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Original Article

Induction of aortic dissection in rats using n-(2-aminoethyl) ethanolamine

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Abstract: This study aimed to establish a stable animal model of aortic dissection and explore the pathogenesis of aortic dissection. Fifteen pregnant (8 weeks) rats were divided into three groups. The rats in the two experimental group received different doses of n-(2-aminoethyl) ethanolamine (AEEA) (100 mg/kg, n = 5; 150 mg/kg, n = 5) daily by intragastric gavage on gestation days 14-20. The rats in the control group received the same dose of normal saline. On the first day of birth, all the surviving newborns from the groups were sacrificed for dissection of aortic vessels, pathological analysis, and immunohistochemistry. It's found that 4 of 43 cubs in the 100 mg/kg AEEA group showed dilatation of the ascending aortic wall, hematoma formation, but no significant endometrial rupture or blood in the media. In the 150 mg/kg dose group, aortic dilatation, tortuosity, intravascular thrombosis and typical intimal rupture were observed and the rate of aortic dissection was 100%. The aortic walls of the control group were smooth and complete, and no aortic dissection was found. Furthermore, compared with the control group, the deficient, broken and disordered elastic fibers were observed in the walls of the aortic vessels in the experimental group, in addition to the reduced amount of collagen I and collagen III. In conclusion, AEEA administered to pregnant rats induced aortic dissection in pups, which may be related to the breakage and separation of elastic fibers and the reduction of collagen fibers.

Keywords: n-(2-aminoethyl) ethanolamine, aortic dissection, pregnant rats, animal model

Introduction

Aortic dissection usually results in aortic endometrial rupture, blood flow into the middle layer of the aortic wall (media), and tearing along the aortic wall [1]. A variety of factors can give rise to aortic dissection, which is a life-threatening condition, with very high mortality [2]. Patients diagnosed with aortic dissection frequently die because of blood vessel rupture and organ ischemia [3]. Unfortunately, aortic dissection remains intractable to treatment, and the underlying causes are unclear. In addition to hypertension and atherosclerosis, arteritis is a specific risk factor for aortic dissection. At present, there are no methods to confirm the relationship between aortic dissection and the above-mentioned risk factors.

Various efforts have been made to establish animal models of aortic dissection. Early aortic dissection models were mainly based on surgical mechanical damage [4, 5]. However, these models were time-consuming, required the use of large animals, and were not suited to studies of the molecular mechanisms of aortic dissection [4, 5]. In recent years, several studies have described chemical and genetic (knockout) methods of aortic dissection [6]. For example, JP Habashi et al. [7] used losartan to an AT1 Antagonist to study aortic dissection in a mouse model of Marfan syndrome. These methods can be applied to small animals, such as rats/mice/rabbits, and the models are conducive to studying the pathophysiology of aortic dissection. Establishing a reliable and stable animal model of aortic dissection is essential for the study of aortic disease. The aim of the present study was to establish such a model, thus laying the foundation for further studies.

Materials and methods

Ethics approval

The Research Ethics Committee of Guangdong General Hospital, Guangdong Academy of

Table 1. Numbers of dissecting aortic aneurysm (DAA) and the newborn pups after the AEEA treatment of dams by gavage

Drugs	Dams	Live pups	Dead pups	DAA
AEEA (100 mg/kg)	5	43	0	4
AEEA (150 mg/kg)	5	40	4	44
0.9% normal saline	5	45	0	0
Total	15	128	4	48

DAA: dissecting aortic aneurysm.

Medical Sciences approved the animal experiment and all the experimental procedures.

Animals and treatments

Sprague Dawley rats were purchased from Guangdong Pharmaceutical University (production license: SCXK (Guangdong) 2013-0034). All the animals were raised in a specific pathogen-free (SPF) environment in the animal center of the north campus of Sun Yat-Sen University (experimental center use license: SYXK (Guangdong) 2012-0081), with professional breeders, a suitable temperature, and sufficient water and fodder.

The chemical n-(2-aminoethyl) ethanolamine (AEEA) was obtained from Sigma-Aldrich (MO, USA) (lot number: VJ1055R3DWB; purity 99.8%). AEEA was diluted 20-fold with 0.9% normal saline to a concentration of 50 mg/ml.

