Cardiac remodeling and functional adaptations consecutive to altitude training in rats: implications for sea level aerobic performance

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Submitted 27 February 2004; accepted in final form 28 July 2004

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Cardiac remodeling and functional adaptations consecutive to altitude training in rats: implications for sea level aerobic performance. J Appl Physiol 98: 83–92, 2005. First published July 30, 2004; doi:10.1152/japplphysiol.00214.2004.—This study questioned the effect of living and training at moderate altitude on cardiac morphological and functional adaptations and tested the incidences of potential specific adaptations compared with aerobic sea level training on maximal left ventricular performance. Sea level-native rats were randomly assigned to N (living in normoxia), NT (living and training 5 days/wk for 5 wk in normoxia), CH (living in hypoxia, 2,800 m), and CHT (living and training 5 days/wk for 5 wk in hypoxia, 2,800 m) groups. Cardiac adaptations were evaluated throughout the study period by Doppler echocardiography. Maximal stroke volume (LVSVmax) was measured during volume loading before and after the study period. Finally, at the end of the study period, passive pressure-volume relationships on isolated heart and cardiac weighing were obtained. Altitude training resulted in a specific left ventricular (LV) remodeling compared with NT, characterized by an increase in wall thicknesses without any alteration in internal dimensions. These morphological adaptations associated with hypoxia-induced alterations in pulmonary outflow and preload conditions led to a decrease in LV filling and subsequently no improvement in LV performance during resting physiological conditions in CHT compared with NT. Such a lack of improvement was confirmed during volume overloading that simulated maximal effort (LVSVmax pretest: NT = 0.58 ± 0.05, CHT = 0.57 ± 0.08 ml; posttest: NT = 0.72 ± 0.06, CHT = 0.58 ± 0.07 ml; NT vs. CHT in posttest session, P < 0.05). Maximal aerobic velocities increased to the same extent in NT and CHT rats despite marked polycythemia in the latter. The lack of LVSVmax improvement resulting from altitude training-induced cardiac morphological and functional adaptations could be responsible for this phenomenon.

In their constant search to improve performance, many athletes invest in considerable resources to train at altitude because hypoxia exposure enhances erythropoiesis. However, there is clear scientific evidence in both humans and animals that training at altitude does not provide any advantage over training at sea level on VO2max and aerobic performance (13, 23). Acclimatization to hypoxia indeed results in cardiovascular and respiratory changes that may negate the training and/or hypoxia physiological benefits. Chronic hypoxia exposure has several cardiac hemodynamic incidences, including increased pulmonary artery pressure (27) and decreased blood plasma volume (37), both of which have been shown to limit LV preload and consequently LV filling (15, 30, 37). Because these hypoxia-induced adaptations resulted in alterations in LV loading conditions, they could play a major role in LV remodeling and functionality changes consecutive to altitude training. Today, very few reports are available on cardiac morphological and functional adaptations after altitude training (22, 39, 44), and conflicting as well as inconclusive results have been found, probably because of bias in experimental designs.

Several authors (4, 9, 13) have recently suggested that a reduction in maximal stroke volume is an important mediator for the classically reported lower maximal cardiac output of acclimatized subjects after returning from altitude (9, 43). Pulmonary hypertension as well as decreased blood plasma volume have been considered to be responsible for LV performance deconditioning (24) and consequently LVSV reduction. LVSV depends on a complex interplay between cardiac size, loading conditions, intrinsic cardiac relaxation, and contractility properties. To the best of our knowledge, mechanisms related to LVSV changes after altitude training have never been studied in a comprehensive way. In addition, no relationships between cardiac morphology or function and heart pumping capacity have been investigated. We hypothesize that living and training at altitude may limit the increase in maximal cardiac pumping capacity classically reported after sea level training via specific LV morphological and functional adaptations.

Another important mediator for the classically reported lower maximal cardiac output after return from altitude is maximal heart rate. Indeed, acclimatization to hypoxia is also responsible for a decrease in maximal heart rate, related to adaptations in both parasympathetic and sympathetic neural tones associated with a reduced cardiac sensitivity to adrenergic stimulation or modulation by other receptors (4, 10, 34). Nevertheless, recent studies have shown that the training state

DURING DYNAMIC EXERCISE INVOLVING a large muscle mass, maximal O2 uptake (VO2max) is primarily set by the rate of O2 delivery to the muscle cells. Hence, a superior cardiac pumping capacity and to a lesser extent O2 carrying capacity allows athletes to achieve a higher VO2max than their sedentary counterparts at sea level (2). It is of importance that the left ventricular (LV) morphological and functional adaptations resulting from the chronic volume overload imposed by repetitive exercise sessions are responsible for a larger stroke volume (LVSV) from rest to maximal exercise in the training state (2, 16).

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prevents the hypoxia-induced decline in maximal heart rate (9, 10).

