HIGHLIGHTED TOPIC | Pulmonary Circulation and Hypoxia

Insights by Peruvian scientists into the pathogenesis of human chronic hypoxic pulmonary hypertension

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Reeves, John T., and Robert F. Grover. Insights by Peruvian scientists into the pathogenesis of human chronic hypoxic pulmonary hypertension. J Appl Physiol 98: 384–389, 2005; doi:10.1152/japplphysiol.00677.2004.—Pulmonary hypertension had long been suspected in high-altitude natives of the Andes. However, it remained for a team of Peruvian scientists led by Dante Penaloza to provide not only the first clear evidence that humans living at high altitude did indeed have chronic, and occasionally severe, pulmonary hypertension, but more importantly, that this was a consequence of structural changes in the pulmonary vascular bed. Novel histological findings by one of the team, Javier Arias-Stella, indicated that hypoxia-induced thickening of the pulmonary arteriolar walls was the primary cause of the elevated pressure. Because the hypertension was not promptly reversed by vasodilators (oxygen inhalation or acetylcholine infusion), they found it differed from acute hypoxic pulmonary vasoconstriction. The team’s other novel findings included a delay in the normal fall in pulmonary vascular resistance after birth and, in adults, a lack of vasodilation with muscular exercise. Furthermore, the altitude-related pulmonary hypertension resolved over time at sea level.

Dante Penaloza; Javier Arias-Stella; lung arteriolar hypertrophy; high altitude; historical review

MORE THAN FOUR DECADES AGO a team of investigators in Peru proposed a new concept for the pathogenesis of hypoxic pulmonary hypertension in high-altitude residents. On the basis of anatomic and hemodynamic correlations, they presented evidence that chronic hypoxia increases the muscularity of the walls of small lung arteries, thereby increasing the resistance to blood flow, resulting in an elevation of pulmonary arterial pressure. Today we take this simple concept for granted, but we should consider that our understanding was not always so clear. The purpose of this history is to focus on a single investigative team, how it was assembled, and how it functioned, despite substantive obstacles, to demonstrate the basis for chronic hypoxic pulmonary hypertension in humans. Because the Peruvian contribution to the development of this concept in relation to other discoveries around the world has been reviewed in detail recently (26), we now present only the highlights from that review.

In 1946 (35), when acute hypoxia was found to raise pulmonary arterial pressure in the cat, one might think that the right heart hypertrophy and failure in high-altitude residents would be attributed, at least in part, to hypoxia-induced pulmonary hypertension. But there was no such prompt clairvoyance. Understanding results from many small steps, not giant leaps. A subsequent study simply confirmed that acute hypoxia raised pulmonary artery pressure in humans at sea level (15). When later studies showed that the elevated pressures were not from a high cardiac output (9), the concept evolved that acute hypoxia likely caused constriction of the small pulmonary arteries. Still, the changes were so small that the normal lung circulation was considered virtually devoid of active control (10). The first report in English of direct measurements of pulmonary arterial pressure in humans living at high altitude was in Morococha, Peru (4,540 m) by Rotta et al. (27). At that time, Andres Rotta was the Chief of the Cardiovascular Laboratory, Instituto de Biologia Andina (IBA), Universidad Nacional Mayor de San Marcos (UNMSM). Rotta et al. attributed their findings of a modest increase in pulmonary artery pressure not to hypoxia per se but rather to polycythemia, increased blood volume, high cardiac output, and abnormal ventilation. Clearly what was missing in the mid 1950s was the concept that sustained hypoxia could induce anatomic narrowing of the pulmonary arterioles and that this was a process distinct from acute hypoxic vasoconstriction and caused more pulmonary hypertension. It remained for Dante Penaloza and his group to make the crucial connection between sustained hypoxia and chronic hypoxic pulmonary hypertension.

Human nature is fascinating. Penaloza and Arias-Stella (Fig. 1) presented the first definitive reports of their exciting new data from Peru (3, 23) at the 1962 Aspen Lung Conference.

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Penaloza, whom we consider the prime mover for the Peruvian other key players, we chose to focus on the person, Dante historical review, at the risk of inadequately acknowledging published in detail by the Peruvian investigators. In the present All of these findings were novel for humans and were pub-

level had prompt resolution of their pulmonary hypertension. In high-altitude natives, the administration of oxygen or

acetylcholine reduced pulmonary arterial pressures by only 15

implying a structural anatomic basis for the increased vascular resistance. However, the finding that pulmonary hypertension occurred in human residents at high altitude (4,540 m) and was due to structural changes induced by the effects of chronic hypoxia on the pulmonary arterioles. Furthermore, the factors considered by Rotta et al. (27) to be primary (“hypervolemia, polycythemia, high blood viscosity, and a certain degree of arteriolar vasoconstriction...”) were considered by Penaloza et al. to be merely secondary.

