Right Ventricular Hypertrophy in Guinea Pigs Exposed to Simulated High Altitude

By ENRIQUE VALDIVIA, M.D.

Guinea pigs exposed to simulated altitudes of 18,000 feet developed right heart dilatation followed by hypertrophy, more conspicuous in the infundibular area of the right ventricle. Under the described experimental conditions, pulmonary artery hypertension may be the etiologic factor.

UNDER conditions of chronic hypoxia, Van Liere\(^1\) reported enlargement of the heart and an increased heart weight-body weight ratio in rats. Using different technics, Takeuchi,\(^2\) Gremels and Starling,\(^3\) and Stickney, Northup and Van Liere\(^4\) all reported dilatation of the heart in experimental acute hypoxia. Kerwin\(^5\) surveyed radiographically large numbers of Peruvian natives living at high altitudes in the Andes Mountains and reported that these individuals have significantly enlarged hearts. In comparing these individuals with those living at sea level, he suggested that perhaps racial and environmental factors may contribute to heart size. Rotta\(^6\) confirmed the work of Kerwin by presenting further radiological evidence of right ventricular hypertrophy by evaluating both chest roentgenographs and electrocardiographs. In the present investigation, guinea pigs born at sea level were submitted to simulated altitudes of 18,000 feet for studies with respect to changes in the cardio-pulmonary system.

METHODS

Atmospheric conditions of 18,000 feet of altitude were reproduced with the use of a steel tank.\(^7\) Control of the barometric pressure was maintained by means of a floating valve by which the air intake was regulated. The temperature was maintained at 24°C; humidity varied between 40 and 80 per cent. In these experiments the steel tank was opened daily for a period of about 1 hour to care for the animals. Animals were removed from the tank and killed at specific periods as indicated in table 1. All animals were fed on a complete dietary ration to which vitamin C was added in excess. After sacrifice the hearts of the animals were removed and fixed in 10 per cent neutral formalin for at least 48 hours. They were then washed in running water for about 4 hours. Heart weights were taken after fixation. The ventricles were then dissected and 4 cross sections made from base to apex. The interventricular septum was divided sagittally in order to separate the two ventricles. The blood clots were removed and the weights of the right ventricle, left ventricle and the total weight of the heart were obtained.

RESULTS

Comparison of the body weights of 22 control (sea level) animals with 25 experimental animals revealed no significant differences. The mean body weight of the control animals was 880 Gm.; the mean body weight of the experimental animals was 850 Gm. For comparison of data, all weights were corrected on the basis of 1 Kg. of body weight and are presented in table 1, together with the absolute figures. Total heart weight, right ventricular weight and left ventricular weights were plotted in relation to time of exposure at simulated high altitude (fig. 1).

When the total heart weights were plotted in relation to weeks in the low pressure chamber, a maximum was reached at approximately 7 weeks. On this basis the experimental results are divided into 2 groups, one composed of animals remaining in the chamber for the first 6 weeks, another of animals remaining at simulated high altitude during longer periods (fig. 1 and table 1). The mean heart weight (corrected) of animals in the chamber 6 weeks was 3.56 Gm. The total heart weight of animals remaining at simulated high altitude up to 28 weeks was 4.30 Gm. This indicates a significant increase in weight when compared with the control animals' heart weight, 2.6 Gm. (mean of 22 animals).

No difference in the weights of the left
TABLE 1.—Body, Heart, Right and Left Ventricle Weights in Control and Experimental Animals

