From the Andes to the Rocky Mountains: A Historical View of High-Altitude Pulmonary Hypertension

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The current understanding of high-altitude pulmonary hypertension (HAPH) is largely attributable to the work of a small cadre of international scientists. The present article discusses the discovery and early investigations into HAPH that now serve as the foundation of our modern understanding of the disease. Further, though HAPH is clearly a distinct entity, we highlight how this early work led to a broader understanding of pulmonary vascular disease—including pulmonary arterial hypertension (PAH)—through the development of translational clinical models of disease, elucidation of hypoxic signaling, and therapeutics applicable to PAH.

INTRODUCTION

The recognition and early scientific investigation of high-altitude pulmonary hypertension (HAPH) is a relatively recent occurrence, with the discovery of HAPH in humans occurring in the mid-1900s. The foundation of our understanding of HAPH was laid by South American investigators working in the Andes, with further development by investigators working in the Rocky Mountains of Colorado. Together, this international team made groundbreaking observations that elucidated the effects of altitude on the pulmonary vasculature and risks to human health. Moreover, their work spurred countless other investigators to expand on our understanding of the effects of acute and chronic hypoxic exposure and the specific structural, cellular, and molecular underpinnings of the pathophysiologic changes seen in the diseased pulmonary vasculature. This has not only expanded our understanding of HAPH but has contributed greatly to our understanding and treatment of pulmonary arterial hypertension (PAH).

BRISKET DISEASE AND BEYOND: THE RECOGNITION OF PULMONARY HYPERTENSION IN ANIMALS

Early Investigations of the Relationship of Pulmonary Artery Pressure and Hypoxia

The first invasive hemodynamic measurements of pulmonary arterial pressure (Ppa) were performed in 1852 in work by Carl Beutner.[1] He measured baseline Ppa in the dog, cat, and rabbit via thoracotomy and cannulation of the pulmonary artery with a monometer. Focusing exclusively on acute changes in Ppa, he ventilated the animals with bellows, observing that halting ventilation for an extended period of time caused an increase in Ppa. Since the experimental animals had undergone bilateral vagotomy, he conjectured that venous blood stimulated cardiac nerves, increasing the force of cardiac contraction, thereby increasing Ppa via an increase in cardiac output.[2] Over the next century, others investigated the effects of respiration on the pulmonary circulation, also demonstrating the early rise in Ppa with various methods of limiting ventilation. The trigger of this phenomenon was reviewed by Wood in 1902,[3] with the potential mechanisms being "first, that it is due to a damming back of the blood; second, that it results from a greater flow to the right heart; third, that it is due to direct contraction of the arteries of the pulmonary circulation." It wasn't until 1946, and the work of Von Euler and Liljestrand, [4] that the modern concept of hypoxia having direct effects on Ppa was discovered. Their work sought to determine how pulmonary vessels react to variations in inhaled gases by ventilating cats with various concentrations of O_2 and CO_2. The most striking finding was that while ventilating the lungs with 100% O_2 caused a small decrease in Ppa, subjecting the lungs to ventilation with 10.5% O_2 caused a robust increase in Ppa. They also noted that this increase in Ppa was not associated with change in left atrial pressure, was larger than the increase in Ppa caused by moderate exercise (assumed to be due to increase in cardiac output), and was not prevented by vagotomy. Thus, they concluded that there was a direct constrictive action of hypoxia on the pulmonary vessels. The exact mechanisms by which hypoxia triggers (directly or indirectly) pulmonary vascular smooth muscle contraction and the possible contribution of pulmonary artery endothelial cells remain incompletely explained and continue to be an active area of investigation.

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The Discovery of Pulmonary Hypertension in Animals With Chronic Hypoxia Exposure

In the late 1800s, ranchers began moving their herds to the fertile grasslands around South Park, Colorado, situated in the Rocky Mountains at 2438 to 3048 m (8000 to 10 000 ft). What appeared to be ideal grazing land for cattle proved to be deadly, with many dying of what the ranchers termed "brisket disease," after the characteristic swelling of the neck tissues that normally comprise the brisket cut. Rather than a scientific curiosity, initial investigations were motivated by the financial strain caused by loss of herds at altitude. In 1913, two prominent South Park ranchers contributed $100 each to the Experimental Station at Colorado Agricultural College for the study of brisket disease. With this, George Glover and Isaac Newsom, a veterinarian and pathologist, respectively, began to explore the cause of brisket disease.[5] They noted the following:

