# Children at High Altitude: Pulmonary and Renal Abnormalities

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■ At elevations above 10,000 feet alveolar hypoxia leads to pulmonary arterial hypertension, arterial hypoxemia, and secondary polycythemia in most persons.[1, 2] The adjustments of adults to this hypoxic environment have been extensively studied but there is relatively little information pertaining to neonates and young children. The only published catheterization study on young children at high altitude is that of Penaloza et al. who reported that in seven infants the average pulmonary arterial pressure was greater than that found in older children or adults.[1] The studies to be described below reveal anatomical abnormalities of the pulmonary vasculature and renal glomeruli in children reared at high altitudes, thus providing an anatomical basis for the pulmonary hypertension observed by Penaloza.

### SUBJECTS

Fifteen children who died in Leadville, Colorado, during the period 1954 to 1960 were selected for study. The altitude of Leadville is 10,150 feet and the mean barometric pressure 525 mm Hg. All children in the study died as a consequence of accidents or as a result of short illnesses including infectious processes. Three were stillborn. Cases with renal or cardiac malformations were specifically excluded. Ages ranged from stillborn to 11 years.

The 80 control infants with whom the Leadville children were compared varied in age from stillborn to 12 years. All had resided near sea level. None were cyanotic or had malformations of the heart, lungs, or kidneys.

## Methods

Previously described methods were used to measure arterial changes in the pulmonary circulation.[3] In each case, multiple blocks of lung and kidney were sectioned at six microns and stained with Verhoeff and van Gieson stains. Duplicate slides were stained with hematoxylin and eosin stains. With the aid of a camera lucida and a planimeter, the relative cross-sectional areas of lumen, intima, and media of small muscular arteries were determined. Cross-sectional areas were also determined for individual nuclei in both intima and media. All arteries found in cross section which had a total diameter of 30 microns or less were measured. All arteries were muscular in type and adjacent to respiratory bronchioles, alveolar ducts or alveoli. Some might classify these vessels as arterioles but we choose not to do so because in the lung the term has been defined in so many different ways.

The mean size of renal glomeruli was determined in a similar manner.[4] Blocks of renal tissue were taken to include the entire cortex. Glomeruli were outlined after projection onto paper with a camera lucida. In the selection process, microscopic fields were chosen in a pattern passing from kidney surface to medulla since glomerular size often varies in the different cortical zones. The glomeruli measured were selected on a random basis in the individual microscopic fields. Using a planimeter, the relative areas of 20 to 40 glomeruli were determined and the mean area calculated for each case. The values determined were relative rather than absolute since measured glomeruli were in varying planes of section. A mean value for glomerular, parenchymal cell density was also determined in each case. Parenchymal cell density was determined in individual glomeruli by dividing the number of parenchymal cells by total glomerular area. Sections from cases under study and from controls were mixed and examined in a random manner to avoid bias.

## Results

For pulmonary arteries of 30 microns or less in diameter, intimal areas were almost identical for high altitude and control cases. In this age group, the intima consists chiefly of endothelial cells. No intimal proliferative lesions were observed. These observations

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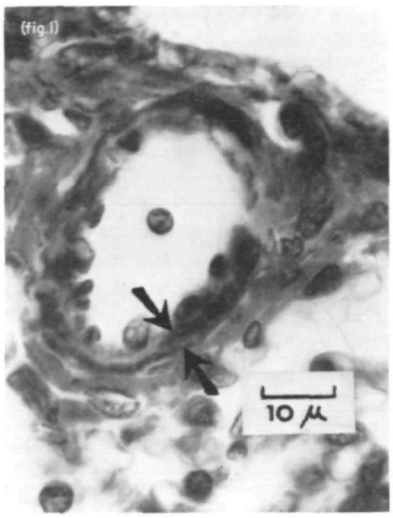


FIGURE 1

*Small pulmonary muscular artery from a 40-day-old nonhypoxic, control infant. The arterial media is seen between the two pointers. (Verhoeff and van Gieson stains.)*

aided further analysis. The relative area of intima was selected as a convenient reference base line to which the arterial medial mass could be compared. As in previous studies,[3, 4] a numerical expression:

$$\frac{\text{area arterial media}}{\text{intimal area} + \text{internal elastic membrane}}$$

was adopted as a relative measure of arterial muscle mass. In each case this value was determined for 15 to 25 arteries.

In infants from high altitude, the medial muscle coat was normal at birth. In most of those who survived three weeks or more this muscle mass did not undergo a normal decrease (figs. 1 and 2). It usually remained at levels intermediate between birth and normal values (fig. 3). The variation in muscle mass from case to case is striking, some children having a near normal mass of arterial muscle and others a greatly increased mass, close to that found at birth.

