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A novel abdominal aortic aneurysm model produced by periarterial application of hydrochloric acid

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Abstract: Previous abdominal aortic aneurysm (AAA) animal modeling methodologies were either expensive or complicated. Here, we developed a novel AAA model which was simple to set up and generated minimal calcification. Twenty-four rats were divided randomly into four groups. Groups 1, 2 and 3 underwent surgery in which 15% hydrochloric acid (HCl) was applied periarterially to the abdominal aorta for 5 min, followed by sacrifice 1 week (group 1), 2 weeks (group 2), and 4 weeks (group 3) after surgery. The maximum aortic diameter (MAD) was measured at surgery and before animal sacrifice. Rats in group 4 were sham-treated. The MADs in group 1, 2 and 3 showed significant dilation compared with group 4, with a mean dilation rate of 33.8% in the first week after surgery. Histopathological examination revealed infiltration of macrophages into the adventitia, obvious apoptosis of smooth muscle cells, and rupture and collapse of the elastic fibers. Furthermore, no calcification was observed in the dilated aorta. The mRNA expression levels of inflammatory factors were at least two-fold higher in group 1 than in group 4, indicating significant inflammatory response in the progression of AAA information. In conclusion, periarterial application of 15% HCl is a convenient and reliable model to create an abdominal aortic aneurysm in rats, and the potential development mechanism may be related to the proinflammatory effects of HCl.
Key words: abdominal aortic aneurysm, chemically induced method, elastic fiber, hydrochloric acid, inflammation

Introduction

Abdominal aortic aneurysm (AAA) represents an abnormal dilation of the aorta that leads to death following rupture. The prevalence of AAA varies in different regions. In China, 0.19% of the population aged >65 years was found with AAA based on a hypertensive population census, almost one-tenth of the prevalence in European countries [1, 2]. The data in the US showed that the prevalence reached more than 10% in 80- to 85-year-old individuals, and AAA is the 10th leading cause of death in men over the age of 55 years [3, 4].

Although traditional surgery and endovascular techniques have been used to treat AAA, procedural-related injuries and complications are inevitable, likely leading to operation failure [5]. Thus, much effort has been exerted to explore medical treatment, and animal models are useful in this regard. Because changes in aortic compliance caused by elastic fiber damage are typical AAA features [6], restoring or improving aortic compliance has always been a key point in basic research.

Since the first animal model reported in 1960, modeling methods have been developed gradually over time, such as genetic manipulation, physical or chemical induction, and the combination of both [7]. Although no perfect model covers all human features, these methods

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provide us with approaches to investigate each specific mechanism involved in AAA development.

The most commonly used model is the chemically induced approach, which includes intraluminal infusion of porcine pancreatic elastase (PPE) and periaortic application of calcium chloride ($CaCl_2$). The former model requires introducing a catheter into a surgically-isolated aortic segment and infusing PPE with persistent pressure [8]. The procedure is relatively complex and time-consuming. The latter model reduces the surgical difficulty; however, the aneurysms are always calcified because of calcium crystal deposition, failing to meet the demands of studying the compliance changes in the aortic wall.

Herein, we developed a novel AAA rat model with peri-arterial application of 15% hydrochloric acid. This model exhibited morphological and histological alterations similar to AAA, as well as considerable aortic wall inflammation. More notably, this model was simple to construct and generated minimal calcification, making it ideal for examining the mechanical properties of aneurysm walls.

Materials and Methods

Animals and materials

This study was approved by the Animal Experiment Committee, Chinese PLA General Hospital (Beijing, China). Male Sprague-Dawley rats (12 weeks of age, 300–350 g in weight) were purchased from the Experimental Animal Center at our hospital and were used for the experiments. Hydrochloric acid (HCl) was purchased from Huahui Chemicals Co. (Beijing, China).

Creation of the AAA model

Induction of general anesthesia was performed using 6% sodium pentobarbital (0.1 ml/100 g body weight). Laparotomy was performed via a midline abdominal incision. The posterior peritoneum was incised. Next, a 1.5-cm segment of the infra-renal abdominal aorta was dissected free from the inferior vena cava, and the collateral arteries were ligated. The proximal and distal dissected aorta was clamped after emptying the blood of this segment. A small piece of gauze soaked with 15% HCl liquid was applied perivascularly for 5 min. A piece of rubber strip was placed between the aorta and vena cava to prevent the latter from contacting HCl (Fig. 1). Finally, the aorta was flushed with saline, and the abdomen was closed in layers.

