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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

The reduction of apnea–hypopnea duration ameliorates endothelial dysfunction, vascular inflammation, and systemic hypertension in a rat model of obstructive sleep apnea

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Abstract

Purpose We aimed to investigate the effect of obstructive sleep apnea (OSA) and apnea–hypopnea duration on endothelial, ventricular function, blood pressure, and inflammation in a rat model.

Methods We established a novel rat model of OSA. Wistar rats were randomized to six groups according to 4-week different treatments: (1) OSA (apnea for 60 s in a 90-s window of breathing [60 s/90 s] with anesthesia), (2) OSA 30 s/90 s with anesthesia, (3) partial recovery (60 s/90 s for 2 weeks, followed by 15 s/90 s for 2 weeks with anesthesia), (4) complete recovery (60 s/90 s for 2 weeks with anesthesia, and then normal breathing for 2 weeks), (5) sham (normal breathing in the device with anesthesia), and (6) control group (normal breathing, normal cage, no anesthesia). We recorded blood pressure, endothelial function, left ventricular function, and inflammation at different time points.

Results Vascular inflammation and endothelial dysfunction occurred in OSA models. More systemic inflammatory and endothelial dysfunction were observed in longer apnea–hypopnea duration group and they were reversed in both partial and complete recovery groups. Left ventricular weight/body weight ratio was significantly higher in the OSA (60s/90s) group than complete recovery, sham, and control groups, which remained unchanged in partial recovery group ($p < 0.05$).

Conclusions Longer apnea–hypopnea duration is related to more systemic inflammatory and endothelial dysfunction, and hypertension and cardiac remodeling. These can be reversed after a period of recovery, which indicates that time parameters for assessing OSA, such as apnea–hypopnea duration, should be considered instead of apnea–hypopnea index only.

Keywords Obstructive sleep apnea · Animal model · Apnea–hypopnea duration · Hypertension

Introduction

Obstructive sleep apnea (OSA) is a common form of sleep-disordered breathing [1], and it is characterized by repeatedly complete or partial obstruction of the upper airway during sleep which leads to cardiovascular sequelae [2]. The severity of OSA and treatment effects have been generally assessed by the apnea–hypopnea index (AHI), an index mainly counting the frequency of apnea–hypopnea episode without combining the duration of breathing cessation and related oxygen desaturation. Recent studies [3, 4] proposed that OSA parameters should contain the duration and desaturation areas of breathing events. They found that even with similar AHI in OSA, target organ impairment and all-cause mortality were diverse. This might be related to longer apnea–hypopnea duration and lower desaturation [5, 6]. Another interesting phenomenon is that nasal surgery can reduce the duration of

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apnea–hypopnea and improve the quality of life and daytime sleepiness, despite an unchanged AHI [7–9].

Bostanci et al. [10] and Asha'Ari et al. [11] also proposed that the apnea–hypopnea duration instead of the AHI is a better polysomnographic parameter that is more accurate for assessing the severity of OSA.

Furthermore, the current target of OSA treatment and prevention of systemic complications are to reduce AHI. Surgical studies showed that blood pressure (BP) was improved by upper airway operation though AHI and body mass index were unchanged [12]. In our previous study [13], we found that the mean apnea–hypopnea duration (but not the AHI) was associated with worse hypertension in OSA. Reduction of the apnea–hypopnea duration irrespective of any changes in AHI (partial recovery) may be more useful for OSA-induced cardiovascular complications.

To test this hypothesis, we designed a rat model of OSA to investigate whether longer apnea–hypopnea duration would induce worse systemic inflammation, endothelial dysfunction, and subsequent hypertension as well as cardiac remodeling. Secondly, we observed if partial recovery could reduce hypertension induced by OSA and whether it would be comparable to complete recovery.

Methods

OSA model

We created a rat model by constructing a device (Fig. 1) that consisted of a body container, head cover, air bag, piston, and controller. When the air bags were inflated, the space between the body container and head cover was constricted, which simulated upper airway obstruction. A vent for the rat's nostrils allowed air flow and was manipulated by the controller and piston. To test this device, Wistar rats were sedated and apnea was induced by the controller. Spontaneous breathing was performed under anesthesia for various durations of time (see below). Blood oxygen saturation of the tail microcirculation (O2C; LEA, Giessen, Germany) was monitored 1 mm away from the epidermis. Bilateral diaphragmatic muscle electromyography was performed by insertion of a pair of stainless-steel electrodes into the medial costal region of the diaphragm [14] after intramuscular injection with ketamine (90 mg/kg) and xylazine (10 mg/kg). The loose ends were tunneled subcutaneously to the dorsum of the rat, externalized, and fixed for use during electromyographic recording sessions. Externalized diaphragm electrodes were connected with gold pin connectors (Compumedics, Victoria, Australia) to ChinL and ChinR signal interface (EMBLA N7000; Middleton, WI, USA). The device was set between 35 and 37 °C. A video of the actual operation of the model is shown in the online resource.

