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Mercaptoethanol Protects the Aorta from Dissection by Inhibiting Oxidative Stress, Inflammation, and Extracellular Matrix Degeneration in a Mouse Model

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

BCDEF 1,2 **Lei Zhang**
BCDE 2 **Changtian Wang**
BCDF 2 **Zhilong Xi**
ABG 2 **Demin Li**
AEG 3 **Zhiyun Xu**

1 Department of Cardiothoracic Surgery, Nanjing Clinical Medical College, Second Military Medical University, Nanjing, Jiangsu, P.R. China
2 Department of Cardiothoracic Surgery, Jinling Hospital, Nanjing, Jiangsu, P.R. China
3 Department of Thoracic and Cardiac Surgery, Changhai Hospital, Second Military University, Shanghai, P.R. China

Corresponding Authors: Demin Li, e-mail: dr.demin@hainan.net, Zhiyun Xu, e-mail: zhiyunx@hotmail.com
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Background: The aims of this study were to investigate the effects of mercaptoethanol treatment on the expression of mediators of oxidative stress, inflammation, and extracellular matrix (ECM) degeneration in a mouse aortic dissection (AD) model.

Material/Methods: Twenty-four 8-month-old C57BL/6J mice were divided into three groups and studied for two weeks: 1) the aortic dissection (AD) Model group (N=8) underwent intraperitoneal injection of angiotensin II (Ang II) (5 ml/kg) three times every 24 h; 2) the mercaptoethanol Treated group (N=8) were given oral mercaptoethanol (2.5 mM); the Normal group (N=8) underwent intraperitoneal injection of noradrenaline (5 mg/kg) three times every 24 h. Sections of mouse aorta were prepared for histology with hematoxylin and eosin (H&E) staining; immunohistochemistry was performed to detect levels of: nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), nuclear factor κB (NF-κB), p65, superoxide dismutase-1 (SOD1), glutamate cysteine ligase catalytic subunit (GCLC), tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and matrix metalloproteinase-9 (MMP9). Quantitative reverse transcription-polymerase chain reaction (RT-PCR) evaluated mRNA expression of SOD1, GCLC, TNF-α, IL-1β, and MMP9.

Results: Mercaptoethanol treatment inhibited Ang II-induced aortic dissection in AD mice, as shown histologically. Mercaptoethanol treatment reduced the expression levels of NFE2L2, NF-κB, p65, TNF-α, IL-1β and increased the expression levels of SOD1, MMP9, and GCLC.

Conclusions: In an AD mouse model, mercaptoethanol treatment inhibited thoracic and abdominal aortic dissection and reduced aortic tissue expression of mediators of oxidative stress and inflammation and increased the activation of ECM signaling pathways.

MeSH Keywords: **Carotid Artery, Internal, Dissection • Medicine, Chinese Traditional • Oxidative Stress**

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Background

Aortic dissection (AD) occurs when the layers of the aorta undergo separation, usually along the smooth muscle of the aortic media [1,2]. Thoracic AD is more common than abdominal AD clinically, but AD is considered to be a potentially life-threatening with a high rate of mortality [1,2]. In AD, blood and thrombus is found in or along the wall of the aorta, which is the major vessel that carries the blood from the heart [3,4]. Clinically, AD is associated with other conditions, including aortic valve insufficiency, aortic rupture, stroke, and cardiac tamponade, and is found in patients with genetic connective tissue abnormalities, including Marfan's syndrome [5]. Clinically, several surgical approaches have been developed to manage AD, usually involving aortic replacement [6]. Both thoracic AD and abdominal AD are known to occur clinically [7]. Clinically, thoracic AD has an incidence 3 per 100,000 individuals per year [8]. However, the mechanisms of occurrence and the associations between abdominal AD and thoracic AD are rarely studied, apart from their associations with hypertension [9].

Recently, animal models for both thoracic and abdominal AD have been established, by genetic mutation, surgery, and the use of drugs, but with variable results [10,11]. A more successful animal model for AD has been recently established with the long-term use of angiotensin II (Ang II) [12,13].

According to previous studies, the pathogenesis of AD has been shown to be due to biomechanical changes in the aortic wall, with dissection occurring when aortic stress exceeds aortic wall strength [14–16]. However, some recently published studies have shown that reactive oxygen species (ROS) can regulate the cellular and extracellular components of the aortic wall in dissecting thoracic aortic aneurysm [17,18]. Also, the extracellular matrix (ECM) in the aortic wall is now considered to be part of a highly dynamic environment that is responsible for its structural integrity [19]. Molecular changes in the aortic wall ECM have also been shown to affect the aortic wall function and stability [20]. The matrix metalloproteinases (MMP) endopeptidases include matrix metalloproteinase-9 (MMP9), which is involved in remodeling the ECM; mercaptoethanol is an antioxidant and free radical scavenger, which may affect ECM integrity [19,20]. Mercaptoethanol is sometimes used in traditional Chinese medicine.

The aims of this study were to investigate the effects of mercaptoethanol treatment on the expression of mediators of oxidative stress, inflammation, and extracellular matrix (ECM) degeneration in a mouse aortic dissection (AD) model.

Material and Methods

Laboratory animals and ethics declaration

A total of 24 specific pathogen-free (SPF) C57BL/6J mice of between 23–25 g in weight, and eight months-of-age, were purchased from the Beijing Fogangren Biotech. Co. Ltd., Beijing, China. The mice were maintained in a 12/12 cycle of light/dark, and at 25±2°C, and fed with the standard commercial diet purchased from CLEA Japan Inc. (Shizuoka, Japan). The mice were allowed to drink water freely.

This study was approved by the Institutional Animal Care and Use Committee of Jinling Hospital, Nanjing, China. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals, of the National Research Council (NRC).

