MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 1806-1813
DOI: 10.12659/MSM.913056

Received: 2018.09.04
Accepted: 2018.11.16
Published: 2019.03.09

Histological, Ultrastructural, and Physiological Evaluation of a Rat Model of Obstructive Sleep Apnea Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

G 1 Yongyi Liu*
B 2 Lu Gao*
F 1 Weinong Lv
B 1 Lin Lin
F 1 Yi Wang
D 3 Hailin He
F 1 Fan Jiang
F 1,2 Fan Feng

1 The Fourth Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, P.R. China
2 Medical College of Jiangsu University, Zhenjiang, Jiangsu, P.R. China
3 Zhenjiang Dantu District People's Hospital, Zhenjiang, Jiangsu, P.R. China

* Yongyi Liu and Lu Gao are first co-authors contributed equally to this work

Corresponding Author: Fan Feng, e-mail: fengfan_514@163.com

Source of support: This study was funded by the National Natural Science Foundation of China (11472118), the Innovation Project of Graduate Training in Jiangsu (CX07B_09x and CX08B_09x), and the Maternal and Child Health Research Project of Jiangsu Province (F201604)

Background: Patients with obstructive sleep apnea syndrome (OSAS) are at an increased risk of cardiovascular disease. The aims of this study were to develop a rat model of OSAS and to validate the use of the model by investigating respiratory and cardiovascular physiological parameters and morphological changes by light microscopy and electron microscopy.

Material/Methods: Sixty 3-month-old Sprague-Dawley rats were assigned to the model group (n=30) and the control group (n=30). The rats in the OSAS model group were injected with 0.1 ml sodium hyaluronate solution into the upper respiratory tract at the junction between the hard and soft palate. After one month, the model and normal rats were compared using tests of respiratory and cardiac function, and histology and electron microscopy of the lung and cardiac tissue.

Results: In the rat model of OSAS, airway obstruction resulted in the collapse of the upper airway. Tests of respiratory function showed that the oxygen partial pressure, oxygen concentration, and oxygen saturation in the model group were significantly lower when compared with the control group. In the model group, histology of the heart showed cardiac myocyte disarray, and electron microscopy showed vacuolar degeneration and mitochondrial abnormalities. The rat model of upper airway occlusion showed pulmonary and cardiac changes that have been described in OSAS.

Conclusions: A rat model of upper airway occlusion resulted in physiological and morphological changes in the lung and heart due to hypoxia, and may be used for future studies on OSAS.

MeSH Keywords: Cardiomyopathies • Hyaluronic Acid • Sleep Apnea, Obstructive

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/913056

2791 2 4 25

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Obstructive sleep apnea syndrome (OSAS) is a common condition type of sleep-disordered breathing more commonly affects middle-aged people with a reported prevalence of between 5–14% [1]. The pathophysiology of OSAS includes recurrent partial and complete upper airway obstruction during sleep, which result in hypoventilation, apnea, intermittent hypoxia, and hypercapnia [2]. The effects of OSAS result in increased respiratory effort, increased sympathetic excitability, changes in sleep structure, and hypoxia, which can result in cardiovascular and cerebrovascular events, metabolic disorders, neurocognitive dysfunction, and other diseases [3,4].

Although progress has been made in the study of OSAS, there are aspects of the pathophysiology that remain to be investigated as there can be a difference in the clinical manifestations and comorbidities in different individuals [5]. There is no safe and effective drug treatment for OSAS [6]. However, the currently recommended first-line treatment for OSAS is the use of continuous positive airway pressure (CPAP), which although effective, is limited by poor patient compliance, which is reported to range from 17–54% [6]. Although pharyngeal occlusion during sleep is the main cause of upper airway collapse, limited understanding of the pathophysiology of OSAS is an important factor that affects the progress of developing new treatments [7]. Therefore, animal models have an important role in investigating the pathophysiological mechanisms, clinical features, complications, and new treatment approaches for OSAS.

