Differences in Cardiac Hypertrophy in Exercise and in Hypoxia

By Edward J. Van Lier, Ph.D., M.D., Barbara Baugh Krames, Ph.D., and David W. Northup, Ph.D.

It is generally known that effective periods of vigorous exercise produce cardiac hypertrophy in rats\(^1\)\(^2\) and in other species also.\(^8\) Experience has shown that it is difficult to produce a significant cardiac hypertrophy in normal, healthy dogs by use of a treadmill. This has been observed by the senior author and was mentioned by Eyster\(^4\) as early as 1928. Cardiac hypertrophy produced by exercise is regarded as a "work hypertrophy" because the work of the heart, including both ventricles, is greatly increased.

Prolonged exposure to hypoxia has also produced cardiac hypertrophy experimentally in animals.\(^5\)\(^6\) One type of hypertrophy is known to occur in men who live at high altitudes.\(^7\)\(^8\) This hypertrophy involves the right ventricle chiefly and is produced presumably by the increased work load imposed by the pulmonary hypertension associated with hypoxia. It is also a "work hypertrophy," but it affects the right ventricle more than the left.

The main purpose of this study was to compare quantitatively, in rats, the grade of right ventricular hypertrophy following exercise with that following exposure to intermittent hypoxia.

Methods

The experiments involved 139 albino rats; 72 of these served as controls and 67 as experimental animals. From the latter, one group was exposed to intermittent hypoxia eight hours daily (except Sunday) for four weeks at a barometric pressure of 303 mm Hg, corresponding to a simulated altitude of 24,000 feet (7,315 m). Another group was subjected to exercise on an electrically driven treadmill, at the rate of one mile per hour. The animals ran two one-hour periods each day (except Sunday) for a total of 60 hours.

When the experiments were completed the control and experimental rats were fasted for 24 hours, and were then weighed and decapitated. The heart was removed, the great vessels were trimmed flush with the surface of the heart, and any remaining pericardium or fat was removed. The blood was expelled from the chambers, the heart washed free of blood and the excess moisture removed with filter paper. The heart was then carefully weighed, and the weight recorded in grams of total heart substance per kilogram of body weight.

The hearts were then fixed in a 4\% formaldehyde solution. The procedure used in partitioning the ventricles followed rather closely that outlined by Keen.\(^9\) The dissection was done under a stereoscopic microscope. Using a fine scissors the atria were first excised as completely as possible. The right ventricle was then separated by inserting one blade of the scissors into the bicuspid opening and holding it closely to the septum while cutting. The incision was carried completely around the free part of the wall, thus separating it from the septum. The papillary muscles were left attached to the free part of the wall. The left ventricular wall was removed in a similar manner by inserting the blade into the mitral opening. In this way the interventricular septum was freed. Each of the parts was then blotted dry and weighed separately.

The weights of the heart changed slightly during the fixation period. A correction factor was established by dividing the original heart weight by the weight of the heart after fixation. The weight of each section of the heart was then corrected. Ratios of these corrected weights to the individual body weights were determined, the average of each calculated, and the mean percent increase in each instance tabulated. The t-test was performed to determine significance.

Results

The data in table 1 show that in both sexes exercise and exposure to intermittent hypoxia produced a significant cardiac hypertrophy both of the right ventricles and of the left...
TABLE 1
Effects of Exercise and of Anoxic Hypoxia on the Right and Left Ventricles of Rats

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Sex</th>
<th>No. of animals</th>
<th>Ratio rt. VW/BW*</th>
<th>No. of animals</th>
<th>Ratio lft. VW/BW</th>
<th>% Increase</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>M</td>
<td>20</td>
<td>0.493</td>
<td>18</td>
<td>0.741</td>
<td>50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>F</td>
<td>25</td>
<td>0.448</td>
<td>25</td>
<td>0.703</td>
<td>57</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Exercise</td>
<td>M</td>
<td>13</td>
<td>0.438</td>
<td>13</td>
<td>0.483</td>
<td>10</td>
<td>.025</td>
</tr>
<tr>
<td>Exercise</td>
<td>F</td>
<td>14</td>
<td>0.448</td>
<td>11</td>
<td>0.520</td>
<td>16</td>
<td>.13</td>
</tr>
</tbody>
</table>

*VW: weight of ventricles; BW: body weight.

