Effects of aging on the cardiac remodeling induced by chronic high-altitude hypoxia in rat

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Chouabe, C., E. Ricci, J. Amsellem, S. Blaineau, Y. Dalmaz, R. Favier, J.-M. Pequignot, and R. Bonvallet. Effects of aging on the cardiac remodeling induced by chronic high-altitude hypoxia in rat. Am J Physiol Heart Circ Physiol 287: H1246–H1253, 2004. First published May 13, 2004; 10.1152/ajpheart.00199.2004.—Effects of chronic high-altitude hypoxia on the remodeling of right ventricle were examined in three age groups of rats: 2, 6, and 18 mo. The extent of right ventricular (RV) hypertrophy (RVH) showed an age-associated diminution. RV cell size and pericellular fibrosis showed a significant increase in the 2- and 6-mo-old exposed rats but not in the 18-mo-old exposed rats compared with control. A hyperplastic response was underscored in the three exposed age groups but appeared less pronounced in the 18-mo-old rats. A significant decrease in the transient outward potassium current (Ito) density was observed in RV cell only in the 2-mo-old exposed group compared with the control group. In the control group, there was a clear tendency for Ito density to decrease as a function of age. The sustained outward current density was modified neither by the hypoxia condition nor by the age. Neither the cytochrome c oxidase activity nor the heat shock protein 72 content in the RV was altered after hypoxic exposure regardless of age. The norepinephrine content in the RV was significantly decreased after hypoxic exposure regardless of age. The sustained outward current density was modified neither by the hypoxia condition nor by the age. The sustained outward current density was modified neither by the hypoxia condition nor by the age. The sustained outward current density was modified neither by the hypoxia condition nor by the age.

CHRONIC HYPOXIA is the main pathophysiological factor in severe disturbances of the cardiovascular system, represented by pulmonary, ischemic, and congenital heart diseases and in cardiopulmonary changes induced by exposure to a high-altitude environment (34).

Adaptation to chronic hypoxia is characterized by functional changes that help to maintain homeostasis with minimum energy expenditure. Besides these protective effects, adaptation to chronic hypoxia may also exert adverse influences on the cardiopulmonary system, including the development of pulmonary hypertension and right ventricular (RV) hypertrophy (for review, see Ref. 30, and references therein).

On the other hand, it is well established that the aging heart is associated with numerous structural changes, including cardiomyocyte hypertrophy, increases in interstitial fibrosis, and cardiac myocyte loss (2, 3, 5).

Only a few studies concerning the influence of age on chronic hypoxia-induced structural and functional alterations in the cardiovascular system have been carried out, and their results are somewhat inconsistent (30).

In the present study, we evaluated the single and interactive effects of chronic hypoxia and aging on the heart. For this purpose, we measured several parameters at the organ, cellular, and biochemical levels after a continuous exposure to hypoxia in rats of three age groups: 2, 6, and 18 mo. Three parameters were measured: 1) the evolution of morphometric and pericellular fibrosis, which are markers of cardiac remodeling and aging (17, 20, 44); 2) the evolution of hyperplasia, which has recently been revealed as significantly contributing to the increase of the cardiac mass in hypertrophy (46); and 3) the density of the transient outward current (Ito), which is a major marker of cardiac cellular electrical remodeling (32). The activity of cytochrome c oxidase (COX) was used as a marker enzyme for mitochondrial oxidative capacity (39). Finally, we measured the expression of heat shock protein 72 (HSP72), which plays a protective role in the myocardium to numerous stress stimuli (21), and the activity of the peripheral sympathoadrenal system, which plays a major role in the adaptive response to hypoxia (15, 31) and aging (23) in regulating cardiovascular events.