Fifteen SPF 8-week pregnant Sprague Dawley rats (250-300 g) were used in the study. Ten rats were treated with different daily doses of AEEA (100 mg/kg, n = 5; 150 mg/kg, n = 5) from the 14th day of pregnancy until the birth day, and five rats of control group received normal saline (150 mg/kg) for the same period. Doses of 100 mg/kg and 150 mg/kg were selected because these were reported previously to be far lower than the lethal dose [8]. All the treatments were administered daily by intragastric gavage at approximately the same time, on 14-20 days of gestation. This period was selected because it is the critical time for vascular formation in newborn pups [9].

Aortic morphology of newborns

All newborn rat pups delivered from pregnant rats (dams) were anesthetized by chloral hydrate on the first postnatal day. The thoracoabdominal aorta was removed from each pup and placed in isotonic saline under an ordinary optics microscope. The surrounding connective tissue was separated carefully during the operative procedure. Aortic tissues, including all the thoracic organs and abdominal distal aorta to the renal arteries, were carefully removed under the microscope. For further morphology studies, the specimens were fixed in 10% paraformaldehyde for 24 h.

The sections were then dehydrated though a series of ethanol and xylene, and finally embedded in dipping wax . Then, the wax blocks were sliced (0.5-mm interval slices, slice thickness of 5 μm). Parts of the slices were retained for immunohistochemistry. Prior to staining, the tissue sections were dewaxed in xylene and hydrated using an ethanol gradient, followed by hematoxylin staining for 2-4 min and washing in water, 1% hydrochloric acid, ethanol, and water for 1-2 s. Then, the tissue sections were washed in warm water (60°C) to back to blue about 10 min, stained with Iraq red for 2-3 min, washed in water, dehydrated, made to be transparent, and mounted. The aortic dissection slices were observed under an ordinary optical microscope. To make it easier to observe the vessels, Masson's staining protocols were used.

Immunohistochemistry study

To detect medium-term aortic changes, the immunohistochemistry of collagen I and III was analyzed using goat anti-type I collagen antibody and goat anti-type III collagen antibody (Southern Biotech, Birmingham, AL, USA), respectively. Biotin-conjugated rabbit anti-mouse IgG and anti-goat IgG (DAKO, Glostrup, Denmark) were used as secondary antibodies. After xylene dewaxing for 10 min, the sections were soaked in hydrogen peroxide treated with citric acid buffer (PH6.0) microwave antigen retrieval, placed in sodium citrate buffer cooking 3 min to expose the antigenic sites and then blocked with normal goat serum, followed by the addition of the corresponding primary antibody, a secondary antibody, and colouration reagent, in turn. The tissue sections were then mounted and observed using a microscope.

Results

General observations

The weight of the pregnant rats increased over time with the administration of AEEA. There were no differences in the maternal weights,