In the present study, considering that chronic exposure to hypoxia has several cardiac hemodynamic consequences that in turn could affect cardiac morphological and functional adaptations consecutive to endurance training, we investigated the effects of a 5-wk highly supervised altitude training camp on LV and right ventricular (RV) morphologies and functions during resting conditions in sea level-native rats. In addition, because cardiac adaptations play a major role explaining maximal aerobic capacity, we also evaluated the involvement of potential cardiac alterations on LV SV changes during overloading conditions simulating a situation encountered during exercise. For ethical and practical reasons, experiments were carried out in rats, animals frequently used in exercise and altitude studies that share several human features of acclimatization to hypoxia and training (18).

METHODS

Animal Model

Sixteen-week-old, sea level-native Dark Agouti male rats, obtained from Harlan Laboratories (Gannat, Puy de Dôme, France), were randomly assigned to live continuously in hypobaric hypoxia including hypoxic aerobic training sessions (CHT rats, n = 14), hypobaric hypoxia (CH rats, n = 14), normoxia including normoxic aerobic training sessions (NT rats, n = 14), or normoxia (N rats, n = 14). This strain was chosen because it presents a high aerobic potential and the typical cardiovascular adaptations encountered by endurance-trained athletes (1). Environments were obtained by using steel chambers fitted with a clear plastic glass door to illuminate and observe the animals (31). Hypobaric hypoxia was obtained by using a specific vacuum pump (Becker Mot63, Rambouillet, France). In each chamber, barometric pressure, humidity, and temperature conditions were continuously estimated by using electronic sensors.

All rats were maintained for 5 wk in their own environment, at a barometric pressure of 760 mmHg [inspired PO2 (PiO2) ≈ 159 Torr, altitude ≈ 80 m] for N and NT or of 550 Torr (PiO2 ≈ 105 Torr, altitude = 2,800 m) for CH and CHT. In addition, to simulate athlete strategies and assess the effect of reacclimatization, all groups were maintained in normoxic conditions without training for 2 days before noninvasive and invasive posttest evaluations. CH and CHT animals were fed ad libitum with free access to tap water. Because of altitude impact on food intake and consequently animal growth (7), a pair-feed model was applied to the two other groups with free access to tap water. Room temperatures were maintained at ~21°C by using air conditioning. Four animals were kept in each cage at the same time on a 12:12-h light-dark cycle. All procedures were performed in agreement with the approval of the French Ministry of Agriculture.

Training Program

Training sessions were conducted in NT and CHT rats during the 5-wk environmental exposure. To supervise training intensities with precision, maximal aerobic velocity (MAV) was evaluated for each rat before and after the study period in normoxia (PiO2 = 159 Torr) and hypoxia (PiO2 = 105 Torr). MAV was also evaluated during the third week of exposure in living environments only to adapt training intensities. Both normoxic and hypoxic MAV were estimated by use of the rats, lightly anesthetized with intraperitoneal ketamine HCl (50 to 75 mg/kg) and xylazine (10 to 15 mg/kg) (29). Samples were quickly analyzed for Hb concentration with a CO-oximeter (Avoximeter 4000, AVOX, San Antonio, KS).

Doppler echocardiography. Cardiac morphology and function were evaluated throughout the 5-wk study period as well as 2 days after return from altitude in normoxia via a noninvasive Doppler-echocardiography method. Rats were lightly anesthetized with intraperitoneal ketamine HCl (50–75 mg/kg) and xylazine (10–15 mg/kg) (29). By using a commercially available echocardiographic machine equipped with a 5- to 8-MHz transducer (HDI 3000, ATL, Phillips, Bothell), a two-dimensional view of the LV was obtained at the level of the papillary muscles. M-mode tracings were recorded through the anterior and posterior walls. End-diastolic anterior and posterior wall thicknesses (AWTd and PWtd, respectively) and LV internal diastolic (LVEDd) and systolic (LVESd) dimensions were measured by using a modified version of the leading-edge method of the American Society for Echocardiography from at least three consecutive cardiac cycles on the M-mode tracings (36). LV mass (LVM) was estimated by using the standard cube formula (8). Endocardial shortening fraction was calculated as \[\frac{\text{LVESd} - \text{LVEdsd}}{\text{LVESd}} \times 100\]. Diastolic relative wall thickness (RWT) was calculated as \[\frac{\text{AWTd} + \text{PWtd}}{\text{LVEdsd}} \times 100\] and was used as an index of LV geometry (8).

Pulsed-wave Doppler spectra of mitral inflow were recorded from an apical four-chamber view. Peak velocities of early diastolic rapid inflow (peak E), atrial contraction filling (peak A), as well as their ratio (E/A) were recorded and served as indexes of diastolic function. Ascending aorta flow was recorded via pulsed-wave Doppler from a suprasternal view (38), permitting measurements of the velocity time integrals (VTI). Aortic annulus diameters (Ao d) were measured at the level of the aortic leaflets during systole from a two-dimensional long axis view of LV. With the use of these measurements, LV SV could be calculated by using the following formula: \[\text{LVSV} = \left(\frac{\text{Ao d}^2 \times 3.14 \times \text{VTI}_{\text{E}}}{4}\right)\] (38). Doppler-echocardiography heart rates were determined in each case.