A flow diagram of the experiment is shown in Fig. 2. Thirty-six 9-week-old male Wistar rats were randomized to six groups. Four experimental groups were studied as follows: (1) OSA was mimicked by closing the vent (apnea) for 60 s, followed by 30-s recovery periods (AHI = 40/h) under anesthesia for 3 h/day for 4 weeks (OSA [60 s/90 s], $n = 6$); (2) OSA was mimicked by closing the vent (apnea) for 30 s, followed by 60-s recovery periods (AHI = 40/h) under anesthesia for 3 h/day for 4 weeks (OSA [30 s/90 s], $n = 6$); (3) partial recovery ($n = 6$), which was the same as in the OSA (60 s/90 s) group for 2 weeks, followed by OSA (15 s/90 s) for the next 2 weeks with the AHI unchanged (AHI = 40/h); and (4) complete recovery ($n = 6$), with OSA (60 s/90 s) for 2 weeks followed by normal breathing. The conversion point of the intervention condition was set at the end of the second week because rats in the OSA (60 s/90 s) group showed a significant increase in BP in 2 weeks in the pre-experiment. Two control groups were studied as follows: (1) sham rats ($n = 6$) were sedated and placed in the device without closing the vent under anesthesia for 3 h/day for 4 weeks; and (2) the control group ($n = 6$) which included rats in normal cages that did not undergo any procedures or anesthesia. Anesthesia was 2% pentobarbital sodium solution. The initial dose of anesthesia was 25 mg/kg intraperitoneal injection. If the rat could not sleep peacefully, then this dose was increased by 20% until the rat did not respond to a shallow stimulus, which simulated the state of sleep. If the rat was agitated during the modeling process, an additional 20% of the initial dose was added. No rats showed signs of complications of anesthesia or complications from the device. Rats were sacrificed at the end of the study and serum and tissues were obtained for analyses (see below). All procedures were approved by the Animal Care and Use Committee of Capital Medical University (AEEI-2015-107). The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No.85-23, revised in 1996).

Cardiac remodeling/blood pressure measurement

Blood pressure measures were taken on days 15 and 30 by a tail-cuff system (BP-2010, Softron, Beijing, China). Cardiac function was evaluated by echocardiography using Vevo 2100 High-Resolution Imaging System (VisualSonics Inc., Toronto, Canada).

Vascular relaxation

Rat thoracic aortas were excised and placed in Petri dishes that contained Krebs-Henseleit solution [15]. Adherent connective tissue was removed, and thoracic aortas were cut into rings 4 mm in length. Each vascular ring was placed in a tissue chamber (10 mL) with Krebs-Henseleit solution bubbled