Currently, animal models of OSAS can be divided into spontaneous and inducible models. In spontaneous animal models, respiratory disturbance may be caused during sleep due to congenital malformation or inherent characteristics [8]. The English bulldog has been reported to the closest animal model to human sleep-disordered breathing and OSAS, with abnormal upper airway anatomy, including enlargement of the soft palate, oropharyngeal stenosis, and central or obstructive apnea during rapid eye movement (REM) sleep, and an arterial oxygen saturation (SaO_2) of below 90% [9]. Brennick et al. reported that mutant New Zealand obese mice with metabolic syndrome and leptin resistance could be used to study the association between OSAS and obesity or metabolic syndrome [10]. Also, a variety of pig with congenital abnormal anatomy of the upper airway has been reported to be suitable for research in OSAS [11]. A Sprague-Dawley rat model that also develops spontaneous hypertension has been used to study sleep apnea [12]. Animal models have been developed using genetic modification, and include the monoamine oxidase A gene knockout mouse model that has been used to study the association between serotonin and OSAS [13]. Although spontaneous animal models of OSAS have shown changes of sleep apnea, the results from studies using these models have been inconsistent, and so increasing numbers of studies have begun to focus on the induced animal models of OSAS.

Induced animal models of OSAS can be divided into intermittent hypoxia models and airway obstruction models. The intermittent hypoxia animal model is easy to develop and can also simulate an important aspect of human OSAS, which is repeated hypoxia and re-oxygenation during sleep [14]. Depending on the species, previous studies with induced animal models of OSAS have used animals, such as piglets, equipped with ventilated masks or animals, such as mice, placed in a special chamber [15,16]. In these induced animal models of OSAS, the animals intermittently inhale inert gases, such as nitrogen, to cause hypoxia, and alternately breathe oxygen or air at the stage of re-oxygenation. Due to the influence of different gas volume and flow rate, intermittent hypoxia cycle duration, and the rise and fall rate of the fraction of inspiration of O_2 (FiO_2) have been shown to be important factors in the differences between different intermittent animal models of hypoxia [17].

However, previous studies that have included induced animal models of OSAS have not been able to simulate human OSAS during apnea due to upper airway occlusion against efforts to rapidly increase and change negative pressure in the chest. Therefore, studies have begun to establish animal models of airway obstruction using a variety of methods. A previously published study showed that tracheotomy, followed by the use of an endotracheal tube to apply intermittent airway pressure could be used [18]. Recent studies have shown that a similar procedure can be used in rats, but required more extensive surgery [18]. The bilateral injection of polyacrylamide hydrogel into the pharyngeal tissue and tongue base of rats induced upper airway stenosis and simulated the anatomical features of human OSAS [18]. However, tissue compatibility with the hydrogel was poor, which resulted in inflammatory nodules that blocked the upper airway [18]. However, sodium hyaluronate gel injection has been shown to have better tissue compatibility and has been used in several types of surgery, including cosmetic surgery [19,20].

Therefore, the aims of this study were to develop a rat model of OSAS using sodium hyaluronate gel injection and to validate the use of the model by investigating respiratory and cardiovascular physiological parameters and morphological changes by light microscopy and electron microscopy. The junction between the hard and soft palate of the Sprague-Dawley rat was previously shown to be the optimal injection site to produce OSAS without completely occluding the respiratory tract, resulting in apnea, intermittent hypoxia, and awakening during sleep, and inducing the same negative intrathoracic pressure changes that occur in human OSAS.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Material and Methods

Laboratory animals and reagents

Sprague-Dawley rats were purchased from the Animal Experimental Center of Jiangsu University. The selected rats were 3-months-old and with a similar weight (mean, 200±10 g), and were randomly assigned to the model group (n=30) and the control group (n=30). Sodium hyaluronate and other chemical reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) or a domestic provider in China, if not otherwise stated. The independent Ethics Committee of Jiangsu University approved the study before it began.

Surgical and injection procedures used in the rat model of obstructive sleep apnea syndrome (OSAS)

Rats in the control group were not treated. Rats in the OSAS model group were given an intraperitoneal injection of 0.2 ml quinolone. Following anesthesia, 0.1 ml of sodium hyaluronate gel (15 mg/mL) was injected into the junction between the soft and hard palate. The two groups of rats were reared separately with the same feeding conditions, to avoid the influence of other factors on the experimental results.

Monitoring of anesthesia and sleep respiration in the rat groups

Three months after modeling, the rats in both study groups were anesthetized in the supine position. Pressure sensors were fixed with a bandage on the abdomen of the rats. Biological measurements of respiration and pressure were collected by using MD3000 Biological Signal Acquisition and Processing System (Huaibei Zhenghua Biologic Apparatus Facilities Ltd., Huaibei, China). Before each rat was tested, the instrument was adjusted to zero, and the respiration curve during 1 min was measured continuously after respiration was stabilized. To better analyze the respiratory pressure patterns in the model group, 10 rats with confirmed OSAS were studied further. In the sleep state, the upper airway and abdominal respiratory pressure were studied in the 10 model rats.