Experimental design

Twenty-four rats were divided randomly into four groups. Three groups were treated with 15% HCl as described above and sacrificed 1 week later (group 1), 2 weeks later (group 2), and 4 weeks later (group 3). Before these rats were killed, the maximum diameter of the treated aorta was re-measured. The other six rats (group 4) infused with saline were deemed the sham group and killed 1 week later. To re-confirm the dilation rate, the maximum intima-to-intima diameter of the treated aorta was also measured with ultrasound before surgery and sacrifice. Next, the aortic samples of all groups were harvested for histological examination and mRNA assessment.

Morphological analysis

The maximum external diameter of the infrarenal aorta was measured using a digital caliper (SMCT, Shanghai, China) prior to treatment and at the time of tissue harvest. Each measurement was performed three times and the mean values were calculated for analysis. The dilation rate was calculated using the following

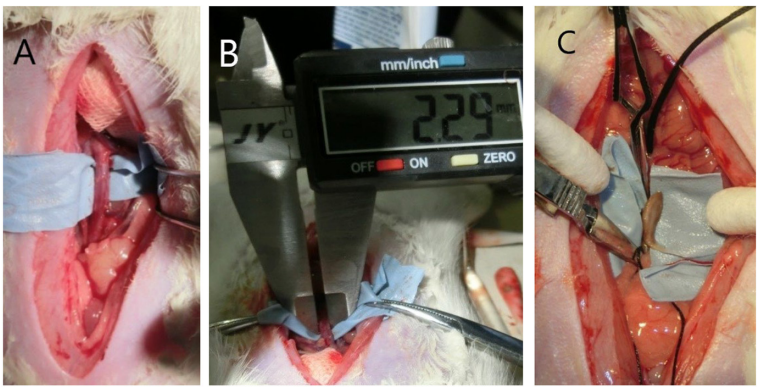

Fig. 1. Model-building surgery. A. The abdominal aorta was separated, and a piece of rubber strip was placed between the aorta and vena cava. B. The aortic diameter was measured using a digital caliper. C. A small piece of gauze soaked with hydrochloric acid (HCl) was applied perivascularly for 5 min.

equation:
Dilation rate (%) = $(D_1 - D_0) / D_0 \times 100\%$,
where D_0 represents the external diameter of the aorta prior to treatment and D_1 represents the mean maximum external diameter of the pathological section.

Histology and immunohistochemistry

The aortic samples were fixed in buffered formalin and embedded with paraffin. The specimens were cut in 5-μm cross-sections and were attached to glass slides. After removing the paraffin, the slides were stained with hematoxylin and eosin and elastic von Gieson to visualize histological changes and the elastic fibers. CD68 staining was also performed to test the presence of macrophages. In addition, to verify the presence of calcification in the hydrochloric acid-treated aorta, Alizarin Red S staining was performed on samples from group 2, while using the healthy aorta as a control.

Assessment of the mRNA expression of inflammatory factors

Because groups 1 and 4 had the same observation period, partial aortic samples of the two groups were used for mRNA detection to initially investigate the potential mechanism of this model. Seven inflammatory factors, tumor necrosis factor (*TNF*)-*α*, interleukin (*IL*)-*1β*, *IL-6*, transforming growth factor (*TGF*)-*β*, CXC chemokine ligand (*CXCL*)-*2*, matrix metalloproteinase (*MMP*)-*9* and *MMP-2*, which are considered important factors in human AAA development, were evaluated. RNA was extracted using an RNA extraction kit (ComWin Biotech, Beijing, China) and was reverse-transcribed into cDNA using universal primers. The single-stranded cDNA was then used in quantitative real-time polymerase chain reaction (PCR) to evaluate the relative expression level of the four inflammatory factors compared with β-actin. Two sets of primers for each inflammatory factor are listed in Table 1. All the samples were examined in triplicate using the Applied Biosystems (ABI 7300) real-time PCR machine. The reactions were run for 40 cycles (95°C for 5 s, 60°C for 31 s).

Statistical analysis

Statistical analysis was performed using SPSS 11.0. All the results were expressed as means ± SEM, which included the aortic diameter and data obtained from real-time PCR. One-way analysis of variance (ANOVA) was used to compare all the data among the groups. *T*-test was used to analysis the real-time PCR results. A P value<0.05 was considered statistically significant.