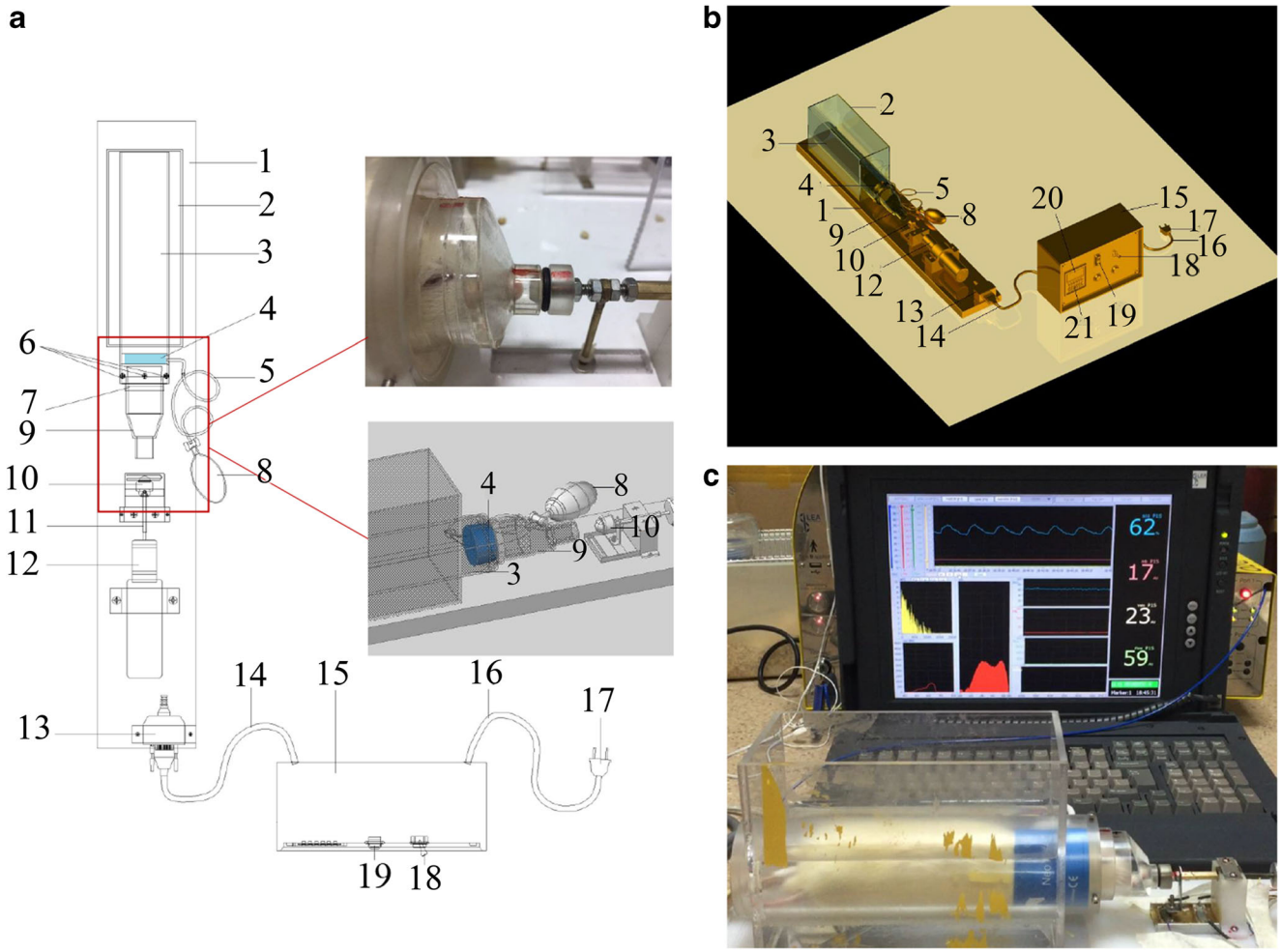


Fig. 1 OSA device. **a**, **b** Design drawing of OSA device. 1. Pedestal; 2. water tank; 3. rat body container; 4. air bag; 5. air pipe; 6. fixator; 7. pontes; 8. pump; 9. head cover; 10. piston; 11. piston rod; 12. motor; 13. USB; 14. USB cable; 15. controller; 16. power line; 17. plug; 18. pause key; 19. switch; 20. viewing screen; 21. control panel; **c** operating diagram

(95% O_2 and 5% CO_2). Rings were mounted isometrically under a previously determined optimum resting tension (15.0 mn). KCl (60 mmol/L) was added to evaluate the vitality of the preparations. After rinsing for three times with Krebs-Henseleit solution and a relaxation time of 40 min, the rings were precontracted with phenylephrine. When the contractile response to phenylephrine reached a plateau and stabilized for 5 min, the relaxation responses to acetylcholine (3 nmol/L,

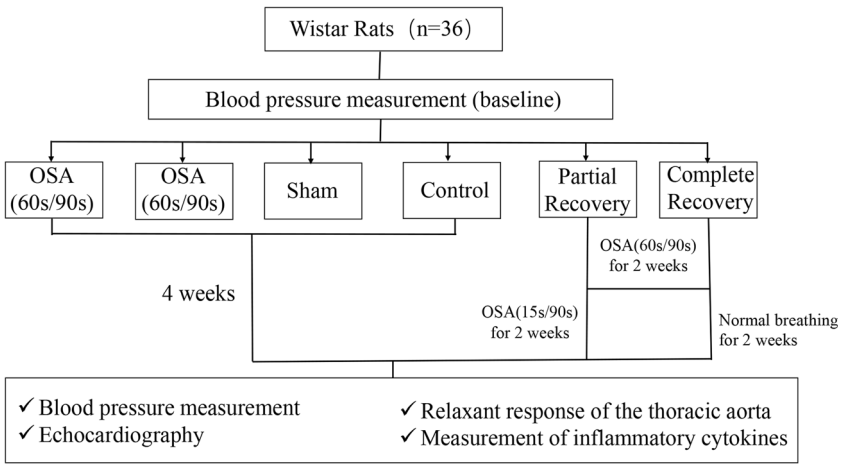


Fig. 2 The flow diagram of experiment

10 nmol/L, 30 nmol/L, 100 nmol/L, 300 nmol/L, 1 μmol/L, 3 μmol/L, 10 μmol/L in sequence) were determined. Changes in isometric force were recorded by myograph (Danish Myo Technology, Aarhus, Denmark). Acetylcholine (ACh)-induced endothelium-dependent relaxations was examined. All drugs and chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA). Unless otherwise noted, all other reagents were from Sigma-Aldrich Company.

Sample preparation and measurement of inflammatory cytokines

Proteins from the thoracic aorta and blood serum were isolated using standard procedures. We designed a custom multiplex panel of 13 Luminex assays to detect relevant cytokines. This panel was designed to encompass the main inflammatory pathways, including chemokine (C-X-C motif) ligand 2, granulocyte-macrophage colony stimulating factor, intercellular cell adhesion molecule-1 (ICAM-1), Interferon-gamma, interleukin-1 beta (IL-1β), IL-10, IL-2, IL-4, IL-6, L-selectin, tissue inhibitor of metalloproteinase-1 (TIMP-1), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor.

Luminex assays (LXSARM; R&D Systems) were performed according to the manufacturer's recommendations using a custom Magnetic Luminex Screening Assay with a Rat Premixed Multi-Analyte Kit (Kit Lot Number L121796; R&D Systems).

Statistical analysis

Variables are presented as mean ± SD. Concentration-response curves were analyzed (GraphPad Prism software, version 5.0, La Jolla, CA, USA). Group comparisons were done by one-way ANOVA with Bonferroni correction. Repeated measured analysis in a general linear model and the independent sample *t* test were used to compare data between days 15 and 30. Two-tailed *p* values < 0.05 were considered significant. All analyses were performed using SPSS 22.0 software for Windows (SPSS Inc., Armonk, NY, USA).

Results

OSA model

Rats that were exposed to the device showed severe OSA with regular intermittent hypoxemia (Fig. 3a). In three different states of OSA (OSA [60 s/90 s], OSA [30 s/90 s], OSA [15 s/90 s]), the mean oxygen desaturation was 13.8 ± 0.8%, 6.8 ± 0.8%, and 4.5 ± 0.5%, respectively. Concurrent respiratory efforts were detected by EMGdi during the apnea (Fig. 3c). These data indicated that this model reasonably reproduced the main measures of OSA, including apnea-caused chronic intermittent hypoxia with concurrent respiratory efforts in OSA in these rats. The state of sedative anesthesia simulated sleep.