Mouse aortic dissection (AD) model and study groups

Established thoracic aortic dissection and abdominal aortic dissection animal models were performed according to the previously published studies described [21,22]. The mice were divided into three groups and studied for two weeks: 1) the aortic dissection (AD) Model group (N=8) underwent intraperitoneal injection of angiotensin II (Ang II) (5 ml/kg) (Oddfoni Bio. Co., Nanjing, China) three times every 24 h; 2) the mercaptoethanol Treated group (N=8) were given freshly prepared oral mercaptoethanol solution dissolved in the drinking water (2.5 mM) (Amresco Inc., Solon, OH, USA); the Normal group (N=8) underwent intraperitoneal injection of noradrenaline (5 mg/kg) (Sigma-Aldrich, St. Louis, Missouri, USA) three times every 24 h.

Histopathological analysis

Tissue samples from the mouse thoracic aorta and abdominal aorta of the AD mice models in the three study groups were fixed, sectioned, and examined by histologically by light microscopy (Figure 1). Briefly, the abnormal (dissected) and the normal aortas were harvested from the aorta and were fixed with the 10% paraformaldehyde. The fixed, paraffin-embedded aortic tissues were sectioned at 4 μm, and stained with hematoxylin and eosin (H&E). Photomicrographic images were evaluated using light microscopy, as previously described [23].

Immunohistochemistry

Immunohistochemistry was performed according to the method previously described [24]. Briefly, the thoracic aorta and abdominal aorta of the mice were sectioned at 4 μm and onto glass slides. Then, the sections were incubated with the 3% H_2O_2 to block endogenous peroxidase activity, and 10% fetal

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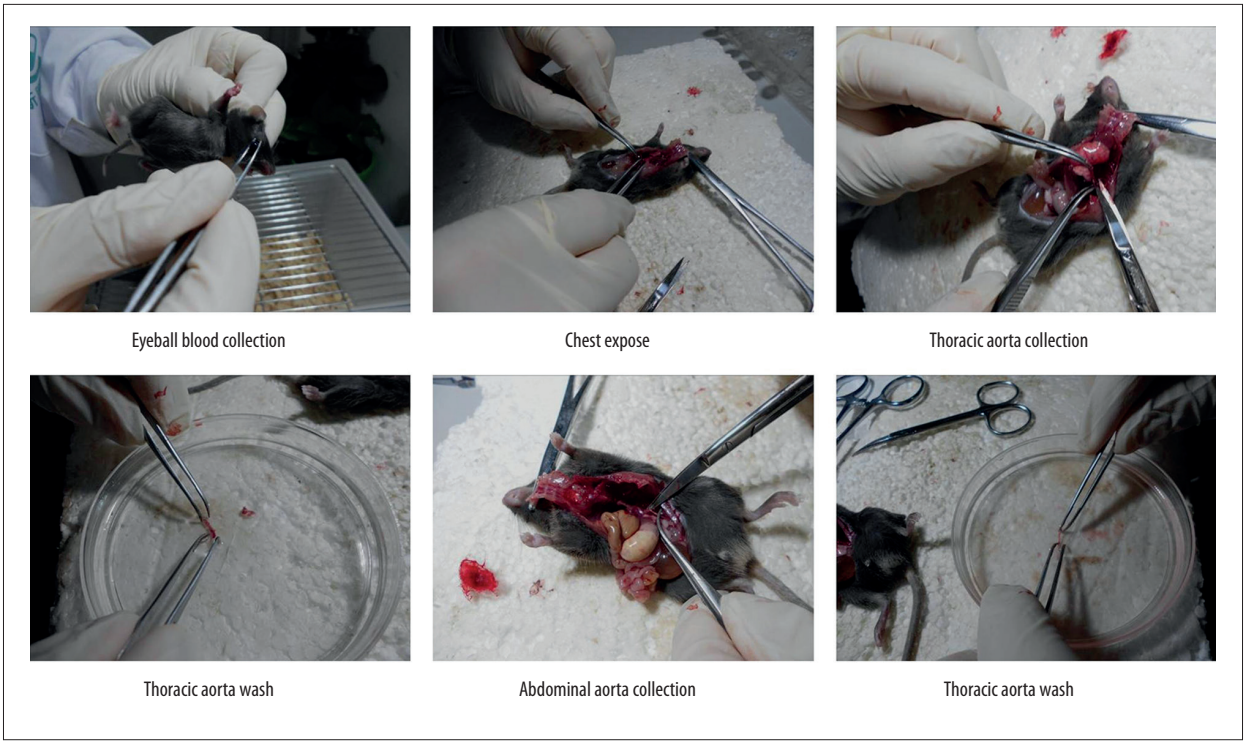

Figure 1. Procedures used for the isolation of the thoracic aorta and abdominal aorta.

bovine serum (FBS) was used to block the non-specific binding of antibodies to the sections.

The aortic tissue sections were incubated with the following primary antibodies: rabbit anti-mouse nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) polyclonal antibody (1: 1000) (Catalogue No. ab137550) (Abcam Biotech., Cambridge, MA, USA); rabbit anti-mouse nuclear factor κB (NF-κB) and p65 polyclonal antibody (1: 1000) (Catalogue No. ab16502) (Abcam Biotech., Cambridge, MA, USA); rabbit anti-mouse superoxide dismutase 1 (SOD1) polyclonal antibody (1: 1000) (Catalogue No. ab13498) (Abcam Biotech., Cambridge, MA, USA); rabbit anti-mouse glutamate cysteine ligase catalytic subunit (GCLC) polyclonal antibody (Catalogue No. ab53179, 1: 1000; Abcam Biotech.), rabbit anti-mouse tumor necrosis factor α (TNF-α) polyclonal antibody (1: 1000) (Catalogue No. ab6671) (Abcam Biotech., Cambridge, MA, USA); rabbit anti-mouse interleukin-1 β (IL-1β) polyclonal antibody (1: 1000) (Catalogue No. ab2105) (Abcam Biotech., Cambridge, MA, USA); and rabbit anti-mouse matrix metalloproteinase-9 (MMP9) polyclonal antibody (1: 1000) (Catalogue No. ab38898) (Abcam Biotech., Cambridge, MA, USA). Primary antibodies were incubated on the tissue sections overnight in a humidified chamber at 4°C. The sections were incubated with the horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG (1: 500) (Catalogue No. ab6721) (Abcam Biotech., Cambridge, MA, USA) for one hour at room temperature.