Pulsed-wave Doppler spectra of the RV outflow were also recorded from a parasternal view of the pulmonary artery obtained at the level of the aorta. Measurements of the pulmonary peak flow velocity (Vpmax), used as a negative index of pulmonary artery pressure (25), and of the velocity time integrals of pulmonary artery flow (VTIp) were obtained. For all variables, measurements represent the mean of at least three consecutive cardiac cycles. Intra- and interobserver Doppler echocardiography variabilityt were evaluated during a previous study in seven 10-wk-old male Dark Agouti rats by means of variation coefficients. Coefficients were all equal to or lower than 9.6% (peak A) with a minimal value for LVEDd (1.4%).

Heart rate. Heart rate was obtained before and after the study period. Subcutaneous thoracic electrodes were set out, and a continuous ECG was recorded in conscious unrestrained animals placed in a dark soundproofed small chamber, under normoxic ambient conditions. ECG recordings were obtained under standard conditions as well as after infusion of isoproterenol (0.2 mg/kg) to get an insight into the effect of our environmental exposure on maximal heart rate (33).
Volume overloading. To mimic (even under nonphysiological conditions) the increase in venous return and, subsequently, preload during exercise and to assess the effect of the different environmental conditions on maximal heart pumping capability, peak $L_{SV}$ was measured during volume overloading conditions by the Doppler-echocardiography method previously described. At the pretest session, rats were anesthetized with a mixture of ketamine HCl and xylazine and were perfused continuously with the same mixture at 1.5 ml/h. Under anesthesia, a cannula was inserted into the right jugular vein. After baseline measurements were carried out over a 5-min steady-state period, warmed Tyrode’s solution was infused at a rate of 20 ml·kg⁻¹·min⁻¹ for 1 min. The $L_{SV}$ was estimated 1, 5, 10, and 15 min after the end of the infusion. The same procedure was applied at the posttest session except that the left femoral vein was cannulated. This allowed $L_{SV}$ to be continuously recorded during the infusion procedure. $L_{SV}$ was also estimated 1, 5, 10, and 15 min after the end of infusion. Heart rate was obtained from echocardiography-Doppler recordings. The reproducibility of $L_{SV}$ values was evaluated in our laboratory in five 10-wk-old male Dark Agouti rats infused with Tyrode’s solution. Individual variation coefficients were equal or lower than 8.9% (fifth minute after Tyrode’s infusion) with minimal values for the first minute after Tyrode’s infusion (5.2%), suggesting a good agreement within our measurements.

Isolated heart and pressure-volume relationships. This model was used to assess the potential changes in passive mechanical properties after different exposures to environmental stress. After hemodynamic variables have been studied, the heart was arrested in diastole with potassium chloride, the atrioventricular groove was ligated, and the lumen over the pressure range of 0 to 2.5 mmHg, and the pressure stiffness constant, $k_1$, was obtained from this portion of the curve. Above 2.5 mmHg, pressure increased exponentially with volume, and stiffness constants $k_2$ and $k_3$ were calculated by fitting one exponential function of the form $P = b + e^{kx}$ to the data from the intermediate pressure range (2.5–10 mmHg) and a second exponential to the upper pressure range (15–30 mmHg) (11).

Heart weight. Immediately after pressure-volume curve measurements, the RV free wall was carefully dissected. Left ventricles were opened and rinsed. Right ventricular free walls and LV plus septa (LV+S) were put into an incubator for 12 h at 60°C and then weighed open and rinsed. Right ventricular free walls and LV plus septa (2.5–10 mmHg) and a second exponential to the upper pressure range (2.5–10 mmHg), and the pressure stiffness constant, $k_1$, was obtained from this portion of the curve. Above 2.5 mmHg, pressure increased exponentially with volume, and stiffness constants $k_2$ and $k_3$ were calculated by fitting one exponential function of the form $P = b + e^{kx}$ to the data from the intermediate pressure range (2.5–10 mmHg) and a second exponential to the upper pressure range (15–30 mmHg) (11).

Statistical Analysis

All values reported are means ± SD. The effects of environmental conditions and training on body weight, maximal aerobic velocities, Doppler echocardiography, and hematological data were assessed by two-way ANOVA with repeated measures, followed when appropriate by post hoc Tukey’s tests, using Statview software (Abacus Concept, Berkeley, CA). Associations between physiological variables were quantified with the Spearman correlation coefficient. Postmortem data were analyzed by a one-way ANOVA followed when appropriate by Tukey’s post hoc tests. The level of significance was set at 0.05.

RESULTS

Body Weight and Hematological Data

Before exposure, no significant differences were found between groups for all parameters (Table 1). Body weight increased significantly ($P < 0.05$) at the end of exposure without any differences between groups being observed. Total Hb markedly increased ($P < 0.05$) in CH and CHT rats at the end of exposure, whereas no modification in this parameter was observed for N and NT rats.