MATERIALS AND METHODS

Animal Model

We used three different age groups of male Sprague-Dawley rats: 2-, 6- and 18-mo-old groups, which correspond to developmental, young adult, and old stage rats, respectively. Although some rats can survive until 30 mo, to follow the normal physiological aging process (23) and avoid adding pathological events due to the impairment of ventricular dysfunction occurring with senescence (5), a period of 12 mo between the adult and old groups can be considered as sufficient to bring out specific aging evolution in the studied parameters. On delivery from the breeder (Ifa Credo; L’Arbresle, France), they were kept for 1 wk under controlled temperature (25 ± 1°C) with a 12:12-h light-dark cycle and with standard food available ad libitum. Complete data were obtained from 60 rats separated into two groups: one exposed to hypoxia and the other serving as control and maintained under normoxic conditions. In each condition, each age group contained 10 rats. Exposed rats were placed in a hypobaric chamber allowing exposition to simulated altitude (≈4,500 m; PO2 ≈12 kPa) without any noticeable accumulation of CO2 as verified with an infrared analyzer. The animals were exposed continuously for 20

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days. Exposure to hypoxia was interrupted for 2 h every 2 days for cleaning the cages, renewing food and water supplies, and weighing the animals; the decompression or ascent and the compression or descent was performed progressively over 30 min (~1.5 kPa/min). Chronic congestive heart failure never occurred in this model, even in 18-mo-old rats. This was confirmed by anatomic examination, which did not show the presence of pleural fluid, hepatic congestion, and ascites, which are the criteria of failure in RV hypertrophy (42). The rats were euthanized under deep pentobarbital anesthesia. All experiments were carried out according to the ethical principles of the French and European Union Council directives for care of laboratory animals.

Histological Studies

Ventricular wall thickness and interstitial collagenic mass measurements were made as previously described (11). Briefly, after aortic retrograde perfusion of the heart, 2-mm-thick transversal ventricular slices were performed with a vibratome, dehydrated, and resin embedded. Measurements of ventricular wall thickness were made from these slices. The finely sliced sections were then silver stained (Gordon-Sweet) to display only the extracellular matrix, and measurements of the extent of collagenic content were obtained on similar transversal myocyte fields (in RV periluminal trabecules; see Fig. 1 in Ref. 11), where only the interstitial endomysial extracellular matrix (see Fig. 4, A and B, in Ref. 11) was present. The software was then elaborated and applied on a QWIN Soft Image System (Leica; Rueil-Malmaison, France).

The hyperplasic response was assessed on the same RV transversal periluminal fields on the Gordon-Sweet silver-stained sections. Comparisons were realized on one section between control and exposed heart, both in the 2-, 6- and 18-mo-old exposed rats. The number of cells (by μm²) was determined by selecting small numerous measured surface areas and averaging 800–1,000 cardiomyocytes/profile. The total surface area of each RV section was then measured, excluding the holes (vascular tissue, artifacts) and the large conjonctive septa. The total theoretic number of cells is the product of these two measurements. Interactive image analysis was performed with AnalySIS (Soft Imaging System, Eloise; Roissy, France).

Heart Weight Measurements and Myocyte Isolation

These procedures were made as previously described (12, 13). The dimensions of freshly dissociated myocytes were assessed by measuring the length and width with a graticule mounted on the lens of a microscope.

Current Measurements

The whole cell configuration of the patch-clamp technique (RK400 amplifier; Biologic; Grenoble, France) was used to record the transient and the sustained outward potassium currents (I_{out}). Glass pipettes (tip resistance: 1–2 MΩ) were filled with a solution containing (in mM) 130 K-aspartate, 5 KCl, 5 MgCl₂, 10 glucose, 3 K₂-ATP, 5 Na₂-phosphocreatine, 0.4 Na₃-GTP, 5 EGTA/KOH, and 10 HEPES/KOH, pH 7.2. The external solution contained (in mM) 135 choline-Cl, 1.1 MgCl₂, 2.5 CaCl₂, 0.5 CdCl₂, 10 glucose, 0.01 atropine sulfate, and 10 HEPES/KOH, pH 7.4. Experiments were performed on isolated RVC at room temperature (20–23°C). When the pipettes were filled with the internal solution, the series resistance ranged from 4 to 5 MΩ and was compensated by 60–80%. Membrane capacitance was systematically measured and was calculated by analyzing the capacitive surge produced by a small voltage step as described previously (12). Depolarizing voltage pulses were delivered at 0.1 Hz from a holding potential of ~80 mV.

Biochemical Investigations

COX activity and quantification of HSP72 were determined on frozen samples of RV and LV muscle, as previously described (18). Norepinephrine (NE) levels were measured in RV and LV according to the HPLC-electrochemical detection procedure previously described (41).