Digital photomicrographic light microscopic images of the aortic histology and immunohistochemistry were captured and observed by using a light microscope (Olympus, Japan). A total of six randomly selected areas (frames) (×200 magnification) were used to evaluate the images.

Quantitative reverse transcription-polymerase chain reaction (RT-PCR)

Total cellular RNA was extracted from the mouse aorta using TRIzol reagent (Beyotime Biotech. Co. Ltd., Beijing, China). The reverse transcription kit (Western Biotech., Chongqing, China) was used to synthesize cDNA, according to the manufacturer's instructions. Then, the synthesized cDNAs were amplified by using the fluorescent dye, SYBR Green I (Western Biotech., Chongqing, China), and conducted in a rapid real-time PCR system (Eppendorf, Hamburg, Germany). The following conditions were used for amplification: 94°C for 4 min, 94°C for 20 s, 60°C for 30 s, 72°C for 30 s, and for 35 cycles. The primers for SOD1, GCLC, TNF-α, IL-1β, MMP9 are listed in Table 1. The amplified mRNAs were loaded onto the 1.5% agarose gels, and the images were digitally captured by using the Ultraviolet (UV) Gel Imager (Shanghai Tianneng Co., Ltd., Shanghai, China). The targeting gene mRNAs were normalized to the GAPDH gene using the comparative threshold cycle ($2^{-\Delta\Delta CT}$) method.

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Table 1. Primer sequences used in reverse transcription-polymerase chain reaction (RT-PCR).

Genes		Sequences	Length
SOD1	Forward	GTGACTGCTGGAAAGGACGG	196 bp
	Reverse	CAATCCCAATCACTCCACAGG	
GCLC	Forward	GCCCTACGGAGGAACGATG	128 bp
	Reverse	CTAGTCTGGGGAATGAAGTGATG	
TNF-α	Forward	CCCTCCAGAAAAGACACCATG	183 bp
	Reverse	CACCCCGAAGTTCAGTAGACAG	
IL-1β	Forward	GCTTCAGGCAGGCAGTATCA	196 bp
	Reverse	TGCAGTTGTCTAATGGGAACG	
MMP9	Forward	CACAGCCAACTATGACCAGGAT	252 bp
	Reverse	GCTGCCACCAGGAACAGG	
β-actin	Forward	GAGACCTTCAACACCCCAGC	263 bp
	Reverse	ATGTCACGCACGATTTCCC	

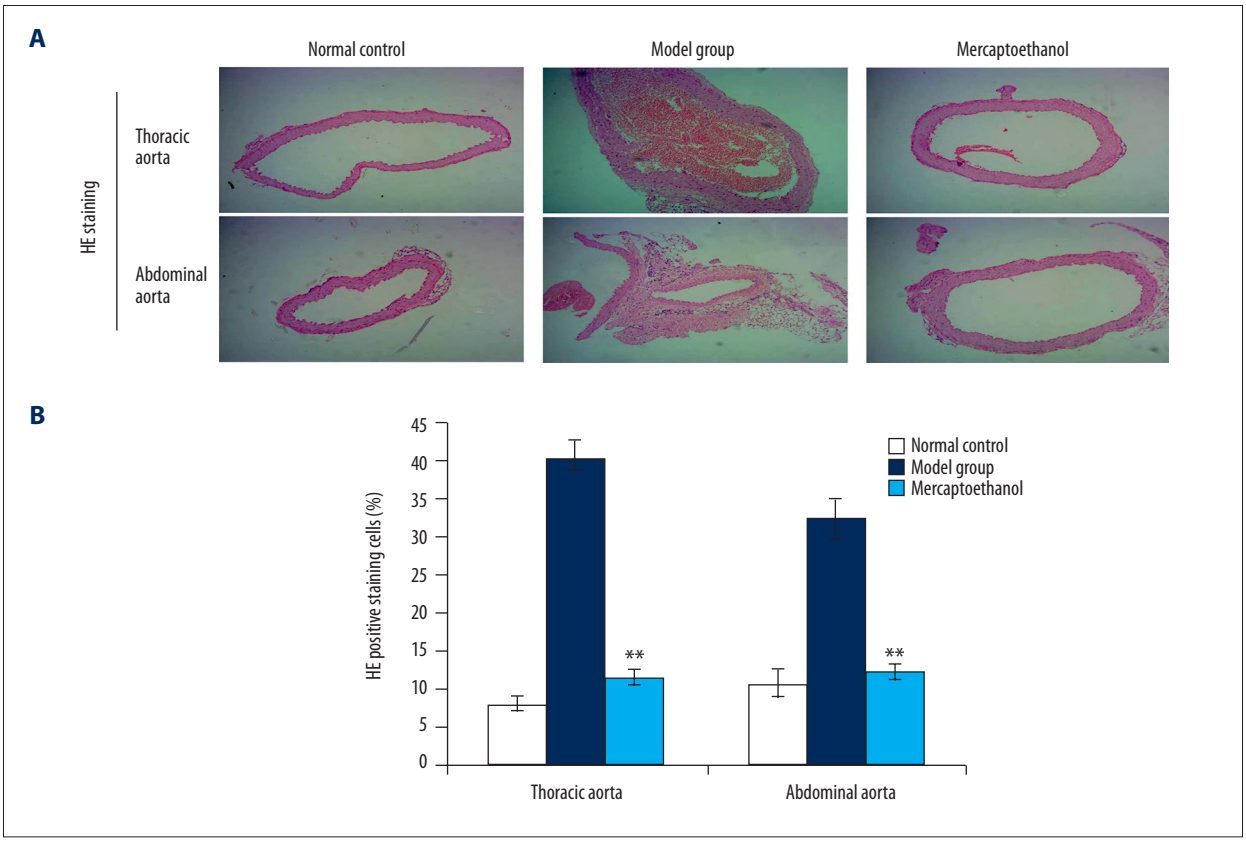

Figure 2. Histological evaluation of the aortic wall following mercaptoethanol treatment. (**A**) Representative light microscopic images of the blood and thrombus inside the dissected aortic wall. Hematoxylin and eosin (H&E). (**B**) Statistical analysis of the histological findings in the aortic wall following mercaptoethanol treatment. ** P<0.01 represents the number of cells in the mercaptoethanol group compared with the Model group. The 'H&E stained positive cells (%)'=the percentage of cells compared with the whole cells in the selected frames.