Table 1. Primers for inflammation factors

TNF-α	F: 5'-TGAGCACAGAAAGCATGATC-3′ R: 5'-CATCTGCTGGTACCACCAGTT-3′
IL-1β	F: 5′-GACCTGTTCTTTGAGGCTGAC-3′ R: 5′-TCCATCTTCTTCTTTGGGTATTGTT-3′
IL-6	F: 5′-CACTTCACAAGTCGGAGGCT-3′ R: 5′-TCTGACAGTGCATCATCGCT-3′
TGF-β	F: 5′-ACTACGCCAAAGAAGTCACC-3′ R: 5′-ACTGCTTCCCGAATGTCTG-3′
CXCL-2	F: 5′-AACATCCAGAGCTTGACGG-3′ R: 5′-CAGTATCTTTTGGACGATCCTCT-3′
MMP-2	F: 5′-GACACTGGTACTGGACCCAC-3′ R: 5′-ACTGTCCGCCAAATAAACCG-3′
MMP-9	F: 5'-CGGAGCACGGGGACGGGTATC-3′ R: 5'-AAGACGAAGGGGAAGACGCACATC-3′
β-actin	F: 5'-GCTCGTCGTCGACAACGGCTG-3' R: 5'-CAAACATGATCTGGGTCATCTTTTC-3'

Results

Morphological changes

All 24 rats underwent surgery successfully. However, one rat each in groups 2 and 3 showed failure to detect changes at the designated time because of severe adhesion of the aorta with the surround tissues, especially with the inferior vena cava. The treated aortas of all the other rats were all successfully isolated, and the maximum diameters were measured. As shown in Fig. 2 and Table 2, the treated aortas presented obvious dilation 1 week after surgery, with a mean dilation rate of 33.8%, while the dilation rate in group 4 was 1.07%. The dilation rate in group 2 was 39.7% and that in group 3 was 43.9%. The dilation rate in groups 1, 2, and 3 showed no statistically significant difference. The treated aortas dilated most rapidly in the first week after the operation and then dilated slowly after 2 weeks. The ultrasonic measurement of the treated aorta shows a same dilation tendency, with a mean dilation rate of 23.9% in group 1, 27.0% in group 2, 29.5% in group 3, and 1.98% in group 4.

Histology changes

As shown in Fig. 3, most of the smooth muscle cells (SMCs) in the media were relatively intact at 1 week, while the SMC nuclei became fragmented at 2 weeks. Samples at 4 weeks showed fewer SMC nuclei, and the medium became collapse compared with that in the other groups. CD 68 staining (Fig. 4) revealed that significant macrophages infiltrated in the adventitia at 1 week, and its number were slightly decreased 2 weeks after surgery. The macrophages were significantly decreased at 4 weeks, but still could be observed. Von Gieson staining (Fig. 5) showed that the elastic fibers ruptured progressively at 1 week and 2 weeks after the