> *During the winter of 1913-1914, one South Park stockman estimates that out of between four and five hundred cattle, he lost thirty calves and ten or twelve older animals. Another man lost 12 during the winter of 1912-1913. Still another says, after several years' experience, he has lost practically all bulls that he shipped in from a low altitude and he figures his loss at about five per cent.… While this may seem small, yet in the aggregate it means many thousands of dollars.*[6]

In their investigations, they quickly excluded feed differences, communicable or infectious etiologies, and other environmental exposures, and determined that it was high-altitude exposure that led to weak pulses, distended neck veins, and edema. Moreover, when affected animals were transported to Denver (a mere 1585 m [5200 ft] elevation), the heart failure resolved. Zeroing in on heart failure as the trigger, they titled their manuscript "Brisket Disease (Dropsy of High Altitude)." With the work of Von Euler and Liljestrand not to come for another 3 decades, the connection between the pulmonary circulation and right ventricular failure was understandably out of reach. However, it is impressive that in just 2 years, Glover and Newsom established the causative agent (altitude) of brisket disease, the resulting heart failure, the "cure" of transport to lower altitude, and also realized that using "native" highland bulls for breeding could improve hardiness. Research interest waned until the 1940s, when one of Newsom's students, Rue Jensen, established through histologic studies that the source of brisket disease was right heart failure, postulating that "atmospheric hypoxia causes pulmonary changes which lead to increased resistance to circulation through the lungs and failure of the right ventricle."

In the late 1950s, two young faculty members at the University of Colorado School of Medicine, Jack Reeves and Robert Grover, intrigued by their observations of pulmonary hypertension (PH) in children with congenital heart disease, began collaborating with Arch Alexander and Don Will, veterinarians at Colorado State University in Fort Collins with a newfound interest in brisket disease. Familiar with the work of Glover, Newsom, and Jenson, along with the acute effects of hypoxia on the pulmonary vasculature as established by Von Euler and Liljestrand, they sought to understand the effects of chronic hypoxia on the pulmonary vasculature. To do this, they established a laboratory on Mount Evans in the Rocky Mountains at an altitude of 3871 m (12 700 ft). Here, they exposed young steers to chronic atmospheric hypoxia for 2 months, performing serial catheterizations demonstrating a marked increase in mean Ppa from baseline of 25 mm Hg to 75 mm Hg. Histologic examination demonstrated marked thickening of the media of the small muscular arteries, with pulmonary arteriograms showing similar findings. Noting that lambs were known to endure altitude with ease, they performed parallel hemodynamic studies that demonstrated that they did not develop PH at altitude.[7] Through this elegant experimental approach, the connection of HAPH with the pulmonary circulation was cemented, coupled with the idea that certain species were more prone to develop HAPH than others.

Later work reinforced the comparative biologic work that Grover performed in those early experiments. Noting the significant variability in rise of mean Ppa that Grover saw in his experiments, two scientists at Colorado State University tested the hypothesis that degree of susceptibility to HAPH was inherited. After 8 years of breeding bulls and heifers that were identified as either susceptible (hyperreactive) or resistant (hyporeactive) based on their degree of severity of HAPH, they had 2 to 3 generations of offspring and were able to clearly show that with exposure to hypoxia the hyperreactive or hyporeactive trait was preserved by selective breeding.[8]

THE DISCOVERY AND DESCRIPTION OF HAPH IN PERU

Much of what is known about HAPH in humans began with physiologic studies in the Peruvian Andes where the partial pressure of oxygen can be as low as 85 mm Hg.[9] In the late 19th century, French physiologists Paul Bert and François-Gilbert Viault first noted polycythemia in individuals resided in Morococha, Peru, a highland town that sits at an altitude of 4540 m (14 895 ft) above sea level with a mean barometric pressure of 445 mm Hg. In 1921, Joseph Barcroft led an expedition of English and American physiologists to Cerro de Pasco, Peru, located at an altitude of 4330 m (14 206 ft). Barcroft performed various physiologic experiments and measurements on his team while in Cerro de Pasco only to offensively and falsely conclude that residents of high altitudes are of lower physical and mental capacity based on his findings. In response to this claim, Carlos Monge Medrano also led an expedition to Cerro de Pasco in 1927 to evaluate cardiopulmonary physiology in the native population. Monge observed that high-altitude residents had polycythemia, increased blood viscosity, increased serum protein, and hyperventilated with a chronic respiratory alkalosis, which he called "La enfermedad de los Andes" or the "disease of the Andes."[10] This condition was later named Monge disease or chronic mountain sickness (CMS). CMS has since been further characterized as a

syndrome seen in some residents living above 2500 m (8202 ft). Findings include hypoxemia, polycythemia, PH, and cor pulmonale, with symptoms similar to those of other chronic respiratory diseases. CMS symptoms have been shown to resolve once a person relocates to sea level for a sufficient period of time.[11,12]

