HIGHLIGHTED TOPIC | Biomechanics and Mechanotransduction in Cells and Tissues

Effect of sustained hypobaric hypoxia during maturation and aging on rat myocardium. I. Mechanical activity

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La Padula, Pablo, and Lidia E. Costa. Effect of sustained hypobaric hypoxia during maturation and aging on rat myocardium. I. Mechanical activity. J Appl Physiol 98: 2363–2369, 2005. First published February 10, 2005; doi:10.1152/japplphysiol.00988.2004.—Long-lasting cardioprotection may be attained by chronic hypoxia. The basal parameters of contractile function and their response to hypoxia/reoxygenation were measured under isometric conditions, in papillary muscles isolated from left ventricle of rats that were submitted to 53.8 kPa in a hypobaric chamber from 7 wk of age and for their lifetime and of their siblings kept at 101.3 kPa. During acclimatization, hematocrit increased, body weight gain decreased, and heart weight increased with right ventricle hypertrophy. Papillary muscle cross-sectional area was similar in both control and hypoxic groups up to 45 wk of exposure. Developed tension (DT) was 34–64% higher in rats exposed to hypoxia for 10, 26, and 45 wk than in their age-matched controls, whereas resting tension was unchanged. Maximal rates of contraction and relaxation showed a similar pattern of changes as DT. Recovery of DT and maximal rates of contraction and relaxation after 60-min hypoxia and 30-min reoxygenation was also improved in adult hypoxic rats to values similar to those of young rats. Heart acclimatization was lost after 74 wk of exposure. Results are consistent with the results of experimental studies using acute anoxia in vitro for testing the myocardial resistance of animals submitted to intermittent hypoxia (1, 30). However, the effects of sustained, long-term simulated high altitude have not been studied. Furthermore, the length of acclimatization for cardioprotection and the age-related differences are still not clear. Moreover, high-altitude hypoxia also exerts adverse influences on the cardiopulmonary system (37).

Acclimatization to chronic hypoxia is characterized by a variety of functional changes that help to maintain homeostasis. Such adjustment may protect the heart under conditions that require enhanced work and, consequently, increased metabolism. It was reported as early as 1960 (28, 37) that the incidence of myocardial infarction is lower in people naturally acclimatized to high altitude (Peru, 4,000 m). Epidemiological observations on the protective effect of high altitude are consistent with the results of experimental studies using acute anoxia in vitro for testing the myocardial resistance of animals submitted to intermittent hypoxia (1, 30). However, the effects of sustained, long-term simulated high altitude have not been studied. Furthermore, the length of acclimatization for cardioprotection and the age-related differences are still not clear. Moreover, high-altitude hypoxia also exerts adverse influences on the cardiopulmonary system (37).

An experimental model of acclimatization to hypoxia has been thoroughly studied in our laboratory (12, 13, 15–17). The advantage of studying animals exposed to simulated high altitude over native populations resides in the fact that environmental and hereditary conditions are controlled. Among the interesting findings in our model was a redistribution of mitochondria in liver, which would serve to improve intracellular O2 diffusion, and an increase in the number of mitochondria in the heart (13). No changes in distribution of mitochondria were detected in heart, where they are mainly interspersed between myofibrils. However, intramyocyte NO may serve a similar role, allowing O2 to diffuse further and to reach more mitochondria through its control on mitochondrial oxygen uptake (39). Furthermore, NO was found to trigger mitochondrial biogenesis in several cell types and tissues, including heart (9, 34, 35, 44, 45, 47). Hypoxic states of the cardiovascular system are undoubtedly associated with the most frequent diseases of modern times. Myocardial hypoxia is the result of a disproportion between O2 supply and demand. Among the most common causes for a reduced O2 supply to the myocardium, hypoxic hypoxia (often described as “cardiac hypoxia”), characterized by a decreased PO2 in the arterial blood but with adequate perfusion, occurs in chronic cor pulmonale, congenital heart disease, and high altitudes. In the myocardium of subjects living permanently at high altitudes, systemic hypoxia can be qualified as physiological.