Blood gas analysis

The rats were anesthetized, and the abdominal aorta was exposed and dissected. Arterial blood was collected with heparin as the anticoagulant, using a method that avoided mixing air oxygen with the arterial blood. The specimens were immediately tested, and the blood gases were analyzed using routine methods.

Histology of the tissues in the rat model of OSAS

The rats were euthanized by carotid artery bleeding and were dissected to collect the upper airway, lungs, blood vessels, heart, and soft palate. The tissues were fixed in 10% neutral buffered formalin, dehydrated in graded ethanol, paraffin-embedded and sectioned at 4 mm onto glass slides. Sections then stained routinely with hematoxylin and eosin (H&E) and with elastin van Giesen (EVG) to detect the elastic fibers. Tissue sections were examined using the HPIAS BX51 optical microscope (Olympus, Tokyo, Japan). The HPIAS-1000 High-Resolution Pathological Image and Word Analysis System (HPIAS-1000) (Wuhan Qianping Image Technology Co. Ltd., Wuhan, China) was used for quantitative comparative analysis of the tissue histology.

Transmission electron microscopy of the tissues in the rat model of OSAS

Tissues from the upper airway, lungs, blood vessels, heart, and soft palate were fixed with glutaraldehyde for 3 hours. Section were cut at 100–200 microns using a microtome. Selected sections were fixed in osmium tetroxide for 1 hour, then rinsed with phosphate-buffered saline (PBS) for 30 minutes. Gradient dehydration included rinsing the tissue sections with graded alcohol, and rinsed in 100% alcohol for 30 minutes, followed by acetone dehydration for 30 minutes. The tissue was placed in a 1: 1 mixture of acetone and embedding agent for 4–6 hours, followed by embedding at room temperature overnight. Tissues were then stained with uranyl acetate and lead citrate. The fixed and stained tissue sections were observed with a JEM-1011 electron microscopy (JEOL Ltd., Tokyo, Japan).

Statistical analysis

Data were shown as the mean ± standard deviation (SD). Statistical significance between the model group and the control group in each experiment was evaluated using the Student's t-test and using Predictive Analytics SoftWare (PASW) SPSS version 18 multilingual (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered as statistically significant.

Results

Airway obstruction induced disorder breathing in the rat model of obstructive sleep apnea syndrome (OSAS)

Under anesthesia, the rats in control group showed uniform respiratory amplitude, the respiratory rate was 50–60 breaths per min, the abdominal respiratory pressure was –3–4 Pa, and the heart rate was 200–240 beats per min, with sinus rhythm. The results of cardiac testing showed that the

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

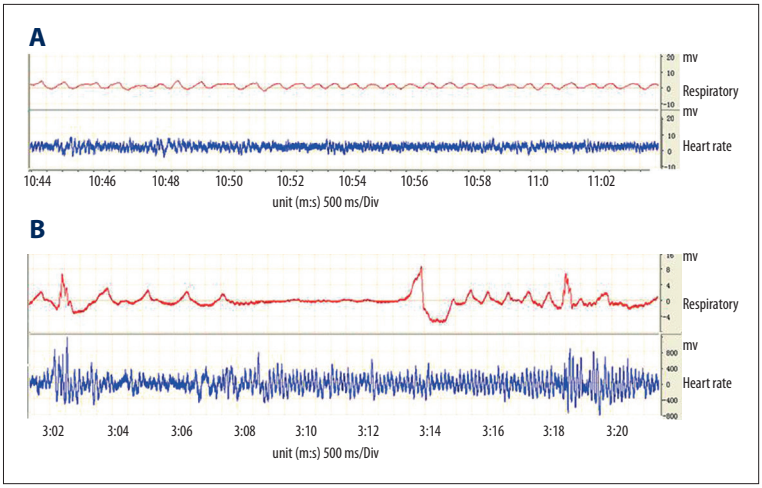

Figure 1. Diagram of the respiratory pressure and heart rate in the rat control group and the rat model group. (**A**) Respiratory pressure and heart rate in the rat control group. (**B**) Respiratory pressure and heart rate in the rat model of obstructive sleep apnea syndrome (OSAS).

Table 1. Comparison of blood oxygen results between the rats in the model group and the control group.

