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Maternal chronic intermittent hypoxia in rats causes early atherosclerosis with increased expression of Caveolin-1 in offspring

Huihuang Lin[1] · Yiming Zeng[1] · Ziyan Wang[2]

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Abstract

Objective The objective of our research was to explore the effects of maternal and postpartum chronic intermittent hypoxia (CIH) exposure on atherosclerosis in adulthood offspring of rats, and the role of Caveolin-1 in the course.

Methods Sixteen rats were assigned to two groups ($n = 8$), maternal normoxia and CIH group. After delivery, two male pups per litter were selected and breastfed for 1 month, which then randomly received postpartum normoxia or CIH. Thus, 4 groups were created as follows ($n = 8$): (1) maternal normoxia and postpartum normoxia group, (2) maternal CIH and postpartum normoxia group, (3) maternal CIH and postpartum CIH group, and (4) maternal normoxia and postpartum CIH group. The offspring were weighed at birth and weaning. After the duration of 12-week experiment, morphological changes, the expression of Caveolin-1 and NF-κB p65 in the aorta were detected.

Results Maternal CIH resulted in significantly lower body weight and thicker intima ($P < 0.001$). CIH upregulated the expression of Caveolin-1 and NF-κB p65 significantly ($P < 0.01$). There was a synergistic effect of maternal and postpartum CIH on the thickening of intima ($P < 0.05$), also on the expression of Caveolin-1 and NF-κB p65 ($P < 0.01$).

Conclusions The results demonstrate that maternal CIH exposure causes a postpartum catch-up growth and early atherosclerotic changes followed by upregulating Caveolin-1 expression. Besides, maternal CIH enhances the atherosclerotic changes caused by postpartum CIH. Oxidative stress probably implicates in above effects.

Keywords Obstructive sleep apnea · Chronic intermittent hypoxia · Atherosclerosis · NF-κB p65 · Caveolin-1 · Rats

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder, and is characterized by collapse of the upper airway. OSA has a high prevalence in the general population, and is associated with a variety of cardiovascular diseases including atherosclerosis [1]. OSA patients often have chronic intermittent hypoxia (CIH), a condition that results in oxidative stress. Increased reactive oxygen species activates the NF-κB signaling pathway and promotes the development of atherosclerotic lesions [2]. Previous study reported that CIH induced atherosclerosis in animals [3].

The prevalence of OSA among women is 2%, and a study about gravidas who underwent first and third trimester overnight polysomnography demonstrated that 8.4% women in the first and 19.7% of women in the third trimester had OSA [4]. Hence, women experience a higher risk of CIH during pregnancy. Barker's fetal origins of adult disease hypothesis imply that harmful intrauterine environment, such as malnutrition and hypoxia, increases the risk of atherosclerosis and other cardiovascular diseases in adulthood [5, 6]. A more recent study showed maternal exposure to persistent hypoxia led to early atherosclerotic lesions in adult rats [7]. However, whether maternal exposure to CIH has similar effects on arteries in adult rats is unknown.

Caveolae, which are 50–100 nm specialized membrane microdomains on cell surface, are implicated in different

✉ Yiming Zeng
zeng_yi_ming@aliyun.com

[1] Department of Pulmonary and Critical Care Medicine, Respiratory Medicine Center of Fujian Province, Second Affiliated Hospital of Fujian Medical University, No. 34, Zhongshanbei Road, Licheng District, Quanzhou 362000, Fujian Province, China

[2] Department of Respiratory, People's Hospital of Fujian Province, No. 602, 817 Middle Road, Fuzhou 350004, Fujian Province, China

biological procedure including macromolecular transcription, lipid metabolism, and signal transduction. As a major component of caveolae, Caveolin-1 is associated with atherosclerosis [8]. Caveolin-1 interacts with many signaling molecules, such as extracellular signal-regulated kinase, heterotrimeric G-proteins, and endothelial nitric oxide synthase through its scaffolding region (Caveolin-1 scaffolding domain, CSD) [9, 10]. However, there is still controversy about the effect of Caveolin-1 in the atherosclerotic lesions. Studies have shown that Caveolin-1 overexpression promotes the apoptosis in vascular smooth muscle cells which induced by oxidized low-density lipoprotein (ox-LDL), thereby, contributing to the formation of atherosclerotic plaques [11]. In contrast, atherosclerotic plaque had lower expression level of Caveolin-1 in hypercholesterolemic rabbits and humans, suggesting that Caveolin-1 may have atheroprotective effects [12, 13]. Importantly, Caveolin-1 is involved in ischemia/reperfusion injury, which also occurs in CIH [14]. In this study, we investigated the effects of maternal and postpartum CIH exposure on atherosclerosis in adulthood offspring of rats, and the role of Caveolin-1 in the course.