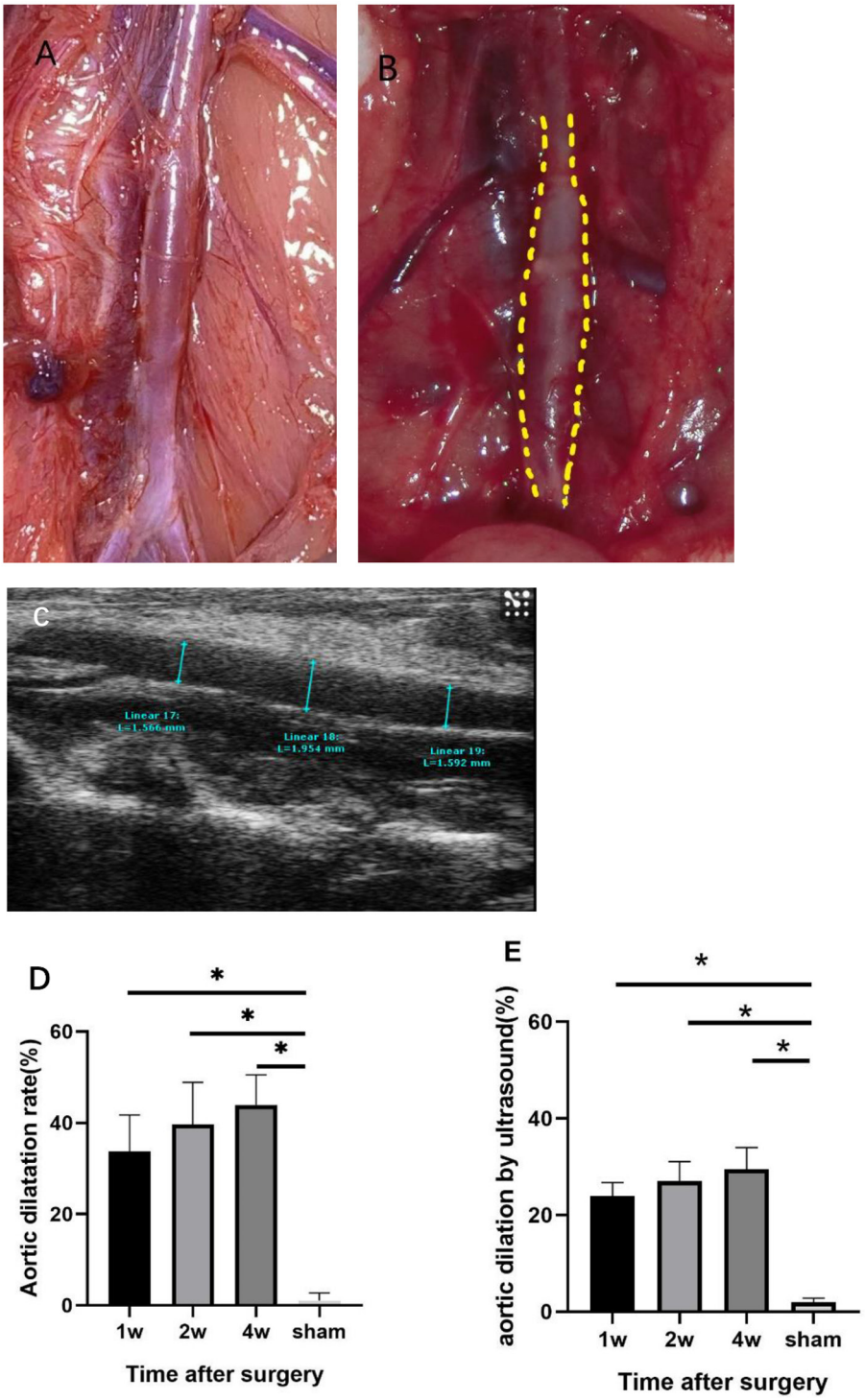

Fig. 2. Morphology of the aorta following treatment with 15% hydrochloric acid (HCl). A. Representative picture of arterial dilation 1 week after surgery. B. Representative picture of arterial dilation 2 weeks after surgery. C. Ultrasound detection of arterial dilation 1 week after surgery. D. The dilation rates measured by the digital caliper. The treated aorta showed the most rapid dilation in the first week after the operation and then started to dilate slowly after 2 weeks. E. The dilation rates measured by ultrasound. **P*<0.05 compared to sham.

operation and collapsed at 4 weeks. Alizarin Red S staining (Fig. 6) showed that no obvious calcification was observed in the HCl treated aorta with the healthy aorta as a control.

mRNA expression of inflammatory factors

All the detected inflammatory factors showed significantly higher mRNA expression in group 1 than in group 4. Considering the mRNA of these factors expressed in

Table 2. Aortic dilation rate measured with the digital caliper in different groups

No.	Goup 1 (D_1/D_0)	Goup 2 (D_1/D_0)	Goup 3 (D_1/D_0)	Goup 4 (D_1/D_0)
1	38.6% (2.87/2.08)	29.4% (2.55/1.97)	34.5% (2.65/1.97)	0 (1.83/1.83)
2	37.6% (2.78/2.02)	54.6% (3.03/1.96)	53.0% (2.54/1.66)	3.0% (2.04/1.98)
3	45.4% (2.89/1.99)	39.2% (2.45/1.76)	43.2% (2.52/1.76)	0 (2.05/2.05)
4	28.1% (2.69/2.10)	37.1% (2.77/2.02)	45.0% (2.93/2.02)	3.4% (1.85/1.79)
5	27.9% (2.52/1.97)	38.0% (2.54/1.84)	44.0% (2.65/1.84)	0 (1.97/1.97)
6	25.1% (2.74/2.19)	-	-	0 (2.01/2.01)
Mean value	33.8%*	39.7%*	43.9%*	1.07%

*P<0.05 vs. group 4; D_0: the external diameter of the aorta prior to treatment; D_1: the maximum external diameter of the pathological section.