<table>
<thead>
<tr>
<th>Time in chamber (weeks)</th>
<th>Body weight (Gm.)</th>
<th>Heart weight (Gm.)</th>
<th>L. vent. weight (Gm.)</th>
<th>R. vent. weight (Gm.)</th>
<th>On basis 1 Kg. body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>920</td>
<td>2.65</td>
<td>1.41</td>
<td>0.90</td>
<td>2.88</td>
</tr>
<tr>
<td>2</td>
<td>890</td>
<td>3.30</td>
<td>1.25</td>
<td>1.10</td>
<td>3.84</td>
</tr>
<tr>
<td>3</td>
<td>820</td>
<td>2.85</td>
<td>1.35</td>
<td>0.85</td>
<td>3.48</td>
</tr>
<tr>
<td>4</td>
<td>1098</td>
<td>3.70</td>
<td>1.50</td>
<td>1.35</td>
<td>3.37</td>
</tr>
<tr>
<td>5</td>
<td>1055</td>
<td>4.00</td>
<td>1.60</td>
<td>1.60</td>
<td>3.70</td>
</tr>
<tr>
<td>6</td>
<td>1096</td>
<td>3.10</td>
<td>1.30</td>
<td>1.30</td>
<td>2.91</td>
</tr>
<tr>
<td>7</td>
<td>1000</td>
<td>3.90</td>
<td>1.50</td>
<td>1.65</td>
<td>3.90</td>
</tr>
<tr>
<td>8</td>
<td>910</td>
<td>2.80</td>
<td>1.25</td>
<td>1.10</td>
<td>3.08</td>
</tr>
<tr>
<td>9</td>
<td>700</td>
<td>2.70</td>
<td>0.94</td>
<td>0.93</td>
<td>3.86</td>
</tr>
<tr>
<td>10</td>
<td>700</td>
<td>3.22</td>
<td>1.42</td>
<td>1.42</td>
<td>4.60</td>
</tr>
<tr>
<td>11</td>
<td>700</td>
<td>3.20</td>
<td>0.92</td>
<td>1.01</td>
<td>4.05</td>
</tr>
<tr>
<td>12</td>
<td>816</td>
<td>2.65</td>
<td>1.00</td>
<td>1.05</td>
<td>3.25</td>
</tr>
<tr>
<td>13</td>
<td>750</td>
<td>2.60</td>
<td>0.80</td>
<td>0.80</td>
<td>3.47</td>
</tr>
<tr>
<td>14</td>
<td>700</td>
<td>2.35</td>
<td>0.85</td>
<td>0.70</td>
<td>3.36</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>902 ± 21</td>
<td>3.14 ± 1.10</td>
<td>1.25 ± 1.35</td>
<td>1.20 ± 1.75</td>
<td>3.48 ± 1.95 ± 1.30</td>
</tr>
<tr>
<td>Control animals</td>
<td>890 ± 37</td>
<td>2.29 ± 1.24</td>
<td></td>
<td></td>
<td>2.60 ± 1.41 ± 0.75</td>
</tr>
</tbody>
</table>

Fig. 1. Total heart weight, right ventricular weight and left ventricular weight of the experimental animals plotted in relation to time of exposure at simulated altitude. Control curve represents mean of 22 control animals.

When the combined weights of the right and left ventricles were subtracted from the heart weight one derives the combined weight of the control animals was 0.75 Gm. (table 1). The mean weight of the right ventricle of the experimental animals remaining in the chamber 6 weeks or less was 1.29 Gm. and the mean weight of the right ventricles of animals remaining within the chamber less than 28 weeks and more than 6 weeks was 1.84 Gm. (table 1). Examination of the plot relating the weight of the ventricle and time in the chamber indicates that the increase in right ventricular weight follows that of total heart weight and the curve is also asymptotic at 7 weeks. A plot of the ratio of the left ventricular weight to the right ventricular weight with relation to time in the chamber represents essentially the reciprocal of the curve of increase in right ventricular weight (fig. 2).
Fig. 2. A plot of the ratio of the left ventricular weight to the right ventricular weight (ordinate) in relation to time in the low pressure chamber (abscissa). Control curve represents mean of 22 control animals.

![Graph showing ratio of left to right ventricular weights over time](image)

Fig. 3. Serial cross sections in 2 guinea pig hearts. Control (left) and animal in low pressure chamber for 28 weeks (right). Note marked enlargement of right atrium (top right) and thickened walls of right ventricle, especially in the infundibular area (second cross section from top).

Fig. 4. Front and posterior views of guinea pig hearts. Control animal (left); experimental animal, 14 weeks in low pressure chamber (middle); guinea pig, 28 weeks in the chamber (right). Notice enlargements of right atrium and ventricle.

atria. From the data in table 1, the corrected mean weights were utilized to determine the mean combined weight of the atria in the 22 control animals, 0.54 Gm.; for animals remaining in the chamber less than 6 weeks, this was 0.87 Gm.; for the animals remaining in the chamber for more than 6 weeks and less than 28 weeks, this was 1.01 Gm. It can be seen that there is a corresponding increase in the weight of the atria, and that this increase in weight is of the same order as that of the right ventricle. From the standpoint of visual examination of the heart, after the animals had remained in the chamber for a period of 2 weeks there was a dilatation of the right ventricle. After 3 weeks in the low pressure chamber, there was a definite hypertrophy of the myocardium of the right ventricle. This becomes conspicuous after 8 weeks or more (fig. 3). This correlates very well with the data demonstrating changes in the weight of the ventricle. Anatomically, enlargement develops at the anterior surface of the heart and was most marked in the area of the infundibulum. Later on the entire right ventricular wall was enlarged (fig. 3), but was most prominent anteriorly (fig. 4). Conspicuous...
enlargement of the right atrium was also present.