TOLERANCE OF THE MYOCARDIUM to oxygen deprivation may be increased by pharmacological intervention, ischemic preconditioning, or systemic hypoxia (37). Chronic normobaric hypoxia (inspired O2 fraction = 0.12) from birth increases the resistance of the isolated neonatal rabbit heart to ischemia (2, 3). Adaptation of rats to intermittent hypobaric hypoxia (53.8 kPa) protects the heart against acute ischemia-reperfusion injury and ischemia-induced arrhythmias and infarction (1, 30). More recently, short episodes of intermittent or continuous hypoxia were shown to induce delayed cardioprotection (11, 47). Although the mechanisms underlying increased resistance to O2 deprivation remain largely unknown, activation of mitochondrial ATP-sensitive K+ channels and increased cellular nitric oxide (NO) steady-state levels, by their effects on the regulation of mitochondrial bioenergetics, appear to be involved in both long-lasting (adaptation to chronic hypoxia) and short-lasting (acute systemic hypoxia and ischemia preconditioning) forms of hypoxic cardioprotection (1, 3, 4, 7, 18, 22, 24, 30, 31, 34, 35, 44, 45, 47).

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The presence of a mitochondrial nitric oxide synthase (mtNOS) (23) has been demonstrated in heart (8, 14, 29), where NO plays a role in contractility (25, 43). Liver mtNOS was reported to be upregulated in mice subjected to acute hypoxia (33).

The aim of the present study was to evaluate myocardial function in the physiological response to hypobaric hypoxia with sustained exposure during maturation and aging. Fully mature adult subjects correspond to ~12 mo old in our animal model. The main basal parameters of contractility and relaxation and their response to hypoxia/reoxygenation were determined in left ventricle (LV) myocardium of rats submitted throughout their lifetime to simulated high altitude. Improvement of heart mechanical activity and posthypoxic recovery developed in acclimatization to hypoxia. The putative role of mtNOS in the mechanism involved is evaluated in the accompanying paper (48).

METHODS

Animals. Seven-week-old male Wistar rats of the CHbbTHOM albino strain were submitted to a simulated altitude of 5,000 m (53.8 kPa = 404 mmHg) in a 2 × 2 × 2-m hypopressure chamber with a 2 × 2 × 1-m prechamber for up to 92 wk, whereas the same number of rats remained as controls at sea level atmospheric pressure (101.3 kPa = 760 mmHg). Both groups were maintained at the same temperature (22°C) on a schedule of 12 h of light and 12 h of dark and had free access to food and water. Chamber pressure was interrupted 20–30 min three times a week for cleaning, replacement of food and water, and periodic body weight control. Pressure changes were achieved slowly, and the renewal of air in the chamber was sufficient to ensure the composition of atmospheric air. After 1, 10, 26, 45, and 74 wk, five rats of each group (one at a time, alternating hypoxic and controls) were used for the study of papillary muscle mechanical activity. After 92 wk, only five control rats were studied, because mortality rate was high in hypoxic rats and they had all died by that time. For globular value determination, three heparinized microhematocrits were filled with blood obtained by cutting the tip of the tail under ether anesthesia, immediately before heart removal. Rats received care in accordance with the 6344/96 regulation of the Argentine National Drug, Food, and Medical Technology Administration and the “Guiding Principles for Research Involving Animals and Human Beings” of the American Physiological Society.

Heart muscle preparations. Hearts were removed under ether anesthesia and flushed with room temperature oxygenated Ringer solution of the following composition (in mM): 128.3 NaCl, 4.7 KCl, 1.35 CaCl₂, 20.23 NaHCO₃, 0.35 NaH₂PO₄, 1.05 MgSO₄, and 5.5 glucose. The LV was opened, and both papillary muscles were removed while submerged in buffer. The chordae tendineae of each muscle was tied with 10-0 nylon suture, which was attached to a Statham force transducer and 9853 coupler (Gould-Statham) mounted on a movable support controlled by a micrometer for accurate length adjustment. The bottom end of the papillary muscle was inserted into a stainless steel spring clip, and the muscle was mounted vertically in a temperature-controlled chamber containing 30 ml of the Ringer solution. The solution was equilibrated with a mixture of 95% O₂ and 5% CO₂, with pH and temperature kept constant at 7.4 and 30°C, respectively. The heart, trimmed of atria and large vessels, was dissected into the LV plus septum and right ventricle (RV), which were weighed separately.

