Original Article

Effect of Simulated Microgravity and its Associated Mechanism on Pulmonary Circulation in Rats*

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Abstract

Objective To study the effect of Simulated Microgravity and its Associated Mechanism on Pulmonary Circulation in Rats.

Methods Rat tail-suspension model was used to simulate the physiological effects of microgravity and changes in pulmonary blood vessel morphology, pulmonary arterial and venous blood pressure, pulmonary vascular resistance, pulmonary vasomotoricity, as well as the regulation of pulmonary circulation by cytokines produced and released by the lung of rats were measured.

Results The walls of pulmonary blood vessels of rats were thickened, and the pulmonary artery was reconstructed with increased pulmonary vascular resistance. The pulmonary blood vessels of rats became more prone to dilation as contractions increased. Rat epithelial Adrenomedulin gene transcription and protein expression were upregulated. The level of basic fibroblast growth Factor of rat was also elevated.

Conclusion Findings from the present study on rats revealed that the microgravity can affect pulmonary blood vessel structure, pulmonary arterial pressure, and pulmonary blood vessel self-regulation and cytokine production.

Key words: Rat; Simulated microgravity; Changes in pulmonary circulation; Regulations of pulmonary circulation

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INTRODUCTION

Previous studies have revealed that microgravity can cause a variety of effects on human body during space flights, including cardiovascular malfunction, osteoporosis, muscular atrophy, and immune suppression[1-2]. It was also reported that microgravity can cause a drop in total blood volume resulting in a low dynamic state of cardiovascular system. Afterwards, down

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regulation of heart contractual adaptation, as well as a decrease in the vasomotoricity[3-5], contribute to side effects such as orthostatic intolerance[6]. As indicated by some of research work, regulation of systemic circulation plays an important role in vascular mechanism during orthostatic intolerance. Meanwhile, recent findings have demonstrated that pulmonary circulation also plays an important role in this process[7-9].

Under microgravity, body fluid shifts to the upper body, then affecting pulmonary circulation. The excess amount of blood quickly passes through the right side of the heart and accumulates in lung. In addition, the mechanical force normally applied to the chest and abdominal cavities disappears in the absence of gravity, causing re-distribution of blood in the lung and change in lung expansion capacity[7,10]. Since the constriction/dilation of pulmonary blood vessel and because pulmonary blood volume can change heart output and blood pressure[11], pulmonary circulation plays a key role in the onset of low endurance and orthostatic intolerance[8-9]. Therefore, the pulmonary circulation system is the major place for redistributed body fluid during microgravity and is also the first defensive line in preventing an excessive burden on the left side of the heart and systemic circulation. Although there were some studies[12-14] focusing on the lung morphology, pulmonary blood volume, pulmonary capillary permeability and vascular permeability factor in microgravity or simulated microgravity and some discussions on the relevant possible mechanisms[7,15], few was reports on the mechanisms of pulmonary blood vessel reconstruction and functional change.

In this study on rats, we hypothesized that simulated microgravity could induce the changes of hemodynamics in pulmonary circulation as well as the secretion and expression of active biological molecules, which, we believe, could finally affect the functions and remodeling of pulmonary vessels. Accordingly, we examined the morphological change of pulmonary blood vessels, measured pulmonary arterial and venous blood pressure and vascular resistance, and assessed the changes in pulmonary vasomotoricity, as well as the effects of locally produced cytokines on the regulation of pulmonary vascular function. The present study focused on how microgravity could affect pulmonary circulation reconstruction and what mechanism was behind in order to gain a better understanding of the important role the pulmonary circulation played in the regulation of orthostatic intolerance and thus providing recommendations for taking preventative measures in future space flights.

MATERIALS AND METHODS

Animals and Reagents

120 male Wistar rats (245±20 g) were obtained from the experimental animal center of the General Hospital of the Chinese People's Liberation Army. Phenylephrine (PE), Acetylcholine (Ach), Sodium Nitroprusside (SNP), and Indomethacin Ethylene Diamine Tetraacetic Acid 2 Na were purchased from Sigma (USA). Adrenomedulin (ADM) detection kit was purchased from East Asia Radio-Immunity Institute (Beijing). ADM Real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) kit and Basic Fibroblast Growth Factor (bFGF) RT-PCR kit were purchased from Pierce (USA).