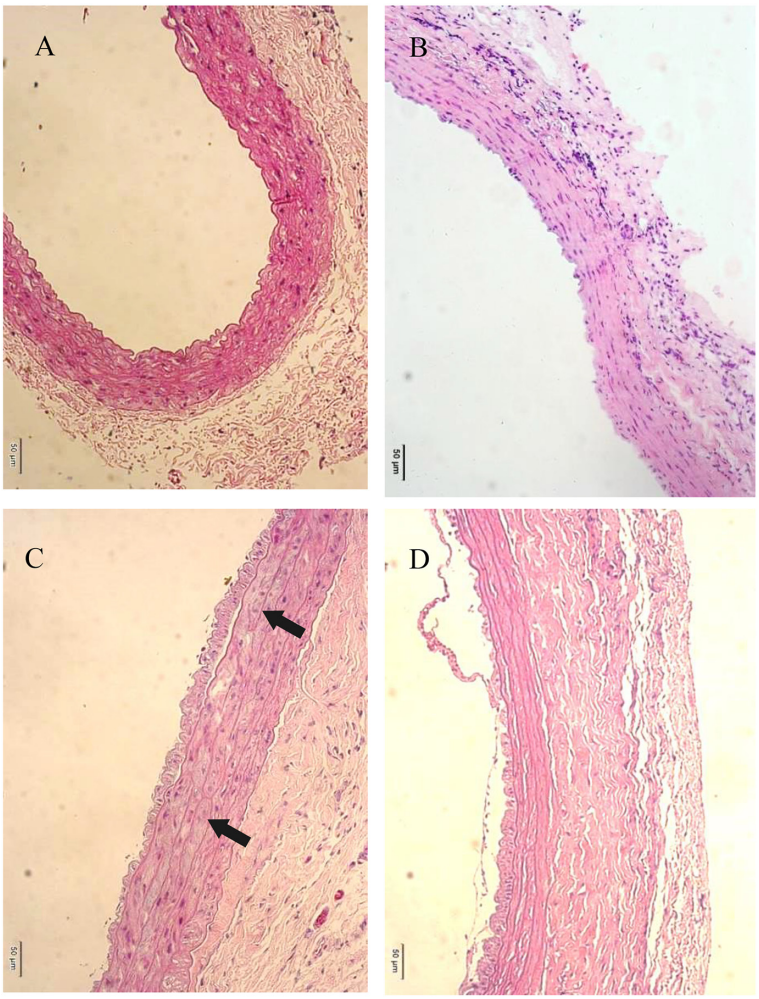

Fig. 3. Histological changes of the dilated aorta in different groups (×40). A. Aorta of the sham group (group 4). B. The dilated aorta 1 week after surgery (group 1) showed mass of inflammatory cells infiltrated into the adventitia, while the media was almost intact. C. The dilated aorta 2 weeks after surgery (group 2) showed a decreased number of the smooth muscle cells (SMCs) in the media and nuclear fragmentation (black arrow). D. The dilated aorta 4 weeks after surgery (group 3) showed that SMCs were seldom observed and the media was thin. Scale bars, 50 μm in (A–D).

group 4 as the baseline, group 1 showed 14-fold higher *IL-6*, 8-fold higher *TNF-α*, 4-fold higher *IL-1β*, 2-fold higher *TGF-β, MMP-2* and *MMP-9*, and 1.5-fold higher *CXCL-2*. Thus, a significant inflammatory response underlies the effect of HCl on the aorta (Fig. 7).

Discussion

This study demonstrated that perivascular application of 15% HCl on the aorta induced aortic dilation. One week after treatment, 100% of the rats had a dilation