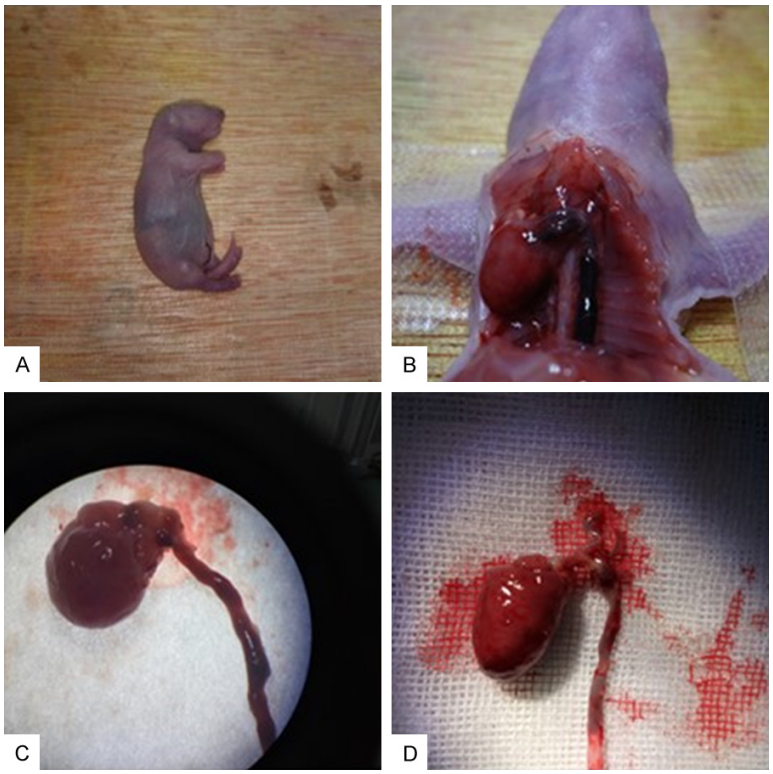

Figure 1. Aortic morphology of newborns in the 150 mg/kg n-(2-aminoethyl) ethanolamine (AEEA) treatment group. Newborn pups in the 150 mg/kg AEEA group (A). An enlarged heart, dilated aorta, and thrombosis observed under a microscope (B). Circuitous vessels in the hearts and aortas isolated from the pups (C, D).

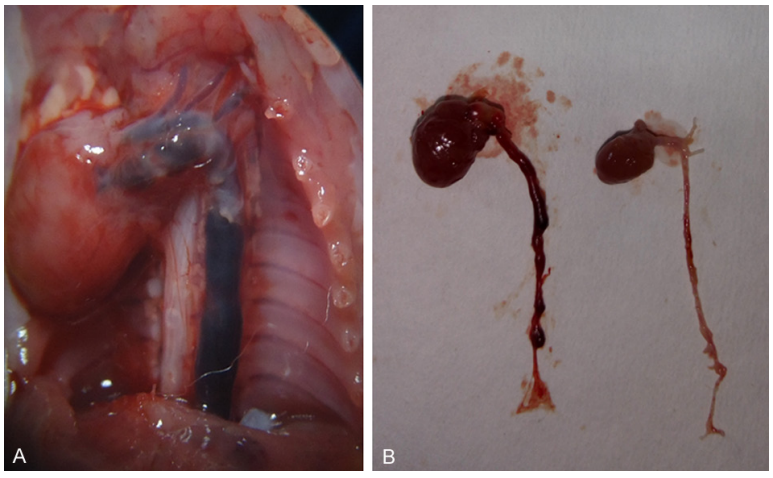

Figure 2. The ascending aorta of the pups. There were two vascular lumens extending from the aortic root of the pups in the 150 mg/kg AEEA treatment group (A). The experimental group (150 mg/kg AEEA treatment group) was characterized by enlarged hearts, expansion of aortic blood vessels, and thrombosis (B, left panel) as compared with the hearts and vessels in the control group (B, right panel).

numbers of stillbirths, litter sizes, or mean pup weights among the groups.

Survival rate of each group

On the delivery day, the total numbers of newborn pups, including stillbirths, in the three groups were recorded. Four pups died in the 150 mg/kg dose of AEEA group, and all the newborns survived in the other two groups. The numbers of surviving pups in each group (100, 150 mg/kg, and control) were 43, 40, and 45, respectively (**Table 1**).

Morphology

On the first day of postnatal day, the rats were anatomized, and then the hearts and aortas were exposed. As observed under a microscope, varying degrees of aortic dilatation was visible in the chests of the newborns in the AEEA group, in addition to extensive tearing of the aorta wall, tortuosity and visible mural thrombosis (**Figures 1** and **2**). The aorta of the normal saline group was smooth, with no dilation or thrombosis (**Figure 2B**).

Hematoxylin & Eosin (H&E) and Masson's staining

The aorta was removed completely and placed in isotonic saline to remove the free surrounding connective tissue. H&E and Masson's staining of cross-sectional slices of isolated aortic tissue helped to understand the changes of the aortic vessels and elastic fibers in the middle aortic wall.