Simulated Microgravity Animal Model

A head-down tail-suspension model for simulated microgravity was used[16-17]. A total of 120 rats were randomly divided into 3 groups: control group (*n*=40), tail suspension 7 day group (TS7d, *n*=40) and tail suspension 14 day group (TS14d, *n*=40). Supine and head-down tilt position were used in each group and the level of head-down tilt was about 30^{o}. Rats in the control group were maintained in the same type of cage without tail suspension and were able to walk freely. All rats were maintained in a room at 22-25 °C under a constant day/night cycle and food and water was provided ad libitum. Principles of laboratory animal care (NIH publication No. 86-23, revised 1985) were followed and implemented. And, the study was approved by the Institutional Review Board (IRB) of the General Hospital of the Chinese People's Liberation Army.

Effects of Simulated Microgravity on Pulmonary Blood Vessel Morphology of Rats

At the end of tail suspension, rats were anesthetized with abdominal injection of 3% sodium pentobarbital (1.5 mg/kg) and were placed face up on an operating table. Lung organ was dissected and removed and gross changes in morphology were detected prior to staining with Hematoxylin and Eosin (HE). Morphology was observed under a light microscope. Lung tissues from the same side were stained with HE and elastin and examined under a light microscope for pulmonary artery remodeling.

Images of arteries with a small diameter (around 100 μm) were taken and analyzed by Image-Pro Plus 6.0 imaging analysis software (Media Cybernetics Inc, USA). Microchanges of lung structure were observed[18] under JAM-1230 electron microscope (JEOL, Tokyo, Japan). Immunohistochemistry staining[19] was used to stain factor VIII using Goat anti factor VIII polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, USA). Lung blood vessels were also visualized with ink perfusion.

Effects of Microgravity on Pulmonary Hemodynamics of Rats

Rats were dissected in order to expose the tracheae. An endotracheal intubation was performed then at the tracheal rings, and a rodent ventilator (HX-300S, Chengdu TME Technology Co, Ltd, China) was connected afterwards for mechanical ventilation. The pulmonary artery was dissected in order to measure volume of pulmonary arterial flow by electrical flowmeter (MFV-3200, Nihon Koden, Tokyo, Japan). Pulmonary arterial and venous blood pressures at supine and head-down -30^{o} position were measured by Millar catheter[20].

Effects of Microgravity on Pulmonary Arterial Vasoregulatory Function of Rats

Endotracheal intubation and ventilation was performed as described in section 3. Rats were dissected and the heart and lung were exposed after anesthetization with abdominal injection of 3% sodium pentobarbital (1.5 mg/kg). A pulmonary artery intubation via right ventricle was made. The left ventricle was cut open and a catheter was intubated into the left atrium. The heart and lung were hung vertically inside the isolated lung perfusion system (Radnoti, USA) and the pulmonary artery and left arterial cannula were connected to a physiology recorder to record pulmonary arterial perfusion pressure (PAPP). The perfusate[21] was injected at a constant rate (13 mL/min) for 20 min using a peristaltic pump. PE (10^{-6} mol/L), Ach (10^{-5} mol/L), and SNP (10^{-5} mol/L) were administered, respectively, and PAPP was recorded. Pulmonary vascular resistance (PVR) was calculated afterwards based on the following formula: PVR=(mPAP-mPVP)/PF.

Effects of Microgravity on Lung Humoral Factors of Rats

ADM Measurement by Radioactive Immunoassay A total of 2 mL of venous blood was taken from the jugular vein catheter and was added into tubes containing 30 μL of 7.5% EDTA2Na and 40 μL of trasylol. The blood was then centrifuged at 3000 RPM at 4 °C for 10 min, and the plasma was isolated and stored at -80 °C for onward analysis. The amount of ADM was measured by an ADM detection kit following the manufacturer's protocol.

Pulmonary ADM Immunohistochemistry Changes in pulmonary ADM expression were tested by immunohistochemistry using rabbit polyclonal antibody against ADM (Abbiotec, San Diego, CA, USA) following kit manual. Stained pulmonary microvascular endothelial cells and pulmonary acinus epithelial cells was observed and positive staining was a brown or dark brown color. Results were calculated then as the number of positive stained cells per 100 cells examined in 5 fields (x400) from each rat and a total of 10 rats per group were sampled for the observation.