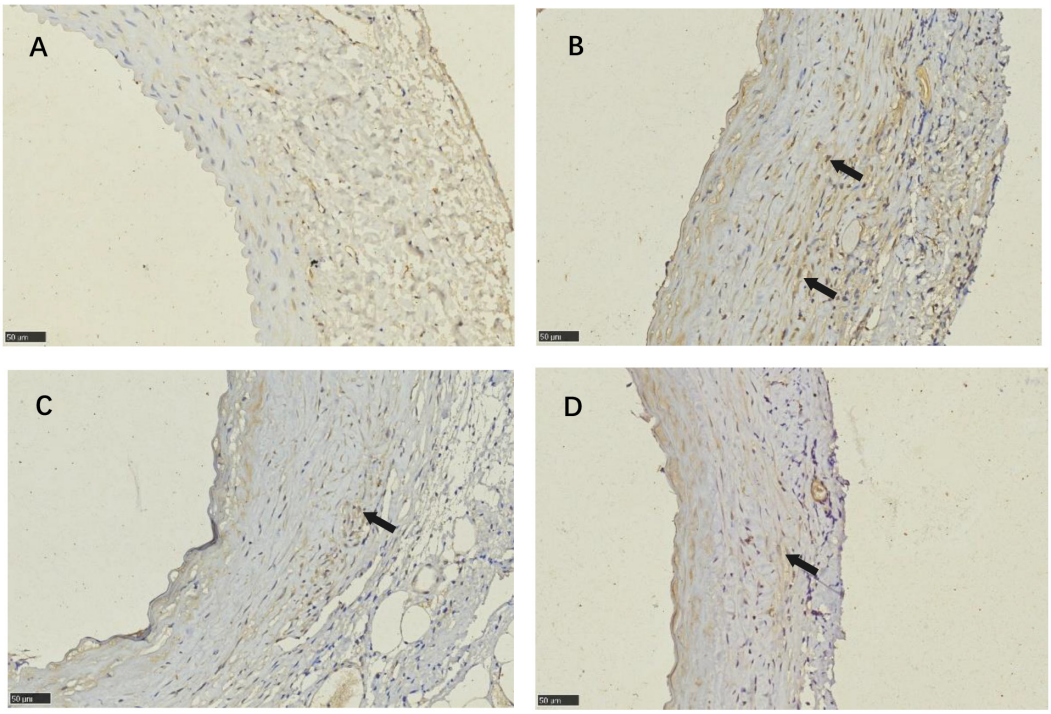

Fig. 4. CD 68 staining of the dilated aorta in different groups (×40). A. Aorta of the sham group (group 4). B. The dilated aorta 1 week after surgery (group 1) manifested significant macrophages (black arrows) infiltrated in the adventitia. C. The dilated aorta 2 weeks after surgery (group 2) showed the macrophages were slightly decreased. D. The macrophages were significantly decreased in the dilated aorta 4 weeks after surgery (group 3). Scale bars, 50 μm in (A–D).

greater than 20% in diameter compared with the initial diameter, and the dilation continued but slowed down at 2 weeks and later. The results were also confirmed by ultrasonic measurement. It should be noted that the dilation rate measured by ultrasound was lower than that by the digital caliper. The reason mainly lied in the intimal hyperplasia caused by HCl, which decreased the lumen of aorta.

Strictly following the definition of AAA, in which the aortic diameter is more than 1.5 times larger than that of the normal aorta, only one rat at 2 weeks after surgery met the criteria. However, if using the threshold of a 20% diameter increase to define AAA [9], the aneurysm formation rate at 1 week after surgery in our experiment could reach 100%.

For all the AAA models, significant dilation in the aorta was mostly observed in mice [10, 11]; however, in rats, aortic dilation shrank if only one induction method was used. Isenburg *et al.* deemed AAA in two-thirds of rats that developed aneurysm with a 20% diameter increase based on only $CaCl_2$ liquid applied perivascularly [9]. Elastase alone was also insufficient to induce AAA stably in rats [12]. Therefore, the two methods were combined to be used for significant aortic dilation in rat experiments. $CaCl_2$ extraluminal application combined with intraluminal elastase infusion increased AAA formation to 51–55% at 1 week with the definition of AAA as a 50% diameter increase [13–15]. Obviously, these methods were complex, particularly intraluminal elastase infusion, which requires pressurized infusion of elastase through iliac-femoral artery access [16]. Periaortic application of $CaCl_2$ or $CaPO_4$, which always leaves calcium deposition on the wall, leads to severe calcification of the treated aorta; thus, it is ineligible to use to study the mechanical property of the aortic wall.

HCl has been used to build an animal model of acute lung injury because of its chemically erosive and proinflammatory effects [17]. In this novel model, HCl promoted mass inflammatory cell infiltration into the adventitia of the aorta that secretes inflammatory factors, leading to elastic fiber damage. Unlike $CaCl_2$ or a mixture of $CaCl_2$ with phosphate, with lasting effects on the aorta because of the deposition of calcium phosphate crystals, HCl is volatile and the chemical injury caused by HCl is transient, while the consequent inflammation would persist for a longer duration. In addition, HCl is a common decalcification agent for bone specimens [18]; thus, the treated aorta would show no calcification. Therefore, this novel model could be used to test the elastic compliance of the aortic wall, providing clues to the mechanical mechanism of the aneurysm.