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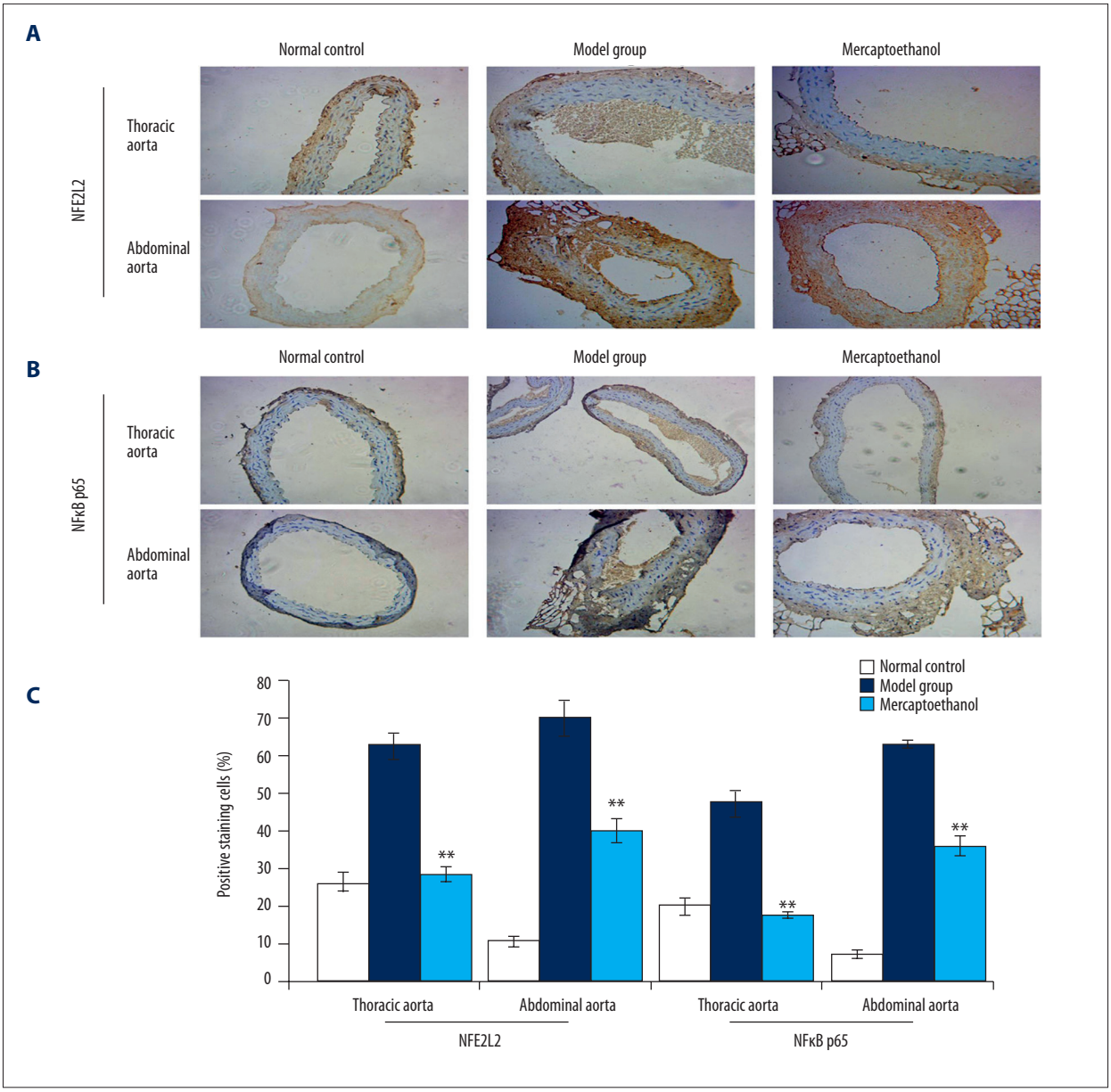

Figure 3. Photomicrographs of representative immunohistochemical images showing the expression of nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), and nuclear factor κB (NF-κB) and p65. (**A**) Representative light microscopic images stained immunohistochemically for nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), and nuclear factor κB (NF-κB) and p65 expression. (**B**) Statistical analysis for the representative immunohistochemically stained images. ** P<0.01 represents the positively-stained cells in the mercaptoethanol group compared with the Model group. The "positively-stained cells (%)"=the percentage of the positively-stained cells out of the total number of cells present in the selected image frame.

Statistical analysis

The data from this study were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, Ill, USA). Data were presented as the mean ± standard deviation (SD) and were obtained from at least six independent experiments. Student's t-test was used for the statistical analysis between two groups. Statistical significance was defined as P<0.05.

Results

Mercaptoethanol inhibited angiotensin II (Ang II)-induced aortic dissection in the AD mouse model

The effects of angiotensin II (Ang II) on the thoracic aorta dissection and abdominal aorta dissection in the AD mice are shown in Figure 2. The aortic histology, using routine hematoxylin and