Statistical Analysis

All values are expressed as mean ± SE (n = number of experiments). Student’s unpaired t-test was used to assess the statistical significance of differences between age-matched control and exposed rats. A one-way ANOVA test was used to determine the statistical significance when more than two groups were compared, in particular, when comparing possible age differences within the same group (control or exposed rats). P < 0.05 was accepted as the level of significance.

RESULTS

Morphometric changes

Figure 1 shows the evolution of the body and heart weights and of the ventricular mass of control and exposed animals in...
the three age groups. Body weight of the 2-mo-old rats increased during the hypoxic exposure, whereas the body weight of the 6-mo-old rats decreased during the first third hypoxic exposure and then began to increase steadily but less than the controls (Fig. 1A). The body weight of the 18-mo-old rats increased regularly during the hypoxic exposure (Fig. 1A). The body weight of control rats increased significantly with age (results not shown). Heart weights were not significantly modified by the hypoxic exposure compared with control animals in all age groups (Fig. 1B) but were significantly increased with age in the control group. The heart weight-to-body weight ratio was significantly increased in the 2-mo-old rats but not in the 6- and 18-mo-old rats (result not shown). The RV weight (RVW)-to-left ventricular (LV) weight (LVW) ratio was significantly increased in all age groups exposed to hypoxia as compared with control animals (Fig. 1C). The ratio increased to 93, 71, and to 59% of controls in the 2-, 6- and the 18-mo-old rats, respectively. This latter result, in agreement with an increase in the RVW, is corroborated by Fig. 2A, which shows a macroscopic illustration of thickening of RV free walls on the exposed specimens in each age group compared with their respective controls at the end of hypoxic exposure. The difference between control and exposed conditions is visible to the naked eye in the three age groups. Even if the thickness of the RV free wall increased in the exposed rats in the three age groups, the reactivity to hypoxic conditions appeared to be more important in the 2-mo-old rats compared with the two other age groups. Indeed, the increase of the RV free wall thickness (Fig. 2B) in the exposed rats compared with control rats was 99.1, 43.7, and 44.1% in the 2-, 6- and 18-mo-old rats, respectively.

Determinants of Increase in RVW

Cardiomyocyte size. As shown in Table 1, RV cells of the 2- and 6-mo-old exposed rats had significantly greater width than those of the control rats. Such an increase was not observed in the 18-mo-old exposed rats. Neither LV myocyte dimensions nor the RV myocyte length was modified by hypoxia in all age groups. The morphometric determination of RV cell dimen-

Table 1. Ventricular myocyte dimensions of control and exposed animals in the three age groups

<table>
<thead>
<tr>
<th>Dimensions, μm</th>
<th>Control</th>
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<th>Exposed</th>
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<tr>
<td></td>
<td>2 mo</td>
<td>6 mo</td>
<td>18 mo</td>
<td>2 mo</td>
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<tr>
<td>Right ventricular myocyte width</td>
<td>26.8±0.7</td>
<td>33.5±0.9†</td>
<td>40.2±1.0‡</td>
<td>34.1±0.7*</td>
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<tr>
<td>Right ventricular myocyte length</td>
<td>122.4±1.7</td>
<td>139.8±1.8†</td>
<td>150.8±2.1‡</td>
<td>122.7±1.5</td>
</tr>
<tr>
<td>Left ventricular myocyte width</td>
<td>26.9±0.7</td>
<td>33.9±0.8†</td>
<td>39.8±0.9‡</td>
<td>27.4±0.7</td>
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<tr>
<td>Left ventricular myocyte length</td>
<td>124.1±1.5</td>
<td>146.5±1.8†</td>
<td>155.9±2.2‡</td>
<td>125.7±1.5</td>
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Values are means ± SE. Sixty right and left myocytes were studied in each condition. *P < 0.001, significant difference between means obtained from the exposed group with those of age-matched control group. †P < 0.0001 vs. control-2 mo, ‡P < 0.0001 vs. control-6 mo; §P < 0.005 vs. control-6 mo.
sions was corroborated by cell-capacitance measurement, which showed a significant increase in the 2- (80%) and 6-mo-old (32%) exposed rats but not in the 18-mo-old (4%) exposed rats compared with control animals (Fig. 3D). A significant difference was also detected for the control group as a function of age.