Maximal Aerobic Velocities

Before exposure, there were no significant differences between groups regarding normoxic MAV as well as hypoxic MAV (Table 1). Whatever the exercise conditions, training induced a significant ($P < 0.05$) improvement in MAV, whereas no modifications were observed for normoxic and hypoxic control groups at the end of the study period. CHT rats improved their MAV to the same extent as NT rats in both normoxia (NT: +16.22%; CHT: +18.5%) and hypoxia (NT: +16.1%; CHT: +20.5%). For both NT and CHT, normoxic MAV was unchanged 2 days after return from altitude (NT: MAV$_{N+2days}$ = 43.7 ± 2.6, MAV$_{N+2days}$ = 44.3 ± 1.8; CHT: MAV$_{N+2days}$ = 44.0 ± 3.7, MAV$_{N+2days}$ = 44.8 ± 4.6 m/min, where subscript N designates normoxia, and subscripts after +2days designate time points immediately and 2 days after return).

Echocardiographic Morphological and Functional Characteristics

LV morphology. Echocardiographic derived data are shown in Table 2 and Fig. 1. Before exposure, no significant differences were found between groups for all morphological data. No modifications were observed in N rats throughout the study period for LVEDd (Fig. 1A), whereas LVEDd progressively

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Table 1. Body weight, maximal aerobic velocity, and hematological data

<table>
<thead>
<tr>
<th></th>
<th>N (n = 10)</th>
<th>Before</th>
<th>After</th>
<th>NT (n = 13)</th>
<th>Before</th>
<th>After</th>
<th>CH (n = 11)</th>
<th>Before</th>
<th>After</th>
<th>CHT (n = 12)</th>
<th>Before</th>
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<tr>
<td>BW, g</td>
<td>243±8</td>
<td>258±23*</td>
<td></td>
<td>237±21</td>
<td>248±25*</td>
<td></td>
<td>244±21</td>
<td>258±21*</td>
<td></td>
<td>244±11</td>
<td>249±14*</td>
<td></td>
</tr>
<tr>
<td>MAVv, m/min</td>
<td>37.6±5.8</td>
<td>35.2±5.3</td>
<td></td>
<td>37.6±3.1</td>
<td>43.7±2.6†</td>
<td></td>
<td>35.4±3.9</td>
<td>35.3±3.7</td>
<td></td>
<td>37.1±4.7</td>
<td>44.0±3.7†</td>
<td></td>
</tr>
<tr>
<td>MAVV, m/min</td>
<td>31.0±3.6</td>
<td>29.3±2.4</td>
<td></td>
<td>32.3±2.5</td>
<td>37.5±3.3†</td>
<td></td>
<td>28.4±3.9</td>
<td>28.1±2.0</td>
<td></td>
<td>31.1±3.1</td>
<td>37.8±2.4†</td>
<td></td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>14.5±1.3</td>
<td>14.5±0.5</td>
<td></td>
<td>13.7±0.9</td>
<td>14.2±0.4</td>
<td></td>
<td>14.7±0.9</td>
<td>16.1±0.9†</td>
<td></td>
<td>14.2±0.8</td>
<td>16.1±0.4†</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. BW, body weight; MAVv, maximal aerobic velocity in normoxia; MAVV, maximal aerobic velocity in hypoxia; Hb, total hemoglobin; N, rats exposed to normoxia; NT, rats exposed to and trained in normoxia; CH, rats exposed to hypoxia; CHT, rats exposed to and trained in hypoxia. *$P < 0.05$ vs. the same group before; †$P < 0.05$ vs. N and CH rats; ‡$P < 0.05$ vs. N and NT rats.
increased in NT rats. The values in this group were significantly higher than those in N rats from the third week onward. On the other hand, LVEDd markedly decreased in CH and CHT rats during the first week of hypoxia exposure. LVEDd in CHT rats showed thereafter a similar pattern as for NT rats and presented 2 days after return from altitude, similar values to those observed in N rats. In CH rats, values remained lower than in the two normoxic groups until the end of the study period. LVEDd showed a significant (P < 0.05) increase with sea level reacclimatization in CH and CHT rats (CH: LVEDd after = 6.38 ± 0.29, LVEDd2days = 6.65 ± 0.18 mm; CHT: LVEDd after = 6.62 ± 0.24, LVEDd2days = 6.79 ± 0.22 mm), whereas no modifications were observed in the two normoxic groups. Only training in normoxia increased LVEDd significantly (Table 2), and no modifications were observed in the two normoxic groups.

**Diastolic function.** Before exposure, no significant differences were found between groups regarding all transmural flow velocity indexes (Table 2). Whatever the group, peak E followed a strictly similar pattern to LVEDd. After 2 days at sea level, peak E increased significantly (P < 0.05) in CH and CHT rats (CH: peak E after = 52.0 ± 2.1, peak E2days = 55.2 ± 1.9 cm/s; CHT: peak E after = 56.3 ± 2.4, peak E2days = 58.5 ± 1.2 cm/s), whereas no modifications were observed in the two normoxic groups. However, values in CH rats remained lower than in N rats. In addition, a significant linear relationship was observed between percentage variation at the posttest session in peak E and LVEDd (r = 0.65, P < 0.05). Peak A did not alter in any of the groups and/or times of intervention. As a result, E/A ratio presented similar kinetics to peak E. Whatever the group and the time of intervention, there were no significant differences concerning heart rate during Doppler measurements.