**Discussion**

The data demonstrating the decrease of the ratio of left ventricle weight to right ventricle weight are comparable to the results reported by Lewis in human subjects. It is most significant that in our experiments there was an increase in the weight of the right heart in the absence of any demonstrable change in the left ventricle, and also gross evidence of predominant hypertrophy and dilatation of the right atrium.

It is impossible to explain our findings on the basis of hypoxia in the myocardium, hyperemia, increased blood viscosity, or general hypertension due to vasoconstriction following exposure to chronic hypoxia. All of these mechanisms would affect both the right and the left heart. The only plausible mechanism remaining, therefore, is pulmonary hypertension. Pulmonary hypertension has been demonstrated in acute hypoxia in the lungs of cats by Euler and Liljestrand; and confirmed in human subjects by Motley and Cournand. Euler and Liljestrand attributed the pulmonary hypertension to vasoconstriction in the pulmonary system. Wiggers and Hurliman discussed also the factor of increased flow through the lungs on the basis of increased cardiac output. It is then not unreasonable to assume that this is the mechanism that produced the right ventricular hypertrophy. The hypertrophy in the atria must then occur in the right atrium. Further sectioning will be necessary to establish this point.

A study of hypertrophy in the right ventricle with relationship to the time subjected to high altitude conditions (table 1 and fig. 1) indicates that the time necessary for the initiation of hypertrophy is indeed short. Additional experiments are being done to determine the latent period, and the precise sequence of this early hypertrophy.

**Summary**

Animals exposed to simulated high altitudes of 18,000 feet for various periods of time were examined to determine what alterations had occurred in the heart. It was shown that there was a progressive hypertrophy of the right ventricle for the first 6 weeks of exposure after which the weight of the right ventricle reached a constant weight. Because a fundamental general mechanism such as anoxia of the myocardium or generalized arterial hypertension would not have caused only hypertrophy of the right ventricle, it was postulated that the effects of high altitude were primarily due to a pulmonary hypertension.

**Acknowledgment**

The author wishes to acknowledge the efficient technical assistance of Gertrude Ableiter, Mary Kuhn, and the Department of Photography and the generous help of Dr. D. Murray Angevine and Dr. Marvin Murray both in the preparation of the manuscript and discussion of this subject.

**Summary in Interlingua**

Animales exponite a simulate altitudes de 5.500 m (=18.000 pedes) durante varie periodos de tempore esseva examine pro determinar qual alterationes habeva occurrite in le cordes. Il esseva trovate que un hypertrophia progressive occurreva in le ventriculo dextere durante le prime sex septimanas del exposition e que subsequentemente le ventriculo dextere manteneva un peso constante. A causa del facto que un mechanismo general fundamental —per exemplo anoxia del myocardio o generalisate hypertension arterial—non haberea causate solmente hypertrophia del ventriculo dextere, il esseva postulate que le effects de grande altitudes es primarimente producete per hypertension pulmonar.

**References**

2. Takeuchi, K.: The relation between the size of the heart and the oxygen content of the arterial blood. J. Physiol. 60: 205, 1925.
4. Stickney, J. C., Northup, D. W., and Van Liere, E.: Cardiac dilatation without hyper-
RIGHT VENTRICULAR HYPERTROPHY AT HIGH ALTITUDE

8 Lewis, T.: Observations upon ventricular hypertrophy with especial reference to preponderance of one or the other chamber. Heart, London, 5: 367, 1913-1914.
Right Ventricular Hypertrophy in Guinea Pigs Exposed to Simulated High Altitude
ENRIQUE VALDIVIA

Circ Res. 1957;5:612-616
doi: 10.1161/01.RES.5.6.612
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1957 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/5/6/612

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/