The paradox of hypoxic pulmonary hypertension (2013 Grover Conference series)

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Just 6 decades ago, the introduction of right heart catheterization provided investigators their very first opportunity to explore the previously inaccessible pulmonary circulation. This marked the dawn of the new era of pulmonary vascular physiology. Just measuring the pulmonary arterial pressure for the first time was noteworthy. Virtually nothing was known about the regulation of the pulmonary blood vessels. Interestingly, one of the very first investigations was to measure the effect of acute hypoxia in man.¹ A rise in pulmonary arterial pressure was noted, but this was erroneously ascribed to a passive response of increasing pulmonary blood flow. Shortly, a follow-up publication acknowledged the overestimation of cardiac output, and when this was corrected, the increase in pressure was attributed to pulmonary vasoconstriction. This was the physiological response to acute hypoxia, but obviously, the effects of long-term chronic hypoxia were completely unknown.

A decade later, in the mid-1950s, two veterinarians, Pierson and Jensen,² documented for the first time significant pulmonary hypertension in cattle with brisket disease on a ranch at 10,000 feet in Colorado. While they recognized that this resulted from an increase in pulmonary vascular resistance (PVR), the etiologic factor was unknown. Speculation ranged from some toxic substance in the tall grass growing at high altitude to excess salt in the drinking water in mountain streams or even the possibility of multiple pulmonary emboli, suggesting a disorder in blood coagulation. This illustrates the complete lack of understanding of the physiology of pulmonary vascular control. Jack Reeves and I were familiar with the early publications demonstrating the increase in pulmonary arterial pressure produced by acute hypoxia in man and so suggested that perhaps the chronic atmospheric hypoxia at high altitude might be the cause of this pulmonary hypertension.

To test this hypothesis, Reeves, Will, a veterinarian, and I³ erected a corral on a mountainside well above timberline at an elevation of 12,700 feet. We took 10 Hereford

steers to this corral, and we made serial hemodynamic measurements over a 6-week period to document the effects of chronic hypoxia on the pulmonary circulation. From control measurements in Denver where the group mean pulmonary arterial pressure was 25 mmHg, pressure doubled in 2 weeks to 50 mmHg, and after 6 weeks at high altitude, mean pressures had tripled to 75 mmHg. Equally impressive was the variability among individuals in their response to this chronic hypoxia. After 6 weeks, pressures ranged from 40 to more than 100 mmHg, but only this single hyperreactive animal had gone into the frank heart failure by the time we had to terminate the project as a result of oncoming winter weather. This was the first investigation documenting in detail the development of pulmonary hypertension in response to chronic hypoxia.⁴

Concurrently, we also studied lambs and rabbits by the same protocol.⁵ These added observations demonstrated the variability among species in their responses to chronic hypoxia. I wondered how humans might fit into this spectrum. A friend of mine, Herb Hultgren⁶ at Stanford, told me of his own experiences of traveling to Peru to investigate reports that a group of investigators in Lima were studying a condition known as high-altitude pulmonary edema occurring in the Andes. Once there he learned that these investigators were also studying the pulmonary circulation in high-altitude natives. Electrocardiothoracic data showed right axis deviation, implying enlargement of the right ventricle.⁷ This in turn suggested the possibility of pulmonary hypertension resulting from the effects of chronic hypoxia at high altitude. Naturally, I was fascinated, but when I searched *Index Medicus* for published references, I found virtually nothing. Later I learned the explanation. The Peruvians had been publishing their work in Spanish in local South American journals such as *Anales Facultad Medicina Lima* not covered by *Index Medicus*. I realized that the only way I was going to see these exciting data was to travel to Peru myself and meet with the individuals who were conducting this research.

I contacted Alberto Hurtado, director of the Institute of Andean Biology in Lima, Peru, and arranged to visit him and his faculty in February 1961. There, my wife and I were introduced to Dante Peñaloza, the individual who had been studying Andean natives in the mining town of Morococha at an altitude of 14,900 feet. With his training in electrocardiography, he had determined that the altitude natives did indeed have a significant rightward shift of the mean QRS axis in the electrocardiogram.⁷ Subsequently, it was he and his colleague Sime who performed right heart catheterizations on 35 of these subjects.⁸ For the record, however, the first direct measurements of elevated pulmonary arterial pressures in Andean natives were made by Rotta et al.⁹ in 1956. I was very impressed when he saw these data firsthand. Group mean pulmonary arterial pressure at rest was 29 mmHg and increased to 60 mmHg during exercise. Similar data that he had collected from 22 subjects at sea level revealed a group mean pressure of 12 mmHg at rest increasing to only 18 mmHg during comparable exercise. Clearly, the human species developed significant hypoxic pulmonary hypertension in response to the chronic hypoxia of high altitude.