Gene Expression Analysis of ADM and bFGF by Semi Quantitative RT-PCR A total of 100 mg of lung tissue were frozen at -80 °C. Gene expression of AMD and bFGF was examined using semi quantitative RT-PCR[22]. In brief, total RNA was isolated using the TRIzol reagent (Invitrogen) following the manufacturer. For RT-PCR, 1 μg total RNA was reverse-transcribed into cDNA with 1 unit/mL M-MLV reverse transcriptase (Invitrogen). Primers were designed using DNAMAN software based on sequences in the NCBI database (Table 1). The cDNAs from all the lung samples were amplified simultaneously using aliquots from the same PCR mixture. After the PCR amplification, 30 μL of each reaction were electrophoresed on 1.5% agarose gels stained with ethidium bromide and Kodak image analysis system (Eastman Kodak, Rochester, NY) was used for image quantification.

Table 1. RT-PCR Primers Sequences

Gene Name	Primer Sequences (5'- 3')	Amplicon Length (bp)
bFGF	F: GTATGAAACGGCGGCTTCTT R: TGAGTCAGCTCTTAGCAGAC	364
β- actin	F: ATCTGACACCACACCTTCTACAATGAGCTGCG R: CGTCATCTCCTGCTTGCTGATCCACATCTGC	838
ADM	F: AGC GCC ACC AGC ACC GAA TAC G R: AGA GGATGG GGT TGG CGA CAC AGT	491
β- actin	F: TGG GTC AGA AGG ACT CCT ATG R: CAG GCAGCT CAT AGC TCT TCT	591

Note. RT-PCR: Real-time Reverse Transcriptase Polymerase Chain Reaction. bFGF: Basic Fibroblast Growth Factor. AMD: Adrenomedulin. F: Fourwar, R: Reverse.

Statistical Analysis

Statistical analyses were performed using SPSS (version 13) and $P<0.05$ was considered statistically significant. Continuous data were presented as mean±standard deviation (M±SD). For the effect of simulated microgravity on vascular morphology and dynamic of pulmonary circulation, differences of measurement data were identified with nonparametric tests. For the effect of simulated microgravity on the regulation of vascular function and the humoral factors in lung tissue, differences of measurement data were examined with one-way ANOVA. The least significant difference method (LSD) was used for the comparation between two-group.

RESULTS

Histological Vascular Morphology

Gross Morphology Lung tissues from the control group appeared normal with homogeneous color and luster and no blood congestion and hemorrhagic spots were observed. However, the tail suspension 7 day- and 14 day- groups displayed uneven color and luster with various degrees of patchy and petechial hemorrhages.

Histological Observation The HE staining of alveoli and arterioles is shown in Figure 1. Alveolar walls in lung tissues had unique shape and size in comparison with the control group, and no blood congestion was observed. Alveolar walls from the TS7d and TS14d groups appeared thinning with sporadic congestion, edema and inflammatory cell infiltration. In the TS7d and TS14d groups, middle layer smooth muscle hypertrophy, vessel wall thickening and stenosis were observed in pulmonary arteriola (diameter 100 μm) and there were certain degrees of vascular hyperplasia and remodeling. Alveoli electron microscopy observation (Figure 2) showed that in the control group, endothelial cells appeared flat with intact internal elastic lamina. But in the TS7d and TS14d group, intima was thickened, and endothelial cells were enlarged, intruding into the alveolar cavity. Pulmonary factor VIII staining (Figure 3) showed that the expression of factor VIII in the TS7d group was significantly higher with increased vascular density as compared to the control group ($P<0.01$). Although the expression and vascular density in the TS14d group was not as high as that in the TS7d group, it was still significantly higher than that in the control group ($P<0.05$). The visualization of pulmonary microvasculature by ink perfusion method is shown in Figure 4. Microvessels