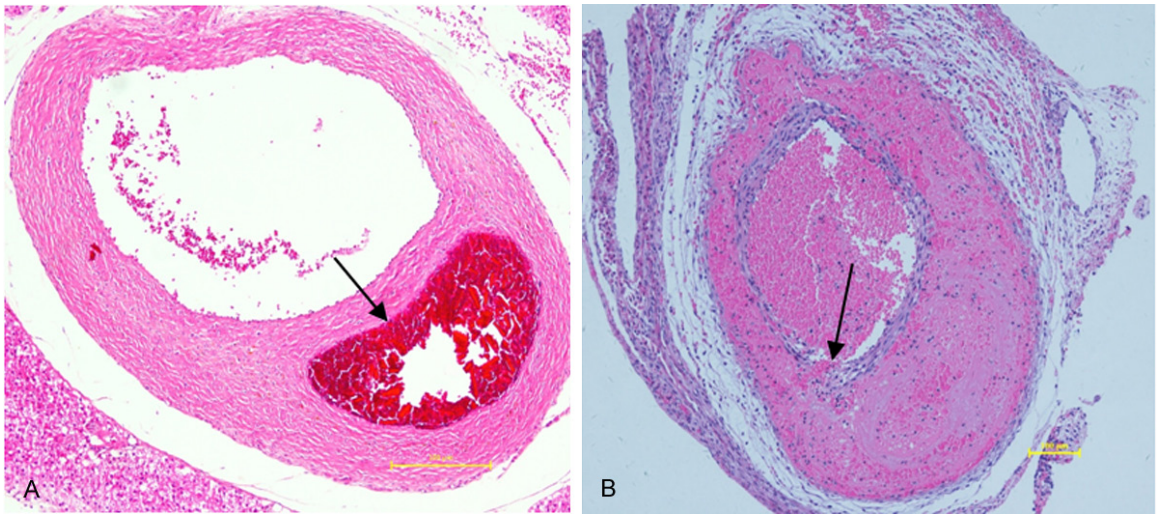

Figure 3. Hematoxylin & Eosin (H&E) staining of of aortic tissues from the 100 mg/kg AEEA group (A) and 150 mg/kg group (B). A hematoma in the media of the aortic vessels (arrow) and a complete intima were observed in the low-dose (100 mg/kg) AEEA group (A). In contrast, a visible breakage was observed in the middle layer of the high-dose (150 mg/kg) AEEA group, in addition to red blood cells (B). Scale bars = 100 μm.