Changes in blood pressure and echocardiographic parameters

Blood pressure data are shown in Fig. 4 and Supplementary Table 1. After 4 weeks of modeling, blood pressure in the OSA groups was significantly higher compared with baseline, and the sham and control groups (all $p < 0.05$) (Fig. 4a–c), especially in the longer OSA (60 s/90 s) group. Increased blood pressure was the most common cardiovascular complication of OSA. After 2 weeks, systolic BP and mean BP were significantly higher in rats in the OSA (60 s/90 s) group compared with those in the OSA (30 s/90 s) group and the sham and control groups (Fig. 4a–c). In the complete recovery group, after 2 weeks of recovery from OSA (60 s/90 s), SBP was significantly reduced (from 126.1 ± 7.1 mmHg [days 15] to 116.7 ± 2.6 mmHg [days 30], $p = 0.012$), but without intra-group difference with sham and control groups (Fig. 4a). In the partial recovery group, after 2 weeks of improvement, systolic BP and mean BP were reduced (Supplementary Table 1), similar to the control group, but significantly higher than the sham group (Fig. 4). The original data are included in the supplemental materials.

Left ventricular weight/body weight ratio was significantly higher in the OSA (60 s/90 s) group (OSA [60 s/90 s]: 2.88 ± 0.24 mg/g; complete recovery 2.56 ± 0.20 mg/g; sham: 2.49 ± 0.34 mg/g; control: 2.47 ± 0.37 mg/g; $p < 0.05$ vs. complete recovery, sham, and control groups). Other echocardiographic parameters were similar among groups at the end of the study (Supplementary Table 2).

Vascular relaxation

Endothelium-dependent relaxations were significantly impaired in the thoracic aortas in the OSA 60 s/90 s and 30 s/90 s groups (Fig. 4d). In the partial recovery and complete recovery groups, endothelium-dependent relaxation was improved. (Fig. 4d).

Inflammatory cytokines

ICAM-1 levels in serum and the thoracic aorta were significantly higher in the OSA 60 s/90 s and 30 s/90 s groups than the sham and control groups (Figs. 5a and 6a). TIMP-1 levels in serum and the thoracic aorta was the highest in the OSA 60 s/90 s group (Figs. 5b and 6b).

Other cytokines were elevated in either serum or thoracic aorta in OSA groups (Figs. 5 and 6, Supplementary Table 3).

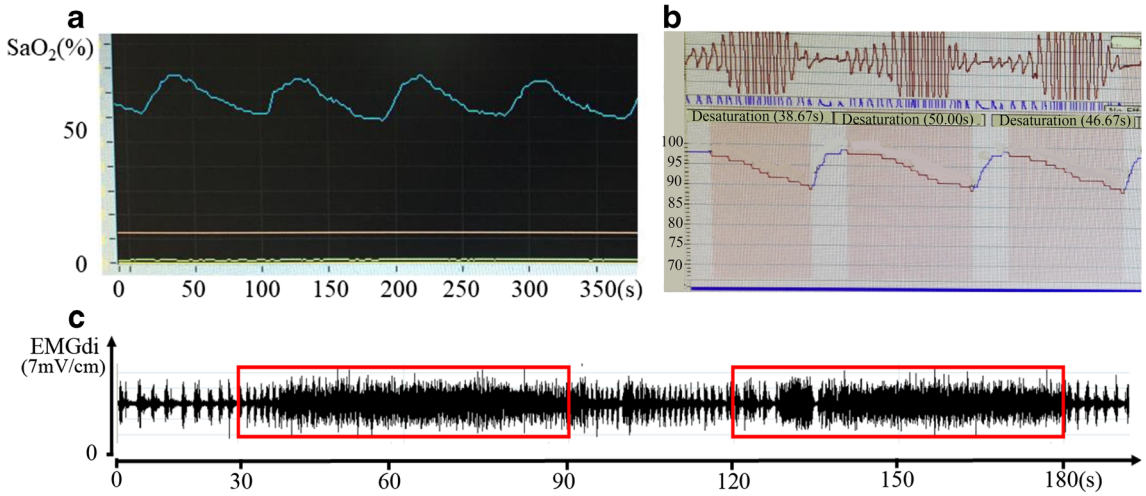


Fig. 3 OSA model results. **a** Intermittent hypoxemia of OSA rats; **b** blood oxygen change waveform of severe OSA patient; **c** EMGdi of OSA rats. EMGdi, diaphragmatic muscle electromyography

TIMP-1 level was markedly reduced in serum and thoracic aorta in the complete recovery and partial recovery groups compared with the OSA (60 s/90 s) group (Figs. 5b and 6b). Levels of other inflammatory cytokines in the thoracic aorta and serum were lower by varying degrees in the complete recovery and partial recovery groups compared with the sham and control groups, but these differences were not significant (Figs. 5 and 6, Supplementary Table 3).