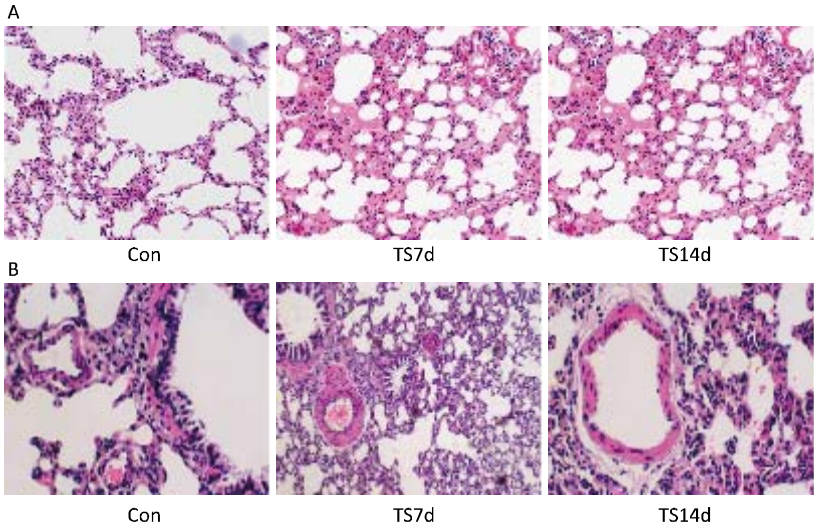

Figure 1. HE staining of lung tissue and pulmonary arteriola. A: Alveolar walls showed unique shape and size in lung tissues from the control group and no blood congestion was observed. Alveolar walls from the TS7d and TS14d group showed thinning with sporadic congestion, edema and inflammatory cell infiltration. B: In the TS7d and TS14d groups, pulmonary arteriola (diameter 100 μm) showed middle layer smooth muscle hypertrophy, vessel wall thickening and stenosis and there are certain degrees of vascular hyperplasia and remodeling. 400× magnification. HE: hematoxylin and eosin staining. Con: control group; TS7d: tail suspension 7 days group; TS14d: tail suspension 14 days group.

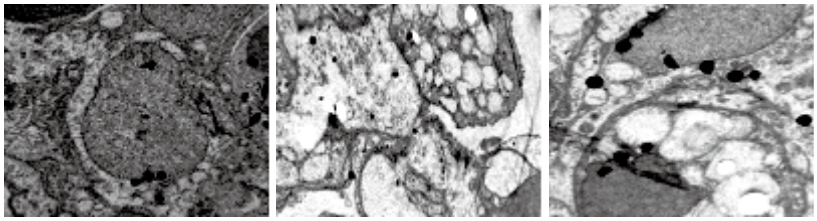

Figure 2. Electron microscopy scanning of alveolar transmission. Endothelial cells in the control group appeared flat with intact internal elastic lamina. In the TS7d and TS14d group, intima was thickened, and endothelial cells were enlarged, intruding into the alveolar cavity. 1000× magnification. Con: control group; TS7d: tail suspension 7 days group; TS14d: tail suspension 14 days group.

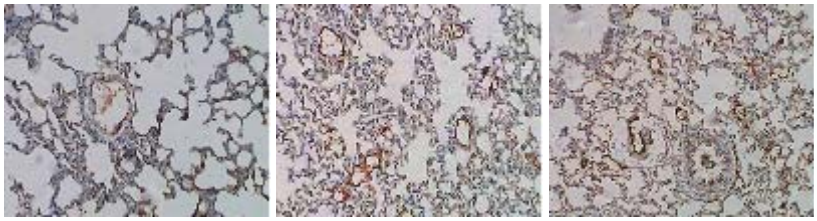

Figure 3. Staining of factor VIII in the lung. The expression of factor VIII in the TS7d group was significantly higher with increased vascular density as compared to the control group (P<0.01). Although the expression and vascular density in the TS14d group was not as high as that in TS7d group, it was still significantly higher than in the control group (P<0.05). 400× magnification. Con: control group; TS7d: tail suspension 7 days group; TS14d: tail suspension 14 days group.

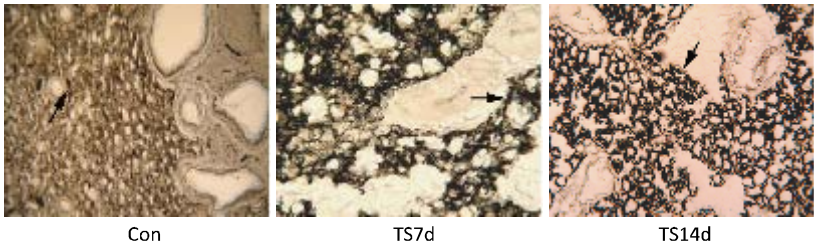

Figure 4. Pulmonary microvasculature Ink perfusion. The TS7d and TS14d group showed pulmonary acinar arterial wall thinning with different degrees of broadening, the internal elastic layer displayed uneven thickness and endothelial cells showed hyperplasia, degeneration and detachment; smooth muscle cells showed hypertrophy and some vascular circle ruptured. 100× magnification. Con: control group; TS7d: tail suspension 7 days group; TS14d: tail suspension 14 days group.