Group	Oxygen partial pressure mmHg	Oxygen content mmol/L	Oxygen saturation %	Oxygenated hemoglobin %	Oxygen capacity mmol/L
Model group (n=30)	85.0±3.4	8.7±1.7	84.0±3.5	83.8±2.9	10.2±2.1
Control group (n=30)	102.0±5.6	10.2±1.6	94.0±2.7	94.0±2.4	10.6±1.4
P-value	0.01	0.02	0.02	0.01	0.58

electrocardiography (ECG) waves were regular with regular morphology and rhythm, and the amplitude of the R wave was no more than 1 mV (Figure 1A).

The model rats showed lethargy and mental fatigue, accompanied by snoring during sleep. Under anesthesia, the model group had irregular breathing, and the negative pressure duration was higher than the positive pressure duration. During breathing, frequent apnea events occur with a frequency of 4–10 events per hour. A large breathing movement followed each apnea event. Before the onset of the apnea event, the rats were in sinus rhythm with a regular rhythm of 300–360/min and the maximum amplitude of R wave was less than 200 mV. During the onset of hypopnea events, fast and uneven QRS waves were visible, and sinus frequency was 450–500/min, reduced P-waves, and an R-wave amplitude of up to 800 mV, as shown in Figure 1B.

Blood gas analysis in the rat model of OSAS

Upper airway collapse severely affected the normal breathing of rats, especially the exchange of oxygen. Blood gas analysis showed differences in blood oxygen content between the control group and the model group (Table 1). The oxygen partial pressure, oxygen content, and oxygen saturation in the model group were significantly lower compared with those in the control group ($P<0.05$). The two indexes of oxygen partial pressure, oxygen concentration ratio and the arterial-alveolar oxygen tension ratio were lower in the model group compared with the control group, but the alveolar-arterial oxygen tension and respiratory index were significantly higher compared with the control group.

Changes in the upper airway wall in the rat model of OSAS

After construction of the rat upper airway stenosis model, the recurrent respiratory changes were consistent with OSAS, which resulted in pathological changes in the respiratory system and the collapse of the upper airway tissue.

Light microscopy and electron microscopy (Figure 2), showed that the surface of the trachea was covered by complex columnar ciliated epithelial cells. The subcutaneous mucosa was mildly edematous, and the surrounding tracheal glands (serous glands) were increased, with retained secretion.

Histological changes in the heart in the rat model of OSAS

Reduced blood oxygen can affect the heart, and so after the rats were anesthetized, the heart rate and heart rate variability (HRV) parameters were compared, including the standard deviation of the normal-to-normal (SDNN) intervals, the

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

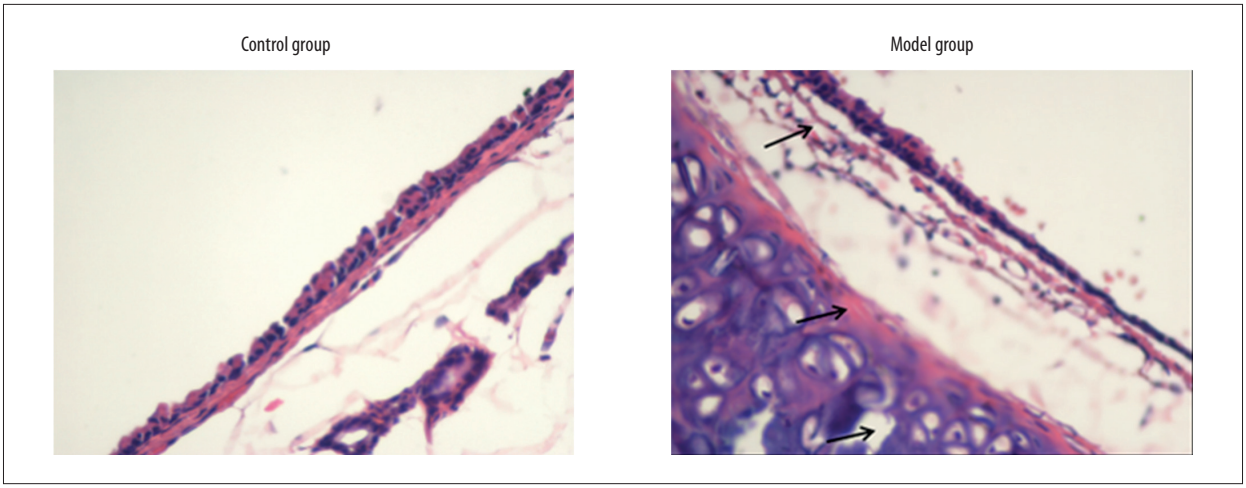

Figure 2. Photomicrographs of the histology of the structure of the tracheal wall of the rats in the model group. Histology of the epithelium of the bronchial mucosa in the rat model of obstructive sleep apnea syndrome (OSAS) shows apoptotic cells and loss of the epithelium, and some epithelial cells are atypical (black arrowhead). Hematoxylin and eosin (H&E). Magnification ×400.