Material and methods

Animal

All experiments were conducted in accordance with National Institutes of Health guidelines. The study protocols were approved by the Standing Committee on Ethics and Animal Experimentation at Fujian Medical University. Seven-day pregnant female Sprague Dawley rats with a body weight of 180–200 g were provided by Center of Laboratory Animals of Chinese Academy of Sciences in Shanghai. Initiation of pregnancy was determined by detection of sperm in the vaginal smear (term = 21 days). All animals were kept at room temperature (19 to 23 °C) under natural light and 55% humidity. The food and drinking water were freely available to rats.

CIH model

We established the CIH rat model as previously described [15]. The oxygen concentration inside the chamber was detected by a portable oxygen analyzer (S-450; IST-AIM). Oxygen and nitrogen gas discharge rate and time were controlled by a made system. Each hypoxia cycle (2 min) took place in the order of 30 s of nitrogen insufflation, 30 s rest, 20 s oxygen insufflation, and 40 s air insufflation. The maximum and minimum oxygen concentrations were 21.32 ± 0.53% and 6.43 ± 0.42%, respectively.

Experimental design

Maternal hypoxia

The rats were placed in the sealed chambers made of Plexiglass and randomly divided into two groups. From the 7th to 21st day of pregnancy, rats in the maternal CIH group ($n = 8$) were exposed to CIH that lasted 8 hours per day from 9:00 to 17:00, for a total of 14 days. Rats in the maternal normoxia group ($n = 8$) were subjected to the same treatment except that the gas insufflated was continuously air.

Postpartum hypoxia

After birth, two male pups of each pregnant rat were randomly selected and breastfed until 1-month-old then weaned to ad libitum laboratory chow. Randomly selected pups from different litters were weighed at birth and weaning. The offspring rats were then randomly assigned as follows ($n = 8$): the maternal normoxia and postpartum normoxia (M_0P_0) group, which was also the control group, the maternal CIH and postpartum normoxia (M_1P_0) group, the maternal CIH and postpartum CIH (M_1P_1) group, and the maternal normoxia and postpartum CIH (M_0P_1) group. Rats assigned to the M_1P_1 and M_0P_1 groups were exposed to CIH lasted 8 hours per day from 09:00 to 17:00, for a total duration of 12 weeks.

Sample collection

At the end of the 12-week experiment, all offspring rats were euthanized and the thoracoabdominal aorta was isolated. Part of the descending aorta was fixed in 10% neutral formalin for histopathological analysis. The remaining aorta was stored at −80 °C until western blot analysis.

Histopathology

The aorta which had been fixed in 10% neutral formalin overnight was made into paraffin-embedded sections. Then the sections were stained with hematoxylin-eosin staining. The morphology of aorta was histologically analyzed by Olympus BH-2 optical microscope. Image Pro Plus 6.0 software was used to measure aortic intima thickness.

Western blot analysis

The aorta was washed with PBS and homogenized in lysis buffer (50 mM Tris-HCl, pH 8.0, 150 mM NaCl, 1% Triton X-100, 100 μg/ml phenyl methane sulfonyl fluoride). The homogenates were further sonicated and then centrifuged for 5 minutes at a speed of 12,000 g at 4 °C. The protein concentration of the supernatant was detected by a BCA protein assay kit (Beijing Dingguo Changsheng Biotech Company, China).

The proteins were separated on SDS-PAGE 10% gels (stacking gel 80 V, separating gel 120 V) and transferred to PVDF membranes (80 V, 90 min). The membranes were blocked with 5% non-fat milk, and probed with monoclonal antibodies against Caveolin-1 and NF-κB p56 (Cell Signaling Technology, USA), respectively. The membranes were then incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG secondary antibody (1:4000) (Beijing Dingguo Changsheng Biotech Company, China). The peroxidase activity was visualized using enhanced chemiluminescence (PIERCE Company, USA). The density of the protein bands was analyzed using software Quantity One. β-actin was used as the internal control.