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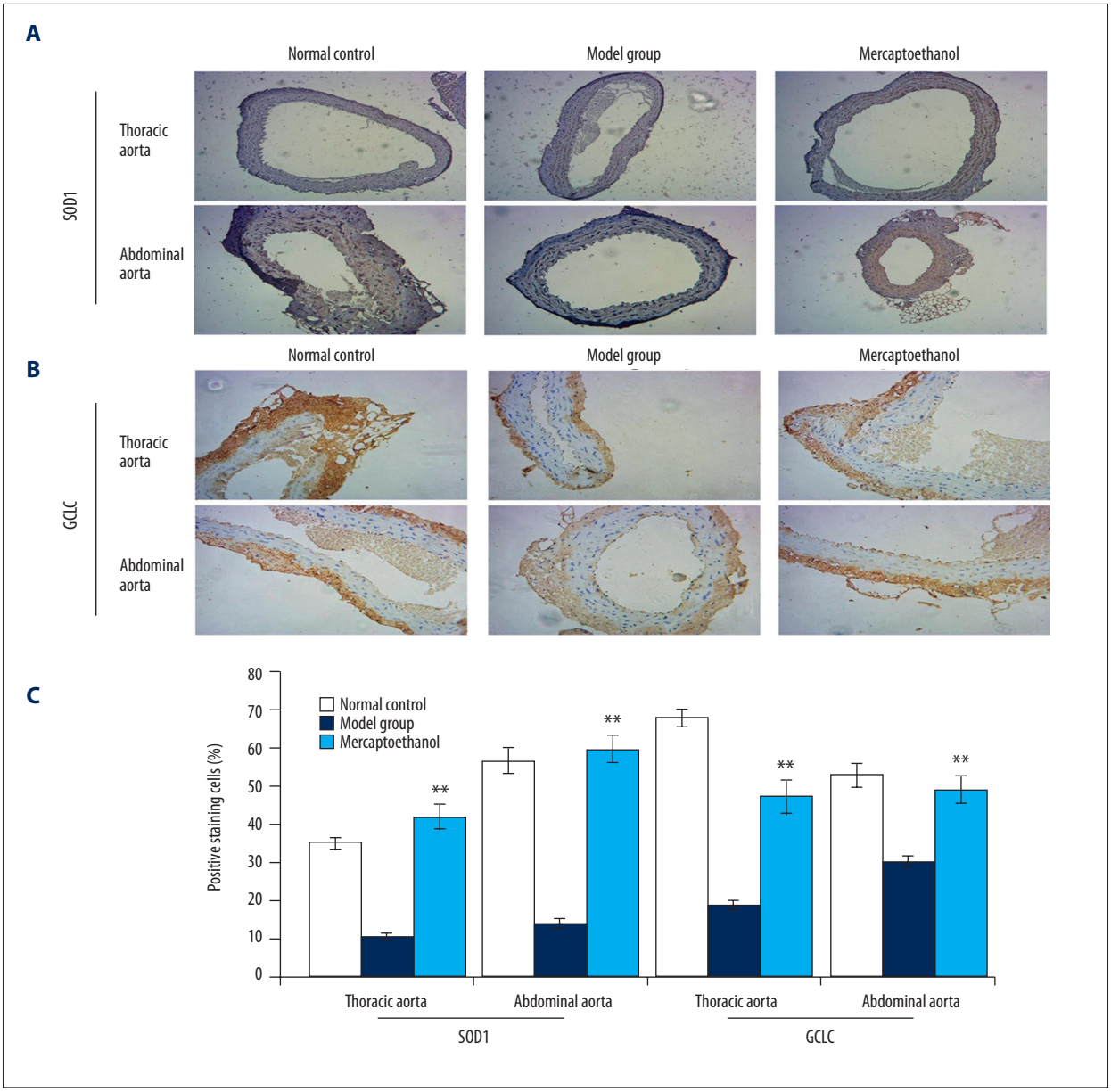

Figure 4. Photomicrographs of representative immunohistochemical images showing the expression of superoxide dismutase-1 (SOD1) and glutamate cysteine ligase catalytic subunit (GCLC). (**A**) Representative light microscopic images stained immunohistochemically for superoxide dismutase-1 (SOD1) and glutamate cysteine ligase catalytic subunit (GCLC). (**B**) Statistical analysis for the representative immunohistochemically stained images. ** P<0.01 represents the positively-stained cells in the mercaptoethanol group compared with the Model group. The "positively-stained cells (%)"=the percentage of the positively-stained cells out of the total number of cells present in the selected image frame.

eosin (H&E) staining, showed blood and thrombus ('blood clot') inside the dissected aortic wall after Ang II treatment (Model group) in both the thoracic aorta and abdominal aorta dissections (Figure 2A). The histology (H&E staining) showed significantly increased numbers of cells in the Model group compared with the Normal group (Figure 2B) (P<0.05). Also, the mercaptoethanol treatment inhibited the Ang II-induced blood and thrombus inside the dissected aortic wall in both thoracic aorta dissection and abdominal aorta dissection (Figure 2A); mercaptoethanol treatment significantly reduced the number of cells on histology (H&E staining) compared with the Model group (Figure 2B) (P<0.05).

