The Terminal Portion of the Pulmonary Arterial Tree in People Native to High Altitudes

By Javier Arias-Stella, M.D., and Mario Saldaña, M.D.

Radiographic evidence of right ventricular enlargement with bulging of the main pulmonary artery and electrovectorcardiographic signs of right ventricular preponderance are common findings in people born and living at high altitudes. Anatomically, the existence of right ventricular hypertrophy has been demonstrated both in adults and children.

Recently, hemodynamic studies have disclosed that these people present, at rest, a mild degree of pulmonary hypertension and increased pulmonary vascular resistance. Children below 5 years of age show higher pulmonary pressure values than older children and adults. Furthermore, different from what occurs in normal persons at sea level, the pulmonary pressure increases markedly during exercise.

The small muscular branches of the pulmonary arterial tree are primarily concerned in determining pulmonary vascular resistance. Therefore, the study of their morphologic characteristics is of paramount importance for understanding the genesis and significance of high altitude pulmonary hypertension. This forms the subject of the present report.

Material and Method

Two autopsy series are studied: one from people born and living permanently in high altitude areas of the Peruvian Andes (from 11,300 to 14,300 feet); the other, used as control, from people born and living at sea level. Subjects of approximately matching ages were considered in both series.

Necropsies at high altitudes were made at Cerro de Pasco (altitude, 14,300 feet), those at sea level were at Lima (altitude, 500 feet).

Acute processes in children of the first 2 years of life, and accidents in the older ages, were the most frequent causes of death. No cases showing pulmonary or cardiovascular pathology were included.

Cases were arranged in two age groups: from 1 month to 2 years and from 6 to 76 years.

The complete lungs were fixed by gentle bronchial injection of 10 per cent formalin and allowed to remain in the same fixative for several days.

The study of a representative sample of the pulmonary arterial vasculature was assured by taking at least 15 tissue blocks per case, following the topography depicted in figure 1. In this way, cortical, medial, and hilar zones in each of the five pulmonary lobes were investigated.

After being embedded in paraffin, the blocks of lung tissue were cut at 6 μ. The sections were stained to show elastic tissue according to the Weigert’s technic and counterstained with Van Gieson’s picro-fuchsin to show connective and muscular tissues.

At the beginning of the study it was apparent that severe vascular lesions like those reported in other forms of pulmonary hypertension do not occur in high altitude cases. On the other hand, we were impressed by the presence of arterial branches showing double elastic laminae and muscle at all ages at peripheral levels, where it has been stated that they are not seen after the age of 6 months. When a detailed analysis was accomplished in normal cases from sea level, it was realized that vessels of arterial type can also be observed at the side of alveolar ducts and alveolar sacs, at any age, by careful scrutiny in a good number of sections. It was obvious, therefore, that in order to make a comparative study, quantification of the frequency of muscular vessels at peripheral levels was as important as the estimation of the amount of smooth muscle contained in the media of arteries.

To avoid bias, sections were labeled with a key number, so that at the time of study it was not known in which series the case belonged.

Histologic Remarks. The terminal portions of the pulmonary arterial and respiratory trees run parallel and in close relationship. Pulmonary arteries extending from the pulmonary hilus to the smallest bronchi belong to the elastic type. They
change to the muscular type, usually, at the level of bronchioles. In the first months of life the muscular pulmonary arteries extend as distally as the alveoli.

Since in this study the muscular arteries of the lung will be classified according to their topographic relation to the ramifications of the respiratory tree, a brief account of the main histologic characteristics of bronchioles, respiratory bronchioles, alveolar ducts, and alveolar sacs will be given.

Bronchioles or terminal bronchioles are tubular structures. When cut transversely they show a continuous circular wall lined by respiratory or high columnar epithelium. Thick muscular bands encircle almost completely the perimeter of the wall. Terminal bronchioles ramify in respiratory bronchioles. These show walls in which portions invested by columnar or cuboidal epithelium alternate with outpouchings of alveoli. Those situated proximally to terminal bronchioles present a few alveoli, leaving intact considerable portions of circumferential wall. Alveoli become more numerous as alveolar ducts are approached, so that one recognizes those respiratory bronchioles more distally situated only by the presence of a short and thin band of muscle that gives support to a strip of low cuboidal epithelium.

Respiratory bronchioles are resolved in several long corridors or alveolar ducts, which have walls beset by alveoli of variable size and depth. Alveolar ducts are devoid of low cuboidal epithelium, a characteristic that permits them to be differentiated from the most distal portions of respiratory bronchioles. Bands of elastic and muscular fibers can be observed at the sites of entrance of alveoli. Alveolar sacs are terminal blind pockets with walls set with alveoli.

