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Review

# Recent Advances in the Development of Experimental Animal Models Mimicking Human Aortic Aneurysms

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Aortic aneurysm is a common and life-threatening disease that can cause death from rupture. Current therapeutic options are limited to surgical or endovascular procedures because no pharmacological approaches have been proven to decrease the chance of expansion or rupture. The best approach to the management of aortic aneurysm would be the understanding and prevention of the processes involved in disease occurrence, progression, and rupture. There is a need for animal models that can reproduce the pathophysiological features of human aortic aneurysm, and several such models have been studied. This review will emphasize recent advances in animal models used in the determination of mechanisms and treatments of aortic aneurysms.

Key Words: Aorta, Aneurysm, Animal model, Research

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## INTRODUCTION

Aortic aneurysm is a degenerative disorder characterized by permanent dilatation of the aortic wall that exceeds the normal diameter by at least 50%. If an aneurysm is left untreated without appropriate management, it progresses to dilate and rupture with high mortality. Recently, with life expectancy increasing, it has become a major cause of death in the elderly population and raises concerns as a socioeconomic issue [1].

Management of abdominal aortic aneurysms still consists of monitoring the disease course without any active treatments or attempts at surgical correction [2]. However, surgical treatments and anesthesia increase morbidity and mortality rates. There have been significant efforts to advance noninvasive endovascular surgery by using stent grafting, but many problems persist, such as endoleaks, stent migration, and limb occlusion [3]. Studies on aortic aneurysms have focused on investigating physical causes and surgical treatments. Early diagnosis of small aortic aneurysms not requiring surgical treatment is more frequent, but problems associated with surgery persist [4].

Ultimately, the best approach to the management of aortic aneurysms is to understand and prevent the processes involved in disease occurrence, progression, and rupture. However, there are no effective non-surgical treatments to prevent progression of early stage disease, or adequate means to monitor disease activity and guide suppressive medical therapies. Information related to this sequence of events is still lacking. A limitation is that human aortic aneurysm tissue for research can only be obtained during surgery. Such tissue is already in late disease stages, and unsuitable for analyzing the occurrence and progression of the disease. Therefore, human studies are restricted to end-stage disease with markedly altered tissue architecture. There is a need for animal models that can reproduce the pathophysiological features of human aortic aneurysm.

In vivo animal models enable researchers to test hypotheses relating to pathogenesis and to investigate potential therapeutic strategies by providing an opportunity to study early stages of disease [5]. Several recently developed animal models of aortic aneurysm have provided novel insights into pathogenesis and pharmacotherapy. We will herein introduce some animal models that have been used, and discuss their relevance to human disease, focusing on contributions to research on aortic aneurysms.

## PATHOPHYSIOLOGY OF AORTIC ANEURYSM

A wide variety of pathologic conditions is associated with initiation, maturation, and eventual rupture of aortic aneurysms [6]. These include proteolytic degradation and inflammation of the aortic wall, and increased biomechanical wall stress. Understanding the underlying pathophysiology is critical for basic research on prevention of initial aneurysm formation and limiting growth and expansion.

Loss of two critical structural elements in the aortic wall, elastin and collagen, contributes to degradation, increasing risk of aneurysm formation. Matrix metalloproteinases (MMPs) derived from macrophages and aortic smooth muscle cells are secreted into the extracellular matrix, which activate collagen and elastin degradation [7]. MMP-1 (collagenase), MMP-3 (stromelysin), MMP-2 (gelatinase A), and MMP-9 (gelatinase B) are the principal proteinases in aortic aneurysms that result in collagen and elastin degradation [8-10]. MMP-2 and MMP-9, which are synthesized by local cells in the aortic wall, including infiltrating macrophages and aortic vascular smooth muscle cells, break down collagen [11,12]. Longo et al. [13] reported that a concerted role of MMP-2 and MMP-9 is required for aneurysmal degradation; both could be targeted for the treatment of aortic aneurysms. The contribution of MMPs to aneurysm formation is highlighted by the beneficial effect on aneurysm expansion of medications that reduce MMP levels. The feasibility of pharmacologically suppressing aneurysmal degeneration was demonstrated by using doxycycline, a nonspecific inhibitor of MMP [14].