The next question for me was inevitable. Might this phenomenon of hypoxic pulmonary hypertension also be manifest in the Rocky Mountains of North America? There was a place to look, the city of Leadville, Colorado, at an elevation of 10,200 feet. When I returned to Denver, I contacted Walt Weaver of the Heart Control Program of Denver, who had demonstrated his skills in organizing and coordinating population surveys. Weaver was intrigued and later in 1961 proceeded to screen all of the students in the Lake County High School in Leadville, all 508 of them. From each student he and his team obtained a medical history, complete physical examination, electrocardiogram, and chest X-ray. The most striking finding was again a right shift in the mean QRS axis in one-third of these students.¹⁰ The obvious implication was pulmonary hypertension. To confirm this I obtained permission from the head of the cardiology division at the medical school in Denver and proceeded to negotiate with the 2 physicians in Leadville, the public health nurse, and the Sisters of Charity of Leavenworth, Kansas, who operated the local St. Vincent's Hospital. All were supportive because they realized that among the population of Leadville there was a subconscious concern for the potential ill health effects of living at such a high altitude. For example, they knew that 10% of adult males developed "thick blood" (excessive polycythemia) and had to have a phlebotomy once a month. I arranged to speak before the student body of Lake County High School, describing the proposed extension of this project by performing right heart catheterization on a se-

lected group of students. They and their parents agreed to cooperate.

In February 1962, a total of 28 students underwent right heart catheterization using the fluoroscopic facilities and support of St. Vincent's Hospital.¹¹ These were performed by John H.K. Vogel, Raymond L. Rose (both research fellows), and me over two separate weekends. The first group of 16 students (Tables 1, 2, subjects LN-JP) was selected for having at least 2 findings suggestive of pulmonary hypertension, such as an increase second heart sound, prominent main pulmonary artery, or right ventricular enlargement. To minimize bias, the second group of 12 students (Tables 1, 2, subjects BL-JJ) lacked any of these signs of pulmonary hypertension; i.e., they were normal by Denver standards. All procedures were completed without incident.

As seen in Figure 1 significant pulmonary hypertension was documented in this group of 28 normal high school students. At rest, the group mean pulmonary arterial pressure was 25 mmHg, increasing to 54 mmHg during exercise (oxygen uptake about 1 L/min). Among the 16 students with clinical signs of pulmonary hypertension, mean pulmonary arterial pressure at rest was 28 mmHg, increasing to 61 mmHg with exercise (Table 2). By comparison, among the 12 students without clinical signs of pulmonary hypertension, pulmonary arterial pressure was just 21 mmHg, increasing to only 44 mmHg with comparable exercise. Clearly, there was good correlation between the clinical picture and the hemodynamic data. Once again, just as with cattle, there was marked variability among individuals in their responses to the chronic hypoxia stimulus.

What was the nature of the increased PVR? To examine the role of vasoconstriction in response to exercise while breathing ambient air, in 22 students this hypoxia was removed by administering 44% oxygen during exercise of the same intensity. This was very effective in reducing the exercise pulmonary arterial pressure by approximately one-third in both groups of students (Table 2). Furthermore, the individual magnitude of this reduction was proportional to the severity of the hypertension while breathing room air. In other words, the higher the initial pulmonary pressure during exercise, the greater the response to 44% oxygen (Fig. 2).