According to their topographic relation with the segments of the respiratory tree, three types of muscular arteries can be distinguished: proximal, intermediate, and distal.

Proximal arteries are those located at the sides of terminal bronchioles; intermediate arteries are those in connection with respiratory bronchioles, regardless of their branching order; distal arteries are those located at the level of alveolar ducts, alveolar sacs, and alveolar septae (fig. 2).

The studies here presented concern proximal and distal arteries.

**Counting of Arteries**

The ratio, number of distal arteries to number of proximal arteries (DA/PA), was calculated in each case. For this purpose all proximal and distal arteries, excepting those cut in longitudinal planes, were counted in the 15 histologic sections. If there was any doubt about the nature of the related air passage, the vessel was excluded. This usually happened at the borders of the histological sections, since distance between the arterial branches and the air channels is variable.

Generally, one proximal artery corresponds to one bronchiole; occasionally, two proximal arteries and very rarely three can be observed at the sides of a single bronchiole. If two arteries were located at opposite sides of a bronchiole they were counted as two independent vessels; on the other hand, when located at the same side of a bronchiole, showing common adventitial tracts, they were counted as a single vessel, since they represent nearby points of branching.

The number of proximal arteries counted per case varied from 48 to 280 and the number of distal arteries, per case, from 52 to 1,356.

**Measurements of Arteries**

The external diameter (ED), the relation of internal diameter to external diameter (ID/ED), and the areas of the media of proximal arteries (S) and of distal arteries (s) were determined.

For these purposes only those arteries cut in an almost perfect transversal plane were considered. In each case, mean values of the measurements were obtained from a minimum of 15 proximal and 15 distal arteries. In some instances, additional blocks had to be studied to reach the required number of measurable distal arteries. Later it was found that this occurred only with sea level cases.

An ocular scale was used for the measurements of arterial diameters. The external and internal diameters of a muscular artery are the diameters of the circles limited by the external and internal elastic laminae, respectively. In each artery, for
PULMONARY ARTERIES AT HIGH ALTITUDES

PROXIMAL LEVEL

DISTAL LEVEL

Figure 2

Representation of the terminal portions of the pulmonary arterial and respiratory trees. The figure in the center illustrates the relationship between the two systems. Lines of division separate the three anatomic levels considered. The histologic patterns more commonly found in each level are depicted in circles. t.b.: terminal bronchiole; r.b.: respiratory bronchiole; alv.d.: alveolar duct; alv.s.: alveolar sac; alv: alveoli; m.a.: muscular artery.

The area of the media of a proximal artery (S) or of a distal artery (s) is given by the formula:

\[ S \text{ or } s \ (\text{in } \mu^2) = \frac{\pi}{4} (ED^2-ID^2) \]

Each of these diameters, a mean value was obtained from two perpendicular measurements.

The relation of internal diameter to external diameter (ID/ED) was calculated in each proximal and distal artery measured.

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These calculations were obviated by the use of an abacus especially constructed for this purpose (approximation: ± 5 per cent from numerically calculated values).

**Estimation of the Amount of Arterial Muscle at Distal Level**

The total area of transverse arterial muscle at distal level per proximal artery (AMDL index), expressed in μ², was calculated by multiplying the mean medial area of distal arteries (s) by the ratio number of distal arteries/number of proximal arteries (ratio DA/PA) as below indicated:

\[ \text{AMDL index (in } \mu^2) = \frac{DA}{PA} \]

With the individual values of the ratio DA/PA and AMDL index, and mean individual values of the external diameter (ED), relation ID/ED, area of the media of proximal arteries (S) and of distal arteries (s), mean values for each age group in both series were obtained. Corresponding mean values of sea level and high altitude groups were compared according to the Fisher t-test, and a 0.05 level of confidence was accepted as significant.

**Limitations and Advantages of the Method**

Classification of the muscular pulmonary arteries, as in the present study, demands a proper identification of the different segments of the peripheral respiratory passages. This can present some difficulties derived from the occurrence of anatomic variances. Furthermore, it is advisable that once familiarity with the histologic criteria has been gained, both problem and control cases should be studied by the same observers.