Statistical analysis

All data are presented as means ± SD (standard deviation). The mean birth weight and body weight at weaning between maternal normoxia and maternal CIH groups were compared by the unpaired Student's two-tailed *t* test. The main effects and the interaction effects of maternal CIH and postpartum CIH on the aorta were interpreted using a general linear model of the univariate process. All other statistical comparisons among the groups were conducted using one-way ANOVA with subsequent Tukey's post hoc test. Differences with $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS 17.0 software.

Results

CIH causes fetal growth restriction and catch-up growth

Birth weight measurements showed that there was significantly lower weight in offspring from maternal CIH group compared to that from maternal normoxia group ($P < 0.001$). However, their body weight had no significant difference after weaning at 1 month of age (Table 1).

Table 1 Body weight of maternal normoxia and maternal CIH pups at birth and weaning (at 1-month-old)

Group	Body weight (g)	
	Birth (day 0)	Weaning (1-month-old)
Maternal normoxia group	5.56 ± 0.55	74.5 ± 3.6
Maternal CIH group	4.46 ± 0.34*	76.7 ± 2.8

*$P < 0.05$ compared with the maternal normoxia group. Data are presented as means ± SD ($n = 8$)

CIH causes atherosclerotic lesions in the aorta

Histological assessment showed that the aorta of rats in the maternal normoxia and postpartum normoxia group had no detectable pathological changes. The thin tunica intima was round and smooth, covered by an integral monolayer of endothelial cells. The internal elastic membrane was also intact. The thick tunica media had regular annular vascular smooth muscle cells and layered elastic membranes. However, the aorta of rats exposed to either maternal CIH or postpartum CIH displayed pathological lesions characterized by inordinate vascular lumen, thickened tunica intima, shredded endothelial cell layer, ruptured internal elastic membrane, thinned tunica media, disordered vascular smooth muscle cells, and unclear elastic fiber layer. The lesions were the most severe in the aorta of rats exposed to both maternal and postpartum CIH (Fig. 1).

CIH causes thickening of the tunica intima in the aorta

Rats in M_1P_0, M_0P_1, and M_1P_1 groups had significantly thicker tunica intima in the aorta than rats in M_0P_0 group ($P < 0.01$) (Table 2). The maternal and postpartum CIH had interaction effect on the thickening of tunica intima significantly ($F = 83.834$, $P < 0.001$). Our modeling results also showed that both maternal and postpartum CIH caused significant thickening of the tunica intima ($F = 39.441$, $P < 0.001$ and $F = 202.180$, $P < 0.001$, respectively). In addition, we found a synergistic effect of maternal and postpartum CIH on the thickening of tunica intima ($F = 9.881$, $P < 0.05$).

CIH increases the expression of Caveolin-1 and NF-κB p65 in the aorta

Our western blot analysis showed that, compared with the M_0P_0 group, other three groups had higher protein levels of Caveolin-1 and NF-κB p65 in the aorta ($P < 0.05$), with the highest levels observed in M_1P_1 group (Fig. 2). We further analyzed the interaction effects of maternal and postpartum CIH on the expression of Caveolin-1 and NF-κB p65, respectively, using a general linear model of univariate procedure. The results indicated that the interaction effects were statistically significant ($F_{\text{Caveolin-1}} = 48.587$, $P < 0.001$ and $F_{\text{NF-κB p65}} = 83.611$, $P < 0.001$, respectively). Results also showed that both maternal and postpartum CIH caused significant increasing in the expression of Caveolin-1 and NF-κB p65, respectively (maternal CIH: $F_{\text{Caveolin-1}} = 49.828$, $P < 0.001$ and $F_{\text{NF-κB p65}} = 75.027$, $P < 0.001$, respectively; postpartum CIH: $F_{\text{Caveolin-1}} = 69.797$, $P < 0.001$ and $F_{\text{NF-κB p65}} = 151.899$, $P < 0.001$, respectively). In addition, we observed a synergistic effect of maternal and postpartum CIH on the