As a further test of reversibility, the effect of the pulmonary vasodilator tolazoline (Priscoline) was examined in a subgroup of 5 students. We had demonstrated that this medication was highly effective in reducing the pulmonary hypertension in children with congenital heart defects.¹² Tolazoline proved to be more effective than simply removing the hypoxic stimulus and reduced exercise pulmonary arterial pressure by 42%. These added observations

Table 1. Leadville catheterization data

Name	Body SA, m ²	O ₂ uptake cc/min rest			O ₂ A-V diff., vol%			Cardiac output L/min, % change					BA O ₂ , sat%			V _E /V _{O₂}			CO ₂ content, vol%	
		Est	Meas	Ex	Rest	Ex		Rest	13% O ₂	Ex	Ex 44% O ₂	Rest	13% O ₂	Ex	Ex 44% O ₂	Rest	Ex	Rest	Ex	
Group 1																				
LN	1.93	295		1,280												33.2				
JF	1.86	278		1,110																
JoK	1.44	190	190	710	3.64		5.22	-9.0	(8.37)		88.3		41.9	33.0	39.6					
VK	1.78	260	275	760	3.85		7.11	1.7	(8.25)		9.21		30.6	29.4	43.7					
IB	1.40	220	215	815		9.58	(5.86)		8.50		90.8		36.7	38.4		31.2				
KL	1.33	220	255	645	4.48		5.69	39.0	(12.51)		90.7		53.0	29.1	35.5					
MLL	1.59	210	235	720	4.19		5.60		(10.49)		90.2		50.2	33.8	34.0					
DW	1.46	200		1,015																
DM	1.80	270	245	1,480	3.57	12.06	6.86		12.28		87.0	85.6	40.8	29.5	36.9	38.0				
JW	1.82																			
TL	1.66	255		1,455	4.33	12.63	5.88		11.53		96.5	88.3			28.3	30.9				
CL	1.52	200	175	900	4.48	9.35	3.90	25.8	9.62		89.7	85.9	38.8	38.2	38.5	35.1				
JD	1.85	285	255	1,635	3.93	11.07	6.48		18.72		93.6	82.9	36.4	32.8	39.8	33.6				
BB	1.60	250	245	1,270	4.26		5.75	19.4	(10.88)	-9.2	87.5		37.9	36.5	35.1					
RH	1.38	220	245	1,050	3.94		6.22	-12.4	(10.38)		96.0		62.8	31.8	34.4					
JP	1.27			765																
Group 2																				
BL	1.70	220	235	895	4.59	8.97	5.12		9.37		95.3	91.5	100.0	79.5	46.8	38.8	36.1	34.1		
LK	1.80	275	290	1,625	4.56	11.43	6.36	24.0	14.21	4.5	95.0	88.4	96.6	78.9	41.0	30.3	34.4	33.8		
TR	1.83	270	330	1,245	6.30	12.04	5.24	5.8	10.34	-29.5	89.5	87.6		75.6	36.6	32.2	41.7	38.4		
RK	1.29	205	260	795		10.12	(5.64)		7.85	24.9		83.4		41.8	30.9		37.8			
JaK	1.29	190	205	570		8.52	(5.27)		6.69			91.1		34.6		36.9				
RR	1.77	270	300	1,580	5.27	11.77	5.69	57.8	13.41	16.6	86.6	86.9	94.2	73.4	30.3	30.7	40.1	36.7		
JCS	1.86	290	290	820	4.28	8.78	6.78	8.1	9.34		94.2	90.8	100.0	80.1	48.1	41.5	36.8	36.0		
MD	1.46	205	245	580	4.73	8.12	5.25	-1.9	7.14	-1.0	96.0	89.3	96.3	89.8	52.6	32.8	31.0	33.9		
SR	1.65	215	230	720	3.72		6.19	16.7	(9.19)	-6.0	90.8		40.9	27.5	37.4					
JKn	1.60	215	205	950	3.66	8.98	5.60		10.57	3.0	94.2	91.1	100.0		43.6	35.6	35.8	31.7		
KK	1.67	220	230	875	4.09		5.62	-5.2	(8.09)		90.3		33.0	26.9	36.6					
JJ	1.50	230	240	1,150	5.25	11.70	4.57	3.2	9.84	10.0	96.2	89.5	100.0	79.9	39.8	31.8	35.9	35.2		
Mean		237	245	1,021	4.36	10.29	5.73	+12.3	10.33	-5.2	92.0	88.6	98.2	79.6	42.1	33.0	36.6	34.9		

Note: Group 1, subjects LN-JP; group 2, subjects BL-JJ.¹¹ A-V diff.: arterial-venous difference in blood oxygen content; BA: brachial artery; Est: estimate; Ex: exercise; Meas: measured; SA: surface area; sat: saturation; V_E/V_{O₂}: ventilatory equivalent for oxygen.