In high-altitude natives, the administration of oxygen or acetylcholine reduced pulmonary arterial pressures by only 15 to 20%, and the lung circulation failed to dilate with exercise, implying a structural anatomic basis for the increased vascular resistance. However, the finding that pulmonary hypertension disappeared when high-altitude natives were taken for 2 yr to Lima near sea level (5, 32, 33) not only demonstrated reversibility of the hypertension but also distinguished it from “primary pulmonary hypertension” as some had assumed. In children and adolescents, the pulmonary vasodilation that normally occurs after birth at sea level was markedly delayed in Moro-

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lar hypertrophy. I was intrigued with our findings and was motivated to make a second excursion to Morococha. This time we did ECG chest mapping using multiple unipolar leads on the front and back surfaces of the thorax in adult residents. The ECG tracings of adults did not show the classical pattern of RVH; instead, the QRS mean vector exhibited great dispersion, so that the ECG interpretation at high altitude became more enigmatic.

When I concluded my residency, I was appointed as Asso-
ant Professor of Medicine. At that time Hurtado was the Dean of the School of Medicine. Because he and Monge knew of my keen interest in electrocardiography, they obtained for me a 3-year fellowship at the Instituto Nacional de Cardiología de Mexico, which then had a well deserved international reputa-
tion in electrocardiography. From 1951 to 1954 I worked with Professor Sodi-Pallares who was then dedicated to experi-

mental electrocardiography. I had the opportunity to discuss with him the ECG mappings obtained in adult natives at altitude and he too was intrigued by the findings.

At his suggestion we obtained ECG mappings there in Mexico City, this time with simultaneous multiple unipolar chest leads recorded at high speed in both normal individuals and in patients with right ventricular hypertrophy of varied etiology. I started this adventure with the cooperation of Joao Tranches, a distinguished Brazilian fellow. When possible we also studied the relationship between our findings and the anatomical features at autopsy. We worked intensively and after two years we were able to understand the spatial se-

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(11). Although the audience included international experts on pulmonary vascular anatomy, pathology, and physiology, they failed to comprehend the implications of what they had seen and heard. Discussions of their papers focused on tangential matters, with no mention of this important concept that was one of the major new ideas to come out of the conference. Obviously their minds were not prepared to accept it. Andre Cournand, who prepared the conference summary (11), did not even mention this major contribution by Penaloza and his colleagues.

Over the years there appeared a flood of publications on the high-altitude lung circulation from this Peruvian team (1–7, 13, 14, 17–25, 28–33). Pulmonary arterial pressures at rest and during exercise, together with histologic findings, provided the first clear evidence that substantial pulmonary hypertension occurred in human residents at high altitude (4,540 m) and was due to structural changes induced by the effects of chronic hypoxia on the pulmonary arterioles. Furthermore, the factors considered by Rotta et al. (27) to be primary (“hypervolemia, polycythemia, high blood viscosity, and a certain degree of arteriolar vasoconstriction...”) were considered by Penaloza et al. to be merely secondary.

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1 The narrative from Dr. Penaloza was extracted from numerous E-mail messages exchanged with us, often in response to our questions.
course, right ventricular hypertrophy in the peculiar ECGs from the natives at altitude.

When I returned to Peru I was reappointed to the School of Medicine and was named investigator of the IBA. It was then that I felt how fortunate I was to be surrounded so soon by a group of students and recently graduated physicians. All of them were anxious to acquire knowledge in electro-vectorcardiography and in high altitude medicine. Amongst these were Francisco Sime, Raul Gamboa, Emilio Maritocorena, Juan Dyer, Max Echevarria, Natalio Banchero, Julio Cruz, Luis Ruiz and many others.

The project to carry out hemodynamic investigations in native children and adults at high altitude was the natural consequence of our electro-vectorcardiographic findings. Those investigations had shown us that in the newborn there is an electric preponderance of the right ventricle at altitude similar to that at sea level [19]. However, after birth these patterns clearly diverged. At sea level, the right ventricular preponderance decreases promptly during the first three months and after 4–6 months there is left ventricle preponderance. In contrast, at 4,540 m the right ventricle predominance decreases slowly and is maintained throughout life [19, 20].

Based on these findings we postulated that at high altitude the postnatal changes in pulmonary artery pressure and pulmonary vascular structure would probably differ from what was already known at sea level. Heath and Edwards [12] had established the relationship between the degree of pulmonary hypertension and the magnitude of the changes in the pulmonary vascular structure in patients with congenital heart diseases. This made us suspect that something similar should exist in other conditions with pulmonary hypertension such as high altitude.