Table 2. Comparison of heart rate and heart rate variation parameters between rats in the model group and control group during sleep.

Group	SDNN/ms	PNN 50%	LF/ms^2	HF/ms^2
Model group (n=30)	45±7	1.2±0.5	73.4±6.2	101.7±8.6
Control group (n=30)	21±4	0.5±0.2	61.2±5.7	49.5±7.4
P-value	0.007	0.024	0.046	0.003

Heart rate variability (HRV) parameters, include the standard deviation of the normal-to-normal (SDNN) intervals, the proportion of the normal-to-normal (PNN) intervals, low-frequency band (LF), and high-frequency band (HF).

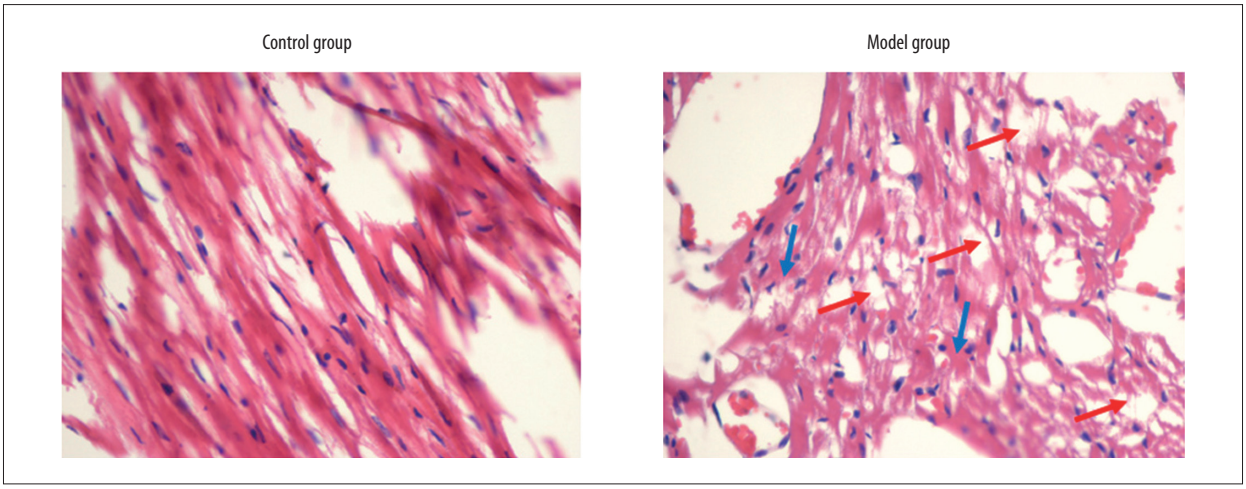

Figure 3. Photomicrographs of the histology of the myocardium of the rats in the model group. Histology of the myocardium in the rat model of obstructive sleep apnea syndrome (OSAS) shows disarray of cardiac myocytes and some of the cardiac myocytes are vacuolated and show degenerative change and myonecrosis (red arrow). Some cardiac myocyte myofibrils are concentrated in the cytoplasm with loss of the transverse lines, and coagulative necrosis (blue arrow). Hematoxylin and eosin (H&E). Magnification ×400.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