from the control group were seemed normal in size with even and smooth distribution; vascular morphology was consistent, endothelial cells were well aligned, the internal elastic layer exhibited a consistent thickness. In the TS7d and TS14d groups pulmonary acinar arterial wall thinning was observed with different degrees of broadening, uneven thickness was evident in the internal elastic layer. In addition, hyperplasia, degeneration and detachment, as well as smooth muscle cells hypertrophy, were observed in endothelial cells and some vascular circle ruptured.

Pulmonary Vascular Pressure and Blood Flow Volume

As showed in Table 2, and compared to the control group at the supine position, the mean Pulmonary Arterial Pressure (mPAP) and Pulmonary Vascular Resistance (PVR) in the tail suspension 7 days group at the supine position were significantly increased (CON: 18.88±1.60 *vs* TS7d: 20.07±0.62, P<0.05), whereas, in the same group, Pulmonary blood Flow (PF) was significantly decreased (CON: 53.91±3.29 *vs* TS7d: 49.47±3.16, P<0.05). An increase was observed also in mean Pulmonary

Venous Pressure (mPVP), but it was not statistically significant (P>0.05). No significant changes in the above parameters were observed in the tail suspension 14 days group at the supine position. The same trend was shown in the tail suspension 7 days head-down tilt -30° position group as compared to the control group with significantly increased mPAP, PF and mPVP (P<0.05). Although there was an increase in PVR, this increase was not statistically significant (P>0.05). The tail suspension 14 days head down group showed similar changes as the tail suspension 7 days group, whereas the tail suspension 14 days head down group had a significant increase of mPAP (P<0.05).

Table 2. Effects of Microgravity on Rat Pulmonary Hemodynamics

		mPAP (mmHg)	mPVP (mmHg)	PF (ml/min）	PVR (Kpa.S/L)
CON	Supine position	18.88±1.60	2.85±0.47	53.91±3.29	2372.25±222.48
	Head-down tilt position	21.01±1.61*	3.91±1.10*	57.34±3.23*	2397.23±353.04
TS7d	Supine position	20.07±0.62△	2.94±0.35	49.47±3.16△	2770.44±123.62△
	Head-down tilt position	21.80±0.99*	3.54±0.43*	52.31±2.58*△	2796.78±250.7△
TS14d	Supine position	19.20±1.60	2.91±0.45	50.08±2.96	2710.34±180.98
	Head-down tilt position	21.40±2.11	3.48±0.51	52.93±3.07	2780.12±239.81

Note. PVR=(mPAP-mPVP)/PF *$P<0.05$, *vs* supine position, △$P<0.05$ *vs CON.* mPAP: mean Pulmonary Arterial Pressure; PVR: Pulmonary Vascular Resistance; PF: Pulmonary blood Flow; mPVP: mean Pulmonary Venous Pressure; CON: control; TS: Tail suspension.

Pulmonary Arterial Perfusion Pressure (PAPP) and Pulmonary Vascular Resistance (PVR) of in vitro Pulmonary Circulation

PAPP significantly decreased in the tail suspension 7 days and 14 days groups as compared to the control group (CON: 16.52±1.91 *vs* TS7d: 14.53±2.37, P<0.05, TS14d: 11.61±1.84, P<0.01, respectively). After intervention with PE, Ach, and SNP, the isolated rat pulmonary artery showed a decreased constriction response to PE (P<0.05) and increased dilation responses to Ach and SNP (P<0.01, P<0.05, respectively) in the TS7d and TS14d groups (Figure 5).