Both smooth muscle hyperplasia and hypertrophy contribute to the increased bulk of pulmonary arterial muscle at high altitude. The ratio: $\frac{\text{number of medial nuclei}}{\text{number of intimal nuclei}}$ was adopted as a relative measure of the number of smooth muscle cells in individual arteries. In normal children there was a progressive decrease in this ratio after birth, suggesting a relative decline in the number of muscle cells (fig. 4). In contrast, this ratio remained at the birth level in some children at high altitude, showing a variable decline in others (fig. 4). A relative muscular hypertrophy at high altitude is suggested by comparing muscle mass with number of medial cells in the Leadville and control cases. In control cases after birth, muscle mass decreased more rapidly than the relative number of smooth muscle cells. In Leadville children often neither change took place (figs. 3 and 4). Thus, at high altitude, some children after birth retain the relatively large pulmonary arterial muscle cells which normally are present only before or at birth. This relative hypertrophy at high altitude appears to be due to retention of cytoplasmic mass of individual muscle fibers since the mean size of individual muscle nuclei is similar in Leadville and in control cases (fig. 5). No abnormalities were found in the pulmonary veins or capillaries of the Leadville children. No smooth muscle was visible in the small pulmonary veins of either the Leadville or control cases.

Data are presented in figure 6 indicating

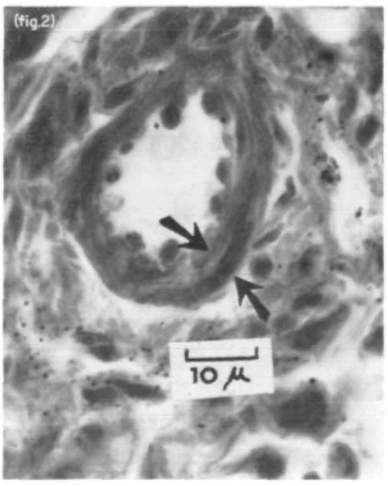


FIGURE 2

*Small pulmonary muscular artery from 40-day-old infant from high altitude. The arterial media, located between the pointers, is thicker than that in control case (fig. 1). (Verhoeff and van Gieson stains.)*

that children at high altitude have normal sized glomeruli at birth. Subsequently glomeruli became abnormally enlarged in all but two of the Leadville children. The density of parenchymal cells in glomeruli of Leadville children was the same as that found in control patients. Since no abnormal cells or tissue were found in these enlarged glomeruli on histologic examination, it is concluded that the enlargement was due to a prolifera-

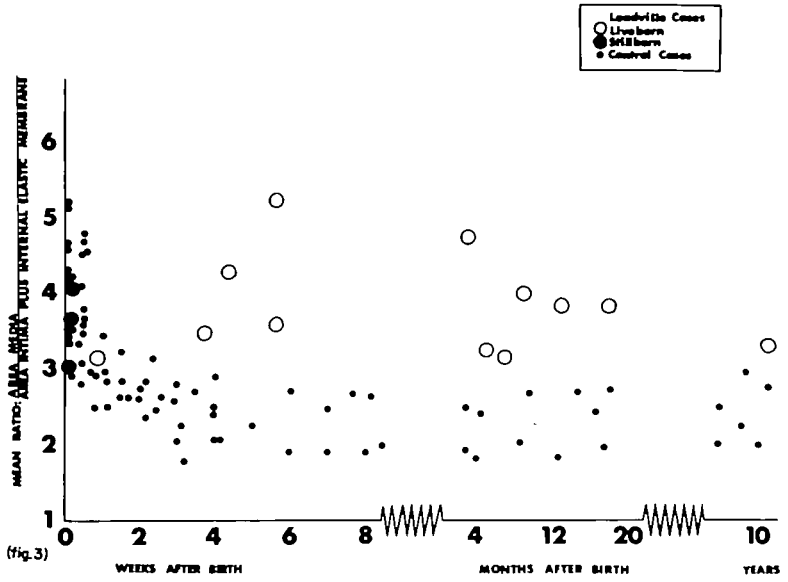


FIGURE 3

*A ratio reflecting arterial muscle mass for small pulmonary arteries is plotted against age for hypoxic and nonhypoxic children. After fourth week of life, values are greater for hypoxic (Leadville) children.*