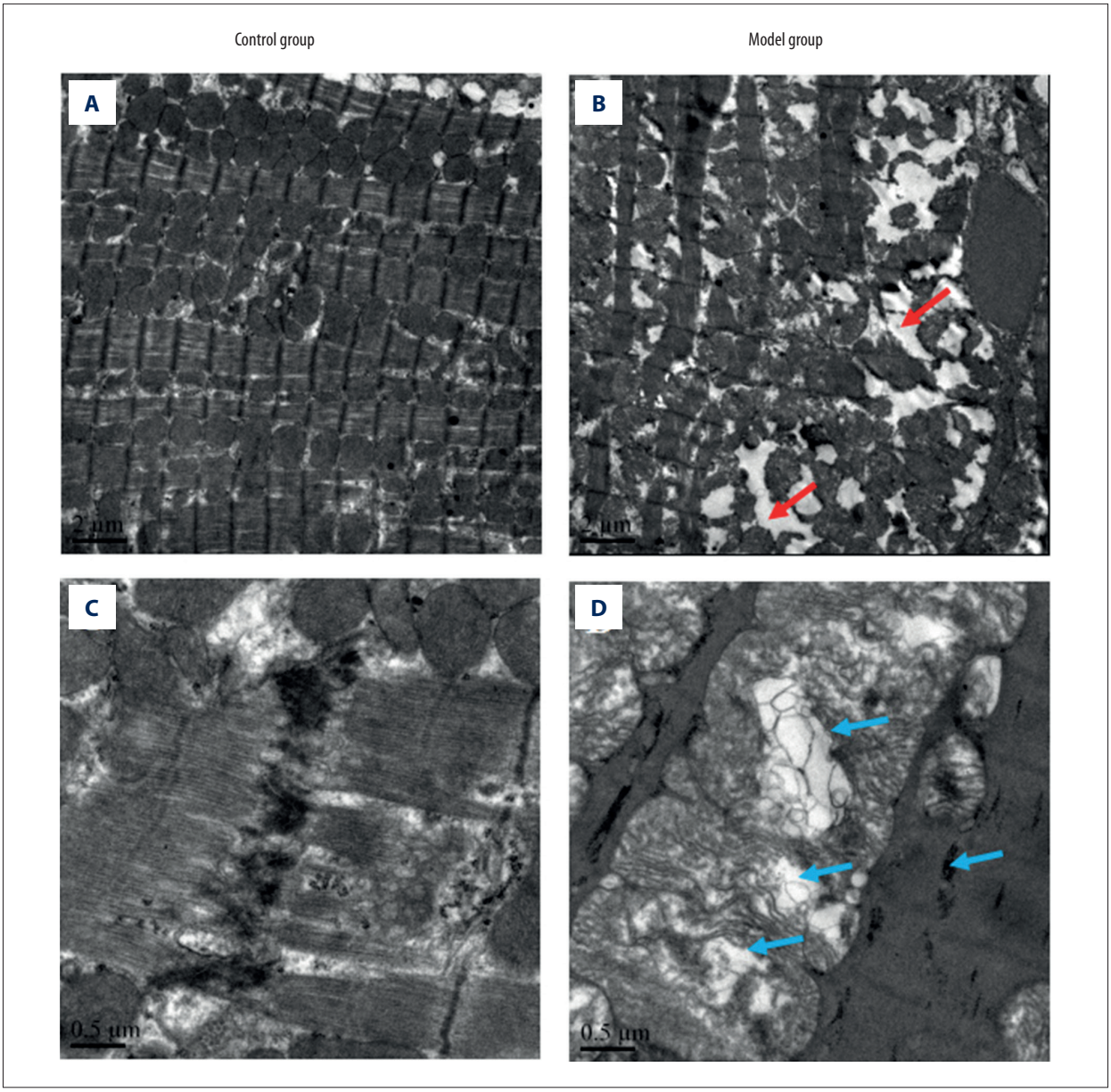

Figure 4. Transmission electron micrographs of the ultrastructure of the myocardium of the rats in the model group. (**A, B**) Images of the ultrastructure of the cardiac myocytes in the rat model of obstructive sleep apnea syndrome (OSAS) shows an irregular arrangement of cardiac muscle fibers, swollen cardiac myocytes, and the focal loss of filaments (red arrows). Magnification ×5,000. (**C, D**) In some regions the myofibril structure is unclear, and the density is increased, which was due to sarcoplasmic coagulation necrosis. The mitochondrial cristae (folds in the inner membrane) contain breaks and vacuolization (blue arrows). Magnification × 20,000.

proportion of the normal-to-normal (PNN) intervals, low-frequency band (LF), and high-frequency band (HF). Cardiac function of the model group was significantly impaired when compared with the control group, as shown in Table 2.

To confirm these effects of OSAS on myocardial structure, light microscopy and electron microscopy changes were found in the heart, as shown in Figure 3. The rats in the OSAS model group showed a disorderly arrangement of cardiac myocytes, with vacuolar degeneration, and some cardiac myocytes showed condensation and coagulative necrosis with diffuse swelling, sarcoplasmic lysis, unclear transverse striations, congested interstitial vessels, but no inflammatory cell infiltrates (Figure 3). These results indicated the OSAS could seriously affect the physiological function of the heart. The electron microscopy changes seen in the cardiac tissue from the rats in the model

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

group are shown in Figure 4. There was diffuse myosin disintegration, cytoplasmic vacuoles, and the myofibril structure was unclear, with sarcoplasmic coagulation necrosis, damage to the mitochondrial cristae, which indicated myocardial myofibril damage.