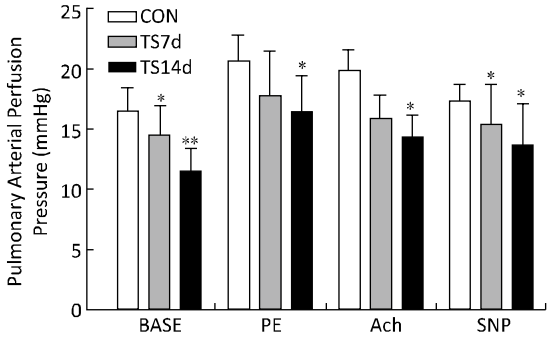

Figure 5. Changes in perfusion pressure under constant flow in isolated rat pulmonary circulation model. PE: Phenylephrine. Ach: Acetylcholine. SNP: Sodium Nitroprusside. Con: control group. *P<0.05 *vs* CON, **P<0.01 *vs* CON.

Rat pulmonary vascular resistance significantly decreased after 7 or 14 days microgravity simulation by tail suspension (P<0.05, P<0.01, respectively), both before and after drug interventions (Figure 6).

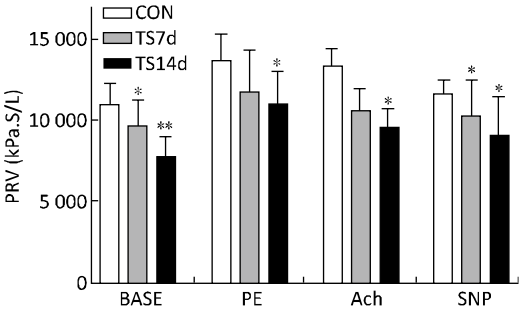

Figure 6. Changes in pulmonary vascular resistance under constant flow in isolated rat pulmonary circulation model. PE: Phenylephrine. Ach: Acetylcholine. SNP: Sodium Nitroprusside. PVR: Pulmonary Vascular Resistance. *P<0.05 *vs* CON, **P<0.01 *vs* CON.

Changes of Intrapulmonary Humoral Factors

Blood ADM levels significantly increased in the TS7d and TS14d groups as compared to the control group (P<0.05 and P<0.01, respectively) as shown in Figure 7. Immunohistochemistry analysis revealed that the majority of positive ADM staining was located in the cytosol and nuclear of bronchial epithelial cells, alveolar macrophages and alveolar

epithelial cells (Figure 8). In addition, as compared to the control group, the expression of ADM and bFGF increased significantly in lung tissues from the TS7d group whereas no change was found in those from the TS14d group. The expression of ADM in the TS14d group was significantly lower than that in the TS7d group (P<0.05) (Figure 9).

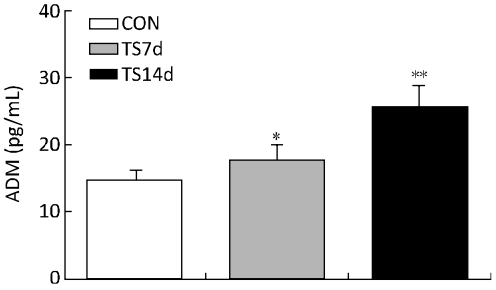

Figure 7. Changes of ADM Concentration in Rat Peripheral Blood. ADM: Adrenomedulin. *P<0.05 *vs* Con. **P<0.01 *vs* Con.

DISCUSSION

Due to the scarce number of space flights and the extremely high cost, researches on the effects of weightlessness on astronauts are largely limited. Therefore, we used a well-accepted animal model in this study in order to mimic microgravity effects. It was revealed that this rat suspension model can well simulate the effects of microgravity during space flights and the subsequent body response[23] and therefore has been widely used. Lung is one of the organs easily affected by gravity. There are huge amounts of body fluids that are redistributed from the lower body to the upper body during weightlessness. Because of the physiological properties of the lung such as low pressure and low resistance, a majority of body fluids will end up in the pulmonary circulation. In this study, HE stains revealed alveolar effusion of red blood cells and pulmonary interstitial edema after 7 and 14 days of simulated microgravity, a phenomenon that was not observed in the control group, indicating

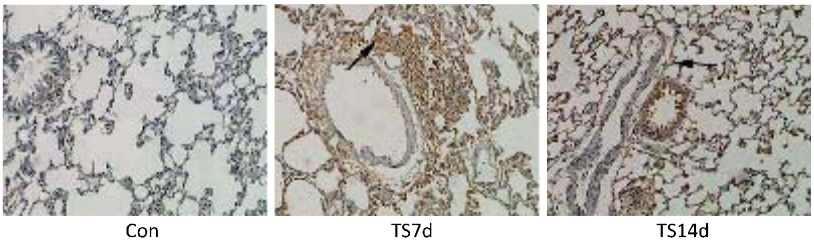

Figure 8. Immunohistochemistry of ADM in lung tissue. ADM expression in TS7d group showed a significant increase compared with that in the control group (P<0.01), the expression decreased in TS14d as compared to TS7d group, yet being still significantly higher than in the control group (P<0.05). 400× magnification. Con: control group; TS7d: tail suspension 7 days group; TS14d: tail suspension 14 days group. ADM: Adrenomedulin.