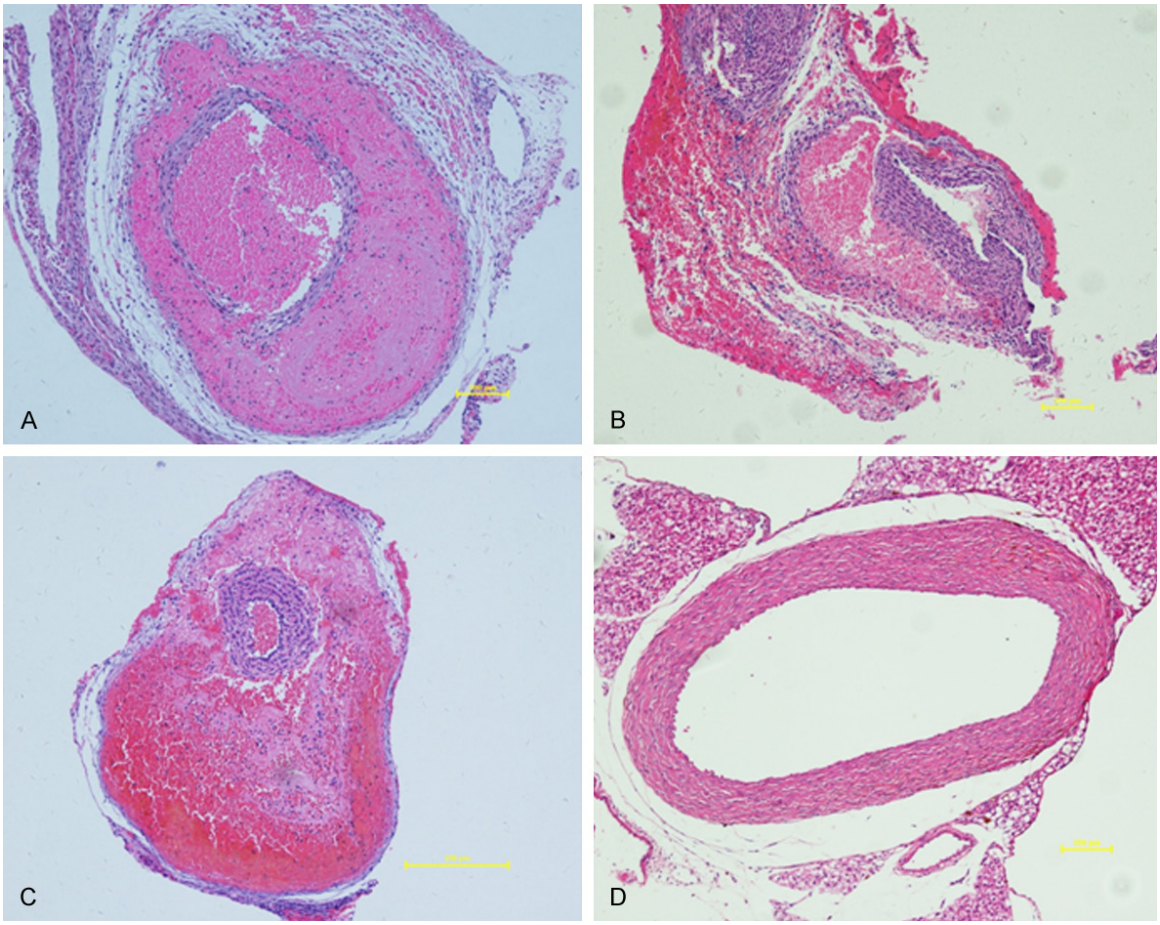

Figure 4. The aortic dissection and full of red blood cells were observed in the aortic vasculature of the newborn rats in the 150 mg/kg AEEA group. Dissecting aortic aneurysm was observed in ascending aorta (A), pulmonary artery (B, left vessel), and descending aorta (C). No aortic dissection was observed in the normal saline gavage group (D). Scale bars = 100 μm.