Papillary muscle mechanical activity. Papillary muscles were allowed to stabilize for 45 min after mounting. Rectangular pulses of 10 ms with an amplitude 20% higher than the threshold of each preparation were digitally delivered by means of a stimulator and data acquisition and analysis software (FP). Contraction frequency was kept constant at 12 beats/min. The muscles were then stretched until maximal developed tension (DT) occurred. The isometric mechanical properties were recorded on a Beckman R511A connected to the force transducer, and simultaneously the computer utilizing FPE digitized and stored the force-pacing signal for later analysis. Resting tension (RT), DT, maximal rate of rise in DT (+T), and maximal velocity of relaxation (−T) were determined. Each data result was the mean of three successive twitches. After recording basal mechanical activity, a 60-min period of hypoxia was established by using a gas mixture of 95% N₂ and 5% CO₂, followed by a 30-min period of reoxygenation (95% O₂ and 5% CO₂), and mechanical events were recorded every 10 min. At the end of each experiment, muscle length was measured with a caliper. The muscle was then blotted dry and weighed, and the cross-sectional area was calculated, assuming the muscle to be a cylinder with a density of 1.0. RT, DT, +T, and −T were normalized for muscle cross-sectional area.

Statistics. Results are expressed as mean values ± SE. The effects of chronic hypoxia and age on measured parameters were analyzed by two-way ANOVA and group-to-group comparisons by using the least significant difference test. The control 23-mo-old group was not included in two-way ANOVA analysis (it lacked its hypoxic counterpart) and was compared with the control 18-mo-old group by unpaired Student’s t-test. A value of P < 0.05 was considered statistically significant.

RESULTS

Biological parameters. Survival was 95, 50, and 25% after 45, 68, and 74 wk, respectively, of exposure to hypobaric hypoxia, whereas at the same times it was 100, 100, and 95%, respectively, in control rats. The mean hematocrit value, an index of adaptation to hypoxia, was increased since the first week of exposure and attained a maximum value by week 10 (Table 1). Body weight gain was delayed by hypobaric hypoxia throughout their lifetime (Table 1). RT decreased with age up to 12 beats/min. The muscles were then stretched until maximal developed tension (DT) occurred. The isometric mechanical properties were recorded on a Beckman R511A connected to the force transducer, and simultaneously the computer utilizing FPE digitized and stored the force-pacing signal for later analysis. Resting tension (RT), DT, maximal rate of rise in DT (+T), and maximal velocity of relaxation (−T) were determined. Each data result was the mean of three successive twitches. After recording basal mechanical activity, a 60-min period of hypoxia was established by using a gas mixture of 95% N₂ and 5% CO₂, followed by a 30-min period of reoxygenation (95% O₂ and 5% CO₂), and mechanical events were recorded every 10 min. At the end of each experiment, muscle length was measured with a caliper. The muscle was then blotted dry and weighed, and the cross-sectional area was calculated, assuming the muscle to be a cylinder with a density of 1.0. RT, DT, +T, and −T were normalized for muscle cross-sectional area.

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relaxation (Fig. 2) followed a similar pattern as DT; +T was significantly higher in hypoxic 8- (67%) and 12-mo-old (61%) rats than in their age-matched controls, whereas the increase in −T by chronic hypoxia was statistically significant in 8-mo-old rats (52%).

**Hypoxia and reoxygenation.** Tolerance to 60 min of hypoxia and recovery during a subsequent 30-min reoxygenation period was examined in the papillary muscles from rats submitted to hypobaric hypoxia for 1 wk (2 mo old, “young”), 26 wk (8 mo old, “adult”), and 74 wk (18 mo old, “old”) from their age-matched controls and from 23-mo-old (“senescent”) normoxic rats.

Contracture tension, expressed as percentage of prehypoxia RT (Fig. 3), showed no differences between age groups during acute hypoxia in controls. Rats exposed to hypobaric hypoxia for 26 wk behaved as controls, whereas rats submitted to hypobaric hypoxia for 1 or

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**Table 1. Biological parameters of rats submitted to 53.8 kPa and of their controls at 101.3 kPa**

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>18</th>
<th>23</th>
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<tbody>
<tr>
<td>Hypoxia, wk</td>
<td>1</td>
<td>10</td>
<td>26</td>
<td>45</td>
<td>74</td>
<td>92</td>
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<table>
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<tr>
<th>Hematocrit, %</th>
<th>C</th>
<th>46.6±0.2</th>
<th>46.6±0.2</th>
<th>46.5±0.2</th>
<th>46.3±1.2</th>
<th>41.7±1.4</th>
<th>38.9±1.3</th>
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<tbody>
<tr>
<td>H</td>
<td>54.9±1.7*</td>
<td>70.9±1.1†</td>
<td>68.2±1.2*</td>
<td>65.1±3.1*</td>
<td>66.6±3.1*</td>
<td>66.6±3.1*</td>
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</tbody>
</table>