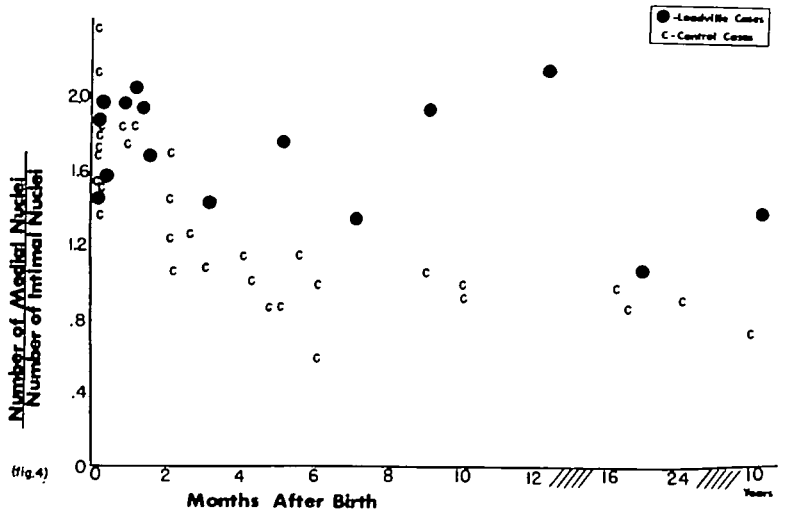


FIGURE 4

*A ratio reflecting number of medial muscle cells for small pulmonary arteries is plotted against age for hypoxic and nonhypoxic children. After four months of life, values are greater for hypoxic (Leadville) children, indicating a larger number of medial cells. This measurement was undertaken in only 32 of the 80 control cases.*

tion of normal glomerular elements. This proliferation may have resulted from an elongation of glomerular loops or an increase in their number; we do not know which process was responsible.

## Discussion

In the current study, stillborn and newborn infants from high altitude had a normal medial mass of smooth muscle in small pulmonary arteries. This suggests that antenatal pulmonary arterial pressures were within normal limits. Such factors as hypervolemia and increased pulmonary blood flow which lead to antenatal hypertension are probably absent in infants born at high altitude.[4–6] Subsequently, the large pulmonary arterial muscle mass present at birth decreased normally

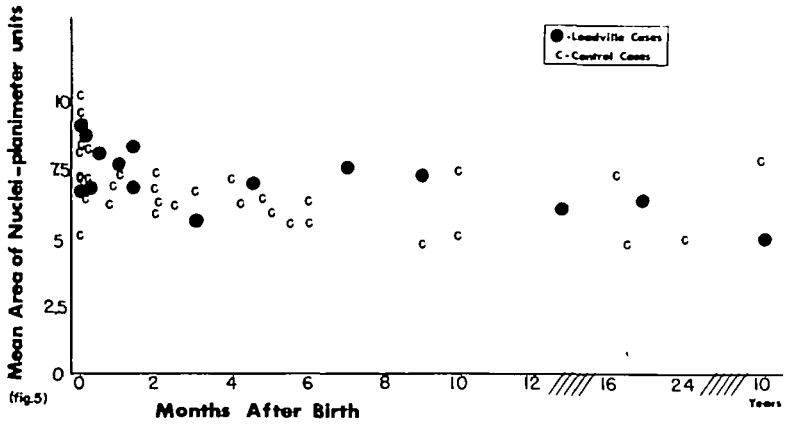


FIGURE 5

*The mean size of individual muscle nuclei in small pulmonary arteries is similar in 15 hypoxic (Leadville) and 32 control cases. Mean values are expressed in arbitrary planimeter units.*

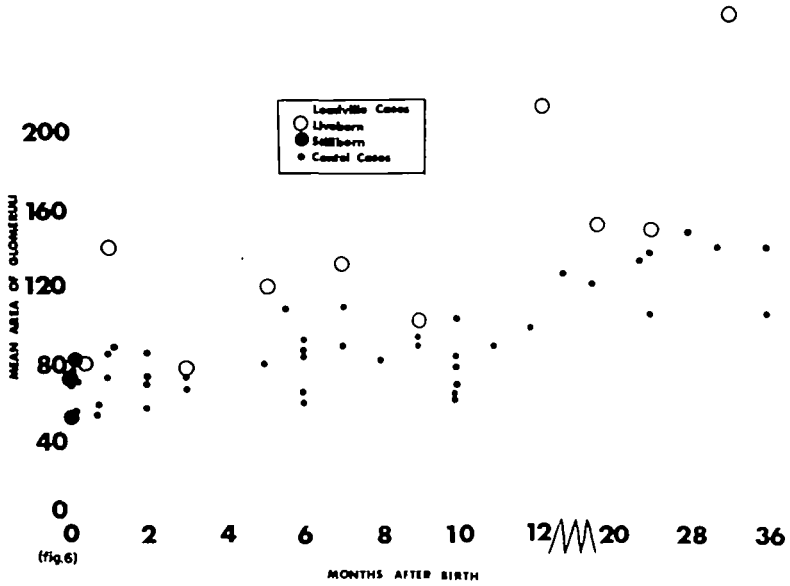


FIGURE 6

*After birth, glomeruli become abnormally enlarged in most children residing at high altitude (Leadville). Renal tissue was available for study in only 13 of the 15 Leadville cases. Mean areas are expressed in arbitrary planimeter units.*