**LV stroke volume.** Data are shown in Table 2 and Fig. 2. Before exposure, no significant differences were found between groups regarding LVSV established under normal physiological conditions. LVSV was not modified throughout the study period in N and CH rats. It progressively increased during sea level training in NT rats, values being significantly higher than those in the other three groups from the second week onward. LVSV, which decreased in the two hypoxic groups during the two first weeks, was maintained thereafter and tended to increase 2 days after return from altitude. A significant linear relationship was observed between the percentage variation at the posttest session in peak E and LVSV (r = 0.56, P < 0.05) as well as in LVEDd and LVSV (r = 0.62, P < 0.05).

**Pulmonary flow.** Before exposure, no significant differences in Vpulm were found between groups (Fig. 3). This parameter remained unchanged throughout the study period in N rats and slightly increased in NT rats, with values being significantly

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Table 2. Morphological and functional left ventricular characteristics by Doppler echocardiography before and 2 days after exposure to different environments

<table>
<thead>
<tr>
<th></th>
<th>N (n = 10)</th>
<th>NT (n = 13)</th>
<th>CH (n = 11)</th>
<th>CHT (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>2 Days after</td>
<td>Before</td>
<td>2 Days after</td>
</tr>
<tr>
<td>LVEDs, mm</td>
<td>4.26±0.18</td>
<td>4.32±0.17</td>
<td>4.22±0.16</td>
<td>4.84±0.31†</td>
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<tr>
<td>LVEDd, mm</td>
<td>7.01±0.21</td>
<td>6.93±0.09</td>
<td>7.00±0.08</td>
<td>7.92±0.28†</td>
</tr>
<tr>
<td>AWTd, mm</td>
<td>0.98±0.03</td>
<td>0.98±0.03</td>
<td>0.98±0.04</td>
<td>1.24±0.06§</td>
</tr>
<tr>
<td>PWTd, mm</td>
<td>1.01±0.04</td>
<td>0.99±0.02</td>
<td>0.98±0.04</td>
<td>1.25±0.05§</td>
</tr>
<tr>
<td>LVM, mg</td>
<td>370±18</td>
<td>372±18</td>
<td>361±12</td>
<td>636±75†</td>
</tr>
<tr>
<td>Ao d, mm</td>
<td>2.49±0.02</td>
<td>2.50±0.02</td>
<td>2.50±0.04</td>
<td>2.50±0.01</td>
</tr>
<tr>
<td>Peak E, cm/s</td>
<td>57.8±1.7</td>
<td>58.0±1.5</td>
<td>59.2±1.7</td>
<td>71.9±4.0†</td>
</tr>
<tr>
<td>Peak A, cm/s</td>
<td>28.0±1.5</td>
<td>28.1±0.9</td>
<td>28.2±1.6</td>
<td>29.5±1.2</td>
</tr>
<tr>
<td>E/A</td>
<td>2.06±0.06</td>
<td>2.06±0.12</td>
<td>2.10±0.12</td>
<td>2.42±0.28§</td>
</tr>
<tr>
<td>SF, %</td>
<td>39.1±1.6</td>
<td>37.6±2.8</td>
<td>39.2±1.9</td>
<td>38.5±1.5</td>
</tr>
<tr>
<td>HRDoppler, beats/min</td>
<td>280±16</td>
<td>289±18</td>
<td>289±15</td>
<td>296±22</td>
</tr>
<tr>
<td>SV, ml</td>
<td>0.36±0.03</td>
<td>0.36±0.06</td>
<td>0.35±0.03</td>
<td>0.51±0.07†</td>
</tr>
<tr>
<td>Qc, ml/min</td>
<td>101.5±15</td>
<td>104.4±8</td>
<td>105.8±7</td>
<td>147.8±16†</td>
</tr>
<tr>
<td>VTtia, cm</td>
<td>7.0±0.4</td>
<td>7.3±0.5</td>
<td>7.3±6.7</td>
<td>9.7±1.1†</td>
</tr>
</tbody>
</table>

*Values are means ± SD. LVEDs: left ventricular end-diastolic diameter; LVEDd: left ventricular end-diastolic diameter; AWTd: end-diastolic anterior wall thickness; PWTd: end-diastolic posterior wall thickness; RWT: relative wall thickness; LVM: left ventricular mass; Ao d: aortic diameter; peak E: peak velocity of early diastolic rapid inflow; peak A: peak velocity of atrial contraction filling; SF: left ventricular shortening fraction; HRDoppler: heart rate during Doppler measurements; SV: stroke volume; Qc: cardiac output; VTtia: velocity time integrals of pulmonary artery flow. **P < 0.05 vs. the same group before; †P < 0.05 vs. the three other groups; ‡P < 0.05 vs. N rats; §P < 0.05 vs. N and CH rats.*
different from those in N rats at the second and the fourth week of the study period. On the other hand, \( V_{pulm} \) progressively decreased in the two hypoxic groups, and values were significantly lower than those of the two other groups from the first week of exposure onward. In addition, \( V_{pulm} \) exhibited a significant increase \((P < 0.05)\) with reacclimatization to sea level in the two hypoxic groups only (CH: +24.3%; CHT: +15.9%). However, values in these groups remained markedly lower than those in the two normoxic groups. Before exposure, no significant differences in VTIR were found between groups (Fig. 3). This parameter remained unchanged throughout the study period in N rats. However, VTIR progressively increased in NT rats, with values significantly higher compared with the other three groups from the third week onward. On the other hand, it progressively decreased in the two hypoxic groups, with values significantly lower than those in N rats from the third to the fifth week of the study period. With reacclimatization, VTIR significantly increased in the two hypoxic groups (CH: +17.2%; CHT: +16.9%), and values 2 days after return.
ing to sea level were not significantly different from those obtained in N rats.