The pathophysiology of this model featured apoptosis

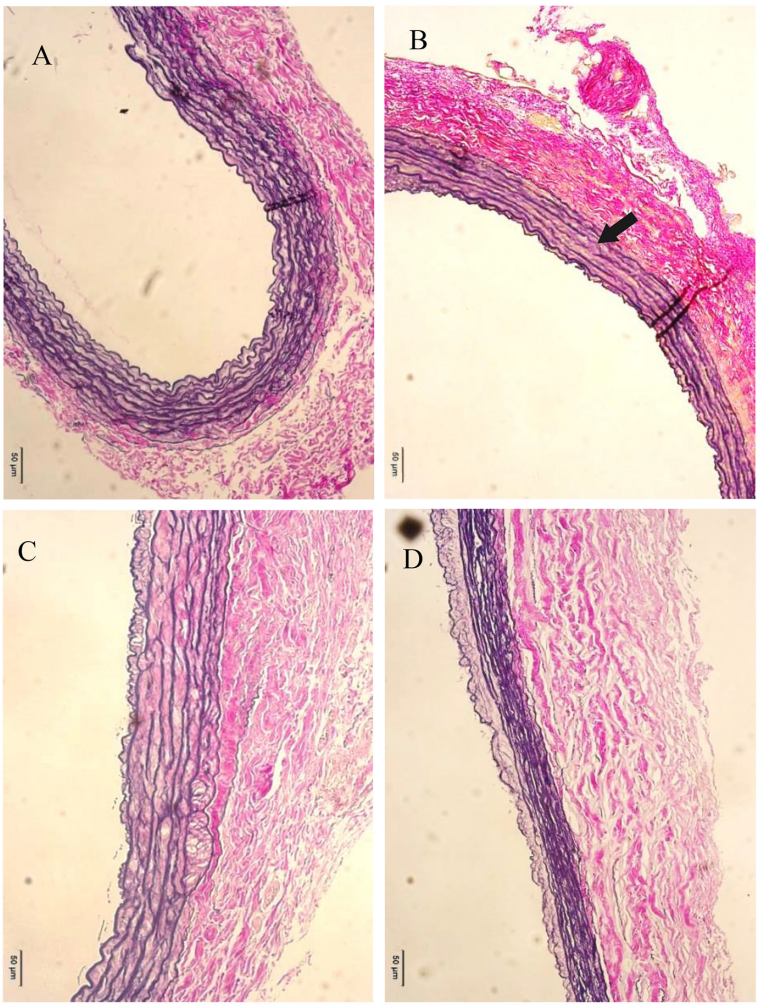

Fig. 5. Elastic fiber changes of the dilated aorta in different groups. A. Aorta of the sham group (group 4). B. The treated aorta 1 week after surgery (group 1) showed rupture of elastic fibers in a limited region (black arrow). C. The treated aorta 2 weeks after surgery (group 2) showed extensive rupture of elastic fibers. D. The treated aorta 4 weeks after surgery (group 3) showed that the elastic layers collapsed. Scale bars, 50 μm in (A–D)

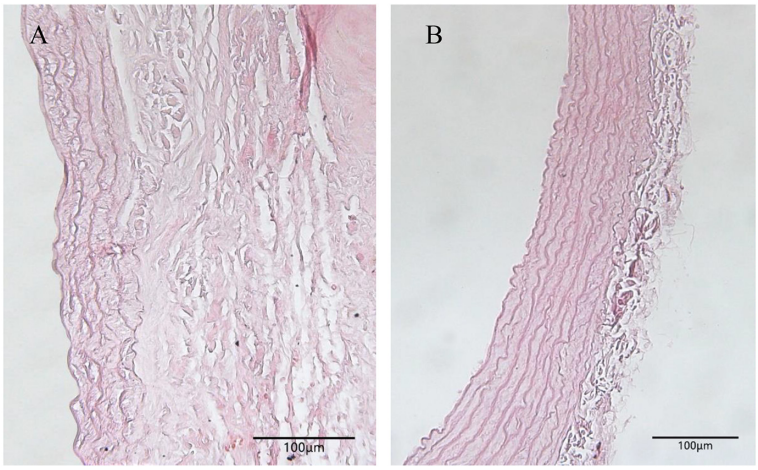

Fig. 6. Alizarin Red S staining of hydrochloric acid (HCl) treated aorta (A) and healthy aorta (B). A. Aorta of the HCl treated segment 2 weeks after surgery (group 2) showed no obvious calcification. B. The healthy aorta was as a control.