<table>
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<tr>
<th>Body weight, g</th>
<th>C</th>
<th>288±22</th>
<th>500±8†</th>
<th>658±3†</th>
<th>681±51</th>
<th>680±19</th>
<th>700±11</th>
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<tbody>
<tr>
<td>H</td>
<td>205±12*</td>
<td>450±3†</td>
<td>530±34†</td>
<td>562±26*</td>
<td>595±77</td>
<td>595±77</td>
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</table>

<table>
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<tr>
<th>Right ventricle weight, g</th>
<th>C</th>
<th>0.26±0.02</th>
<th>0.31±0.03</th>
<th>0.31±0.01</th>
<th>0.30±0.06</th>
<th>0.29±0.02</th>
<th>0.32±0.03</th>
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<tbody>
<tr>
<td>H</td>
<td>0.29±0.02</td>
<td>0.49±0.01†</td>
<td>0.59±0.03†</td>
<td>0.55±0.02*</td>
<td>0.56±0.02*</td>
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</table>

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<thead>
<tr>
<th>Left ventricle weight, g</th>
<th>C</th>
<th>0.68±0.05</th>
<th>0.99±0.06†</th>
<th>1.07±0.04</th>
<th>1.18±0.07</th>
<th>1.62±0.07†</th>
<th>1.29±0.10†</th>
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<tbody>
<tr>
<td>H</td>
<td>0.59±0.03</td>
<td>1.11±0.06†</td>
<td>1.15±0.06</td>
<td>1.28±0.06</td>
<td>1.29±0.02*</td>
<td>1.29±0.02*</td>
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</table>

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<thead>
<tr>
<th>Papillary muscle length, mm</th>
<th>C</th>
<th>10.5±0.7</th>
<th>10.6±0.3</th>
<th>11.3±0.2</th>
<th>11.0±0.3</th>
<th>11.1±0.5</th>
<th>9.3±0.4†</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>9.7±0.4</td>
<td>10.4±0.2</td>
<td>10.6±0.5</td>
<td>10.4±0.5</td>
<td>11.0±0.3</td>
<td>9.3±0.4†</td>
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<tr>
<th>Papillary muscle area, mm²</th>
<th>C</th>
<th>0.76±0.06</th>
<th>0.96±0.05</th>
<th>1.36±0.13†</th>
<th>1.66±0.12</th>
<th>2.10±0.22†</th>
<th>1.54±0.16†</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.60±0.07</td>
<td>0.87±0.04</td>
<td>1.26±0.25†</td>
<td>1.47±0.09</td>
<td>1.02±0.15†</td>
<td>1.02±0.15†</td>
<td></td>
</tr>
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</table>

Values are means ± SE; n = 5 rats in each group (10 papillary muscles). H, rats submitted to 53.8 kPa; C, controls at 101.3 kPa. *P < 0.05 vs. control; †P < 0.05 vs. previous age group.

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Fig. 1. Resting tension (RT; circles) and developed tension (DT; squares) of papillary muscles from rats submitted to hypobaric hypoxia (open symbols) and of their controls at sea level atmospheric pressure (solid symbols). Values are means ± SE. *P < 0.05, hypoxic vs. control; †P < 0.05 between age groups.

Fig. 2. Maximal rates of contraction (+T; squares) and relaxation (−T; circles) of papillary muscles from rats submitted to hypobaric hypoxia (open symbols) and of their controls at sea level atmospheric pressure (solid symbols). Values are means ± SE. *P < 0.05, hypoxic vs. control; †P < 0.05 between age groups.
74 wk to hypobaric hypoxia developed a significant decrease in the onset of contracture tension, indicating the lack of effective adaptation at these two time points. During reoxygenation, RT recovered prehypoxia values in all of the groups, and in young rats RT was decreased further, attaining 60–70% of the baseline values.

