Cardiopulmonary Function During Six Weeks Exposure to Simulated High Altitude in Growing Rats

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Abstract An attempt was made, by using a control chamber, to elucidate how the cardiopulmonary function of the growing rat is affected by chronic exposure to a hypoxic condition. Thirty-five male Wistar rats were divided into 7 groups at 5 weeks old: C₀, examined at 5 weeks old; T₃, T₆, exposed to a hypobaric-hypoxic condition (simulated 2,500 m altitude) from 5 to 8 and 11 weeks old; T₁₇, exposed to the hypobaric-hypoxic condition from 5 to 11 weeks old then kept at a normobaric-normoxic condition (simulated sea level) until 22 weeks old; C₃, C₆, C₁₇, control groups for T₃, T₆, T₁₇, respectively, kept at the normobaric-normoxic condition. Ambient temperature, relative humidity, and CO₂ concentration were maintained at 25°C, 60%, and 500–1,500 ppm, respectively. Morphological, electrocardiographical, and haematological examinations were performed under the sea level condition. The exposure depressed the gain in body weight progressively and prolonged the QT interval. The increase in the heart weight of the exposed group continued after the return to the sea level, but the increased adrenal weight during the exposure was restored by the return. Notable increases in erythrocyte count, Hb concentration, Hct value, and the weight of the right ventricular free wall were observed in T₃. However, these increases were depressed thereafter. Enlargement of the variation in mean QRS axis and increases in MCV, MCH, and the lung weight/body weight were revealed in T₆. In general, the results obtained in this experiment were similar to those observed in a natural high altitude environment. It was considered that the most influential factor for the cardiopulmonary function at high altitudes was the decrease in oxygen tension and that the animals altered their physiological conditions for achieving new stability through the process of adaptation to a high altitude environment.

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It is well known that physiological adaptation in the cardiopulmonary system occurs in man and animals native to or exposed to high altitudes. It has been presumed that the cardiopulmonary changes observed at high altitudes are mainly concerned with the level of oxygen tension^{1,2,3)}. In a natural high altitude environment, the living body is affected by a complex of many meteorological factors. Therefore, this investigation was designed to discriminate only the effects of oxygen tension from those of other factors by using a control chamber⁴⁾. The aim of the present study is to elucidate how the cardiopulmonary function of the growing rat is affected by chronic exposure to a hypoxic condition.

Materials and Methods

Thirty-five male Wistar rats were raised for one week preliminarily from 4 to 5 weeks old in a control chamber (Shimadzu, SCA-102Z)* under a normobaric-normoxic condition (simulated sea level), and then divided into the following 7 groups: C₀, non-exposed and examined at 5 weeks old; T₃, T₆, exposed to a hypobaric-hypoxic condition equivalent to 2,500 m altitude from 5 weeks old and examined at 8 and 11 weeks old, respectively; T₁₇, exposed to the hypobaric-hypoxic condition from 5 to 11 weeks old, and then raised under the normobaric-normoxic condition and examined at 22 weeks old; C₃, C₆, C₁₇, control groups for T₃, T₆, T₁₇, respectively, raised under the normobaric-normoxic condition.

The chamber was composed of main- and sub-cabinets, in which the simulations of 2,500 m altitude and sea level conditions were performed, respectively. The exposed groups were returned to the sea level condition every two days for 1.5 h to be fed according to normal procedures for rats and to be measured for body weight with the control groups. Ambient temperature, relative humidity, and CO₂ concentration were continuously maintained at 25°C, 60%, and 500–1,500 ppm, respectively, and light control (12 L and 12 D) was also performed.

All observations were carried out on the rats anesthetized by urethane (primal dose 0.8 g/kg i.p. and supplemental dose 0.4 g/kg s.c.) under a normobaric-normoxic condition out of the chamber. The exposed groups were examined by the next day of their return to the sea level at each examination. Electrocardiograms in limb leads were recorded with a biophysigraph (Sai-ei, 180 system). Mean QRS axis was calculated from the records of LI and LIII, and QT and PP intervals were measured from the record of LII. For the blood samples collected from the abdominal aorta, erythrocyte count, Hb concentration, and Hct value were measured with a Micro Cell Counter (Toa Medical Electric, CC-108), by azide methaemoglobin method, and by micro capillary method, respectively. Thereafter, all rats were killed by bleeding and the weights of the heart, the lungs, and the adrenal glands in raw material were measured by Mettler (Siebel-Seiko, H-10). After the heart was fixed in a 10% neutral formalin solution for one week, the weights of the right ventricular free wall (R) and the left ventricular free wall plus the ventricular septum (L+S) were measured according to Fulton's method⁹.