Endomysial Fibrosis

The Gordon-Sweet stain underscores the total collagenic component. Figure 3, A and B, illustrates the endomysial and perivascular collagenic fibrosis. Figure 3C shows the quantitative evolution of endomysial fibrosis in the trabecular cardiomyocyte fields. In the control group, a significant increase was noted only in the 18-mo-old rats compared with the two other age groups. Moreover, the heart of the 18-mo-old rats showed numerous areas of fibrosis in periluminal trabecules compared with the two other groups of age (results not shown). In the exposed group, a significant increase was observed in the 2-mo-old (18.3%) and 6-mo-old (9.3%) rats, but not in the 18-mo-old rats compared with the control animals.

Changes in Whole Cell Potassium Current Density

Figure 4A shows representative $I_{\text{to}}$ recordings elicited by a step depolarization to +60 mV in RVC isolated from control and exposed 2-mo-old rats. Figure 4, B–D, shows mean current density-voltage relationships of $I_{\text{to}}$ and $I_{\text{sus}}$ in RVC from control and exposed animals in the three age groups. In the control groups, there was a clear tendency for $I_{\text{to}}$ density to decrease as a function of age even if the comparison of the 2- and 6-mo-old animals was just at the limit of significance. A significant decrease in $I_{\text{to}}$ density was also observed in the 2-mo-old exposed group compared with the control group (by...
The density of $I_h$ during depolarizing steps to $+60\,\text{mV}$ from a holding potential of $-80\,\text{mV}$. Dotted line represents the zero current level. $B-D$: mean current density-voltage relationships of transient outward current (squares) and sustained current (circles) in control (open symbols) and exposed (solid symbols) rats. Bar values are means $\pm\text{SE}$ derived from 10 to 14 right ventricular myocytes isolated from 2 rats in each condition and for each age group. The transient outward current was measured as the difference between the peak outward current and the current at the end of 600-ms depolarizing pulses, whereas sustained current was measured at the end of 600-ms depolarizing pulses with respect to zero of the analog-to-digital converter. The difference concerning the transient outward current between control and exposed groups was significant ($P<0.0001$) between $+10$ and $+60\,\text{mV}$ only in the 2-mo age group, whereas this difference was significant ($P<0.05$ or $<0.01$) among the three control age groups.

Morphometric Changes

Weight and wall thickness. The significant reduction of body weight in adult rats exposed to chronic hypoxia confirms previous studies (12, 27, 36). The body weight curves indicate that the age of the experimental animal modifies its response to high-altitude stress (Fig. 1A). Weight loss in response to chronic high-altitude exposure has been attributed to reduced caloric consumption (6) or to increased metabolic rate produced by the hypobaric-hypoxic stress (29).

As expected, chronic hypobaric hypoxia induced an isolated RVH as evidenced both by the increase in the RVW/LVW ratio that acts as a sensitive detector that is independent of body weight (Fig. 1C) and by the increase of the RV free wall thickness (Fig. 2). Our findings indicate that there is an age-associated diminution in the extent of the hypertrophic response at the organ level. These results are in variance with those obtained in rats exposed either to intermittent hypobaric hypoxia (27) or to chronic normobaric hypoxia (26), which showed an age-associated increase of the RVH. The reason for this discrepancy is not clear but it cannot be related to animal strain difference or to differences in the inciting stimulus (22).

Cardiomyocyte Size

In our experimental model, the measurements of myocyte dimensions (Table 1) and myocyte membrane capacitance (Fig. 3D) confirm and extend our previous data (12) and show that the increase in RVW is partly due to an enlargement of cardiomyocytes (i.e., myocyte hypertrophy) in the 2- and 6-mo-old rats but not in the 18-mo-old rats. An age-associated diminution in the extent of the hypertrophic response was also
detected at the myocyte level, and such a response was not recorded in the 18-mo-old rats. An upper limit to cellular hypertrophy in terminally differentiated cardiomyocytes could explain this latter result in the old age group.

**Endomysial Fibrosis**

Measurements of pericellular fibrosis in RV (Fig. 3C) show an increased endomysial total collagen in the 18-mo-old control rats. This is in agreement with the results of Thomas et al. (45) obtained on LV that show an increase in fibrosis, consequential to the natural aging process.