During acute hypoxia, DT showed no statistically significant differences between the groups and, after 60 min of hypoxia, all of them were within the range of 0.1–0.5 g/mm² (Fig. 4), which represents 8–15% of prehypoxia values. Force recovery during reoxygenation was significantly higher in adult hypoxic rats (71%) than in their controls (57%). Senescent animals only recovered 23% of the baseline value.

During hypoxia and reoxygenation, +T (Fig. 5) and −T (Fig. 6) showed a behavior similar to DT. Maximal rate of contraction recovered 82% in adult hypoxic rats and 69% in controls and only 32% in normoxic senescent rats. Posthypoxic recovery of the maximal rate of relaxation was 93% in adult hypoxic rats and 69% in their age-matched controls, whereas in senescent rats it was only 30%.

DISCUSSION

In the present study and for the first time, experimental animals were submitted to hypobaric hypoxia for their entire lifetime. Hypoxic rats showed the well-known increase in hematocrit in response to the enhanced expression of erythropoietin mediated by the hypoxia-inducible transcription factor-1 (42), which also serves in the oxygen-dependent regulation of other genes (10, 32, 41), and is now recognized as the main regulator of oxygen homeostasis in the body (19). Hypoxia-inducible transcription factor-1 has been associated with the weight loss in response to chronic hypoxia (41) that occurs with a marked decrease in fat content and with retardation of growth (17).

Cardiac hypertrophy followed the exposure to hypobaric hypoxia, mainly due to an increase in RV mass associated with the pulmonary hypertension that accompanies altitude acclimatization. LV weight was not significantly changed by hypoxia. The similar profile in the increase in cross-sectional area of papillary muscles in both rat groups up to 12 mo old seems...

Fig. 3. RT in percentage of baseline values of papillary muscles from rats submitted to hypobaric hypoxia (open symbols) for 1 (circles), 26 (squares), and 74 wk (triangles), from their controls at sea level atmospheric pressure (solid symbols), and from 99-wk-old control rats (diamonds) during a period of hypoxia and reoxygenation. Values are means ± SE. *P < 0.05, hypoxic vs. control; #P < 0.05 vs. closest age group.

Fig. 4. DT by papillary muscles from rats submitted to hypobaric hypoxia (open symbols) for 1 (circles), 26 (squares), and 74 wk (triangles), from their controls at sea level atmospheric pressure (solid symbols), and from 99-wk-old control rats (diamonds) during a period of hypoxia and reoxygenation. Values are means ± SE. *P < 0.05, hypoxic vs. control; #P < 0.05 vs. closest age group.
to exclude the possibility that thicker muscles may experience local hypoxia in the central portion and decrease contractile parameters. The decrease in area in 23-mo-old controls and 18-mo-old hypoxic vs. previous age groups indicates that muscle atrophy occurs earlier during aging under hypoxia.

RT and DT, which can be extrapolated to diastolic and systolic function, respectively, in intact hearts, decreased with age until 4 – 8 mo and afterward were not significantly changed up to senescence. Decreased RT, which can be assimilated to LV end-diastolic pressure at whole heart level, would translate into an adaptive improvement of diastolic function as DT decreases with age. Reports in the literature on changes in diastolic and systolic functions during aging are not consistent (6, 26, 38). Because most studies compare only two or three age groups, contradiction may arise from the particular selection of such ages. One of the main findings of this study was that the decrease in DT was less pronounced in hypoxic rats of 4, 8, and 12 mo. Indeed, chronic hypoxia retarded the age-associated decline of heart contractility. Therefore, on maturation, systolic function in hypoxic animals remained similar to that of younger rats. From 8 mo old on, papillary muscles not only developed less force but also contracted and relaxed more slowly, as shown by +T and −T. In hypoxic rats, the decline in these parameters was again less marked than in controls.

Adaptation of adult rats to intermittent high-altitude hypoxia for 5 wk increased RV contractile function, determined as developed pressure, maximal rate of pressure development, and maximal rate of pressure fall (27). The increase of the same parameters in the LV as reported in this study suggests that they are caused by adaptation to hypoxia rather than by RV hypertrophy.