Heart Rate

Before exposure, no significant differences were found between groups for heart rate under normal resting conditions (N: 415 ± 22; NT: 416 ± 24; CH: 405 ± 15; CHT: 410 ± 26 beats/min) and after isoproterenol infusion (N: 507 ± 18; NT: 505 ± 13; CH: 502 ± 19; CHT: 510 ± 18 beats/min). The same results were obtained at the end of the study period regarding heart rate under normal resting conditions (N: 411 ± 23; NT: 390 ± 24; CH: 401 ± 20; CHT: 401 ± 27 beats/min). Moreover, values were not different in each group from those obtained at the pretest sessions. However, heart rate established after isoproterenol infusion significantly ($P < 0.05$) decreased in CH rats compared with pretest, and values in this group were significantly lower than those of the other three groups (N: 507 ± 18; NT: 504 ± 16; CH: 487 ± 13; CHT: 503 ± 10 beats/min). The hypoxia-induced decrease in heart rate response to isoproterenol infusion was not observed in CHT rats.

Fig. 3. Pulmonary peak flow velocity ($V_{pulm}$) and velocity time integrals of pulmonary artery flow ($VTI_R$) throughout the study period. Values are means ± SD. $§P < 0.05$ vs. N and NT rats; $\dagger P < 0.05$ vs. the 3 other groups.

Fig. 4. Left ventricular stroke volume ($LV_{SV}$) during volume overloading conditions before (A) and 2 days after (B and C) the study period. T, time corresponding to T0. Values are means ± SD. $\dagger P < 0.05$ vs. the 3 other groups. $§P < 0.05$ vs. CH rats.
**Volume Overloading Conditions**

Before exposure (Fig. 4A), no significant differences were found between groups in LVSV before and up until 15 min after maximal preload stress with infusion of Tyrode’s solution. At the end of the study period, N, CH, and CHT presented no significant differences in LVSV before and after this maximal preload stress (Fig. 4B). However, LVSV values shifted upward in NT rats, and a higher resting LVSV associated with an increased maximal flow generating capacity of the heart was noted in this group compared with the other three groups (Fig. 4B). Interestingly, LVSV kinetics during the infusion of Tyrode’s solution were similar in the four groups up until the 30th second. Values plateaued thereafter for CH, CHT, and N, whereas they continued to increase up to the first minute for NT (Fig. 4C).

**LV End-Diastolic Pressure-Volume Relationships**

Data are shown in Fig. 5. Ventricle volumes measured in the potassium-arrested heart significantly increased in NT rats at transmural pressures from 0 to 30 mmHg compared with the other three groups. Indeed, LV pressure-volume relationship shifted rightward in NT rats. On the other hand, no differences were found between N, CH, and CHT rats. In addition, no differences were found in the stiffness constants between groups for $k_1$ (N: 32 ± 9; NT: 26 ± 4; CH: 32 ± 6; CHT: 26 ± 11), $k_2$ (N: 7.4 ± 2.1; NT: 7.7 ± 1.2; CH: 7.1 ± 2.2; CHT: 6.9 ± 2.2), and $k_3$ (N: 7.1 ± 1.1; NT: 6.9 ± 2.2; CH: 7.6 ± 2.3; CHT: 8.3 ± 2.0).

**Heart Weighing**

At the end of the study period, altitude and sea level training resulted in a LV hypertrophy. Indeed, LV+S mass values in NT and CHT were statistically ($P < 0.05$) higher than those in the two sedentary groups (N = 146 ± 6, NT = 163 ± 11, CH = 139 ± 12, CHT = 156 ± 6 mg). On the other hand, RV mass was significantly ($P < 0.05$) lower in N compared with CH and CHT, and in NT compared with CHT (RV mass: N = 39 ± 2, NT = 42 ± 3, CH = 44 ± 3, CHT = 48 ± 2 mg). Because both hypoxia and training affected RV mass, training at altitude induced a greater RV hypertrophy than living only at altitude.

**DISCUSSION**

The major finding of the present study using a rat model was the limitation of maximal heart pumping capacity after altitude training compared with sea level training. Specific cardiac morphological and functional adaptations consecutive to hypoxia training seem mainly responsible for this result. The involvement of other factors influencing cardiac preload as well as afterload also appear to play a part.