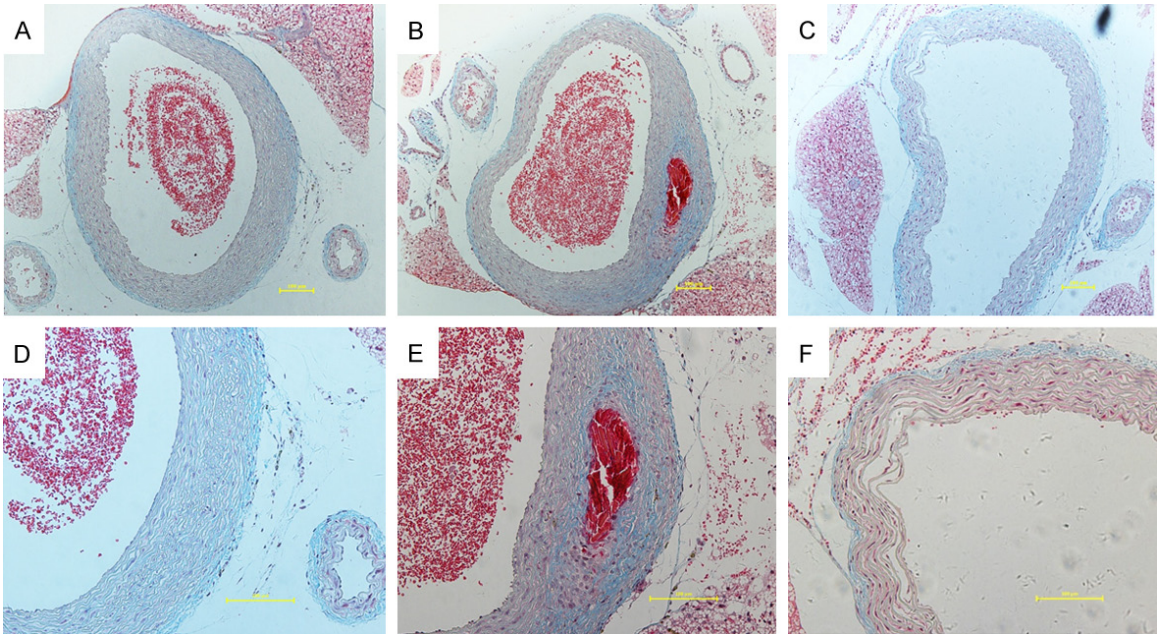

Figure 5. Masson's staining from the control group (A and D), 100 mg/kg AEEA group (B and E), and 150 mg/kg group (C and F). Elastic fibers were dyed blue. In the control group, the elastic fibers were intact (A and D). Scattered and fractured fibers (B and E) and separated fibers (C and F) were observed, with these features more obvious in the 150 mg/kg AEEA group than the 100 mg/kg AEEA group. Scale bars = 100 μm.

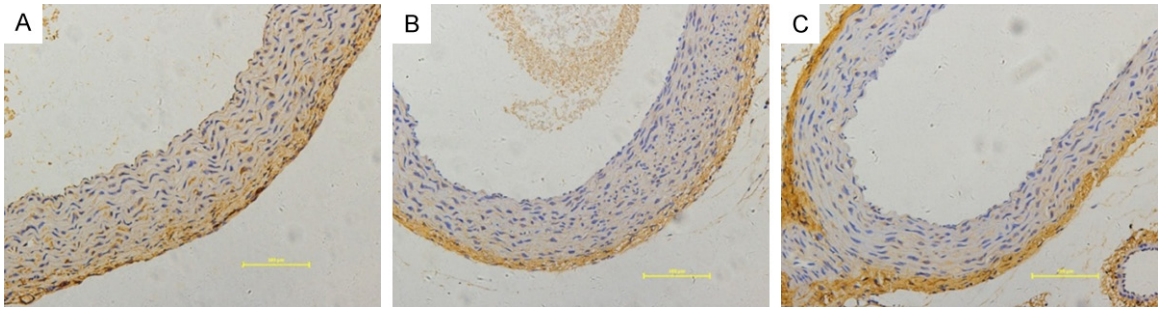

Figure 6. Immunostaining with collagen type I antibody showed that collagen type I was localized predominantly in the adventitia of the aorta of the newborns. The media of the ascending aorta in the newborns in the control group showed obvious positive staining (A). The experimental group showed a lack of staining for collagen type I in the media of the ascending aorta (B: 100 mg/kg AEEA; C: 150 mg/kg AEEA). Scale bars = 100 μm.

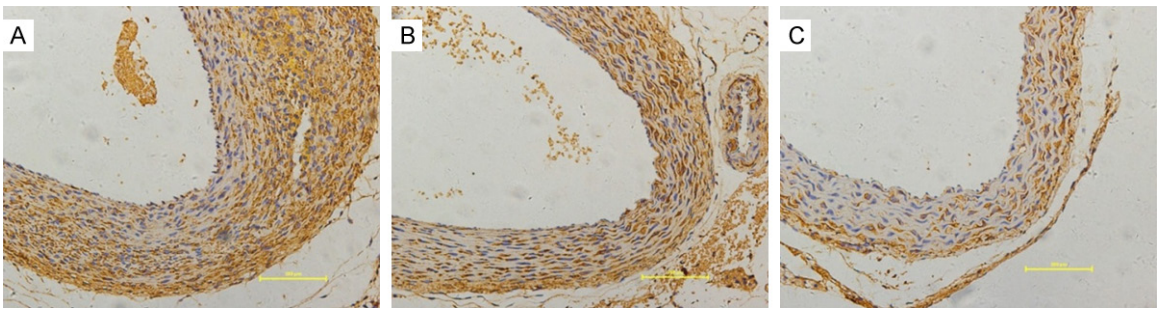

Figure 7. Immunostaining with collagen type III antibody showed that collagen type III was localized predominantly in the adventitia of aorta of the newborns. The media of the ascending aorta in the newborns of the control group showed obvious positive staining (A). The experimental group showed a lack of staining for collagen type III in the media of the ascending aorta (B: 100 mg/kg AEEA; C: 150 mg/kg AEEA). Scale bars = 100 μm.