Testing our hypothesis made it necessary for us to carry out direct measurement of the pulmonary arterial pressure in altitude natives, children, adolescents and adults. At that time, we only had direct evidence of pulmonary hypertension in four adult natives at altitude [27] and the authors provided no satisfactory interpretation. It was also essential that we examine the correlation between hemodynamics and the postnatal changes of the heart and the pulmonary vascular structure at high altitude. For these anatomical studies I contacted Javier Arias-Stella. He and I were very close friends ever since our studies at the university. Now, we both were professors at the same school of medicine and appointed as heads of our departments, Cardiology and Pathology, respectively. Javier was, at that time, investigating endometrial cytology and had made a seminal discovery which is known as the “Arias-Stella phenomenon.” Javier promptly showed high interest in our hypothesis, and it was then that we planned to carry out parallel investigations, hemodynamic and anatomic, of the pulmonary circulation in children and adults native to high altitude.

Morococha, a mining town located at 4,540 m with a population of about 6,000, was the logical place to conduct these studies since Hurtado had already established a research laboratory there [Fig. 2]. In those days there did not exist the limitations of today with respect to research on human beings and so our project involving cardiac catheterization was approved by the NIH. Sime did many of the procedures and I had the roles of organizer and monitor [Fig. 3], with the valuable help of the other team members. The individuals were selected at random. The selection was not based at all on the electrocardiogram or on clinic signs of pulmonary hypertension. The adult natives at altitude were enlisted through an agreement with the Peruvian Army from a group of soldiers who volunteered in exchange for their transfer to sea level after the investigations. Other adult natives offered themselves up for the investigation for remuneration. Some subjects had investigations awake and asleep [Fig. 4]. The children and adolescents were selected by agreement with the parents based on payment and the opportunity for their children to attend schools on the coast. The Instituto Nacional Pedagogico offered scholarships for them in Lima. This offer was facilitated because the founder and Director of this Instituto was my brother (Doctor Walter Penaloza, renowned teacher, philosopher and later the Peruvian Ambassador to Germany).

To summarize our principal findings, the adults had mild pulmonary hypertension at rest (mean pulmonary artery pressure 28 mmHg) [23, 24] that doubled during light exercise (60 mmHg) [6] with no pulmonary vasodilation. Young children had significantly more pulmonary hypertension (mean pulmonary artery pressure 45 mmHg) [17, 31] than adults, but this regressed to the levels seen in high altitude adults as the children grew older. In post mortem studies the high altitude residents had developed a distinct pulmonary arterial anatomy characterized mainly by the presence of large amounts of muscle in the small arteries with muscular extension into precapillary vessels (arterioles) normally devoid of muscle [3, 4]. Together, these findings strongly supported our hypothesis that this muscularization of distal pulmonary vessels provided an anatomic basis for the increased pulmonary vascular resistance and resulting pulmonary hypertension in this high altitude population.

During the conduct of these studies, there was some political upheaval. In 1960 there was a crisis at the School of Medicine, UNMSM. A group of communist students prevailed in the University Council, and Hurtado, then the Dean of the School of Medicine, with 90% of the faculty, resigned. Two years later, under Hurtado’s leadership the professors who had resigned founded a new university, Universidad Peruana Cayetano Heredia (UPCH). As a result of a contest, I was appointed Professor of Medicine. A new altitude institute was created.
with the name of High Altitude Research Institute (HARI) and I was named Chief of the Cardiovascular Laboratory. We promptly developed a research project for hemodynamic studies in children and adults at high altitudes. The US Public Health Service approved this project and awarded us research grants.

For the conduct of research in Peru 50 years ago, one must remember that although research was encouraged, it had to be on the investigator’s own time and at his personal expense. No one was paid to do research (or even to teach). We were expected to support ourselves from the private practice of medicine. As a result of this cultural reality, one had to be truly dedicated to pursue research activities. We had to be active practitioners first, and researchers second, and our economic survival depended on the former. For me, it was a family tradition to obtain spiritual satisfaction by performing investigative activities. It has been of the highest value in our lives. At the beginning of my clinical practice of Cardiology I considered it unethical to receive professional fees from the patients, yet I had to support myself.

Writing this essay has brought pleasant memories, particularly the human warmth that I received at IBA beginning when I was a student. Hartado’s affection and support lasted until his death. Also, I recall the satisfaction of being surrounded by many collaborators that came to the laboratory as if attracted by a magnet. Most of them continued on as associate investigators. The enthusiasm and harmony amongst all the team members was remarkable. Whether we were carrying out studies at sea level or at altitude, each one of them contributed his own ideas, knowledge and unique personality. In this pleasant environment that remained with us during many years, I must include the medical staff, technicians and nurses.