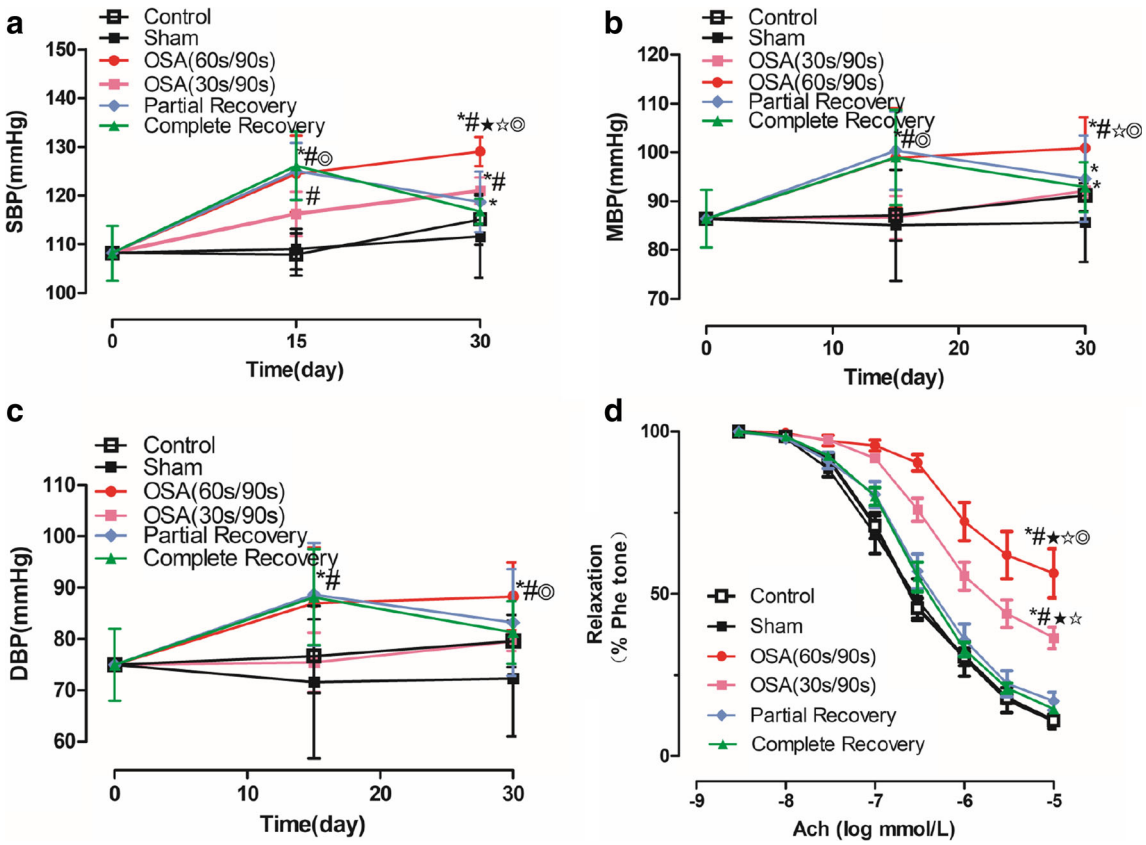


Fig. 4 Blood pressure change during 4 weeks and EDRs impairment in thoracic aortas. **a** SBP change in the six groups; **b** MBP change in the six groups; **c** DBP change in the six groups; **d** EDRs impairment in OSA rats' thoracic aortas. $^{*}P < 0.05$ vs. sham, $^{\#}P < 0.05$ vs. control, $^{\bigstar}P < 0.05$ vs. partial recovery, $^{\star}P < 0.05$ vs. complete recovery, $^{\circledcirc}P < 0.05$ vs. OSA (30 s/90 s). EDRs, endothelium-dependent relaxations; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure

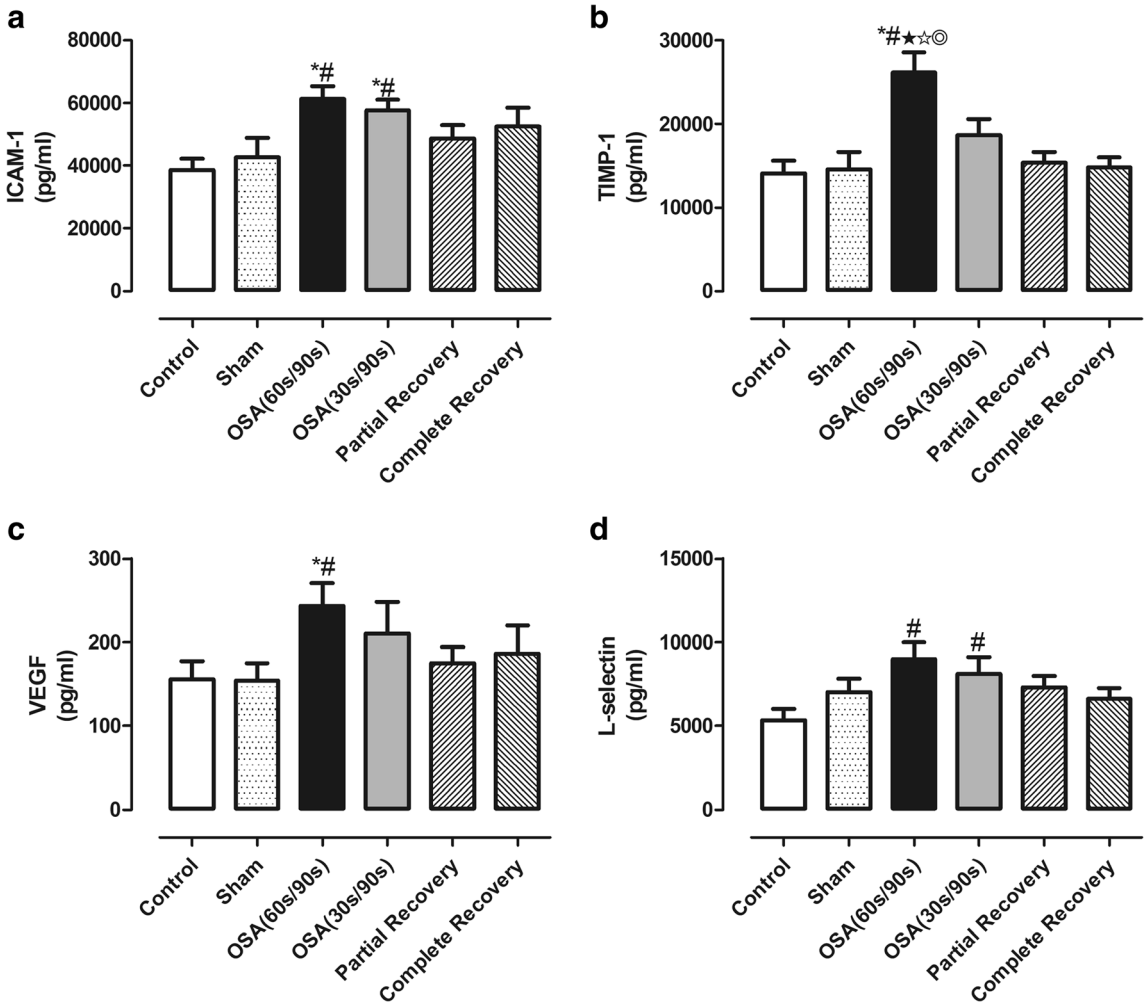


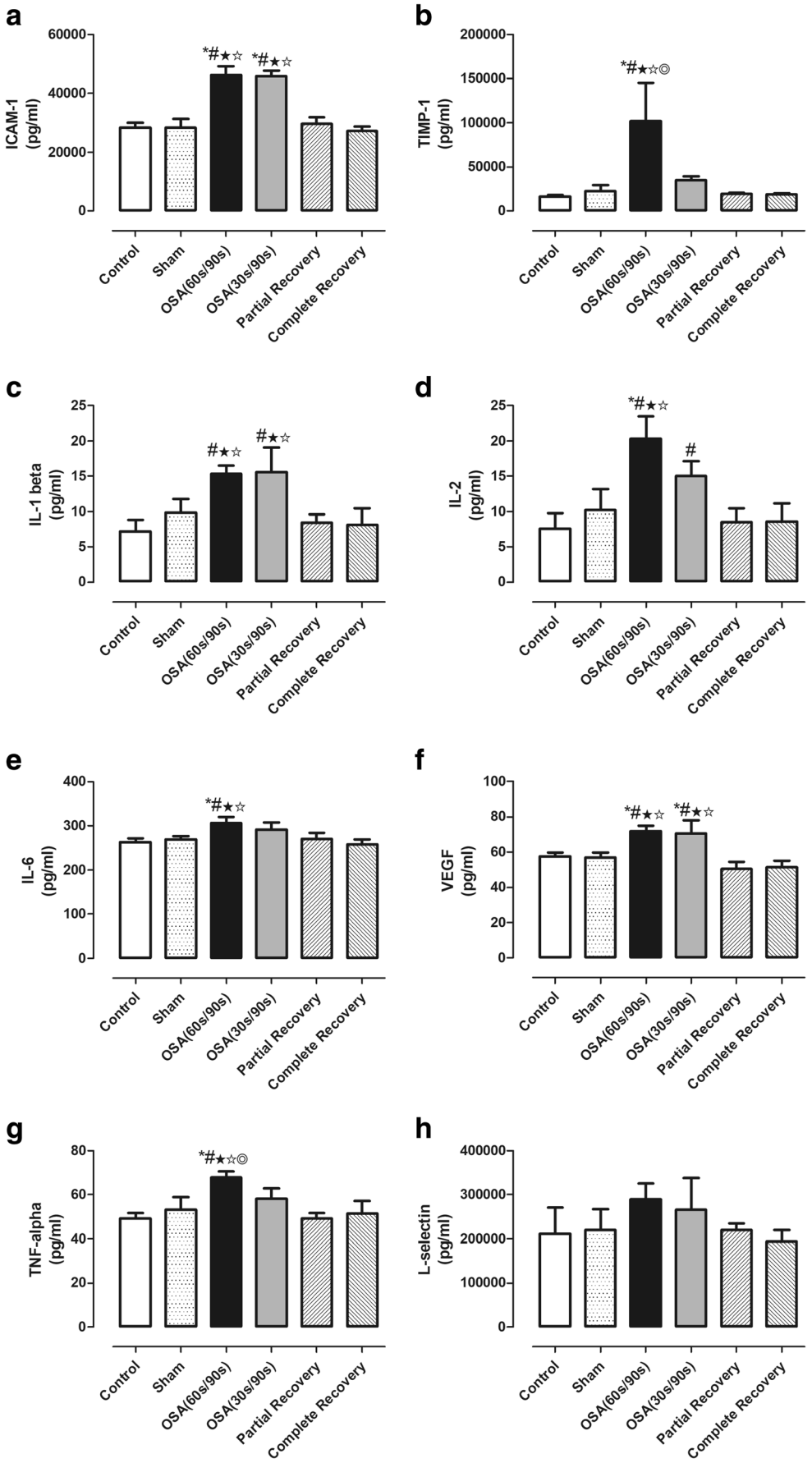
Fig. 5 Level of inflammatory cytokines of thoracic aorta. **a** ICAM-1 in thoracic aorta increased in OSA for 4 weeks and reversed by complete recovery or partial recovery; **b** TIMP-1 in thoracic aorta increased in OSA (60 s/90 s) for 4 weeks and reversed by complete recovery or partial recovery; **c** VEGF in thoracic aorta increased in OSA (60 s/90 s) for 4 weeks and reversed by complete recovery or partial recovery; **d** L-selectin in thoracic aorta increased in OSA for 4 weeks and reversed by complete recovery or partial recovery. $^{*}P < 0.05$ vs. sham, $^{\#}P < 0.05$ vs. control, $^{\bigstar}P < 0.05$ vs. partial recovery, $^{\star}P < 0.05$ vs. complete recovery, $^{\circledcirc}P < 0.05$ vs. OSA (30 s/90 s). ICAM-1, intercellular cell adhesion molecule-1; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor

Discussion

The novel rat model of OSA used in this study confirmed two main physiological features of OSA—chronic intermittent hypoxia with concurrent respiratory efforts, which reflected an increase in negative pressure in the chest. After 2 and 4 weeks, blood pressure in the OSA groups was significantly increased, which is the most common cardiovascular complication of OSA. With the extension of apnea–hypopnea duration, blood pressure in the rats was significantly increased. These results are consistent with the chronic intermittent hypoxia model [16].

The chronic intermittent hypoxia model [17] and artificial upper airway stenosis model [18, 19] are the two most common types of OSA rat models. The main limitation of the chronic intermittent hypoxia model is that it only mimics

Fig. 6 Level of inflammatory cytokines in serum. **a** ICAM-1 in serum increased in OSA for 4 weeks and reversed by complete recovery or partial recovery; **b** TIMP-1 in serum increased in OSA (60 s/90 s) for 4 weeks and reversed by complete recovery or partial recovery; **c** IL-1 beta in serum increased in OSA for 4 weeks and reversed by complete recovery or partial recovery; **d** IL-2 in serum increased in OSA for 4 weeks and reversed by complete recovery or partial recovery; **e** IL-6 in serum increased in OSA (60 s/90 s) for 4 weeks and reversed by complete recovery or partial recovery; **f** VEGF in serum increased in OSA for 4 weeks and reversed by complete recovery or partial recovery; **g** TNF-alpha in serum increased in OSA (60 s/90 s) for 4 weeks and reversed by complete recovery or partial recovery; **h** L-selectin in serum showed no difference among six groups. $^{*}P < 0.05$ vs. sham, $^{\#}P < 0.05$ vs. control, $^{\bigstar}P < 0.05$ vs. partial recovery, $^{\star}P < 0.05$ vs. complete recovery, $^{\circledcirc}P < 0.05$ vs. OSA (30 s/90 s). ICAM-1, intercellular cell adhesion molecule-1; TIMP-1, tissue inhibitor of metalloproteinase-1; IL, interleukin; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor-alpha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ICAM-1 (pg/ml)
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Control
Sham
OSA(60s/90s)
OSA(30s/90s)
Partial Recovery
Complete Recovery

chronic intermittent hypoxia of OSA and does not include other important physiological aspects of OSA. Additionally, this model is not flexible enough to simulate OSA with various apnea–hypopnea durations and AHI conditions. The artificial upper airway stenosis OSA model typically uses tracheal intubation or operation on experimental animals with anesthetic simulation of the sleep state. This model involves external automated devices to simulate intermittent hypoxia and intrathoracic negative pressure of OSA. The pathophysiology of this OSA model, which requires good surgical skills, is closer to the real state of OSA. However, this OSA model causes greater damage to animals than other models, thus restricting this model to short-term studies. The ideal OSA model requires the following features: (1) sleep apnea caused by upper airway obstruction; (2) accompanied by hypoxemia and breathing effort during apnea; (3) ability to mimic clinical symptoms or complications of OSA; and (4) observable sleep patterns and changes in secondary organ function (e.g., the heart, brain). Our OSA model meets most of these criteria and mimics sleep during sedative anesthesia. This model can also flexibly simulate the condition of OSA with different AHIs and apnea–hypopnea durations.

In this study, we have shown that the apnea–hypopnea duration was highly associated with vascular inflammation, endothelial dysfunction, and hypertension. This is in line with our previous study on the association between mean apnea–hypopnea duration and the severity of hypertension [13]. In the present study, the mean oxygen desaturation and the apnea–hypopnea duration were strongly significantly correlated. This might be due to the fact that the apnea–hypopnea duration was the only factor affecting mean oxygen desaturation. Even if the AHI was unchanged, a longer apnea–hypopnea duration (deeper oxygen desaturation) induced a worse systemic inflammatory response and impaired endothelial function, and resulted in increased blood pressure. Importantly, partial or complete recovery reversed the hypertensive response and lowered vascular inflammation and endothelial dysfunction. Therefore, the apnea–hypopnea duration is an important parameter in OSA. A reduction in the apnea–hypopnea duration may be the best index to target with therapy to prevent cardiovascular complications in patients with OSA.