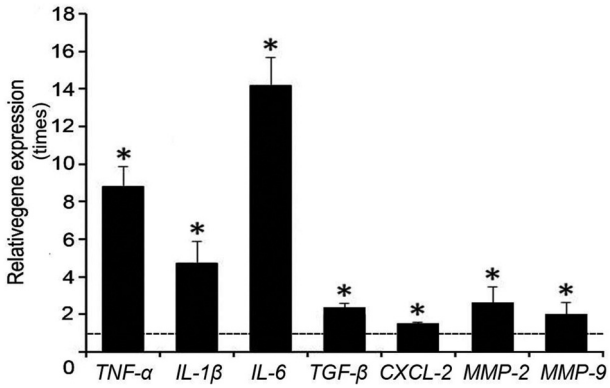

Fig. 7. Relative quantitative gene expression of specific inflammation factors by comparing groups 1 and 4. The gene expression levels of the seven factors in group 4 were deemed the baseline (dotted line). The gene expression levels in group 1 were at least 1.5 times higher than that in group 1. **P*<0.05 compared to group 4.

of smooth muscle cells, rupture and collapse of elastin, and infiltration of inflammatory cells, which mimic changes in human AAA [19]. The changes in different groups reflected the dynamic pathological progress of the treated aorta. Surprisingly, the dilation rate among rats at 1 week, 2 weeks, and 4 weeks after surgery showed no statistical difference. The cause may be due partly to the inflammation caused by HCl not lasting sufficiently long to induce extensive damage to the aortic wall, as evidenced by the manifestation of macrophages, which is a representative kind of inflammatory cells in AAA formation and development. The treated aorta appeared infiltration with significant macrophages at 1 week and 2 weeks after surgery,and less macrophages left at 4 weeks. Additionally, Diehm *et al.* revealed severe structural damage in the infrarenal aortic aneurysm neck that was not yet significantly dilated [20], providing clues that aortic dilation might not necessarily be consistent with the severity of pathophysiological changes.

TNF-α, IL-1β, IL-6, TGF-β, CXCL-2, MMP-2 and *9* are important inflammatory factors with a high correlation to AAA. The human aneurysm wall shows higher expression of *TNF-α* and *IL-6* than that of the normal aorta, while no differences in *IL-1β* and *TGF-β* [21]. Besides, *CXCL-2, MMP-2* and *9* were detected in human or animal AAA walls [22–24]. In our model, *IL-6* and *TNF-α* were the two most significantly expressed factors, and the other factors were at least 1.5 times higher in expression than the sham, indicating an extensive inflammation induced by HCl, and multiple inflammatory pathways participating in the aneurysm formation. Honestly, 15% HCl may cause chemical corrosion on the aortic wall, but this effect should not be overemphasized. As the pathological change of this model was a progressive process, the aortic dilation was not seen immediately after the HCl application. Because the current study is a preliminary investigation of the potential mechanism of this model, additional studies are needed to further explore the mechanism of this model.

There were some limitations of this model. First, the proportion of the aorta with a 50% diameter increase was low. However, its simple operation process and the pathophysiological changes made it a suitable model for AAA study, particularly to explore the mechanical mechanism of the aneurysm. Second, HCl could cause injury of the surround tissues and operators. Thus, a thick piece of rubber strip is needed to protect the aorta from the surroundings, and the experimental segment of the aorta should be emptied and clamped to prevent thrombosis.

In conclusion, periaortic application of 15% HCl for 5 min could be used to build an aneurysm model that mimics the inflammatory and histological changes in human AAA. This model seldom shows calcification and is suitable to investigate the mechanical properties of AAA. More efforts are needed to explore the potential mechanism of this model.

Authors' Contributions

All authors participated in the design, interpretation of the studies and review of the manuscript; RW, XJC, ZYW and CD conducted the experiments under JX and WG's direction. RW and XJC wrote the manuscript, and WG revised it.

Conflict of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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