Human pulmonary artery catheterization was then a novel technique, having first been performed in 1945 by Cournand in a subject with mitral stenosis and resultant PH.[13] By the 1950s, acute anoxia had been demonstrated to result in elevations in Ppa but the effects of chronic hypoxemia on the pulmonary circulation were still unknown. Rotta and colleagues[14] studied 4 groups of Peruvian men: lifelong sea-level natives, lifelong high-altitude natives, those who immigrated to high altitude 1 year prior to the study, and high-altitude natives with CMS. Performing the first hemodynamic studies demonstrating HAPH in humans, they found that Ppa and right ventricular (RV) pressures were elevated in all high-altitude groups compared with those at sea level. The rise in pressures was lowest in the immigrant group and highest in the CMS group. In the CMS group, Ppa and RV pressures slightly decreased with the administration of oxygen, but these changes were not seen in other groups. They postulated that this suggested that there were mechanisms other than hypoxic pulmonary vasoconstriction that led to the changes in the pulmonary circulation in long-term high-altitude residents with HAPH.[14]

In an effort to clarify the prevalence of HAPH, Penazola et al performed electrocardiographs and vectocardiographs of 1090 Peruvian natives ranging from newborns to 60 years of age. Of these, 650 were residents of Lima at sea level while 440 lived in Morococha. All newborns demonstrated evidence of RV hypertrophy (RVH), reflective of the right-heart–dominant circulatory system in utero. These findings resolved within a few weeks at sea level but persisted lifelong at high altitudes.[15,16] Following this, they performed a series of cardiac catheterizations in high-altitude newborns, children ages 1 to 5 years and 6 to 14 years, and men ages 17 to 34 years. Newborns at sea level and high altitude had an average mean Ppa of approximately 60 mm Hg. While the mean Ppa quickly normalized for newborns at sea level, the decline was much slower and remained elevated into adulthood for high-altitude residents. At high altitudes, the average mean Ppa was 45 mm Hg at ages 1 to 5 years, 28 mm Hg at ages 6 to 15 years, and 28 mm Hg in adults. In comparison, the average mean Ppa at sea level in adults was 12 mm Hg. Cardiac output, right atrial pressures, and pulmonary capillary wedge pressures were similar at different altitudes.[17,18]

During this period, fueled by the electrocardiographic work and hemodynamic studies, Arias-Stella and colleagues performed groundbreaking histopathologic studies that for the first time elucidated the pathogenesis of HAPH. To confirm the findings of the electrocardiographic studies, autopsies were performed to evaluate the hearts of residents of low and high altitudes who died of noncardiopulmonary causes. In total, 241 natives with ages ranging from newborn to 80 years of age were examined. All newborns had a greater right heart mass compared to the left heart. The left heart became dominant between the ages of 1 day to 3 months, although RVH was still present. The RVH resolved between 3 and 23 months at sea level but persisted to varying degrees in all age groups at high altitude. The left ventricular mass was similar for a given age group at low and high altitudes.[19,20] Hypothesizing that altitude altered the pulmonary vascular structure, they performed histologic examination of the distal pulmonary arterial branches of 30 subjects native to sea level and 20 subjects native to altitude—all of whom died in accidents or from acute noncardiopulmonary disease. The ages of the subjects ranged from newborn to 76 years, and they found that the newborns had no differences—all had the characteristic fetal pattern of increased smooth muscle cells in the small pulmonary arteries and muscularization of the arterioles. However, they found that children and adult subjects at altitude retained this phenotype, with thickened vascular walls and lumen narrowing in comparison to the sea level subjects.[21,22] For the first time, structural changes in the pulmonary vasculature were identified as the primary cause of HAPH, rather than polycythemia, cardiac output, or hypervolemia.