Discussion

Obstructive sleep apnea syndrome (OSAS) is a form of sleep-disordered breathing that has serious clinical consequences and can result in anatomical changes in the lungs, heart and other major organs [1]. Imaging studies have identified pharyngeal anatomical abnormalities in patients with OSAS [21]. Previous studies have shown that a narrow pharyngeal airway and anatomical changes of the pharyngeal lumen were associated with pharyngeal collapse during sleep, which is the main cause of OSAS [22]. Pharyngeal structural abnormalities that contribute to upper airway obstruction and collapse involve the dilator muscles of the soft palate, lateral pharyngeal wall, and the epiglottis [23].

A previous rat model of OSAS used multiple injections of the oropharynx with sodium hyaluronate [24]. This method was easy to use to create the rat model, but resulted in acute laryngeal obstruction and post-traumatic infection after multiple injections, and was considered to be an excessive model of acute hypoxia with a low success rate [24]. However, in the present study, the creation of the rat model of OSAS with the use of sodium hyaluronate injections under the submucosa at the junction of the hard and soft palate resulted in stenosis of the rat airway, and the model was successful without complications such as infection or nodule formation. Also, the rat model of OSAS resulted in respiratory characteristics that were similar to human OSAS, which indicated the hypoventilation caused by collapse of the upper airway might be the main cause of OSAS. To investigate the effect of OSAS on respiratory function, the tracheal wall structure and upper airway of rats in the OSAS model group was shown to collapse, which seriously affected the breathing rhythm of the model group, resulting in reduced blood oxygen levels. Chronic hypoxemia combined with hypercapnia might explain the association between OSAS and the occurrence of cardiovascular disease.

In the present study, blood gas measurements showed that in the OSAS rat model, oxygen saturation, oxygenated hemoglobin, and oxygen capacity were reduced when compared with the control group. The resulting hypoxia resulted in similar symptoms to those found in human OSAS, and long-term hypoventilation would explain the chronic respiratory and circulatory diseases associated with OSAS clinically.

The cardiac effects of OSAS in humans have shown to result in changes in cardiac morphology, that were associated with changes in cardiac function [25]. Cardiac myocytes in patients with OSAS have been shown to become disorderly, with vacuolar degeneration, indicating lack of oxygen due to myocardial ischemia which may explain the clinical association between OSAS and cardiac disease, including heart failure. These cardiac morphological findings were also present in the rate model of OSAS, which showed variability in the heart rate and changes in the cardiac indices when compared with the rats in the normal control group. Therefore, the rat model of OSAS developed in this study appeared to provide a good animal model for the study of systemic pathological changes associated with OSAS.

In conclusion, in a rat model of OSAS that used the injection of sodium hyaluronate gel into the upper airway, significant alteration in the mechanical characteristics of the upper airway included airway collapse, which resulted in sleep-disordered breathing. Morphological changes observed by light microscopy and electron microscopy showed that changes in the cardiac structure of rats in the model were early pathological indicators of OSAS, and these cardiac changes require further study. This animal model appeared to closely replicate the changes described clinically in OSAS and might provide a useful animal model for future studies on the pathogenesis of OSAS.

Conclusions

A rat model of obstructive sleep apnea syndrome (OSAS) was developed using injection of sodium hyaluronate gel at the junction of the hard and soft palate, resulting in upper airway collapse and shear stress on pharyngeal tissues. Rats in the OSAS model developed cardiac changes that were consistent with hypoxia. It is hoped that this animal model may be used for future studies on OSAS

Conflict of interest

None.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

References:

1. Xie J, Yu W, Wan Z et al: Correlation analysis between obstructive sleep apnea syndrome (OSAS) and heart rate variability. Iran J Public Health, 2017; 46(11): 1502–11
2. Wali SO, Abalkhail B, Krayem A: Prevalence and risk factors of obstructive sleep apnea syndrome in a Saudi Arabian population. Ann Thorac Med, 2017; 12(2): 88–94
3. Maekawa M, Shiomi T: [Sleep apnea syndrome (SAS) and ischemic heart disease (IHD).] Nihon Rinsho, 2000; 58(8): 1702–6 [in Japanese]
4. Borys JM, Boute D: Obstructive sleep apnea syndrome: A frequent complication of obesity. Biomed Pharmacother, 1994; 48(3–4): 137–41
5. Zamarron C, García Paz V, Riveiro A: Obstructive sleep apnea syndrome is a systemic disease. Current evidence. Eur J Intern Med, 2008; 19(6): 390–98
6. Jin F, Liu J, Zhang X et al: Effect of continuous positive airway pressure therapy on inflammatory cytokines and atherosclerosis in patients with obstructive sleep apnea syndrome. Mol Med Rep, 2017; 16(5): 6334–39
7. Can M, Uygur F, Tanrıverdi H et al: Effect of continuous positive airway pressure (CPAP) therapy on IL-23 in patients with obstructive sleep apnea. Immunol Res, 2016; 64(5–6): 1179–84
8. Yang L, Hu Y, Zhang X: [An animal model of obstructive sleep apnea syndrome.] Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2012; 26(12): 569–72 [in Chinese]
9. Petrof BJ, Pack AI, Kelly AM et al: Pharyngeal myopathy of loaded upper airway in dogs with sleep apnea. J Appl Physiol, 1994; 76(4): 1746–52
10. Brennick MJ, Kuna ST, Pickup S et al: Respiratory modulation of the pharyngeal airway in lean and obese mice. Respir Physiol Neurobiol, 2011; 175(2): 296–302
11. Powell NB, Riley RW, Troell RJ et al: Radiofrequency volumetric reduction of the tongue. A porcine pilot study for the treatment of obstructive sleep apnea syndrome. Chest, 1997; 111(5): 1348–55
12. Liu K, Liu XS, Xiao L et al: NADPH oxidase activation: A mechanism of erectile dysfunction in a rat model of sleep apnea. J Androl, 2012; 33(6): 1186–98
13. Real C, Popa D, Seif I et al: Sleep apneas are increased in mice lacking monoamine oxidase A. Sleep, 2007; 30(10): 1295–302
14. Davis EM, O'Donnell CP: Rodent models of sleep apnea. Respir Physiol Neurobiol, 2013; 188(3): 355–61
15. Li B, Zhao LM, Xiu QY et al: An experimental study on the mini pig model of obstructive sleep apnea syndrome. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi, 2005; 22(3): 565–69
16. Seo YJ, Ju HM, Lee SH et al: Damage of inner ear sensory hair cells via mitochondrial loss in a murine model of sleep apnea with chronic intermittent hypoxia. Sleep, 2017; 40(9)
17. Lee EJ, Woodske ME, Zou B, O'Donnell CP: Dynamic arterial blood gas analysis in conscious, unrestrained C57BL/6J mice during exposure to intermittent hypoxia. J Appl Physiol, 2009; 107(1): 290–94
18. Tang S, Zhou XF, Hu K: Advances in animal models of obstructive sleep apnea. Chin J Tuberc Respir Dis, 2016; 39(1): 54–58
19. Zhou ZQ, Sui ZF, Liu C: Clinical trial on safety and efficacy of an injectable cross-linked sodium hyaluronate gel for moderate and severe nasolabial groove. J Practical Dermatol, 2016; 9(1): 20–23
20. Hu JC, Fan DJ, Lin XT et al: Safety and efficacy of sodium hyaluronate gel and chitosan in preventing postoperative peristomal adhesions after defunctioning enterostomy. Medicine, 2015; 94(51): e2354
21. Coxson HO, Eastwood PR, Williamson JP, Sin DD: Phenotyping airway disease with optical coherence tomography. Respirology, 2011; 16(1): 34–43
22. Segal Y, Malhotra A, Pillar G: Upper airway length may be associated with the severity of obstructive sleep apnea syndrome. Sleep Breath, 2008; 12(4): 311–16
23. Morrison DL, Launois SH, Isono S et al: Pharyngeal narrowing and closing pressures in patients with obstructive sleep apnea. Am Rev Respir Dis, 1993; 148(3): 606–11
24. Song KY, Xu P, Shi YH: [Experimental study on rat OSAS model.] Acta Academiae Medicinae Zunyi, 2012; 3: 189–92 [in Chinese]
25. Bodez D, Damy T, Soulat-Dufour L et al: Consequences of obstructive sleep apnoea syndrome on left ventricular geometry and diastolic function. Arch Cardiovasc Dis, 2016; 109(8–9): 494–503

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]