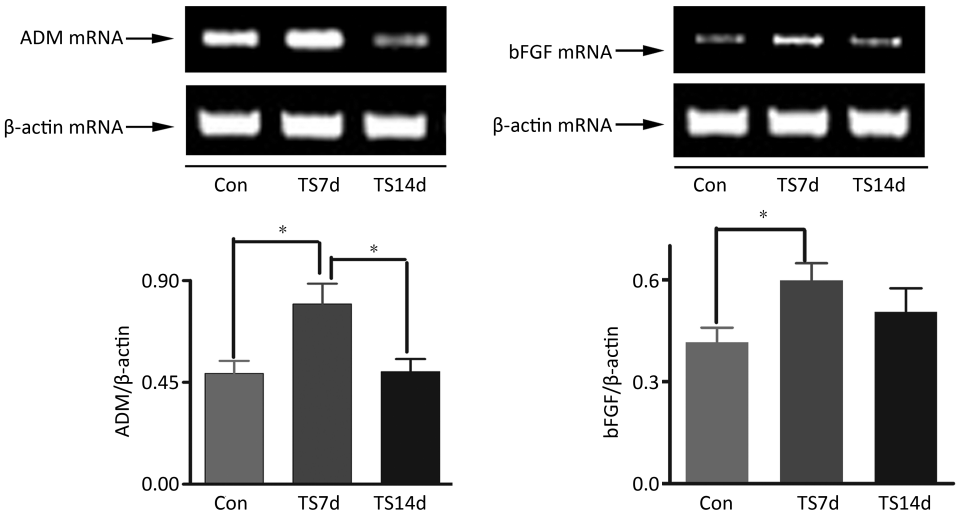

Figure 9. ADM and bFGF RT-PCR results in lung tissues from each group of rats. ADM: Adrenomedulin. *P<0.05 *vs* 7d-HU and Con.

that weightlessness caused a certain degree of damage to rat lung tissues[24]. We also examined the staining of elastic fibers of pulmonary blood vessels and it was revealed that the simulated microgravity induced the changes of pulmonary vascular structure[25]. The ultrastructural changes observed in the present study indicated that rat vascular endothelial cells function, protein synthesis and metabolism were very active, and smooth muscle cells were hyperproliferative. Timewise, the changes in pulmonary artery and microvascular happened at the early stages of the simulated microgravity[26]. Previous work done by Langille[27] found that it only took a very short number of days for the arterial vascular remodeling to happen after local hemodynamic changes.

The significant increase of pulmonary microvascular Factor VIII protein expression, as well as the increases in microvascular density in the TS7d and TS14d groups, indicating that the pulmonary microvascular structure underwent remodeling by the simulated microgravity and the main reason for this remodeling could be likely due to acute shear stress caused by tail suspension. A recent study by Tian reported that abnormal expression of genes and proteins of weightlessness was observed due to compensatory reconstruction in pulmonary blood vessels[28]. Meanwhile, in our studies, the increased protein expression of Factor VIII was identified, which demonstrated that simulated microgravity could induce angiogenesis in the lung. There were also possibilities of verification of microvascular density. The increased expression of Factor VIII and microvascular density may be induced by changed hemodynamics in pulmonary circulation, which may facilitate the secretion of some factors contributing to the vascular remodeling, such as ADM and bFGF, etc.