To classify arteries according to their topographic position in relation to the air passages represents an attempt to study a given segment of the pulmonary vascular tree, thus permitting a valid comparison among cases. It should be realized that proximal and distal levels actually comprise segments of considerable length of the pulmonary arterial vasculature. If possible, it would certainly be useful to study more limited portions of the pulmonary arterial tree. On the other hand, there is no question that the type of identification of arteries that was used in the present investigation obviates some of the limitations that occur when other criteria are used. If, for instance, arteries are classified according to the length of their external diameter, several problems arise. The presence of various degrees of contraction can make different vessels look alike. Furthermore, since age and body size are certainly reflected in the size of arteries, to a given external diameter correspond different segments of the pulmonary arterial tree.

It has already been mentioned that the quantification of the number of vessels with muscular media at peripheral levels is as important as the study of the morphologic characteristics of the individual arteries (size, area of the media, thickness of the wall). This is precisely the information gathered from the ratio DA/PA applied in this study. Since it is accepted that one of the earlier changes in pulmonary hypertension is the muscularization of peripheral vessels normally devoided of muscle, abnormally higher values of this ratio are indirect evidence of pulmonary arterial hypertension.

One of the most demanding problems, when studying the lung in pulmonary arterial hypertension, is to know the amount of arterial muscle at distal level. The AMDL index gives, in a simple manner, reliable information on this question.

Finally, it should be stressed that changes in the pulmonary parenchyma (atelectasis, hyperinflation) do not alter the value of the DA/PA ratio, and, therefore, the validity of the calculations of the AMDL index.

**Results**

**Number of Distal Arteries/Number of Proximal Arteries (Ratio DA/PA)**

Table 1 summarizes the findings at high altitudes and at sea level. In both age groups

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Ratio—Number of Distal Arteries to Number of Proximal Arteries at High Altitudes and at Sea Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month - 2 Years</td>
<td></td>
</tr>
<tr>
<td>Source of cases</td>
<td>No. cases</td>
</tr>
<tr>
<td>High altitudes</td>
<td>8</td>
</tr>
<tr>
<td>Sea level</td>
<td>8</td>
</tr>
<tr>
<td>t</td>
<td>4.7178</td>
</tr>
</tbody>
</table>

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a statistically highly significant greater mean value of the ratio DA/PA was found in high altitude cases. In figure 3 individual values are shown. It is interesting to note that, with a single exception in the younger age group, none of the high altitude subjects presented ratios falling into the normal range of sea level cases. Some of the high altitude cases showed a ratio eight to 10 times greater than the age-matched sea level control. Wide variations in the value of this ratio occurred among high altitude cases. Contrarily, the sea level cases varied through a short range.

**External Diameters of Proximal and Distal Arteries**

In the younger age group the mean individual values of the external diameter in the proximal arteries varied from 67μ to 260μ at high altitudes, and from 50μ to 251μ at sea level. In the distal arteries, the external diameters from 19μ to 72μ at high altitudes and from 19μ to 68μ at sea level.

In the older age group the mean individual values of the external diameters of proximal arteries varied from 95μ to 472μ at high altitudes and from 95μ to 496μ at sea level. In the distal arteries, extreme values of the external diameter ranged from 28μ to 170μ at high altitudes and from 30μ to 184μ at sea level.

As shown in table 2, no significant differ-

**Table 2**

**Measurements of Proximal and Distal Vessels at High Altitudes and at Sea Level**

<table>
<thead>
<tr>
<th>Source of cases</th>
<th>1 Month - 2 Years</th>
<th>6 - 76 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal vessels</td>
<td>Distal vessels</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>External diameter in μ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High altitude</td>
<td>132</td>
<td>11.0</td>
</tr>
<tr>
<td>Sea level</td>
<td>150</td>
<td>16.6</td>
</tr>
<tr>
<td>t</td>
<td>0.1191</td>
<td>0.3386</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.00</td>
<td>&lt;0.00</td>
</tr>
</tbody>
</table>

| Ratio—internal/external diameters |
| High altitude | .77 | .018 | .052 | .79 | .018 | .052 | .83 | .017 | .064 | .87 | .014 | .053 |
| Sea level | .79 | .025 | .073 | .84 | .009 | .026 | .89 | .010 | .044 | .90 | .008 | .033 |
| t | 0.7053 | 2.5119 | 2.8373 | 2.0059 |
| p | <0.00 | <0.00 | <0.10 | <0.00 |

| Area of the media in μ² |
| High altitude | 5272 | 805.3 | 2377.8 | 437 | 35.9 | 101.6 | 12462 | 877.7 | 3284.3 | 771 | 67.2 | 251.5 |
| Sea level | 4242 | 693.8 | 1962.4 | 359 | 21.1 | 59.7 | 9387 | 889.4 | 3288.1 | 1047 | 135.5 | 507.0 |
| t | 0.9687 | 1.8624 | 2.4666 | 1.8225 |
| p | <0.00 | <0.00 | <0.00 | <0.00 |

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No significant difference in the medial surface has been found in the distal arteries of the younger age group between high altitude and sea level cases. Therefore, the significantly lower ID/ED ratio found at high altitudes suggests a condition of arterial vasoconstriction.