Results

The increase in body weight of the exposed group was depressed progressively in accordance with the time of exposure as shown in Fig. 1.

Though the adrenal weight of the exposed group increased during exposure, it was reduced by the return to sea level (Fig. 2).

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Fig. 1. Growth curve in body weight in control (○) and exposed (●) groups. Each mark represents a mean $\pm$ S. D.. *: significant difference between control and exposed groups ($P < 0.05$).

Fig. 2. Correlation chart of adrenal weight and body weight. The line which connects the marks (mean values in each group) with the arrows indicates the changing process of the correlation between both parameters during the experiment in control (○) and exposed (●) groups. See the text for the explanation of C_i and T_i .

The relative weight of the heart to the body weight in the exposed group tended to be greater than that of the control group. This tendency was observed more clearly after the return to sea level than in the exposure period (Fig. 3).

Fig. 4 shows the correlation between R weight and (L+S) weight in both groups. The exposed group showed a notable increase in R weight in the first 3 weeks

Fig. 3. Correlation chart of heart weight and body weight. Footnote is the same as in Fig. 2.

Fig. 4. Correlation chart of R weight and (L+S) weight. See the footnote in Fig. 2. R: the right ventricular free wall, L: the left ventricular free wall, S: the ventricular septum. The vertical arrow indicates a significant difference in R/(L+S) ratio between C_3 and T_3 ($P < 0.05$).

Fig. 5. Regression line of PP and QT intervals in control (○) and exposed (●) groups. The data of C₀ (●) were used for obtaining both regression lines.

Fig. 6. Variation of mean QRS axis in control (○) and exposed (●) groups. The hatched zone represents the maximal-minimal range of the control group.

of exposure, as indicated by the large R/(L+S) ratio of T₃.

Fig. 5 shows the regression lines of PP and QT intervals in both groups. The slope of the line in the exposed group was obviously greater than that in the control group ($P < 0.05$).

The fluctuation of mean QRS axis in the control group was confined within a narrow range. On the contrary, the range of the exposed group was expanded especially in T₆ and T₁₇ as shown in Fig. 6.

The lung weight of the exposed group increased linearly, while the rate of increase for lung weight in the control group was depressed in C₆. Therefore, the increase in lung weight due to exposure was accentuated after 6 weeks exposure ($P < 0.05$) as shown in Fig. 7.

Fig. 7. Correlation chart of lung weight and body weight. See the footnote in Fig. 2. The vertical arrow indicates a significant difference in the lung/body weight ratio between C₆ and T₆ ($P < 0.05$).

Fig. 8. Changes in blood properties in control (○) and exposed (●) groups. Each mark represents a mean $\pm$ S. D.. *: significant difference between control and exposed groups ($P < 0.05$).

Fig. 8 shows the process of changes in erythrocyte count, Hb concentration, and Hct value in both control and exposed groups. All measurements of these parameters in the exposed group were significantly larger than those in the control group at the 3rd week from the onset of exposure ($P < 0.05$). However, the changes in these parameters in the exposed group leveled out thereafter.

Discussion

It has been reported in several works that adaptive changes in the heart occur in all individuals over 2,000 m altitude⁶⁾, and cardiac failure appears over about 3,000 m altitude⁷⁾. Based on these works, the conditions of high altitude simulation in this experiment were determined at 2,500 m altitude in order to observe with certainty the adaptive changes in the cardiopulmonary system.

From the depression in the gain in body weight in the exposed group, it was assumed that the simulative conditions of this experiment laid stress on the rats, as was also suggested by the process of changes in the adrenal weight.

Including the results obtained at the 11th week from the return to sea level (22 weeks old), the changes in physiological parameters produced by the exposure were classified into two types: a reversible type represented by the changes in adrenal weight and blood properties, and an irreversible one represented by the changes in heart weight and mean QRS axis.