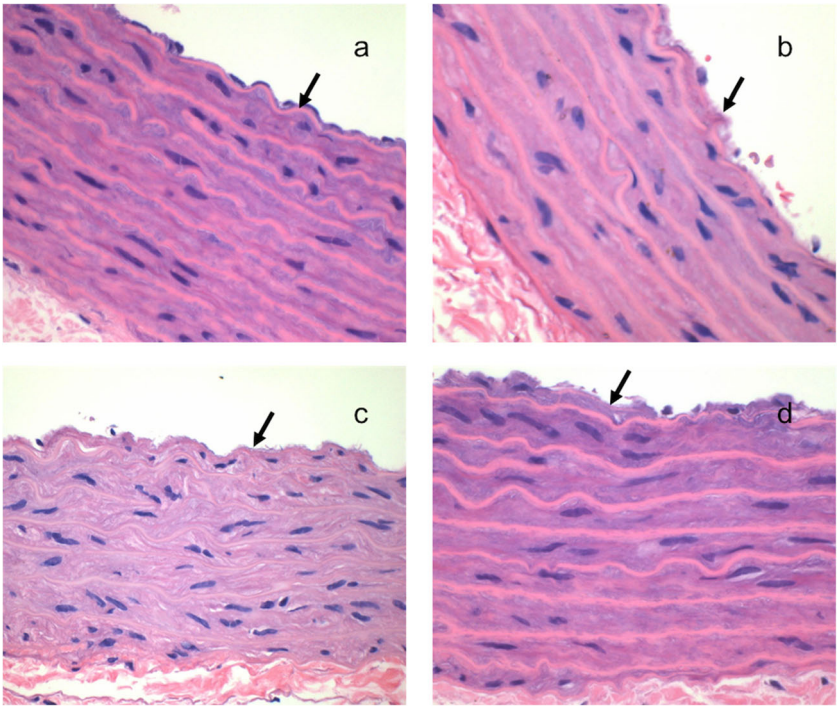

Fig. 1 Morphological changes in the aorta of rats with hematoxylin-eosin (HE) staining. **a** The aorta of rats in the maternal normoxia and postpartum normoxia group had no detectable pathological changes. **b** The aortas of rats exposed to maternal CIH only and **d** rats exposed to postpartum CIH only, the two groups displayed pathological lesions characterized by inordinate vascular lumen, thickened tunica intima, shredded endothelial cell layer, ruptured internal elastic membrane, thinned tunica media, disordered vascular smooth muscle cells, and unclear elastic fiber layer. **c** The aorta of rats exposed to both maternal and postpartum CIH displayed the most severe lesions. Arrow indicates the endothelial cell layer. Magnification×400

upregulation of Caveolin-1 and NF-κB p65 expression ($F_{\text{Caveolin-1}} = 26.136$, $P < 0.001$ and $F_{\text{NF-κB p65}} = 20.906$, $P < 0.001$, respectively).

Correlation analysis

Our correlation analysis indicated the expression level of Caveolin-1 and NF-κB p65 was positively correlated ($r = 0.848$, $P < 0.001$). Moreover, the levels of Caveolin-1 and NF-κB p65 were positively correlated with the thickness of the artery intima ($r = 0.811$, $P < 0.001$ and $r = 0.880$, $P < 0.001$, respectively).

Table 2 The thickness of tunica intima in the thoracic aorta

Group	The thickness of tunica intima (μm)
M_0P_0 group	1.555 ± 0.259
M_1P_0 group	3.800 ± 0.543*
M_1P_1 group	6.440 ± 0.977*
M_0P_1 group	5.692 ± 0.708*

*$P < 0.01$ compared with the M_0P_0 group. M_0P_0 maternal normoxia and postpartum normoxia, M_1P_0 maternal CIH and postpartum normoxia, M_1P_1 maternal CIH and postpartum CIH, M_0P_1 maternal normoxia and postpartum CIH. Data are presented as means ± SD ($n = 8$). Statistical comparisons among the groups were conducted using one-way ANOVA with subsequent Tukey's post hoc test

Discussion

In this study, rats underwent intermittent hypoxia cycles of 2 min each, which had the effects similar to that of moderate OSA. In our previous study, the continuous gas exchange prevented carbon dioxide accumulation in the chamber, and the lowest oxygen saturation was approximately 70% [15]. We showed that maternal CIH resulted in a fetal growth restriction and a catch-up growth in the study. Our findings also demonstrated that maternal exposure to CIH caused early atherosclerotic lesions in 4-month-old rats, along with upregulation of Caveolin-1 and NF-κB p65 protein expression. These changes were aggravated in conjunction with postpartum CIH. These results suggest that maternal and postpartum CIH cause atherosclerotic lesions in rats by inducing oxidative stress, which upregulates Caveolin-1 expression through activating NF-κB p65 pathway.