In the 150 mg/kg AEEA group, intimal rupture of the vessel walls was observed, in addition to blood flow in the media. Thus, the media was filled with red blood cells. Aortic dilatation and dissecting aortic aneurysm were also observed. In the low-dose (100 mg/kg) AEEA group, only interhemispheric hematomas were observed. In the normal saline group, the vasculature was intact and no aortic dissection was observed (**Figures 3** and **4**).

The elastic fibers determine the elasticity of the vascular wall. In the control group, the elastic fibers were intact. Scattered and fractured fibers and separated fibers were observed in the 100 mg/kg AEEA group and the 150 mg/kg AEEA group, respectively. In addition, these features were more obvious in the 150 mg/kg AEEA group than the 100 mg/kg AEEA group (**Figure 5**).

Immunohistochemistry

The middle aortic wall consists of elastic fibers and collagen fibers, which exert an anti-stress effect. Collagen fibers are mainly composed of collagen I and III. As shown by the results of immunostaining with collagen type I antibody compared with the control group, the amount of collagen I was significantly reduced in the experimental group. Furthermore, the reduction of collagen I was more obvious in the high-dose (150 mg/kg) AEEA group than in the low-dose (100 mg/kg) AEEA group (**Figure 6**). In both experimental groups and the control group, the amount of collagen I in the ascending aorta was less than in the descending aorta. The immunostaining findings with collagen type III antibody were consistent with those observed for collagen I (**Figure 7**).

Discussion

Aortic dissection is a life-threatening disease, with an annual incidence of ranges from 5 to 30 cases per million people, depending on the prevalence of risk factors in the study population [10]. The incidence rate of aortic dissection is higher in China, and those affected are younger than in other countries. Patients usually die of blood vessel rupture and organ ischemia, although timely surgery and effective conservative medical management can reduce mortality. Although aortic vascular disease has been the focus of research attention internationally since 1948, the underlying cause of aortic dissection remains unclear. Compared with common cardiovascular disorders, such as coronary heart disease and high blood pressure, the clinical diagnosis and treatment of aortic dissection are difficult. Studies have shown that the risk of sudden death with aortic dissection is three times higher than with coronary heart disease [11]. Reducing blood pressure and thus preventing extension of the dissection is the main focus of treatment of aortic dissection [12].

At present, the consensus is that the mechanism of aortic dissection involves external or internal forces, which result in aortic intima dissection and weakening of the media, leading to blood flow and tearing of the vessel walls [13]. The middle layer of the aortic wall is mainly composed of vascular smooth muscle cells (VSMCS) which can be ranged two different phenotypes, i.e., a contractile phenotype and a synthetic phenotype. Synthetic phenotype has a stronger proliferation and migration ability to synthesize extracellular matrix, which is made up of elastic fibers and collagen fibers [14]. The ability plays an extremely important role in maintaining the integrity, compliance and compression capability of the normal aorta wall [15, 16]. Previous research revealed that changes in the media of the aortic wall contributed to the formation of aortic dissection [17, 18]. Reports also indicated that elastic fibers were more important than collagen fibers in the thoracic aorta [19]. Furthermore, elastic fiber breakage in the media of aortic wall was demonstrated in an animal model of aortic dissection [20]. As the exact cause of aortic dissection is not known, it is difficult to establish an ideal experimental animal model. Establishing a reliable and stable aortic dissection animal model for the etiologic study of aortic disease is essential.

As noted earlier, previous research aimed at developing an animal model of aortic dissection including living models and vitro models. In contrast, recent research has increasingly focused on living models, which were more suited to in-depth studies of the molecular mechanisms of aortic disease [21]. Early animal models of aortic dissection involved large animals, such as dogs and pigs, and also included using

surgical interventions to study aortic dissection [22]. Today, small stable reproducible animal models of aortic dissection are favored instead [23]. Such models can be better able to shed light on the pathogenesis of aortic dissection and adapt to the appropriate drug treatment.