TABLE 2
Effects of Exercise and Anoxic Hypoxia on the Ratio, Weight of Left Ventricular Wall/Weight of Right Ventricular Wall, LV/RV

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Sex</th>
<th>No. of animals</th>
<th>Ratio LV/RV</th>
<th>Difference</th>
<th>&quot;t&quot;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control rats</td>
<td>For hypoxic group</td>
<td>M</td>
<td>20</td>
<td>3.22</td>
<td>0.53</td>
<td>3.509</td>
</tr>
<tr>
<td></td>
<td>For exercised group</td>
<td>M</td>
<td>13</td>
<td>3.75</td>
<td>0.37</td>
<td>1.556</td>
</tr>
<tr>
<td></td>
<td>For hypoxic group</td>
<td>F</td>
<td>25</td>
<td>3.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For exercised group</td>
<td>F</td>
<td>14</td>
<td>3.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental rats</td>
<td>Hypoxic group</td>
<td>M</td>
<td>18</td>
<td>3.06</td>
<td>0.64</td>
<td>3.280</td>
</tr>
<tr>
<td></td>
<td>Exercised group</td>
<td>M</td>
<td>13</td>
<td>3.70</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Hypoxic group</td>
<td>F</td>
<td>25</td>
<td>3.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercised group</td>
<td>F</td>
<td>11</td>
<td>3.76</td>
<td>0.72</td>
<td>3.396</td>
</tr>
</tbody>
</table>

ventricles. The per cent increase of the weight of the right ventricular wall relative to that of the left ventricular wall was greater after intermittent hypoxia than after exercise. The data show also that exercise produced about the same per cent increase of weight in both right and left ventricular walls.

Table 2 summarizes control data and the effects of exercise and of anoxic hypoxia on the left ventricular/right ventricular ratio in both male and female rats. A significant difference was found between the male control rats used in the exercise and hypoxia groups. This difference will be discussed later. The difference between the two female control groups was not statistically significant.

The data in table 2, comparing male rats exposed to hypoxia with those subjected to exercise, indicate that the LV/RV ratio is significantly lower in the hypoxic group. This was also found to be true when the female exercised and hypoxic rats were compared. The smaller values, 3.06 and 3.04, indicate a predominance of right ventricular hypertrophy in those animals subjected to intermittent hypoxia.

Discussion

EFFECT OF HYPOXIA

The data in table 1 and table 2 indicate clearly that rats exposed to intermittent hypoxia show a relatively greater hypertrophy of the right ventricle than exercised rats. The significant increase in weight of the right ventricle in both sexes exposed to anoxic hy-
poxia indicates that there has been an increased work load on that chamber, presumably due to the increased pulmonary pressure. There is also some left ventricular hypertrophy which, at least in acute hypoxia, is probably caused by increased cardiac output.

When the left ventricular/right ventricular ratio (table 2) of male control rats used for the exercise experiments was compared with that of the control rats used for hypoxia it was observed, as previously mentioned, that there was a significant difference. It is difficult to account for this except on the basis of random variation. The difference between the male exercised and hypoxic rats was significant but in view of the control series this may not be an entirely meaningful figure. Nevertheless the values obtained from male hypoxic and male exercised rats compare very favorably with those of the females subjected to the same conditions.

That pulmonary hypertension exists in animals during hypoxia was first shown by von Euler and Liljestrand in 1946. In the following year Motley et al. also found this to be true in man. Since that time numerous workers have described pulmonary hypertension with concomitant right ventricular hypertrophy at high altitudes or at simulated high altitudes. As far as the authors are aware, the pulmonary arterial pressure in the rat has not been measured during hypoxia. This has been done, however, in dogs, cats, and rabbits, and a distinct rise of pulmonary arterial pressure was found. It can be assumed that rats probably would be affected in similar fashion, particularly when exposed to severe degrees of hypoxia.