In exposed rats, the increase in the collagenic component reported in the 2- and 6-mo-group compared with control groups (Fig. 3C) may contribute to the increase in the RVW observed in those groups (Fig. 1C). Nevertheless the evolution of pericellular fibrosis seems also to be age dependent as it decreased from the 2- to 6-mo-old exposed groups until being not detectable in the 18-mo-old exposed group, compared with controls.

Myocardial fibrosis results from the imbalance between collagen biosynthesis and degradation. An hypertrophy associated with pressure overload (but not with volume overload) induces an increase in collagen fibers number and size (review in Ref. 20). In the RV free wall, collagen I was essentially found in the epimysial but also in perimysial and endomysial situations where it is associated with collagen III and IV (this latter one being present with laminine in the basal laminae) (9, 38). Because the different collagen types have specific functions (types I, III, and IV providing resistance to tension, structural maintenance in extensibility, and anchoring of cell to cell, respectively), the particular evolution of each collagen type will be interesting to underscore for the characterization of our experimental hypoxia-induced hypertrophy (20).

**Putative Hyperplasia**

Hyperplasia was a possible explanation of the increase in RV wall thickness without a significant increase in fibrosis or myocyte hypertrophy. It is still generally believed that compensated cardiac hypertrophy is mainly caused by myocyte hypertrophy, hyperplasia of the nonmuscle cells (essentially fibroblasts), and fibrosis. Nevertheless, it was often suggested during the past 15 yr (2, 4, 5, 44) that adult cardiomyocytes may not all be terminally differentiated cells and that mitotic divisions of myocytes could constitute a growth reserve for severely damaged myocardium (4, 44). It has recently been proven that a myocyte turnover occurred in myocardium with an enhancement of myocyte replication; this concerns acute pathological states (4), as well as the hypertrophy generated by chronic stimuli developing a mild ventricular dysfunction (as in human aortic stenosis). In this latter case (46), the replication would even exceed from 4- to 15-fold that of the acute pathological states. The last studies showed (by immunofluorescence and confocal microscopy) that the replicating myocytes originate from the activation of cardiac stem cells committed with the cardiac myocyte lineage. So it seems now definitely acquired that hyperplasia significantly contributes to the increase in the cardiac mass in hypertrophied human myocardium. This seems to be corroborated on our model; a rapid checking on Gordon-Sweet-stained sections showed that the number of RV myocytes increased in rats exposed to chronic hypoxia compared with controls (data not shown). We found a cellular increasing ratio between control and exposed specimens (young group 25%, adult group 26%, and old group 10%). The apparent downregulated hyperplastic response in the 18-mo-old rats is an interesting result. The reason could be the loss of proliferative capacity of the cardiac stem cells and the concomitant age upregulated cell loss as proposed by Anversa et al. (4) (reviewed in Ref. 43). At any rate, this will complicate the estimation of the newly formed myocytes, in the old specimens, whatever the methodology used.

**Changes in Whole Cell Potassium Current Density**

The reduction in \( I_{K} \) density induced by chronic hypobaric hypoxia confirms and extends our previous results (12). Such a response is the most consistent finding in hypertrophied ventricular myocytes regardless of the species or the experimental conditions.

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Fig. 5. Evolution of cytochrome \( c \) oxidase (COX) activity (A), heat shock protein 72 (HSP72) content (B), and norepinephrine content (C) in the three age groups in control and exposed rats. For both conditions and for each age, \( A-C \) show the mean data \( \pm \) SE derived from 8 to 10 animals. Significantly different from control: *** \( P < 0.001 \), + \( P < 0.0001 \) vs. Contr.-2 mo and/or Contr.-6 mo.
method of hypertrophy production (32). As for the myocyte hypertrophy response and for the pericellular fibrosis response, an aging-related decline was observed at this subcellular response level (Fig. 4). In addition, an age-dependent decrease in $I_{Na}$ density was also observed in control groups. If this latter result agrees with previous ones (10, 47), it is in contrast with two studies showing either no variation (even a downward trend) or an increase in $I_{Na}$ density as a function of age (24, 25).