In our study, mPAP, mPVP, and PVR significantly increased in the simulated microgravity group as compared to the control group. Owing that the pulmonary artery is an elastic vessel, the vascular compliance is determined by the amount of collagen fiber present in the vascular wall. Previous research work has ever shown a great amount of collagen deposition in large and medium sized pulmonary arteries during pulmonary hypertension, together with decreased pulmonary vascular compliance and increased pulmonary resistance[29]. We also found in our study the significantly increased mPAP and PVR while the position of rats changed to head down in both the control and simulated microgravity groups, indicating changes in hemodynamics after redistribution of body fluids to the upper body during microgravity. Moreover, similar changes were observed between TS7d and TS14d groups. As we know, the redistribution of body fluids is a kind of weightlessness effects, which can be simulated by rat tail suspension and human head-down bed rest models[30]. The acute response effects of cephalic fluid shift generally occur in the first week, entering a new adaptation period onwards. Consequently, it is possible to find the similar results about the changes of hemodynamics in pulmonary circulation after simulated microgravity is induced by tail suspension.

Morphological examination detected arterial stenosis, distortion of arterial elastic plates, hyperplasia of middle layer smooth muscle and adventitia collagen fibers in the lung tisue of rats. These changes directly caused pulmonary hypertension and increased pulmonary resistance. After all, microgravity could induce remodeling of pulmonary vascular structure.

Tension of rat pulmonary blood vessel contributes to the regulation of pulmonary circulation. The contractile and relaxant reaction plays a certain role in local redistribution of pulmonary blood and other body fluids[31]. Then a question is raised by whether microgravity can affect the contractile and relaxant reaction of pulmonary blood vessels. To eliminate the possible neurological and humoral effects, we used an isolated pulmonary perfusion system[32] was used in our present study inorder to examine the effects of microgravity on pulmonary contractile and relaxant reaction. And our results showed that after tail suspension for 7 and/ or 14 days, perfusion pressure in isolated rat pulmonary artery under constant flow decreased significantly as compared to the control group. Meanwhile, rat pulmonary vascular resistance decreased after tail suspension for 7 days, and then some improvement was observed after 14 days, possibly due to the damages at early stage caused by microgravity to the intact layers of vascular smooth muscle and endothelium, which regulated vascular contractile and relaxant reaction and maintained proper tension of blood vessel walls.

We believe that it is possible for the contractile and relaxant reactions to be decreased when blood vessels were damaged and imperfect. Findings from our study showed that after 7 or 14 days of simulated microgravity, the contractile response of rat pulmonary artery to PE diminished whereas the

relaxant response to Ach and SNP was enhanced. This is in consistent with previous findings by Daniel et al.[7] that under microgravity SNP enhanced vascular dilation through endothelial released NO. It might be suggested therefore that microgravity can cause increased compliance and enhanced relaxant reaction, allowing pulmonary blood vessels to relax more easily.

Under the microgravity, self-regulatory function of pulmonary vascular is affected. It is well known that certain pulmonary humoral factors participate in pulmonary vascular regulation; for example, ADM can dilate blood vessel and reduce blood pressure[33]. Hardt et al.[34] once administrated inhalablly the ADM to patients with pulmonary hypertension who were waiting for lung transplantation. And the pulmonary arterial pressure of these patients significantly decreased, indicating a regulatory effect of ADM on pulmonary blood pressure. Another humoral factor, bFGF, supposedly promotes cell proliferation and angiogenesis, therefore participating in pulmonary vascular remodeling[35]. In this study we found a significant increase in plasma ADM levels and lung ADM expression by immunohistochemistry after 7 and 14 days of simulated microgravity. Results from RT-PCR demonstrated an increased gene expression of ADM and bFGF in rat lungs in simulated microgravity groups and this was possiblly due to that microgravity could cause the increased pulmonary blood flow, which applied more shear force to the endothelial cells and, as a result , the transcription, translation and secretion of ADM in epithelial cells increased, causing vasodilative effects. Moreover, the upregulations of ADM and bFGF were more significant in the TS7d group than in the TS14d group. The hemodynamics of vessels such as shear stress on endothelial cells might affect the expression of related genes. The mPAP and PVR in the TS14d group decreased compared with those in the TS7d group and these changes of hemodynamics would affect the shear stress on endothelial cells of pulmonary vessels and finally induce the corresponding changes in gene expression.

CONCLUSION

Simulated microgravity can cause damages in the lung tissue, the pulmonary vascular remodeling and the increases in pulmonary vascular resistance in rats. Meanwhile, local factors play important roles in pulmonary vascular regulation in rats. The amount of accumulated pulmonary blood volume is relatively increased under the microgravity together with impaired pulmonary vascular constriction.

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