Several sea level studies have shown that an artificial increase in Hct improves aerobic performance and $V_{O2max}$ (5, 40). In our study, despite their marked increase in total Hb, normoxic MAV in CHT rats improved to the same extent as in NT. Such a result has been classically reported in several recent studies performed in humans and animals (13, 23, 41). It can be argued that part of this result might be explained by the fact that CHT rats trained at a similar relative and therefore lower absolute intensity than NT rats. However, several studies have shown similar increases in normoxic MAV and $V_{O2max}$ in rats trained at equal absolute intensities at moderate altitude (i.e., 2,400 m) or sea level. Maximal cardiac output constitutes one potential candidate for this apparent paradox regarding the effect of training and living at altitude on normoxic MAV (9, 24). A decrease in maximal cardiac output after chronic hypoxic exposure has been frequently reported (9, 43) and partly attributed to a reduction in maximal heart rate (HRmax) on account of a downregulation of cardiac adrenergic receptor density (10, 34). This hypoxia-induced decrease in HRmax was evident in our CH rats as shown by heart rate after isoproterenol infusion. However, it is very unlikely that CHT rats exhibited a decrease in HRmax during exercise at peak effort because the diminished cardiac response to $\beta$-adrenergic agonist was not observed in this group. Similar results have been obtained recently by Favret et al. (9, 10), who showed that the training state prevented the hypoxia-induced downregulation of $\beta$-adrenergic receptor density and sensitivity in LV and RV. It could be argued that our results were not obtained under exercise conditions. However, Favret et al. (9) did not report any differences between HRmax established at peak effort and after isoproterenol infusion (10 $\mu$g/kg) in rats. Our results provide clear scientific evidence, however, of a limitation in LSVmax increase after training in CHT compared with NT rats, which if extrapolated to maximal exercise conditions, might well lead to lower maximal cardiac output in the former group. Under physiological conditions, resting LSV increased after training in NT rats (Table 2, Fig. 2), which is well in accordance with previous reports in humans and animals (9, 16). Surprisingly, such an enhancement in LSV was not observed in CHT. Moreover, LSV values during the infusion of Tyrode’s solution shifted upward in NT rats only. This methodological approach served to increase central blood volume (which is known to be depressed after chronic hypoxia exposure) as well as venous return and subsequently cardiac preload, thus simulating a situation encountered during exercise. Although LSVmax was not obtained during physical exercise, these results highlight a limited maximal cardiac output in NT rats compared with the other three groups.
pumping capacity of the heart after altitude training compared with sea level training. On the basis of these findings, it is reasonable to postulate that the marked increase in O\textsubscript{2} carrying capacity in CHT compared with NT rats was counterbalanced by reduced maximal cardiac output, leading to a similar net O\textsubscript{2} delivery to active muscles and subsequently maximal aerobic improvement.

Very few studies have investigated the effects of living and training at altitude on sea level LV\textsubscript{SV\textsubscript{max}}. Henderson et al. (23) showed in rats acclimatized and trained at 2,400 m an increase in LV\textsubscript{SV\textsubscript{max}} similar to that observed after a training program of equal absolute intensity performed under normoxic conditions. Favret et al. (9) likewise reported in rats living at high altitude but training at sea level no difference in the LV\textsubscript{SV\textsubscript{max}} increase compared with rats living and training at sea level. It is, however, very difficult to compare the results of these aforementioned studies with ours, because of the different altitudes and/or training program strategies.

The major result from this study was that this apparent limitation in LV\textsubscript{SV\textsubscript{max}} improvement after training in CHT rats was mainly accounted for on the basis of specific altitude-induced cardiac remodeling affecting LV filling. In accordance with results commonly reported in humans (32) and animals (26, 45), sea level training induced in NT an increase in LV internal cavity dimensions as well as wall thicknesses. Different cardiac remodeling was, however, observed in CHT, characterized by an increase in LV wall thicknesses with no changes in internal dimensions, leading therefore to a major increase in LV relative wall thickness. Such an adaptive process in LV dimensions has undoubtedly serious incidences on LV filling capability and subsequently LV performance, as our volume overloading results demonstrate.

Several authors have reported that volume overload imposed by chronic exercise acts as a major determinant of LV hypertrophia in sea level endurance athletes (17, 37). It is therefore very likely that alterations in loading conditions due to chronic hypoxia exposure and repetitive exercise sessions were responsible for this specific cardiac remodeling in CHT. At altitude, several hemodynamic adaptations are known to occur, including decreased plasma volume (42, 35, 37) and pulmonary hypertension (27), which are both involved in limiting LV preload. For evident methodological reasons, blood volume was not assessed in the present work. However, LVEDd and peak E, two indexes highly sensitive to blood volume changes (6), were similarly affected throughout the study period, supporting the argument for an alteration in blood volume in CHT rats. Indirect evidence of pulmonary hypertension was shown also in CHT by the decrease in \(v_{\text{pulm}}\) (25). Pulmonary arterial pressure is increased after chronic hypoxia as a result of pulmonary vasoconstriction, vascular remodeling, and increased blood viscosity (20). Marcus et al. (30) reported that pulmonary hypertension reduced LV filling at rest but also during exercise by decreasing blood delivery. CH rats presented the same adaptations as CHT rats regarding LV internal dimensions, probably due to the same underlying mechanisms. Thus even repetitive exercise sessions did not serve to prevent the hypoxia-induced alteration in cardiac dimensions as well as in loading conditions.