Fig. 3. Left: Dr. Francisco Sime during heart catheterization of a volunteer subject, who is performing supine cycle exercise. Right: Dr. Dante Penaloz observing the cardiac monitor during heart catheterization. (Courtesy of Drs. Sime and Penaloz.)

Fig. 4. At high altitude at any age, acute hypoventilation during sleep (sueño) accentuates hypoxemia and pulmonary hypertension. Vigilia, awake; transicion, transition. Figure shows the pressure response obtained in 1960 in our first patient, a normal 5-yr-old girl at 4,540 m. [Reproduced with permission from Sime et al. (34).]
Historical Perspective

in both the sea level and altitude laboratories. Finally I emphasize the friendly relationship we had with our test subjects. This was truly a “golden era” in my career.

Unforgettable experiences were the visits we received from renowned investigators, amongst them, Hans Hecht, who arrived in Peru sent by the NIH to visit our laboratories in Lima and Morococha and to verify the progress in our investigations. Another unforgettable visit was that of Bob and Estelle Grover in 1961. Interchanging ideas on human pulmonary hypertension in the Andes and the experimental hypoxic pulmonary hypertension induced in calves in Colorado by Grover, Reeves and others were very illuminating. It was a pleasure for us to incorporate Bob as a Correspondent Member of the Peruvian Society of Cardiology. An amusing story on his stay in Peru was his spectacular acute mountain sickness episode (soroche) while visiting Morococha. This has been published by Bob under the heading “High adventure in Peru,” as a part of his article Pulmonary hypertension: The price of high living [36].

SUMMARY

A number of important factors came together to make possible the large body of research by Penaloza and his colleagues. The Andes Mountains themselves provided nature’s own human laboratory, which, in the first half of the 20th Century, was recognized and exploited by medical academic pioneers such as Mongé father and son, Hurtado and Rotta. A unique body of evidence suggestive of pulmonary hypertension in altitude residents resulted. This was followed by new tools for investigation (cardiac catheterization), new concepts (hypoxic pulmonary vasoconstriction), and international cooperation and funding (principally from the United States).

Concurrently, there appeared a young scientific leader, Dante Penaloza, who could assemble a team made up of faculty (cardiologists, pulmonologists, pathologists, physiologists) and medical students, and who could get the cooperation of the military, mine operators, and subjects. From the intense work of this team, including that of Javier Arias-Stella, a new concept was substantiated in humans, namely, that chronic hypoxia acting to remodel lung vessels has a more profound effect than does acute hypoxic vasoconstriction. Muscular arteries become more muscular (medial hypertrophy), and new muscle appears in the peripheral arterioles where no muscle existed before. Not only does the sheer mass of new muscle impinge on the arteriolar lumina but the muscle also has a contracture-like high tone, and both factors act to impede blood flow. To overcome the resistance created by these muscle-bound vessels, higher pressure is required to maintain blood flow. Dante Penaloza led the Peruvian investigations that demonstrated for the first time this anatomic basis for “chronic hypoxic pulmonary hypertension” in humans.

The future direction of science is unpredictable. Penaloza and colleagues could hardly have predicted that the blunted vasodilatation they observed in their high-altitude residents reflected lung arteriolar walls that were not just thickened but also had a fundamentally altered behavior. Since their work, physiologists have shown the complexities of calcium flux in hypoxic pulmonary arteriolar smooth muscle cells. Further recent understanding is that when the hypoxia is chronic, the sensitivity of the contractile machinery to intracellular calcium is remarkably increased. Although Penaloza would have known that phosphorylation of myosin caused smooth muscle cells to contract, he could not have known that the phosphorylation of the myosin light chain was also under the control of another system of (Rho) kinases and that in chronic hypoxia this system promotes a contracted state of the lung vascular smooth muscle (16). Of course the origin of the cells that thickened the arteriolar walls would also not have been known in the 1960s, when attention was limited to the smooth muscle in the arteriolar media. Then the conventional wisdom was that hypoxia caused hyperplasia and hypertrophy of the cells resident in the vascular wall. The concepts could not have been imagined that circulating cells originating from the bone marrow might be brought via the bronchial and pulmonary capillary circulations to the pulmonary arteriolar adventitia and that these cells could be transformed into vascular mesenchyme (8). Currently these are new ideas that are stimulating exciting research, but they build on the foundation laid by Penaloza and his colleagues four decades ago.

ACKNOWLEDGMENTS

The authors acknowledge the Colorado Center for Altitude Medicine and Physiology.

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GRANTS

This work was supported by National Institutes of Health (NIH) Specialized Center of Research Grant HL-57144 and NIH Program Project Grant HL-14985.

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