The cause of pulmonary hypertension during both acute and chronic hypoxia is still not thoroughly understood. It has been suggested by a number of workers that hypoxia produces pulmonary hypertension through vasoconstrictor effects, but this view is not accepted by all investigators. Fishman maintains that there is no convincing evidence that the autonomic nervous system is directly involved in the regulation of normal pulmonary circulation during hypoxia.

Recently Aviado has reviewed critically the action of acute hypoxia on the pulmonary circulation. In essence, he states that it is generally agreed that pulmonary artery pressure rises during hypoxia and that increased cardiac output could contribute to the pulmonary hypertension. He believes there is strong evidence that hypoxia by sympathetic stimulation causes constriction of the lung vessels (probably due to chemoreceptors). Furthermore, hypoxia, by increasing discharge of the adrenal medulla, causes cardiac stimulation, increases venous return, and may also produce pulmonary constriction.

**EFFECT OF EXERCISE**

Cardiac hypertrophy was established by making rats run on an electrically-driven treadmill. This method was chosen rather than others, such as aortic constriction or pulmonary ligation, because exercise is more physiologic, it can be regulated better and, even more important, it requires no surgical procedures. Another cogent factor was that exercise has been used for many years in our laboratory in order to produce cardiac hypertrophy in the rat.

All rats do not run equally well on a treadmill, and close supervision is required during the exercise periods. Although most rats can be trained to run satisfactorily, an occasional rat refuses to run. One difficulty experienced in exercising rats was that their feet became bruised. There seems to be no way to prevent this, and occasionally a rat had to be removed from the series. It should be mentioned that two one-hour periods each day must be regarded as strenuous exercise. Parenthetically, it might be added that vigorous swimming will also produce significant cardiac hypertrophy. Water may, however, influence the body temperature of the rat, and furthermore, there is danger that some water may enter the lungs and produce hypoxia.

The increase of heart weight produced by exercise is thought to be caused by enlargement of the myocardial fibers produced by the increased work load. It is, therefore, a work hypertrophy. The exact nature of the stimulus...
CARDIAC HYPERTROPHY

to myocardial hypertrophy in man and experimental animals is not known. There are a number of current hypotheses, such as nutritional deficiency of the myocardium, excessive hormonal secretion, increased external work of the cardiac chambers, myocardial dilatation, and others. Recently Badeer has proposed a hypothesis, which he admits has not as yet been entirely proved. He has written that the chronic increase of myocardial metabolic rate per beat per unit mass of tissue probably constitutes the stimulus for hypertrophy. He believes that this is the most favored hypothesis and is more inclusive than any other in explaining hypertrophy. He states further that conditions which increase the force of contraction of the wall of a cardiac chamber for a short period are accompanied by an increase in the oxidative metabolism of the myocardium per unit mass of tissue per beat. If these conditions are maintained over long periods, hypertrophy of muscle fibers develops. This hypertrophy increases the contractile force of the wall because the wall becomes thicker, and it restores the myocardial metabolic rate per unit mass of tissue per heart beat. He suggests that this hypertrophy may be considered as a useful response from the standpoint of myocardial energetics.

It is interesting to note that cardiac hypertrophy, produced either by exercise or by subjecting animals to an effective simulated altitude, regresses if the exercise is discontinued or if exposure to hypoxia is stopped. There is some evidence that cardiac hypertrophy regresses completely in somewhat less than three weeks (unpublished work).

Summary

A group of rats, including both sexes, was exercised on an electrically-driven treadmill at the rate of one mile per hour for two hours daily to a total of 60 hours. Another group, also including both sexes, was exposed to intermittent hypoxia for eight hours daily, six days per week, for four weeks at a barometric pressure of 303 mm Hg corresponding to a simulated altitude of approximately 24,000 feet (7,315 m). All these animals showed significant hypertrophy of both ventricles.

Exercise produced about the same percentage of weight increase in the right and also in the left ventricular walls. The per cent increase of the right ventricular wall relative to that of the left ventricular wall was greater after intermittent hypoxia than after exercise. The ratio of left ventricular weight/right ventricular weight was significantly less in the hypoxic group than in the exercised group. This indicates a relative right ventricular hypertrophy produced by the intermittent hypoxia. Reasons are given to indicate that the pulmonary hypertension associated with hypoxia is the cause of this right ventricular predominance.

References

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