Table 2. Leadville catheterization data

Name	Age sex	Mean QRS axis	No. yr	Leadville	Rest		Mean PA pressure, mmHg			Resting mean wedge pressure	Mean BA pressure, mmHg					
					Hct %	Hgb, g%	Rest	Ex	Ex 44% O ₂		13% O ₂	Rest	Ex	Ex 44% O ₂	13% O ₂	
Group 1																
LN	16M	100	Birth				23	47		11						
JF	17M	120	12				27	86	58	5						
JoK	15M	110	Birth	45	14.7		33	59	34	(19) 57	6		79	82	81	73
VK	17M	120	Birth	55	16.9		45	70	49	(59) 70	13		93	102	114	102
IB	15F	120	Birth	48	16.8		42	66	35	(23) 29	9		83	98		
KL	13M	120	2	40	14.4		25	51	34	(24) 35	11		88			
MLL	16F	120	Birth	42	15.7		24	45	30	(19) 21	14		79			
DW	15F	120	Birth				44	109			12					
DM	18M	110	13	48	17.4		27	59	51	(37) 37	9		67	106		
JW	17M	120	6				27	56		(56) 70	8					
TL	15M	100	1.5	50	15.8		16	36	25		8		81			
CL	15F	120	14	43	15.1		22	40		(19) 20	10		72	102		66
JD	15M	110	Birth	50	16.2		23	89	81		10		76			
BB	15M	120	4	50	17.4		27	54	34	(16) 38	6		74	110	104	76
RH	14M	123	5 mo	44	15.8		22	41	27	(17) 18	6		77	109		84
JP	13M	130	Birth				19	72	36	(16) 25	5					
Group 2																
BL	17F	80	Birth	42	14.3		18	26	22	(17) 19	9		82	104		88
LK	16M	123	Birth	48	16.4		24	54	38	(21) 27	10		102			90
TR	17M	80	Birth	50	16.7		11	51	22	(21) 38	8		75	97	89	75
RK	13M	90	Birth	45	15.2		22	54	27		7		73	94		
JaK	12F	90	Birth	47	15.2		20	43		(18) 20	7		66	82		
RR	15M	123	Birth	45	15.5		19	56	33	(16) 33			81		97	80
JCS	15M	-15	Birth	45	15.0		21	39	23	(21) 22			79	98		
MD	14F	60	Birth	43	14.5		21	23	18	(16) 18	7		74	85	73	84
SR	16F	60	Birth	45	14.8		24	51	29	(27) 56	11		80	100		94
JKn	15F	60	Birth	42	14.3		19	49	42		6		83		105	
KK	16F	80	13	49	16.2		20	26	21	(17) 18	7		80	91	89	86
JJ	15M	80	Birth	49	15.6		29	67	38	(30) 43	10		97	123		
Mean	15			46	15.6		25	54	35	(23) 32	9		80	99	94	83

Note: Group 1, subjects LN-JP; group 2, subjects BL-JJ.¹¹ BA: brachial artery; Ex: exercise; Hct: hematocrit; Hgb: hemoglobin; PA: pulmonary artery.

Figure 1. Pulmonary arterial (PA) pressures in 28 individuals at rest and during supine leg exercise.¹¹

suggested a major vasoconstrictor component to the increased PVR. Fifty years ago when tolazoline was in clinical use, the *Physicians' Desk Reference* suggested a variety of possible mechanisms for the vasodilator effect of this imidazoline, including direct action on vascular smooth muscle. Despite our much greater understanding of pulmonary vascular control, to my knowledge, the specific mechanism underlying the vasodilator action of tolazoline remains unknown.

One normal response to residents of high altitude is an increase in hemoglobin concentration and hematocrit, i.e., polycythemia.¹³ Indeed, excessive polycythemia was common among adult males living in Leadville. However, in these adolescent high school students, excessive polycythemia was not a problem, although, as would be expected, both females and males did have higher values of hemoglobin (mean 15.6 g%) and hematocrit (mean 46%) than their counterparts at lower altitude (Table 2). In fact, 4 males had hematocrits of 50%. But would this raise blood viscosity enough to contribute significantly to the increase in PVR? Robert Naeije (this conference) raised this question with reference to the first data collected by Rotta et al.⁹ at the much higher altitude of 14,900 feet in Morococha, Peru. That was back in 1956, when pulmo-

nary vascular control mechanisms had yet to be disclosed (as with “brisket disease,” above). Rotta postulated that hypervolemia, polycythemia, and high blood viscosity were probably the causative factors of high-altitude pulmonary hypertension. At that time, neither he nor anyone else knew anything about hypoxic pulmonary vasoconstriction or vascular remodeling. When in 1961 Peñaloza was asked about those viscosity-related factors, he replied, “Those are merely secondary.”¹⁴ He would probably say the same thing about a hematocrit of 46% in Leadville.