in some of the Leadville children but not in others. This may well be correlated with the finding that some children at high altitude have pulmonary arterial pressures as low as those found at sea level while others have pressures as high as those normally present at birth.[1, 2, 7, 8] In cattle at high altitude, pulmonary arterial pressure can be directly correlated with pulmonary arterial muscle mass in individual animals.[9] Contraction of the increased arterial muscular mass may be correlated with the increased pulmonary arterial pressure response to exercise noted in children at high altitude.[1, 2] Children who show such a hyperreaction to exercise are usually the same children who hyperreact to increased hypoxia.[2] In general the pulmonary arterial changes in Leadville children resemble those recorded in children developing alveolar hypoxia at low altitudes due to alveolar hypoventilation.[10]

The present study extends our knowledge of the pulmonary arterial muscular response to hypoxia at the cellular level. It is now clear that the reduction in muscle mass observed in normal infants in the first two weeks after birth is due largely to the loss of cytoplasm from individual smooth muscle cells. This might be compared to the rapid loss of sarcoplasm from skeletal muscle fibers with disuse.[11] It appears that the neonatal loss of pulmonary arterial smooth muscle cytoplasm, normal at low altitude, does not occur in many children at high altitude. This phenomenon at high altitude may reflect a continuation of the prenatal vasomotor stimulus if the thesis is correct that hypoxemia or alveolar hypoxia helps to maintain the high pulmonary vascular resistance normally found in fetal life.[10, 12] The present study also shows that postnatal hypoxia can prevent the relative decrease in number of arterial medial cells which normally occurs within a few months of birth.

It seems likely that the increased pulmonary arterial muscle mass present at high altitude is the cause as well as the consequence of the hypertension. The increased pulmonary arterial pressures recorded in residents at high altitude decrease only slightly following the injection of acetylcholine or the inhalation of a gas mixture which raises the alveolar $pO_2$ to values normal at sea level.[13, 14] When long-term human or bovine residents at high altitude are returned to sea level it takes weeks or months for the pulmonary arterial hypertension to disappear.[14, 15] In fact, pulmonary hypertension persists after hypervolemia and polycythemia have disappeared.[14]

An increased medial muscle mass in individual pulmonary arteries is not the only vascular abnormality found in children at high altitude. Arias-Stella and Saldana found an increased number of precapillary vessels adjacent to alveolar ducts with a muscular media.[16] They did not find an increased muscle mass about individual arteries as reported in the present study. This may be related to the probable inability of Arias-Stella's method to demonstrate medial hypertrophy when arteries are dilated. Since pulmonary arteries are dilated in adults at high altitude, it is probable that they are dilated in children as well.[3] The dilatation has been related to an increased blood volume which apparently exists at all ages.[3, 7]

The renal glomerular changes found in Leadville children resemble those found in children with cyanotic types of congenital cardiac malformations.[17] In both groups, glomeruli enlarge after the first month of life. This enlargement is due to a proliferation of normal glomerular elements. Several factors present in children at high altitude may be responsible for the enlargement. These factors include increased blood volume, increased blood viscosity, arterial hypoxemia, and reduced renal parenchymal oxygen tension. Increased blood volume and viscosity are associated with abnormal glomerular enlargement in a variety of disorders before and after birth. These include recipient twins with the monochorionic, cross-placental, transfusion syndrome, adults with chronic cor pulmonale and the aforementioned infants with cyanotic types of cardiac malformations.[4, 17, 18] Infants with cardiac malformations and adults with chronic cor pulmonale

often have arterial hypoxemia as well. A role for renal parenchymal hypoxia is suggested by the observation that individuals with sickle cell anemia have glomerular enlargement in the inner cortex where reductions in parenchymal oxygen tension are presumably most severe.[19] Current information does not make it possible to decide which of these factors may be significant at high altitude.

The glomerular changes suggest the possibility of an increased glomerular filtration surface. However, it may be difficult to ascertain what the influence of the glomerular changes is on renal function because of concomitant changes in blood volume, renal parenchymal oxygen tension, and blood viscosity. It would be interesting to know if residents at high altitude eventually develop the sclerotic glomerular lesions found in some older patients with cyanotic congenital cardiac malformations.[20]

## Summary

Changes in pulmonary arteries and renal glomeruli were assessed in children born and resident at high altitude (Leadville, Colorado). The hypoxia appears to arrest normal neonatal decrease of pulmonary arterial smooth muscle in some of these children. No abnormalities were found in pulmonary veins or capillaries. A quantitative study also demonstrated enlargement of renal glomeruli in the hypoxic children after the first month of life, apparently due to a proliferation of normal glomerular elements.

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