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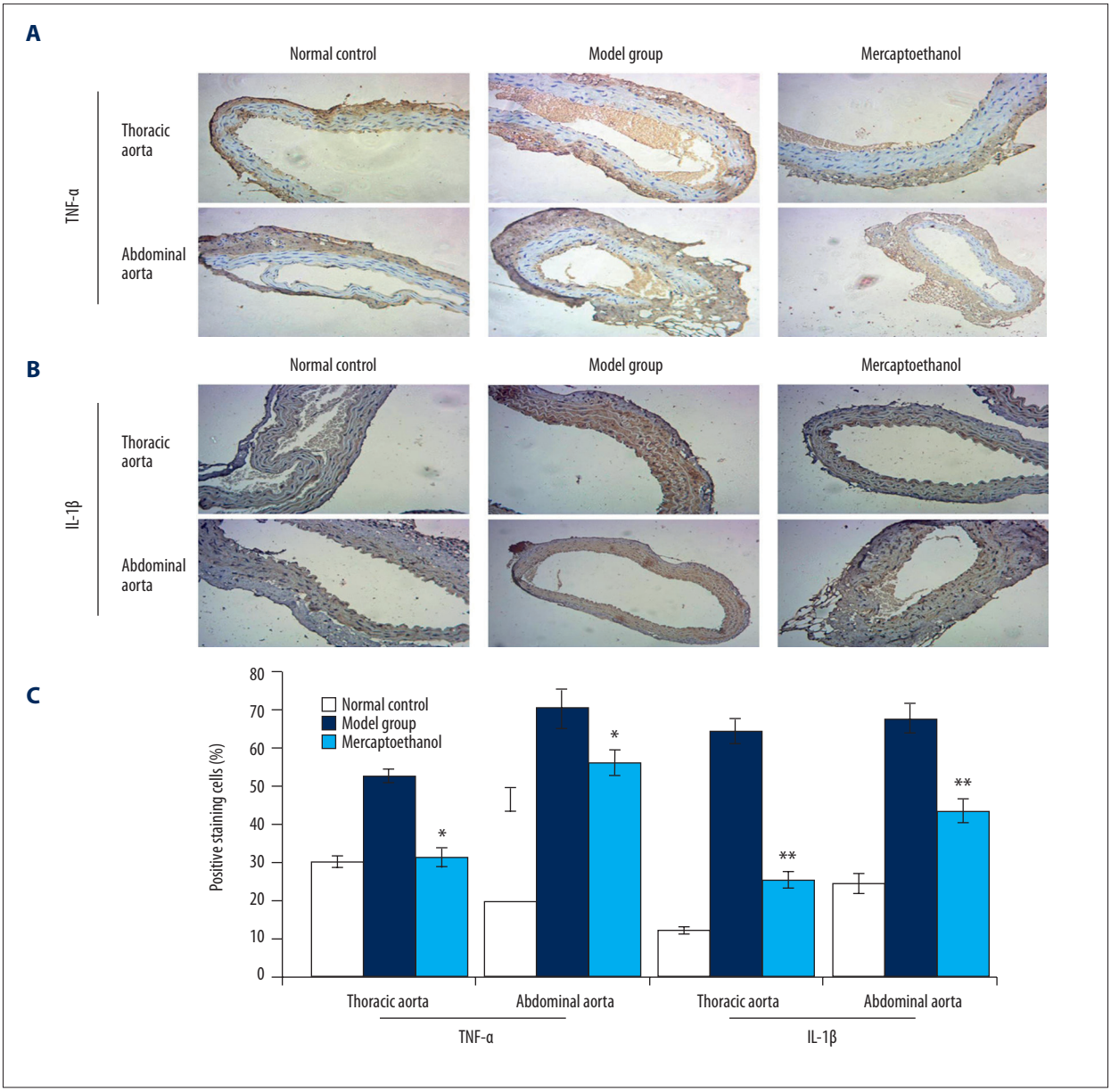

Figure 5. Photomicrographs of representative immunohistochemical images showing the expression of tumor necrosis factor α (TNF-α) and interleukin (IL)-1β. (**A**) Representative light microscopic images stained immunohistochemically for tumor necrosis factor α (TNF-α) and interleukin (IL)-1β. (**B**) Statistical analysis for the representative immunohistochemical images. ** P<0.01 represents the positively-stained cells in the mercaptoethanol group compared with the Model group. The "positively-stained cells (%)"=the percentage of the positively-stained cells out of the total number of cells present in the selected image frame.

Mercaptoethanol decreased nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) and nuclear factor κB (NF-κB) and p65 expression in the AD mouse model

In this study, the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), and NF-κB and p65 expression were studied using immunohistochemistry. The results showed that both NFE2L2 and NF-κB and p65 stained cells in the Model group were significantly increased compared with the Normal control group (Figure 3) (P<0.05) in both thoracic aorta and abdominal aorta in AD mice. Meanwhile, the mercaptoethanol treatment significantly decreased the NFE2L2 and NF-κB and p65 expression compared with the Model group (Figure 3, P<0.05) in both the thoracic aorta and the abdominal aorta in AD mice.

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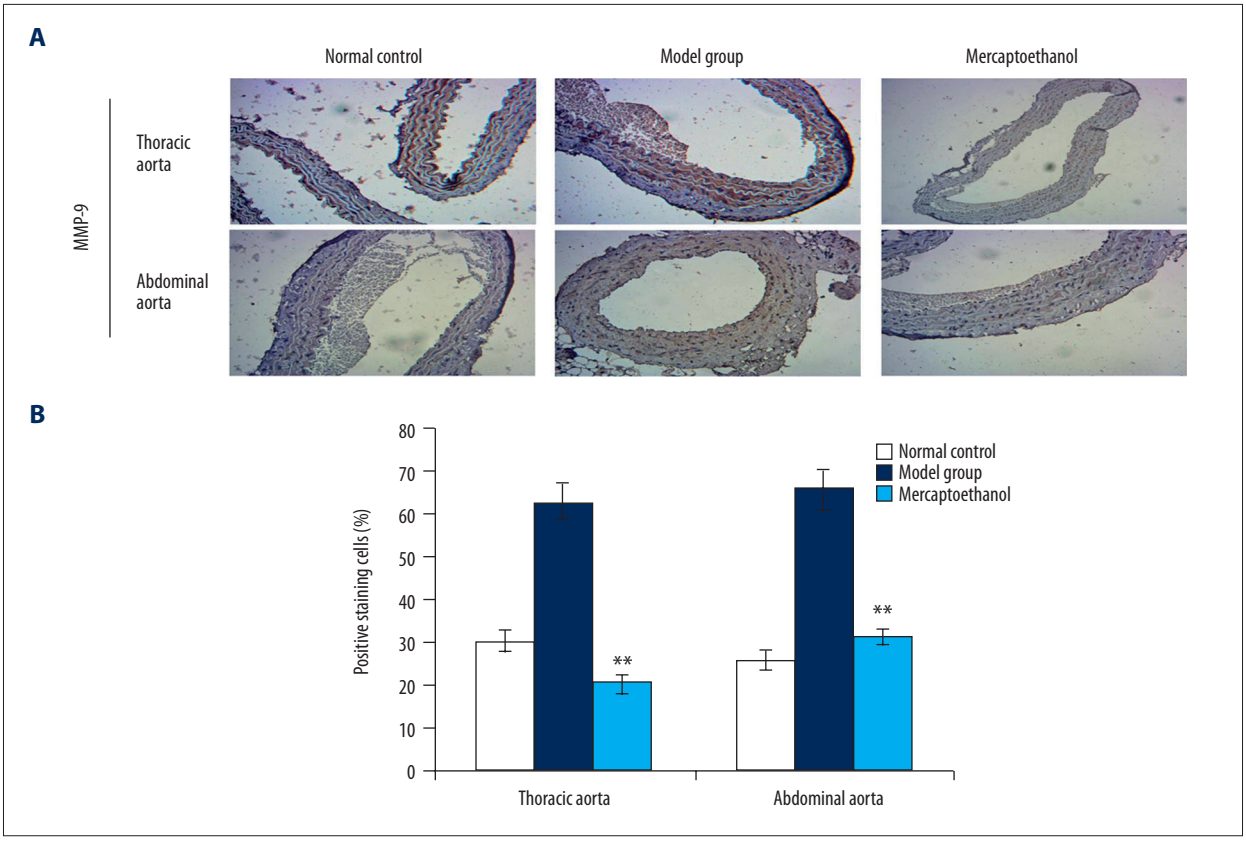

