th>Arterial pressure mmHg</th>
<th>Right Atrial pressure mmHg</th>
<th>Cardiac Output L/min</th>
<th>Heart Rate b/min</th>
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**Figure 3.** Top: A sharp rise in the number of publications on experimental therapies for pulmonary arterial hypertension (PAH) coincided with landmark publications describing the molecular phenotype of the disease on human tissues (see text). The search engine Scopus was used with query to Pulmonary Arterial Hypertension AND Experimental Therapies within the years 1990 and 2011. Derived from Sutendra and Michelakis. **Bottom:** The current survival of a patient with PAH is similar to that of a patient with metastatic breast cancer (Stage III) while the cost of therapy for a patient with advanced PAH is much higher compared with that for metastatic breast cancer. BMPR II indicates bone morphogenetic protein receptor II; and NOS, nitric oxide synthase.
This was until the first articles studying molecular changes in human pathology specimens started appearing in the literature, describing an activated vasoconstriction axis (eg, by endothelin 1)\(^{19}\) and a suppressed vasodilator axis (eg, endothelial nitric oxide synthase).\(^{20}\) This coincided with a sharp rise in the number of publications on potential therapies for PAH (Figure 3). Now scientists had identified targets in human tissues, a great example of the importance of translational work. Soon, the first randomized trials on epoprostenol\(^21\) and bosentan\(^22\) (as well as sildenafil shortly thereafter)\(^23\) were published. Along with the seminal description of a potential genetic basis of PAH (loss of function mutations on bone morphogenetic protein receptor II),\(^24,25\) offering additional therapeutic targets, they further accelerated the rate of increase in publications on PAH therapies, a rate that continues to rise (Figure 3).

Prostacyclins, endothelin antagonists, and phosphodiesterase type 5 inhibitors were shown to improve the quality of life of patients and symptoms, and all helped to increase awareness and interest in the disease, engaging young researchers and clinicians and triggering the creation of organized PAH clinics in essentially all major tertiary care centers.\(^12\) But they fail to reverse the disease and prolong survival. Most of them were primarily developed for use in systemic arterial diseases, not in PAH. The environment they created however was fertile and allowed for an explosion of knowledge and the discovery of novel therapies that offer hope for further progress.\(^12,26,27\) This is urgently needed, because the mortality of PAH remains similar to that of metastatic breast cancer, while the cost of treatment of a patient with PAH is much higher (not including the cost of transplant) (Figure 3). Combined with the fact that the typical patient is a woman in her reproductive years, the impact on society is huge.

## A Patient Asks Questions

In summary, the first two articles in the compendium review our current understanding of the clinical syndrome and our clinical approach within modern, research-intensive multidisciplinary PAH clinics. The subsequent three summarize what seem to be the 3 most exciting recent and evolving developments (and potential paradigm shifts) in our understanding of PAH: the metabolic theory and the inflammatory theory of PAH as well as the inclusion of the RV as part of a comprehensive diagnostic and therapeutic approach to the RV-pulmonary artery unit. The last article is dedicated to what is probably the single most important step in our understanding of PAH in the past 20 years: the identification of a genetic basis for PAH; a concept that after the discovery of mutations in bone morphogenetic protein receptor II continues to expand. All the faculty contributing to this compendium are clinician scientists and were asked to keep in mind the questions posed by a patient, as if they were answering the same questions in the clinic, in addition to providing the newest information and the state of the art on their subject.

Here is the description of an actual typical patient and the questions she poses:

K.M. is a 30-year-old, newly married molecular biologist who had worsening dyspnea on exertion during the past 6 months. She recently started having fluid retention in her feet and experienced an episode of near-syncope after running up the stairs with groceries. She did not have any other medical problems or a history of hereditary diseases in her family. She was on no medications and lived a healthy lifestyle. Her family physician eventually ordered a chest x-ray film and an ECG that showed evidence of enlarged pulmonary arteries and right ventricular hypertrophy. Her physical examination, in addition to the edema, showed a jugular venous pressure of 10 cm H\(_2\)O, a prominent pulmonary valve sound and a moderate systolic murmur compatible with tricuspid regurgitation. An echocardiogram showed a hypertrophied RV with moderate decrease in the RV function, moderate tricuspid regurgitation with no other valvular disease, and normal left ventricular size and function. Based on that, she was referred to a PAH clinic. Blood work was unremarkable, a ventilation/perfusion scan showed no evidence of pulmonary embolism, and pulmonary function tests showed no evidence of airway disease. She underwent heart catheterization that showed right atrial pressure: 10 mm Hg; mean pulmonary artery pressure: 60 mm Hg; cardiac output: 3.5 L/min; pulmonary artery wedge pressure: 10 mm Hg; left ventricular end-diastolic pressure: 9 mm Hg; heart rate 100 mm Hg; arterial pressure: 130/80 mm Hg. Based on this information, she was diagnosed with idiopathic PAH at the time of her catheterization. Remarkably, her chest radiograph, ECG, physical findings, and hemodynamic parameters are quite similar to the case presented by Dresdale et al\(^4\) in 1950 (Figure 2).