The improved contractility of acclimatized myocardium implies an increase in myocardial oxygen consumption, unless a more efficient contraction in terms of energy utilization occurs. Several mechanisms have been proposed to be involved in increasing the efficiency of myocardial contraction (37). Acclimatization to high altitude was reported to lower the specific activities of several sarcolemmal ATPases and, at the same time, to increase their affinity for ATP, which permits a more...
efficient utilization of ATP (37). A selection of metabolic pathways or substrates with a higher energy efficiency would decrease the oxygen requirements (37). Although chronic hypoxia did not change the efficiency of oxidative phosphorylation, as measured by the ADP-to-oxygen consumption ratio in isolated cardiac mitochondria, a better oxygen diffusion from blood vessels to mitochondria and an enhanced aerobic capacity of the tissue provided by an increase in the number of mitochondria in acclimatized heart, along with a decrease in mitochondrial mean size and, therefore, an enlarged surface-to-volume ratio (13, 46), would increase oxygen extraction from the tissue. The increase in mitochondrial NO (48), through modulating the activity of the respiratory chain by reversible inhibition of cytochrome oxidase, would allow oxygen to diffuse further and to reach more mitochondria (39), providing another way of increasing oxygen extraction, which could help make the heart more efficient.

One of the main findings of this study was that, on reoxygenation after a 60-min period of hypoxia, mechanical function was significantly improved in rats submitted to hypobaric hypoxia for 26 wk compared with normoxic controls. This protective effect was not observed in young rats after only 1 wk of exposure to hypoxia and in rats of old age (18 mo). The situation at 26 wk represents the acclimatization after 10–45 wk of hypoxia (4–12-mo-old rats), whereas the time points at 1 and 74 wk of hypoxia indicate a too short time for adaptation and a final aged state, respectively. Moreover, the onset of contracture tension developed during in vitro hypoxia, an index of high-energy phosphate depletion and intracellular calcium overload, was earlier in rats submitted to hypoxia for 1 and 74 wk than in all of the normoxic animals, indicating a decreased resistance to ischemia, whereas 26-wk hypoxic rats behaved as controls, indicating an effective adaptation.

It was observed that, although basal contractile parameters of control senescent rats were not statistically different from those of old ones, the senescent animals showed a significant loss of the ability to recover during reoxygenation. A reduced tolerance of the aged myocardium to ischemia has been reported (5, 26).

Chronic systemic hypoxia has been found to improve the postischemic systolic function in several experimental models. As early as 1958, Kopecky and Daum showed an improved contractile recovery of the RV after in vitro anoxia in rats exposed to intermittent high-altitude hypoxia in a hypopressure chamber (reviewed in Ref. 30). This finding was later repeatedly confirmed and extended to other models of intermittent hypobaric hypoxia, which showed an increased cardiac tolerance to all major deleterious consequences of acute oxygen deprivation, such as myocardial infarction, contractile dysfunction, and ventricular arrhythmias (1, 30, 35, 37). Another model, developed to reproduce cyanotic congenital heart disease, showed that adaptation to chronic normobaric hypoxia in infant rabbits confers cardioprotection against subsequent ischemia (2–4, 18, 31, 44, 45). The beneficial effects of chronic hypoxia were found on both ventricles (31). In contrast, 14 days of sustained hypoxia in adult rats protected RV from ischemia-reperfusion damage but failed to improve postschematic LV function (21). In the present study, we show a cardioprotective development in the papillary muscle of the LV from adult rats during sustained hypobaric hypoxia, provided that the duration of the exposure is long enough.

The improved condition of hypoxic hearts to handle hypoxia reoxygenation was lost at advanced age. Although no prior study has been reported on the effects of chronic hypoxia in aged hearts, human and animal studies suggest that aging is a limiting determinant for the myocardial protection achieved with ischemic preconditioning (5, 20, 40). Because recovery of the muscles from old (18 mo) hypoxic rats was similar to that of old controls, and much better than that of senescent (23 mo) controls, decreased survival under hypoxia may be ascribed to other adverse influences of chronic hypoxia as the development of pulmonary hypertension, which may result in congestive heart failure (37). Loss of acclimatization involving an exaggeration of pulmonary hypertension (chronic mountain sickness) is frequent in aged people living at high altitude in the Andes.

In conclusion, adaptation to sustained hypobaric hypoxia in adult rats increased the functional capacity of the myocardium and its recovery after hypoxia and reoxygenation. Heart acclimatization was developed during several months (from 4 to 12 mo) of exposure to 5,000-m simulated altitude and was lost after 18 mo of exposure. The biochemical mechanisms that may contribute to the observed effects on myocardial contractile function are addressed in the accompanying paper (48).

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