**Total Area of Transverse Arterial Muscle at Distal Level per Proximal Artery (AMDL Index)**

Table 3 shows that the mean values of this index were statistically highly significantly greater for high altitude cases in the two age groups ($p < 0.001$). The individual values of the AMDL index are shown in figure 4.

**Discussion**

The present study has disclosed that the terminal portion of the pulmonary arterial tree of people born and living at altitudes from 11,300 to 14,300 feet above sea level differs structurally from that of normal sea level inhabitants of comparable ages. A greater amount of arterial muscle in the more distal segments of the pulmonary arterial tree has been demonstrated in high altitude subjects, from the age of 1 month onward. This greater amount of arterial muscle results not from hypertrophy of the media of the arteries but from the presence of a muscular media in a considerable number of the more peripheral pulmonary arterial branches (figs. 5 and 6).

Evidence has been found that some degree of arterial vasoconstriction occurs in the distal arteries of the younger age group cases (1 month to 2 years) at high altitudes. In the older age group (6 to 76 years), true hypertrophy of the media of the proximal arteries has been demonstrated.

**Figure 4**

Area of transverse arterial muscle at distal level per proximal artery (AMDL index) in individual cases.

**Area of Arterial Media**

A statistically greater mean value of the arterial medial surface was found in the proximal arteries of high altitude cases in the second age group (table 2).
Hemodynamic studies performed at high altitudes have demonstrated the existence of mild hypertensive arterial levels in the lesser circuit of people from such areas.\textsuperscript{11–13, 20}

Up to now a clear idea on the mechanisms that originate and maintain the pulmonary hypertension at high altitudes was lacking. Since it was found that the cardiac output was normal, Rotta et al.\textsuperscript{11} ruled out the possibility of an augmented pulmonary blood flow as a factor. Instead, they thought that an elevated blood viscosity secondary to the increased red cell volume could play a significant role. According to Burton,\textsuperscript{21} however, anomalous blood viscosity can be omitted as a factor in the production of pulmonary hypertension. Furthermore, the observation exists that pulmonary hypertension is not a common finding in polycythemia vera.\textsuperscript{22}

Recently it has been shown that high altitude pulmonary hypertension is associated with an increased pulmonary vascular resistance.\textsuperscript{12, 13} One may ask, consequently: which are the anatomic changes, if any, in the pulmonary arterial bed of high altitude subjects that can be related to the existence of an increased pulmonary vascular resistance?

Campos and Iglesias\textsuperscript{8} thought that the capillary engorgement they observed in the lungs of autopsied people from high altitudes could explain the existence of pulmonary hypertension. This explanation cannot be accepted, since the vascular resistance in the pulmonary circuit is established at a precapillary level. Furthermore, normal values of pulmonary wedge pressure have been demonstrated in high altitude subjects.\textsuperscript{12, 13}

The results of the present study give, indeed, an answer to the above question. The presence of a greater number of peripheral pulmonary arterial branches with muscular media in people from high altitudes means that their pulmonary arterial trees have a reduced total cross-sectional luminal area at distal level. Furthermore, this pattern is more effectively provided for, than that in persons at sea level, to influence the $r^4$ factor of Poiseuille's law,\textsuperscript{21} determining an increased pulmonary vascular resistance. The existence of some degree of vasoconstriction of the distal arteries in the younger ages, as suggested by our data, would be responsible for the higher values of vascular resistance observed in high altitude children when compared with adults.\textsuperscript{13}

The pattern of the pulmonary arterial tree in high altitude lungs can result from a delayed and incomplete involution of its fetal characteristics. This possibility agrees with previous observations of the heart and pulmonary trunk structure at high altitudes. It has been shown that the right ventricular hypertrophy of fetal life does not subside after birth\textsuperscript{10} and is maintained up to adulthood in high altitude dwellers.\textsuperscript{8} Likewise, the elastic configuration of the pulmonary trunk observed in the fetus and newborn, that normally changes at sea level by the third month, is retained up to the first decade in high altitude children,\textsuperscript{23} resembling that which occurs in congenital cardopathies with pulmonary hypertension from birth.