The role of pulmonary vascular remodeling in the increase in PVR must certainly be considered. It is well established that hypoxia, per se, will stimulate growth of the smooth muscle cells in the walls of small pulmonary arteries.¹⁵ Investigators take advantage of this fact when they use rats as a model for studying hypoxic pulmonary hypertension. The Peruvian scientist Dante Peñaloza, together with his associate in pathology Javier Arias Stella, made a major contribution to the understanding of hypoxic pulmonary hypertension in humans when they presented the first evidence that chronic hypoxia increases the muscularity of the walls of small lung arteries, thereby increasing the resistance to blood flow, resulting in the elevation of pulmonary arterial pressure.^{14,16} I saw this histological evidence during my trip to Lima in 1961, and so

Figure 2. Decrease (Δ) in mean pulmonary arterial (PA) pressure with 44% oxygen during exercise ($n = 22$).¹¹

when I organized the conference Normal and Abnormal Pulmonary Circulation held in Aspen, Colorado, in 1962, I arranged for Peñalosa and Arias Stella to present these remarkable discoveries for the very first time outside of Peru.^{8,16} Their data indicated that hypoxia-induced thickening of the pulmonary arterial walls was the primary cause of the elevated pressure in the Andean natives. But what about the residents of Leadville, Colorado? To date there are no histological studies of lungs from this population, and so the role of pulmonary vascular remodeling remains unknown.

In clinical patients with known hypertension, one of the major symptoms is reduction in exercise capacity. Improvement in the distance they can walk in 6 minutes is used as an indicator of the effectiveness of therapy. But the residents of Leadville with pulmonary hypertension seem to have no limitation in their capacity for exercise. Reeves and I have demonstrated that the atmospheric hypoxia at Leadville's altitude has a significant impact on the oxygen transport system. Members of Kentucky's state champion high school track team had a 25% reduction in maximum oxygen uptake throughout a 3-week sojourn in Leadville.¹⁷ Conversely, high school track runners from Leadville had a comparable increase in maximum oxygen uptake during a sojourn in Kentucky.¹⁸ However, this change in exercise capacity has nothing to do with the presence or absence of hypoxic pulmonary hypertension.

So this is the paradox of hypoxic pulmonary hypertension. Unquestionably, this places a significant increase in right ventricular afterload. Yet the right heart appears to handle the increased workload with no apparent difficulty in this Leadville population of healthy, very active adolescents. What is the hemodynamic difference between them and patients with pulmonary vascular disease or idiopathic pulmonary hypertension? Current thinking considers the vascular nature of the pulmonary vascular obstruction to be important. What about the compliance or stiffness of the large pulmonary arterial trunks? Classically, PVR considers the ratio of an unvarying mean pressure to a nonfluctuating constant blood flow of normal viscosity. Nothing could be further from reality. Blood enters the pulmonary circulation as a series of ejections from the beating heart, with the resulting pulsatile flow having a variable frequency from 1 to 3 Hz, not to mention harmonics. These pulses of blood create a pressure oscillating between a rapid rise during systole and a slower decline during diastole. The vascular impact should be evaluated as impedance, not simplistic PVR.¹⁹ And how is right ventricular function modified by these variables? How does it respond? A broadening appreciation of this more complex hemodynamic picture is being reflected by journal article

titles such as "Pulmonary vascular input impedance is a combined measure of PVR and stiffness and predicts clinical outcomes better than pulmonary vascular resistance alone in pediatric patients with pulmonary hypertension."²⁰ Incidentally, these concepts and their potential importance are not new, as a paper entitled "On-line impedance analysis system for studying the pulmonary vascular response to hypoxia"²¹ appeared from our cardiovascular pulmonary laboratory 37 years ago.

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