In these two studies, ventricular myocytes were used without analyzing their regional provenience (i.e., RV myocytes, LV subepicardial or subendocardial myocytes) while there is a clear regional distribution of $I_{Na}$ density (1, 8), and thus the mean result could be greatly influenced by the relative proportion of these different myocytes. This experimental bias could explain the absence of variation in $I_{Na}$ density reported on aged Wistar rats (24) because a decrease was reported by others on the same rat strain (10, 47). Concerning the increase in $I_{Na}$ density reported on aged Fischer 344 and Long-Evans rat strains (25), the greatest part of the discrepancy might be attributable either because the study was performed on myocytes in primary culture or most probably because of the strains of rats used. Indeed, similarities but also differences with respect to morphological changes that accompany aging in these different rat strains have already been noted (23). In our study, the absence of effect of hypoxia in $I_{Na}$ density is certainly because aging per se cause a decrease in this current density and that hypoxia could not induce further decrease.

**Biochemical Data**

**COX activity.** Chronic hypoxia leads to biochemical adaptations of the myocardial cell affecting the pathways of energy production (35). Activity of COX, a marker enzyme for the mitochondrial oxidative capacity (39), was nearly the same in homogenates from RVs and LVs and was essentially unaffected by chronic hypoxia in each age groups (Fig. 5A). Such a result is similar to the data of Rumsey et al. (40) obtained on younger rats (4 day old) but with more severe hypoxic conditions (10% O₂ atmosphere, corresponding to an altitude of ~6,000 m during 40 days). Contrary to Paradies et al. (33), we did not find an age-dependent decrease in the COX activity in control rat heart mitochondria. The discrepancy between these two studies might be attributable to the fact that their rats were older (26 mo old) than those used in our study (18 mo old). We cannot rule out the possibility that significant changes could have been detected at later stages of life.

**HSP72.** Heat shock proteins constitute a universal, intracellular response to stress. Among them, the HSP72, expressed in the normal, unstressed mammalian cells, is primarily induced in response to stress (21). In our study, HSP72 content was not increased in RVs and LVs by chronic hypoxia among the three age groups or between the control and exposed individual age groups (Fig. 5B). The present results are in agreement with those of Comini et al. (14), which showed that congestive heart failure, but not compensatory hypertrophy, was a specific stimulus for the induction of HSP72 in the heart. Nevertheless, we cannot exclude the possibility that significant changes could have been detected soon after the beginning of hypoxic exposure but was no longer present after 20 days of hypoxia. Such a behavior was reported for the rat heart HSP70 mRNA in response to aortic banding (21).

The absence of modification concerning the COX activity and HSP72 content confirms our previous data showing that the model of cardiac hypertrophy induced by chronic simulated high-altitude exposure is a physiological mild hypertrophy model (19).

**NE content.** Chronic hypoxia exposure triggers the autonomic nervous system and increased the cardiac neuronal activity (15, 37). These responses play a major role in the cardiovascular adaptations to offset the decrease in tissue oxygen supply. With the higher levels of NE in the RV than in the LV in the adult and the decrease of ~70% in the RV and LV NE contents with advancing age, our data agree with previous results (14, 23). In RV hypertrophy induced with monocrotaline, no modification in ventricular content of NE was reported compared with control (14). In contrast, in RV hypertrophy induced by chronic high-altitude hypoxia, our results show a significant specific decrease in the RV content of NE, whatever the age. No change was recorded in the LV part of the heart. These data confirm (15, 28) and extend previous results by reporting a specific effect of chronic hypoxia on the RV and no age-related effect of chronic hypoxia on the RV NE content decrease and on the cardiac adrenergic response to hypoxia. The role of NE in cardiovascular hypertrophic remodeling has been reported (16). The age-related decrease in the RV NE content in the old rats might be part of mechanisms contributing to the reduced RV remodeling in the 18-mo-old rats exposed to hypoxia. It has been shown that sympathetic NE depletion by reserpine in rat heart causes a decrease in $I_{Na}$ density in ventricular myocytes (7). The role of NE content decreases in the reduction of $I_{Na}$ density in the chronic high-altitude hypoxia model and in aging remains to be determined.

In conclusion, the present study shows that besides a myocyte hypertrophy and a fibrosis, the remodeling induced by chronic hypoxia in the RV could also result of a myocyte hyperplasia. Such a possibility is validated by the recent findings of Anversa et al. (4, 46). Moreover, our study shows that the natural aging process decreases the degree of heart remodeling (at morphological and electrophysiological levels) induced by chronic hypoxia. These aging-induced changes in cardiac plasticity may play important roles in the decreased myocardial function in the elderly, in whom pulmonary diseases are frequent.

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