The increase in Hb concentration observed in the exposed group was considered to be an adaptive response to a hypoxic condition, since it meant an increase in the oxygen capacity of the blood⁸⁾. The erythrocyte count of T_6 was no more different from that of C_6 , which suggests that the size and Hb content of the erythrocyte were changed. In fact, the values of MCV and MCH in T_6 were greater than those in C_6 ($P < 0.05$). Therefore, the mechanism involved in the increase in Hb concentration was mainly due to the increase in the number of the erythrocytes in T_3 , and due to the increase in Hb content of the erythrocyte in T_6 , respectively.

As it has been reported, an increase in Hct value can be considered to induce a high blood viscosity⁹⁾ and to increase the pulmonary vascular resistance¹⁰⁾, and the occurrence of right ventricular hypertrophy is assumed by an increase in $R/(L+S)$ ratio⁶⁾. In this experiment, considerable increases in both Hct value and $R/(L+S)$ ratio were observed in the first 3 weeks of the exposure. Moreover, the exposed group showed a prolongation of QT interval, which is often observed in cardiac hypertrophy. Therefore, it was presumed that the right ventricular hypertrophy had been produced in the exposed group owing to the increase in the pulmonary vascular resistance. The enlargement of the variation of mean QRS axis in T_3 may be connected with this right ventricular hypertrophy; on the other hand, the considerable enlargement in T_6 may have resulted from the alteration of the heart position in the thorax as suggested by the increase in lung weight.

In the present study, the high altitude simulation was performed by decompression alone in order to create hypoxic conditions under constant conditions of ambient tem-

perature, relative humidity, CO₂ concentration, and lighting. In general, the results obtained in this simulative experiment were similar to those observed in a natural high altitude environment composed of many meteorological factors in the aspects of morphological^{8,11)}, electrocardiographical¹²⁾, and haematological^{13,14)} changes. In our preceeding report⁴⁾, we indicated that the main influential factor of a hypobaric-hypoxic condition on the cardiopulmonary function was the decrease in oxygen tension based on the observations in the rats exposed to hypobaric and/or hypoxic conditions. It was considered, therefore, that the most influential factor for the cardiopulmonary function of man and animals at high altitudes was the decrease in oxygen tension.

In this experiment, physiological parameters were altered by exposure, but the process of the alteration during the exposure was different for each parameter. For example, the initial changes evoked by exposure were great in the blood properties and the weight of the right ventricle in T₃, but the increase in lung weight or the enlargement of the variation of mean QRS axis appeared later in T₆. From the results obtained in this experiment, it was presumed that the animals altered their physiological conditions to achieve a new stable condition with the process of adaptation to a high altitude environment.

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低酸素環境が成長期ラットの心肺機能に及ぼす影響

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慢性的な低酸素暴露が，成長期ラットの心肺機能に及ぼす影響を明らかにするために，コントロールチャンバーを用いて実験を行なった。

5週令の Wistar 系雄ラット 35 匹を 7 群に分けた。5週令で観察する群を C₀，標高 2,500 m 相当の低圧低酸素環境に 5 週令から暴露し，8 および 11 週令で観察する群を T₃，T₆，11 週令まで暴露したのち海面相当の常圧常酸素環境にもどし，22 週令で観察する群を T₁₇ とし，それぞれの群に対して海面相当で飼育する対照群 C₃，C₆，C₁₇ を設けた。温度，湿度，および二酸化炭素濃度はそれぞれ常に 25°C，60%，および 500～1,500 ppm に制御した。各群に対して，形態的，心電図的，血液学的検査を常圧常酸素条件下で実施した。

暴露群では対照群と比べて，成長にともなう体重の増

加が抑圧され，QT 間隔は延長し，心臓重量も大きい傾向にあったが，暴露による副腎重量の増大は，常圧常酸素環境へ戻すことにより回復した。赤血球数，Hb 濃度，Hct 値，および右心室重量は T₃ 群で大きく増加したが，その後の増加は抑圧された。T₆ 群では，平均電気軸のバラツキが大きくなり，肺重量体重比ならびに MCV，MCH が大きくなった。

高地環境下でみられる心肺系の典型的な変化が低酸素暴露のみによって生じたことから，心肺機能にとって酸素分圧の低下が多くの高地環境要因の中で最も重要な作用因子であり，高地環境への適応過程として生理状態の安定に向け段階的な変化が生ずる可能性が示唆された。

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