Figure 6. Photomicrographs of representative immunohistochemical images showing the expression of matrix metalloproteinase-9 (MMP9). (**A**) Representative light microscopic images stained immunohistochemically for matrix metalloproteinase-9 (MMP9). (**B**) Statistical analysis for the representative immunohistochemical images. ** P<0.01 represents the positively-stained cells in the mercaptoethanol group compared with the Model group. The "positively-stained cells (%)"=the percentage of the positively-stained cells out of the total number of cells present in the selected image frame.

Mercaptoethanol decreased expression of inflammatory mediators in the AD mouse model

In this study, the inflammatory factors, including tumor necrosis factor α (TNF-α), interleukin (IL)-1β, were also detected by using the immunohistochemical assay. The result showed that highly inflammatory responses were triggered in the Model group (Figure 4A), including the enhanced levels of TNF-α and interleukin-1 β (IL-1β) compared with the Normal control group (Figure 4B, P<0.05). Meanwhile, TNF-α and IL-1β levels in mercaptoethanol treated group were significantly decreased compared with the Model group (Figure 4, P<0.05) in both the thoracic aorta and the abdominal aorta in the AD mice.

Mercaptoethanol inhibited the expression of mediators of oxidative stress in the AD mouse model

The effects of mercaptoethanol on the expression of mediators of oxidative stress in AD mice showed that superoxide dismutase-1 (SOD1), glutamate cysteine ligase catalytic subunit (GCLC) levels were significantly downregulated by Ang II in the Model group (Figure 5, P<0.05) in both thoracic aorta and abdominal aorta in AD mice.

Mercaptoethanol reduced the expression of matrix metalloproteinase-9 (MMP9) in the AD mouse model

In this study, the extracellular matrix (ECM)-associated factor, matrix metalloproteinase-9 (MMP9) was detected in the aortic wall, and the expression of MMP9 was significantly increased in the Model group compared with the Normal group (Figure 6, P<0.05). Also, mercaptoethanol treatment significantly reduced MMP9 expression when compared with the Model group (Figure 6, P<0.05) in both the thoracic aorta and the abdominal aorta in AD mice.

Mercaptoethanol regulated the expression of mediators of inflammation, oxidative stress, and ECM-associated factors in the AD mouse model

In order to support the findings of protein expression demonstrated using immunohistochemistry, reverse transcription-polymerase

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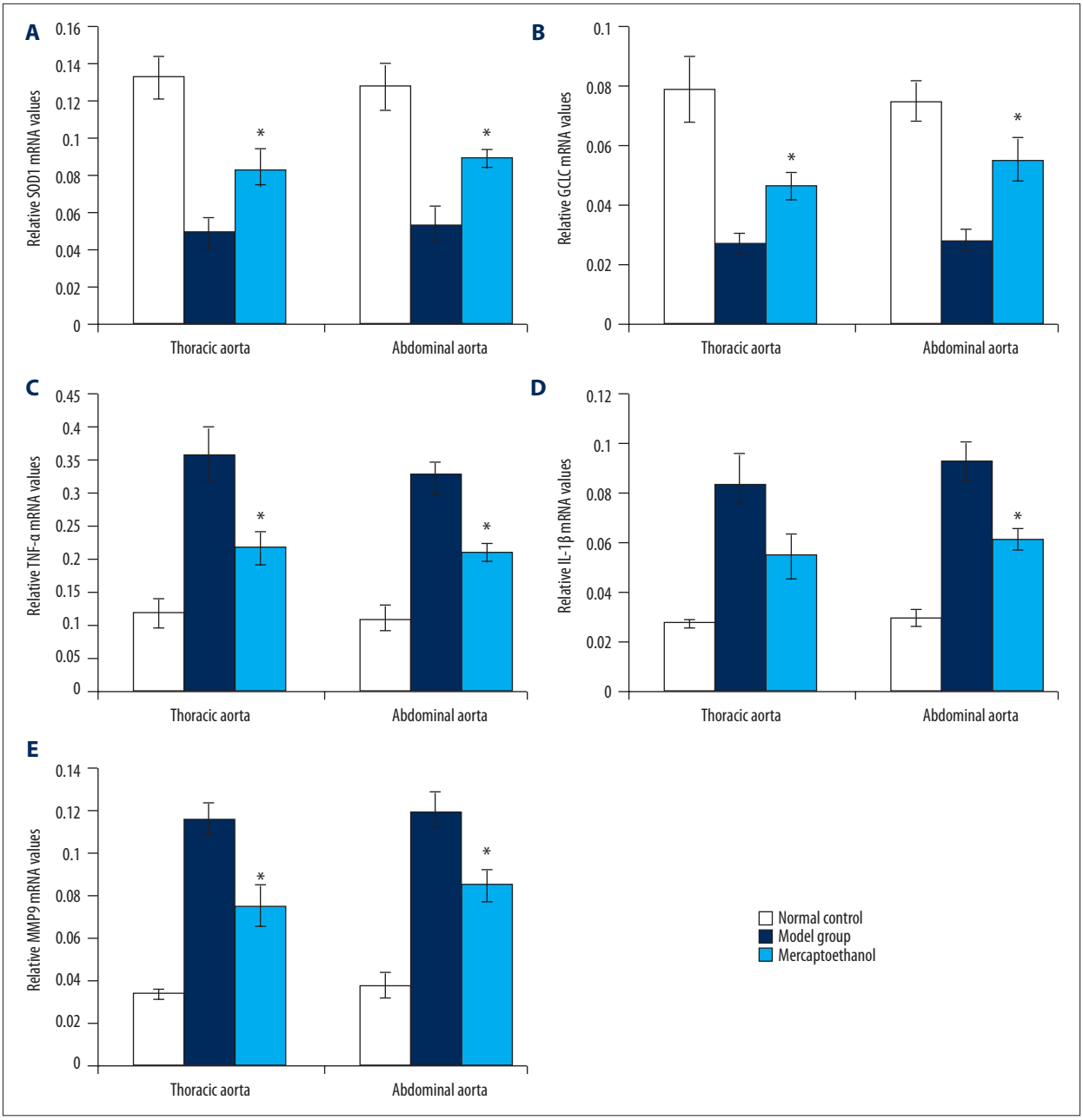