Different from previous studies, we described a new aortic dissection model involving newborn rats exposed to AEEA, a semicarbazide, which inhibits a vascular enzyme, semicarbazide-sensitive amine oxidase in the present study. We then conducted a morphological and pathological study of the aortic vessels of newborns from rats administered AEEA by intragastric gavage at 14-20 days of gestation. As also shown by the results, the amount of collagen was association with damage to the vessels.

The experimental method used herein was first described by Xu et al. in 2014 [8]. They compared the formation of aortic dissection in neonatal rats administered different doses of AEEA by gavage and intraperitoneal injection. Their results indicated that an intragastric route was safer than an intraperitoneal route, with a higher rate of aortic dissection found in rats that received intragastric gavage. In this study, after administering 100 mg/kg and 150 mg/kg of AEEA to pregnant rats by intragastric gavage, the incidence of aortic dissection reached 100% and no fatal toxicity in both groups of neonatal rats. Their results suggested that AEEA could be safely administered by gavage to pregnant mice on 14-20 days of gestation at doses of 100 mg/kg and 150 mg/kg. On dissection, the aortas of the newborn pups could be observed by the naked eye and in pathological sections. As aortic dissection was observed at both doses, they concluded that 100 mg/kg was a safer and more effective dose. We used the same experimental method as Xu et al. and administered AEEA (100 mg/kg and 150 mg/kg) daily by gavage to pregnant rats on 14-20 days of gestation. The newborn pups were anatomized to obtain intact aortic vessels. In the present study, four of 43 cubs in the 100 mg/kg AEEA group showed dilatation of the ascending aortic wall and hematoma formation. In the H&E stained sections, no significant endometrial rupture or blood in the media were observed, as is typical in aortic dissection. In the 150 mg/kg dose group, aortic dilatation, tortuosity, and intravascular thrombosis were observed in 40 neonatal rats. The typical intimal rupture seen in aortic dissection was enhanced by H&E staining, and the rate of aortic dissection was 100%. The results were different from Xu et al. Thus, we concluded that 100 mg/kg was not the best concentration and that an AEEA dose of 150 mg/kg by gavage to pregnant rats, which resulted in aortic dissection in all the newborn rats, was the most successful aortic dissection animal model. The aortic walls of the control group were smooth and complete, with no sandwiching of vasculars. These findings indicate that the concentration of AEEA is vital in the formation of aortic dissection.

Aortic dissection causes splitting of the media of the aortic wall. The media is composed of VSMCS and proteins, including collagen and elastin fibers [20]. In the present study, Masson's staining revealed obvious breakage of elastic fibers of the media of the aortic wall and disordered rows of fibers in the AEEA groups. In contrast, these fibers were intact and in orderly rows in the control group. The immunohistochemical analysis also showed changes in the collagen fibers of the media. Compared with the control group, the amount of collagen I and collagen III was significantly reduced in the 150 mg/kg AEEA experimental group, with more obvious reductions in the ascending aorta than in the descending aorta. The abnormalities identified in the present study in elastic and collagen fibers suggest that cross-linking of elastic and collagen fibers seems to play an important role in the integrity, elasticity, and tensile forces of the aortic wall. Without effective cross-linking, the walls of the aorta are weakened and are characterized by broken elastic fibers and disordered collagen fibers. These changes make the aorta vulnerable to external shocks, resulting in tearing of the media of the aortic wall, and ultimately lead to the formation of aortic dissection.

In conclusion, we established an animal model of aortic dissection model, with a 100% incidence rate, using a drug-induced approach. The mechanism underlying the induction of aortic dissection by AEEA remains unclear. One possible mechanism is the inhibition of the formation of effective cross-linking of elastic and collagen fibers in the media of the aorta, followed by tearing of the media and formation of the sandwiching. The aortic dissection animal model established herein can be expected to assist research on the etiology and mechanism of aortic disease.

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Disclosure of conflict of interest

None.

Authors' contribution

ZHD performed the experiments, collected and analyzed the data, wrote the manuscript, and participated in the design of the experiments. WHH performed the experiments, collected and analyzed the data, and wrote the manuscript. JHL conceived the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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