LV remodeling in CHT differed from that obtained in CH rats as no LV wall thickness was observed in the latter. LV remodeling in CHT rats was in fact comparable to that obtained by using training models of pressure rather than volume overload (21, 32). It is interesting to note that altitude exposure is accompanied by a rise in systolic and diastolic blood pressures, which is moreover exacerbated during exercise (43, 46). Consequently, a potential hypoxia-induced blood pressure increase could have also been involved in the specific cardiac remodeling encountered in CHT rats by means of an increase in afterload, especially during exercise. At each training session, exercise brought about an increase in O\textsubscript{2} supply to active muscles. It is therefore also reasonable to hypothesize that, considering the evident reduced LV preload and filling, energy requirements were matched by an increase in cardiac contractile force, leading therefore to an increase in wall thickness.

Considering the absence under physiological conditions of changes in LV end-diastolic pressure by endurance training (14) or chronic hypoxia exposure (31), LV pressure-volume relationship curves allowed us to have a good index of LV size independent of loading conditions. In this context, the increase in LV internal dimensions in NT rats was confirmed by the rightward shift in the LV pressure-volume relationship. Similar results have been previously reported after aerobic training in rats by Libonati (28). It is notable, however, to highlight that such results were not observed in CHT rats, reinforcing the lack of change in LV internal dimensions in this group after altitude training.

Today, very few reports are available on cardiac morphological changes after altitude training, and conflicting as well as inconclusive results have been found (22, 39, 44). It is very likely that the discrepancies between these results and ours are explained on the basis of different altitudes and/or training programs. Indeed, Haykowsky et al. (22) reported no modifications in any of the morphological echocardiographic parameters estimated in elite swimmers after 5 wk at an altitude training camp of 1,848 or 1,050 m. Svedenhag et al. (39) reported, in a study incorporating no control group, an increase in LVM after a 1-mo training period at 1,900 m, because of a slight increase in internal diameters and wall thicknesses. Finally, an echocardiographic analysis performed by Weng et al. (44) reported that altitude training (1,890 m for 4 wk) was not associated with alterations in LV morphological and functional parameters. However, it is also possible that the discrepancies between these results and the present study are accounted for on the basis of differences in species. Hence, because the data were obtained by using a rodent model, caution should be exercised with application to human subjects.

LV\textsubscript{SV} depends on a complex interplay between morphological factors, other factors related to loading conditions, and cardiac intrinsic contractility and relaxation properties. Some of our results obtained during resting conditions, if reasonably extrapolated to maximal effort, likewise support the involvement of hemodynamic variables in limiting LV\textsubscript{SV\textsubscript{max}} increase after living and training at altitude. This may imply pulmonary hypertension as Henderson et al. (23) reported in rats that had lived and trained at altitude compared with normoxic control trained rats, significant higher pulmonary arterial pressure during a maximal effort performed at sea level. Actually, Marcus et al. (30) found a corresponding association between the decrease in LV blood delivery due to primary pulmonary
hypothesis and the reduced \( LV_{SV_{\text{max}}} \) by the Frank-Starling mechanism.

Finally, increased blood viscosity may have also contributed to a reduction in \( LV_{SV_{\text{max}}} \) via an elevated cardiac afterload, as suggested by the observation that lowering Hct at constant blood volume substantially increased \( LV_{SV_{\text{max}}} \) of the acclimatized rats (19). Villafuerte et al. (42) reported that maximal cardiac output markedly decreased along with increasing Hct by means of raised viscosity and diminished venous return.

To conclude, overall, our results showed in a rodent model a limitation of maximal heart pumping capacity after altitude training compared with sea level training, explained by specific morphological and functional adaptations. These specific cardiac adaptations were likely due to a combination of factors, including morphological parameters, playing a major role, as well as hemodynamic variables, related to preload (combined effects of increased pulmonary vascular resistance and decreased blood plasma volume) and afterload (elevated blood viscosity and systemic peripheral resistances) conditions. Because of the impact of these specific cardiac adaptations on maximal stroke volume, and considering that maximal stroke volume makes a crucial and substantial contribution to maximal aerobic capacity, our findings could well clarify why similar sea level aerobic performance values are frequently reported after altitude and sea level training camps despite the marked increase in \( O_2 \) carrying capacity generated by chronic hypoxia exposure.

**Limitation of the Study**

The major limitation of the present work was that \( LV_{SV_{\text{max}}} \) was not obtained during maximal exercise. Our results regarding effects of training and living at altitude on heart pumping capability could therefore not be extrapolated to reflect peak effort. Nevertheless, \( LV_{SV_{\text{max}}} \) obtained during volume overloading reported by Fletcher et al. (11) provides a good index of maximum pumping ability of the heart. Moreover, Blomqvist and Saltin (3) reported a strong linear relationship in humans between the maximal stroke volume obtained during exercise (\( SV_0, \text{ml} \)) and the magnitude of the increase in maximal stroke volume after volume overloading (\( \Delta SV, \text{ml} \)) (\( \Delta SV = 0.51 SV_0 - 48; r^2 = 0.49; P < 0.05 \)).

**REFERENCES**