A week later she came to her clinic appointment where oral therapy was to be started. She was remarkably calm and admitted to having read hundreds of Internet pages on PAH and already having contacted patients with PAH through her local PAH patient group. She asks:

1. Why am I really so short of breath? My oxygen levels are not that low…
2. How long do I have to live?

The answers are given in the first article by Lai et al: PAH: The clinical syndrome. The authors discuss how the cardiovascular-pulmonary physiology in PAH explains the symptoms, the hemodynamics, and the prognosis of patients with PAH. They review basic diagnostic approaches to the disease as well as the molecular mechanisms that have led to the current approved therapies of PAH. The authors use several algorithms that have been developed based on large outcome studies in PAH and attempt to calculate the expected survival of our patient. This is almost an impossible question to ask or to answer and yet is one of the most common ones asked. Our patients will appreciate an answer based on hard evidence, to the best of our ability.

3. You mentioned that there are 3 classes of medications available to me; which is the best? Will I eventually be on all of them?
4. Should I be optimistic about the future? It seems that there are so many cures for PAH in animal research but the currently available therapies do not cure the disease—why?
5. You mentioned there will be many research trials in the future that I may consider. How should I be best informed on which one is the most promising?

The answers are given in the second article by Zamanian et al: Current Clinical Management of PAH. Here, a team of young faculty, all clinician scientists that run the PAH clinic at Stanford University, describe how they approach their patients with PAH in an era where molecular biology, genetics, randomized trials, and guidelines all merge. Their approach to patients with PAH and their treatments can be seen as a model for a tertiary care clinic that in addition to standard clinical care provides options for discovery and clinical research.

6. I am fit and watch my diet, but my triglycerides are high and I read that my lung blood vessels have the same metabolism to that of a tumor. What does this mean and how important is it for my condition?

The answer is given in the third review by Paulin and Michelakis: The Metabolic Theory of PAH. The article summarizes the evolving metabolic theory of PAH. The theory proposes that many of the diverse causes of triggers of PAH are a part of a generalized, cancer-like, metabolic remodeling that involves not only the pulmonary arteries but other organs as well, including perhaps the RV, the skeletal muscle, or the bone marrow. The theory suggests that these mitochondrial and metabolic changes are not secondary to the disease process but are causal and thus can be therapeutically targeted.

7. I read that there is a lot of inflammation in my blood and in my lungs, as if I had an infection, but I don’t have fever. What does this mean and how important is it for my condition?

The answer is given in the next article by Rabinovitch et al: Inflammation and Immunity in the Pathogenesis of PAH. The authors review the evolving inflammatory theory of PAH. The theory proposes that immune and inflammatory cells are activated in PAH and through paracrine signaling facilitate or cause many of the molecular abnormalities that have been described in this disease. The theory suggests that these changes are not secondary to the disease process but primary, suggesting that they could be therapeutically targeted.

8. I met this patient in the PAH group meeting… She has lower pulmonary artery pressures than I do, but she is much sicker….What does that mean; how is it possible?

The answer is given in the article by Ryan and Archer: The Right Ventricle in PAH (but also discussed in the first article by Lai et al). The question is reasonable and not a paradox; yet it is commonly misunderstood even by practicing physicians: because the disease progresses and the RV fails, it is unable to generate contractile force and the recorded pulmonary pressures are lower, but the patient feels worse because of the decrease in the cardiac output. The authors describe our current appreciation that RV function is the most critical parameter in the morbidity and mortality of PAH and thus should be approached in parallel to the pulmonary vascular remodeling. They describe critical differences between the RV and the left ventricle and summarize our progress in our understanding of RV failure, which is not necessarily similar to what we know about left ventricular failure.

9. Why me? I am not aware of anybody else in my family ever being diagnosed with this disease, dying prematurely or having similar symptoms.

10. I wish to have children. Should I be concerned about passing this disease to my children and are there any tests I can take to know for sure?

The answer is given in the last article by Austin and Loyd: the genetic basis of PAH (but also discussed in the first article by Lai et al). The authors review the evidence for mutations and disturbed signaling in the bone morphogenetic protein receptor II axis in heritable PAH, possibly the most important discovery in PAH for the past 15 years. They also discuss many novel mutations that have recently been added to the list of involved genes in PAH. They discuss the penetrance and the role of these mutations in the pathogenesis of PAH and give practical answers to the questions of our patient, which are typically among the most frightening for the young patients newly diagnosed with PAH.

Michael Servet did not burn alive in vain….Servet’s and Forssmann’s passion for knowledge is infusing an army of young researchers and experienced clinicians with more energy for discovery. Our patients will continue to suffer but not for long. Perhaps the answer to their prayers is somewhere hidden in this compendium.

Disclosures

Michelakis is a member of the Bayer clinical trial steering committee on riociguat (<$5000 total, past 5 years). He is a consultant in United Therapeutics (<$5000 total, past 5 years). He is a member of the faculty of Entelligence (a committee selecting young faculty proposals for a young investigator award in the field of pulmonary hypertension).

References


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