Previous studies in rodent reported that maternal CIH could cause growth restriction and low birthweight in offspring [16, 17]. Consistent with the finding, our results showed offspring from maternal exposure to CIH had lower birth weight. The result indicated that maternal CIH could lead to intrauterine growth restriction, which was an effort to protect against low oxygen, and establish oxygen supply–demand balance [18]. At weaning, no differences were found in the body weight between maternal CIH and normoxia pups in our study, which showed maternal CIH induced a postpartum catch-up growth after low birthweight in offspring. Recent animal studies also confirmed the observation that maternal hypoxia resulted in

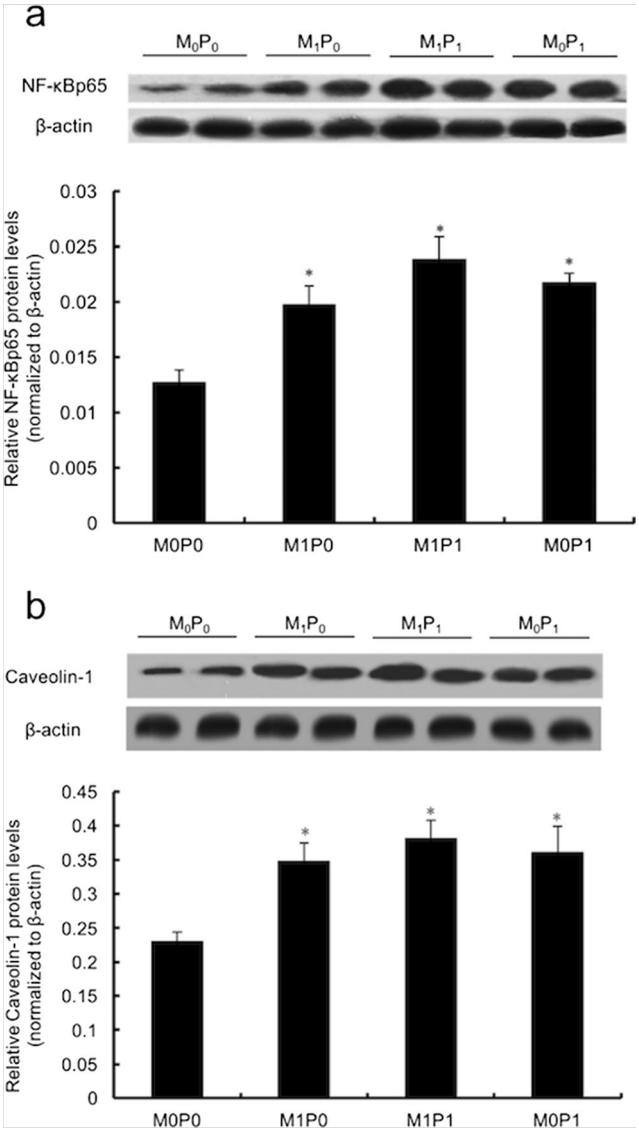

Fig. 2 The protein expression of NF-κB p65 (a) and Caveolin-1 (b) in the aorta. Aortas were harvested, homogenized, and centrifuged. Samples from the supernatant were subjected to western blot analysis. Protein bands were quantified by densitometric analysis. β-actin was used as the internal control. Compared with the M_0P_0 group, the protein levels of NF-κB p65 and Caveolin-1 in the aorta were significantly higher in all other groups, with the highest levels observed in the M_1P_1 group. $^*P < 0.05$ compared with the M_0P_0 group. M_0P_0 maternal normoxia and postpartum normoxia, M_1P_0 maternal CIH and postpartum normoxia, M_1P_1 maternal CIH and postpartum CIH, M_0P_1 maternal normoxia and postpartum CIH

intrauterine growth retardation of infants who showed rapid early postpartum growth [7, 17]. Catch-up growth is beneficial in early period, but is also considered as a hazard in adult life. Several studies in human and animal have provided evidence that offspring who suffered from a low birthweight followed catch-up growth were particularly prone to develop cardiovascular disease in adulthood [7, 19, 20]. In the present study, the alternations in the body weight of rodent corroborated the previous studies and presumable may be associated with the aortic morphological changes of the offspring rats.