The hypertrophy of the muscular media of the proximal or larger muscular arteries in high altitude subjects of the older age group (6 to 76 years) can be interpreted as a secondary change to pulmonary hypertension, since the same feature was not observed in the younger age group.

It would remain to be explained why the

\begin{table}
\centering
\caption{Area of Transverse Arterial Muscle at Distal Level per Proximal Artery (AMDL Index)}
\begin{tabular}{lcccccc}
\hline
Source of cases & \multicolumn{2}{c}{1 Month - 2 Years} & \multicolumn{2}{c}{6 - 76 Years} \\
 & Mean ($\mu^2$) & SE & SD & Mean ($\mu^2$) & SE & SD \\
\hline
High altitude & 2405 & 433.2 & 1225.3 & 3298 & 197.7 & 739.8 \\
Sea level & 467 & 122.8 & 347.4 & 1232 & 310.2 & 1161.0 \\
\hline
\textbf{t} & 6.0462 & & & & 5.6155 & \\
\textbf{p} & <0.001 & & & & <0.001 & \\
\hline
\end{tabular}
\end{table}
Figure 6

Thirty-three-year-old man from Cerro de Pasco. Panoramic view and magnifications to show distal pulmonary arteries. In the low-power view (× 106) three distal pulmonary vessels provided with muscular medias and double elastic lamina are illustrated. The magnifications show the details of these vessels. Distal artery 1, 70μ of external diameter (× 657); 2, 67μ of external diameter (× 708); and 3, 76μ of external diameter (× 631). Observe the absence of intimal changes and the normality of lung parenchyma. Stained with Weigert's fuchsin-resorcin and Van Gieson's picro-fuchsin.

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postnatal involutionary changes in the pulmonary arterial tree are so modified at high altitudes. Certainly, here one has to consider the influence of hypoxia on the pulmonary circulation. The studies of Grover and Reeves,24 in bovines from sea level placed at high altitudes, have demonstrated that hypoxia has, as an acute phenomena, a vasoconstrictive effect on the pulmonary arteries. If hypoxia becomes prolonged, hypertrophy of the muscular media of the pulmonary arteries ensues. Thus, it is a strongly suggested possibility that the delayed and incomplete involution of the muscular content of the distal arterial vasculature observed in human beings at high altitudes may be a consequence of hypoxia acting at birth and thereafter.

Finally, a word must be said in regard to the wide variations of the DA/PA ratio and of the amount of arterial muscle at distal level (AMDL index) found at high altitudes. This should be related to the different altitude levels from which the cases came. Recently, Cruz et al.25 have demonstrated that pulmonary hypertension is higher at higher altitudes. Elsewhere we have demonstrated that differences in altitude levels are reflected in the elastic structure of the pulmonary trunk.23

Summary and Conclusions

The terminal portion of the pulmonary arterial tree has been investigated in two autopsy series of normal subjects who died of acute processes or accidents. One, from subjects who were born in and lived permanently in Andean villages of Peru above altitudes of 11,300 feet; the other, used as control, from people who were born at and lived at sea level. High altitude and sea level cases were distributed in two age groups: from 1 month to 2 years (16 cases), and from 6 to 76 years (28 cases).

The muscular pulmonary arteries were classified according to their topographic relation with the air channels. Proximal arteries were defined as those located at the sides of terminal bronchiolo. Distal arteries are those situated at the level of alveolar ducts and alveolar saes.

In the two age groups, statistically significant greater mean values of the ratio of the number of distal arteries to the number of proximal arteries were found in the high altitude cases, indicating that in them there exists a more extensive muscularization of the peripheral pulmonary arterial branches.

Evidence has been found that some degree of vasoconstriction is present at high altitudes, in the distal arteries of the younger age group.

In the second age group (6 to 76 years) the proximal arteries of high altitude cases were found to have a hypertrophied media, a change apparently secondary to the pulmonary hypertension.

A significantly greater amount of arterial muscle at distal level per proximal artery was found in the high altitude cases of the two age groups studied.

It is suggested that at high altitudes, the greater muscularization of the distal pulmonary arterial branches is the result of a delayed and incomplete involution of the fetal characteristics of the pulmonary arterial tree brought about by hypoxia acting from birth.

The results give an anatomic basis for understanding the genesis of high altitude pulmonary hypertension.

Acknowledgment

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References


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