Our finding of significantly increased inflammatory cytokines in the OSA (60 s/90 s) group may be responsible for the impaired endothelial dysfunction. After the partial or complete recovery period, this effect was reversed. A longer apnea–hypopnea duration and associated deeper desaturation may lead to more severe endothelial dysfunction [5]. Consistent with our findings, other studies have reported that levels of systemic inflammatory markers (TNF-α, ICAM, IL-6, and selectins) were significantly higher in patients with OSA compared with control subjects [20, 21]. Additionally, circulating adhesion molecules (ICAM-1 and vascular cell adhesion molecule-1) are associated with endothelial dysfunction [22]. When the endothelial monolayer becomes inflamed by the inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α), endothelial cells begin to express selective adhesion molecules on their surface. This process facilitates the interaction between leucocytes and the vascular endothelium and then contributes to endothelial vasodilator dysfunction. Biomarkers of endothelial dysfunction (ICAM-1) and low-grade inflammation (IL-6 and TNF-α) are also associated with greater arterial stiffness [23], and this may be related to the development of hypertension in OSA. When the apnea–hypopnea duration was reduced to 15 s per 90 s, blood oxygen saturation was reduced by approximately 4 to 5%. Therefore, we speculate that lowering the apnea–hypopnea duration may relieve downstream oxidative stress and inflammatory responses and blood pressure.

Another major sequela of OSA is the changes in cardiac function and structure [24]. We found that TIMP-1 levels in serum and the thoracic aorta and the left ventricular weight/body weight ratio were significantly increased in the OSA 60 s/90 s group. This cardiac remodeling improved after the complete recovery period. However, after the partial recovery period, only TMIP-1 levels were improved. This finding is consistent with previous studies that showed that elevated serum and tissue TIMP-1 levels were correlated with diastolic dysfunction [23], myocardial fibrosis [25], and hypertensive cardiac remodeling [26]. In community-based studies, higher circulating TIMP-1 levels are predictive of incident hypertension [27]. TIMP-1 is a driving force in promoting cardiovascular remodeling in hypertension [26] and myocardial fibrosis [25] through a mechanism that is independent from its MMP-inhibitory function. TIMP-1 is synthesized by several cell types. Transcription of TIMP-1 is regulated by similar cytokines that control MMP expression, including TNF-α, IL-1, and IL-6 [28]. Oxidative stress, growth factors, and pro-inflammatory cytokines (IL-6, IL-1, and IL-1β) modulate TIMP-1 expression via the ERK1/2 and p38 MAPK pathways [29]. Therefore, decreased TIMP-1 levels following stopping apnea or hypopnea could be due to the alleviation of the effects of pro-inflammatory cytokines and markers. This could result in downregulation of nuclear factor-κB, and subsequently, TIMP-1 expression. In addition, however, cardiac remodeling may be induced by episodes of repeated increased respiratory effort and the associated chest negative pressure induced by OSA. We found that an increased respiratory effort occurred within 15 s of the apnea period (Fig. 2c). This suggested that although the apnea–hypopnea duration may be reduced, the negative chest pressure still happened and this may be associated with cardiac remodeling.

In this study, only the apnea–hypopnea duration affected the degree of the mean oxygen desaturation. However, many factors affect blood oxygen saturation clinically, such as apnea–hypopnea duration, awakening threshold, and

complications. However, whether the event duration or the degree of oxygen desaturation or a combination of both are the main causes of vascular dysfunction, inflammation, and hypertension remains unclear. Therefore, follow-up clinical studies should be performed to examine the relationship of the apnea–hypopnea duration and oxygen desaturation and subsequent damage to target organs. Moreover, the difference in responses at 4 weeks in rats that were exposed to occlusions for the whole 4 weeks versus those with partial/complete recovery program may partly be due to the duration of exposure. Two OSA groups were used to simulate the state of OSA for 4 weeks with the same AHI and different apnea–hypopnea duration without treatment. Partial/complete recovery groups were used to mimic the state after OSA treatment. Clinically and experimentally, early intervention is beneficial even if only partial.

There are several limitations to our study. First, sleep fragmentation which is an important component of OSA cannot be determined in the current model because of a lack of electroencephalographic monitoring. This type of monitoring is difficult in this animal model. Secondly, similar to other artificial airway stenosis OSA models, the use of sedation during the experiment further complicates the viability of this model as a surrogate reporter of OSA. Therefore, we only investigated a limited period of exposure (3 h/day) that could also induce an elevation in blood pressure in only 2 weeks of modeling in the OSA 60 s/90 s group. Third, systolic BP in the control group increased on day 30 which was a relatively unexpected result. Based on the calculation of sample size, more than six rats in each group should be included for comparing systolic BP. Because of the small sample size, there was the possibility of a type 1 error when interpreting systolic BP findings. However, our study showed some important findings and provides the foundation of the next large-scale experiment. This study was a pilot experiment and will hopefully be useful in the clinical situation of OSA. Finally, this research raises questions about the role of apnea–hypopnea duration in OSA. Whether surgery or other treatments can sufficiently reduce the apnea–hypopnea duration to treat OSA remains to be confirmed in further clinical research.

Conclusion

Our study shows that a longer apnea–hypopnea duration induces a worse systemic inflammatory response, endothelial dysfunction, severe hypertension, and other cardiovascular complications. Adequate partial recovery with or without a change in the AHI can achieve the same therapeutic effect as complete recovery from OSA in terms of lowering blood pressure and by eliminating the systemic inflammatory response. Our findings suggest that other breathing parameters besides the AHI might be important in the pathogenesis of OSA-induced end-organ damage. Further studies are required to confirm these findings in humans.

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Authors' contributions WH and WY performed the study design and experiment operation and were major contributors in writing the manuscript. LQ and SH performed the sample preparation and measurement of inflammatory cytokines. ZH performed the isolation of rat thoracic aortas. QY performed the study design and data collection. FF analyzed and interpreted the data. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate All procedures were approved by the Animal Care and Use Committee of Capital Medical University (AEEI-2015-107). The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No.85-23, revised 1996).

Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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