Figure 7. Reverse transcription-polymerase chain reaction (RT-PCR) analysis shows the expression of mRNA for tumor necrosis factor α (TNF-α), IL-1β, superoxide dismutase-1 (SOD1), glutamate cysteine ligase catalytic subunit (GCLC) and matrix metalloproteinase-9 (MMP9). (**A**) Superoxide dismutase-1 (SOD1). (**B**) Glutamate cysteine ligase catalytic subunit (GCLC). (**C**) Tumor necrosis factor α (TNF-α). (**D**) Interleukin (IL)-1β. (**E**) Matrix metalloproteinase-9 (MMP9). * P<0.05 represents the relative mRNA expression in the mercaptoethanol group compared with the Model group.

chain reaction (RT-PCR) was used to measure the levels of mRNA expression of TNF-α, IL-1β, SOD1, GCLC, and MMP9. The results indicated that the mercaptoethanol significantly increased the SOD1 (Figure 7A) and GCLC (Figure 7B) levels compared with the Model group, and significantly increased the TNF-α (Figure 7C), IL-1β (Figure 7D) and MMP9 (Figure 7E) levels compared with the Model group (all P<0.05).

Discussion

This study used an established mouse model of aortic dissection (AD) to study the expression mediators of inflammation, oxidation, and extracellular matrix (ECM) factors with and without treatment with mercaptoethanol, including nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), nuclear factor κB (NF-κB),

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p65, superoxide dismutase-1 (SOD1), glutamate cysteine ligase catalytic subunit (GCLC), tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1β), and matrix metalloproteinase-9 (MMP9). This study showed that mercaptoethanol treatment inhibited Ang II-induced aortic dissection in AD mice, as shown histologically. Mercaptoethanol treatment reduced the expression levels of NFE2L2, NF-κB, p65, TNF-α, IL-1β and increased the expression levels of SOD1, MMP9, and GCLC.

Aortic dissection (AD), whether or not it is associated with complete aortic rupture, results from a structural breakdown in components of the thoracic or abdominal aortic wall [25]. According to the previously published studies, the aortic wall could be impaired by many factors, including the oxidative stress, mechanical injury, and inflammatory mediators [26–28]. In this study, we used angiotensin II (Ang II) to produce the mouse AD model, and the findings of this study supported previous studies and showed that oxidative stress, and increased expression of inflammatory mediators, as well as factors affecting the ECM were involved in dissection of the aorta in the AD mouse model.

In this study, the histology of the mouse aortas, using hematoxylin and eosin (H&E) staining, showed blood and thrombus ('blood clot') inside dissected aortic wall following Ang II treatment (Model group) in both thoracic aorta dissection and abdominal aorta dissection. Mercaptoethanol is an antioxidant and free radical scavenger, which may affect ECM integrity, and is sometimes used in traditional Chinese medicine. In this study, mercaptoethanol treatment inhibited the Ang II-induced aortic dissection, as demonstrated by reduced amounts of blood and thrombus ('blood clot') in the dissected aortic wall. These changes have previously been reported in a clinical study that showed a temporal change of leukocytes and chemokines in aortic dissection patients [29].

In this study, mercaptoethanol treatment in the AD mouse model significantly reduced the expression of NFE2L2, NF-κB, and p65, which may indicate that mercaptoethanol protects the aortic wall of AD mice by inhibiting the NF-κB signaling pathway. This finding has been previously reported in a study that showed that the NF-κB pathway participated in the development of abdominal aortic aneurysm [30].

The findings from this present preliminary study in the AD mouse model showed that the inflammatory response was activated in the AD Model group, and that mercaptoethanol significantly inhibited the expression of inflammatory mediators, including TNF-α and IL-1β. The accumulation of the TNF-α and IL-1β are associated with tissue injury, and the accumulation of the TNF-α and IL-1β may have had this effect in the AD mice [31]. It is also of interest that the treatment of AD mice with mercaptoethanol reduced the inflammation of the aortic wall that was associated with aortic wall injury, which suggests that the mercaptoethanol protects the aortic wall of AD mice from mediators of inflammation.

A previously published study has shown that the oxidative stress is involved in the etiopathogenesis of AD [32]. The findings of the present study support a possible role mercaptoethanol in upregulation of anti-oxidative stress molecules, including SOD1 and GCLC, both of which may have a role in protecting against oxidative stress-induced aortic wall injury in AD mice. In this study, the ECM degeneration was also involved in the thoracic and abdominal aorta dissections in AD mice, which was consistent with the findings from a previous study [33]. Our results also showed that a key factor of the ECM degeneration system, MMP9, was significantly decreased following mercaptoethanol treatment. Although the present study in the AD mouse model showed some interesting findings, this was a small and preliminary study with several limitations. The methods used in this study, immunohistochemistry and RT-PCR, are semi-quantitative methods. Therefore, in future studies, a larger number of AD mice and the additional use of techniques such as the Western blot assay should be performed to evaluate protein expression.

Conclusions

In an AD mouse model, mercaptoethanol treatment inhibited thoracic and abdominal aortic dissection and reduced aortic tissue expression of mediators of oxidative stress and inflammation and increased the activation of ECM signaling pathways.

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