PARALLEL SCIENCE IN THE ROCKY MOUNTAINS

The comprehensive work being done in South America was being published in local journals that were elusive to their North American counterparts who had been studying bovine HAPH. Hearing of the studies by Penaloza and colleagues, Grover traveled to Peru in 1961 and became fully aware of the extensive hemodynamic and histologic work they had performed.[23] Inspired by this, Grover and a cadre of physician-scientists from the University of Colorado sought to determine if there was evidence of PH at 3094 m (10 150 ft) in Leadville, Colorado—the highest incorporated town in the United States, but also markedly lower in elevation than the 4572 m (15 000 ft) of their Peruvian counterparts. Initially, an electrocardiographic study was carried out, wherein the entire high school population of 508 subjects underwent physical exam, chest radiograph, and electrocardiogram. In comparison to similar subjects from a lower altitude, they found an electrocardiographic preponderance of rightward deviation, suggesting RV enlargement.[24] This study was followed by a hemodynamic follow-up in 1962, where 28 healthy and asymptomatic individuals residing in Leadville who were 12 to 17 years of age underwent resting and exertional right heart catheterization. Sixteen of these children had 2 findings of PH—either on examination (increased P2), chest radiograph (enlarged pulmonary vasculature or right atrium), or electrocardiogram (right axis deviation)—while 14 had no objective evidence of PH. The results were striking in that 10 of the 28 subjects had a resting mean pulmonary arterial pressure (mPAP) ±25 mm Hg. Also notable was that, with exercise, many of the subjects had significant increases in mPAP that were exaggerated in comparison to subjects at sea level.[25] Interestingly, one of the subjects with particularly severe

PH in this study relocated to sea level, and after 11 months underwent repeat right heart catheterization, demonstrating normalization of resting Ppa.[26] This reversibility was further studied by the South American group, where Sime et al[27] studied the effects of relocating high-altitude natives to Lima. The study included 11 young healthy male volunteers born around Cerro de Pasco with baseline studies performed in Morococha, then repeated after living in Lima for 2 years. They found that hypoventilation decreased but did not normalize and the heart rate decreased while the cardiac index increased. In addition, the mPAP and average pulmonary vascular resistance normalized. This normalization was not seen with supplemental oxygen alone, which further supported the primary role of structural remodeling in the pathophysiology of HAPH.[27]

RESULTING LEGACY AND CONTRIBUTIONS TO THE MODERN PARADIGM OF PAH

While the initial identification and understanding of HAPH was motivated by the economic interests of cattle farmers, an international group of scientists appreciated the potential impact of HAPH on human populations and dedicated their careers to this pursuit. By the mid-1960s, the South American investigators and Coloradoan counterparts firmly established the demonstrable increase in resting Ppa in both natives and newcomers to altitude, and that this was often associated with polycythemia and other findings of CMS. Further, they were able to show that in children born at altitude, the normal regression of RVH and pulmonary vascular smooth muscle with corresponding fall in pulmonary arterial pressure and resistance was aberrant and persisted later in life, establishing the histopathologic basis for HAPH. Finally, they established that exercise—even in healthy individuals—was accompanied by an intensified increase in Ppa and blunting of the normal exercise-related decrease in pulmonary vascular resistance.

This fundamental work led to decades of work elucidating the mechanistic underpinnings of altitude- and hypoxia-induced alterations of the pulmonary vasculature, including the pathobiologic differences between acute hypoxic vasoconstriction, and the hypertrophy or hyperplasia of pulmonary arterioles and RV remodeling observed with chronic hypoxia and altitude exposure. Recognizing the interspecies variability in development of HAPH, reproducible rodent models of hypoxia-induced PH were developed, which along with continued application of the bovine model have greatly aided our mechanistic understanding of PH. These models recapitulate the remuscularization of previously nonmuscularized arterioles, along with hypertrophy of muscularized precapillary pulmonary arteries. Further, they also demonstrate vascular-specific inflammatory responses that have more recently been recognized as a driver of PH, with enhanced perivascular expression of inflammatory mediators and influx of neutrophils and macrophages.[28] These later developments also led to the discovery of vasoactive mediators that contribute to the vasoconstriction and remodeling seen in PH, including nitric oxide, prostacyclins, and endothelin. Recognizing the parallels with experimental PH and the human disease state of PAH, these have all served as therapeutic targets that have significantly improved symptoms and outcomes for those afflicted.[29]

While these discoveries led to the development of a greater understanding of the pulmonary circulation and undoubtedly led to enhanced understanding of PAH, HAPH demonstrates a distinct difference in comparison to the family of diseases that comprise World Health Organization group 1 PAH. As opposed to PAH, which is progressive, subjects with HAPH demonstrate reversibility when relocated to sea level. Further, PAH characteristically results in significant exertional limitation, while subjects with HAPH paradoxically demonstrated no apparent exercise limitations despite the increased RV afterload, hinting at a fundamental difference between those with HAPH and PAH—and a point of future studies that can be leveraged to further our understanding of both disease states.

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