Thickening of the tunica intima is considered as a symbol of arterial endothelium injuries, and occurs in early atherosclerotic lesions. In this study, the morphological changes of the aorta induced by CIH, which included inordinate vascular lumen, shredded endothelial cell layer, ruptured internal elastic membrane, thinned tunica media, disordered vascular smooth muscle cells, and unclear elastic fiber layer, were consistent with that of early atherosclerotic lesions reported in previous studies [21]. Importantly, exposure to maternal and/or postpartum CIH significantly increased the intimal thickness, a key index of the severity of atherosclerotic lesion. Collectively, the findings demonstrated that maternal CIH increased the risk of atherosclerosis in rats.

Oxidative stress is implicated in the formation of atherosclerotic lesions. NF-κB is a key regulator of gene transcription in response to oxidative stress. Ischemia/reperfusion results in production of reactive oxygen species, which activates the expression of NF-κB p65 through multiple signaling pathways [22]. The hypoxia/reoxygenation cycle of CIH is as the ischemia/reperfusion process. Our previous studies have shown that postpartum CIH promotes the formation of early atherosclerotic lesions, along with increased NF-κB p65 expression. Our study found that maternal CIH in rats also increased NF-κB p65 expression in the artery. Furthermore, we found NF-κB p65 expression was positively correlated with the intimal thickness of rat aorta. Atherosclerosis is a chronic inflammatory disease [23]. NF-κB p65, which is detected in atherosclerotic plaques, upregulates a variety of inflammatory cytokines involved in the development of atherosclerotic lesions [24]. Therefore, we believe that CIH promotes formation of early atherosclerotic lesions through inducing oxidative stress and followed activation of NF-κB p65 pathway.

In the present study, we found that maternal CIH increased Caveolin-1 expression in the aorta of rats. Our results also demonstrated the level of Caveolin-1 was positively correlated with that of NF-κB p65. Previous study has showed that ox-LDL increases Caveolin-1 via NF-κB pathway [25]. Therefore, we think that maternal CIH also upregulates Caveolin-1 expression through activating NF-κB p65 pathway. Previous studies indicated that Caveolin-1 probably had a pro-atherosclerotic or anti-atherosclerotic effect depending on cell type and environment [26–29]. Our study showed Caveolin-1 expression was positively correlated with the intimal thickness of the aorta, suggesting that maternal CIH-induced Caveolin-1 expression might promote the formation of early atherosclerosis in rats. Caveolae participates in the division of different signaling pathways. Caveolin-1, as a major caveolae protein, regulates many signaling molecules concentrated in caveolae. It has been reported that increased Caveolin-1 expression may promote inflammation and cell apoptosis, thereby, contributing to the development of

atherosclerosis [10]. However, it is also possible that Caveolin-1 is expressed in response to CIH to protect cells against the CIH insult. The actual effect of Caveolin-1 on the formation of atherosclerotic lesions following CIH is not fully understood and is the focus of our future study.

Previous studies have demonstrated that maternal hypoxia increases the heart susceptibility of rats to ischemia/reperfusion injury [30]. Our study found that maternal CIH caused more severe pathological changes of the aorta compared with postpartum CIH. In addition, we found a synergistic effect of maternal and postpartum CIH on the thickening of intima. These results suggest that maternal CIH sensitizes the aorta to postpartum CIH-induced intimal thickening. The synergistic effects were also found on the expression of Caveolin-1 and NF-κB p65.

In conclusion, results from this study demonstrate that the rats expose to maternal CIH during days 7 to 21 of pregnancy can result in a postpartum catch-up growth after low birthweight and cause early morphological changes of atherosclerosis in adulthood. Furthermore, maternal CIH enhances atherosclerotic changes caused by postpartum CIH in rats. CIH-induced oxidative stress probably implicates in above effects, through activation of NF-κB p65 pathway followed increasing Caveolin-1 expression.

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Compliance with ethical standards

All experiments were conducted in accordance with National Institutes of Health guidelines. The study protocols were approved by the Standing Committee on Ethics and Animal Experimentation at Fujian Medical University.

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

Ethical approval The animal experiments were performed after approval from the Standing Committee on Ethics and Animal Experimentation at Fujian Medical University.

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