Chronic transmural inflammation is a prominent histologic feature of aortic aneurysms [15]. Lymphocytes and macrophages are found in the adventitia and media of aortic aneurysms in greater concentration than in the normal aorta [16]. When such cells invade aortic tissue and create an inflammatory environment, the process of elastin and collagen breakdown and aneurysm formation begins. Tissue levels of proinflammatory cytokines, such as tumor necrosis factor-$\alpha$, interleukin (IL)-1$\beta$, IL-8, interferon-$\gamma$, and IL-6, are all consistently upregulated in patients with aneurysms [17]. Recent studies showed that limiting inflammation with drugs can reduce aneurysm formation in animal models [18-20].

Hemodynamic stress on the aortic wall is an obvious important factor in aneurysm development and rupture. Compared with the thoracic aorta, the infrarenal abdominal aorta is prone to aneurysmal enlargement due to a combination of differences in structure, composition, and biology of the wall, as well as differences in hemodynamic flow and biomechanical forces [21]. The infrarenal segment is subject to higher levels of oscillating flow and reflected pressure waves than the suprarenal segment, resulting in a higher level of aortic wall tension [22]. Shear stress caused by altered hemodynamics, and wall tension caused by blood pressure acting on the curved aneurysm wall, is a signal for collagen remodeling [23]. Understanding biomechanical factors may help improve assessment of the risk of aneurysm growth and rupture.

## ANIMAL MODELS OF AORTIC ANEURYSMS

### 1) Genetically predisposed or engineered animal models

The broad breasted bronze turkey was the first animal model reported to develop spontaneous rupture of dissecting aneurysms [24,25]. Supplementation of feed with various compounds, such as $\beta$-aminopropionitrile (BAPN) and diethylstilbestrol, increased risk of rupture [26,27]

The blotchy mouse, with a mutation on the X-chromosome that leads to abnormal copper absorption, developed spontaneous aortic aneurysms [28]. Because copper is a cofactor for lysyl oxidase (Lox), which is important in the crosslinkage of elastin and collagen, these mice have defective tissue. Mice with a genetically engineered deficiency in Lox died in the perinatal period due to ruptured thoracic aortic aneurysms [29]. Electron microscopy showed highly fragmented elastic fibers and discontinuity in the smooth muscle cell layer in the aortic wall. Lox was therefore proposed as an enzyme with an essential role in the resilience and tensile strength of the arterial wall.

High fat diets fed to apolipoprotein E (ApoE) and low-density lipoprotein (LDL) receptor knockout mice promoted the formation of aortic aneurysms [30]. Aortic aneurysms formed under mature atherosclerotic lesions showed medial elastolysis, dilatation of the lumen, and the presence of necrotic cores with a predominant lipid component. Because most reports on these mice focused on the development of atherosclerosis, there are limited data on aortic aneurysm development. For this reason, subcutaneous infusion of angiotensin II in hyperlipidemic

strains has been widely employed, generating data of mechanistic and pharmacologic relevance [31-33].

Aneurysm development in both the thoracic and abdominal aorta has been noted in mice with MMP-3 or tissue inhibitor of MMP-1 deficiency [34,35]. The lack of specificity for the region may reflect a generalized destruction of extracellular matrix. However, some of these mice are not suitable as models because they died from early-stage ruptured aneurysms, or aneurysms developed at atypical locations.

### 2) Elastase infusion models

Temporary infusion of porcine pancreatic elastase into an isolated segment of infrarenal aorta produced aneurysmal degeneration in rats [36]. This rat model has been modified to produce aortic aneurysms in mice [37]. The rationale for development of aortic dilatation was based on an influx of inflammatory cells, increased production of MMPs, and destruction of medial elastin [38]. These findings supported the hypothesis that elastolytic activity within the media plays a key role in aneurysm formation.

The procedure of elastase infusion involves the introduction of a catheter via the femoral artery into the infrarenal aorta, and isolation of a segment of the abdominal aorta. The aorta is clamped at the level of the left renal vein and ligated around the catheter 1cm distally. This isolated segment is perfused with 2 ml of elastase for 2 hours. The elastase results in extensive destruction of the elastin network with immediate aortic dilatation followed by aneurysm formation. After 1-2 weeks, gradual expansion in the corresponding area can be confirmed, and tissues that are histologically similar to human aortic aneurysms can be obtained.

In the elastase infusion model, administration of indomethacin [38] and doxycycline [39] significantly attenuated aneurysm formation, presumably because of inhibition of MMPs. Recently, it was reported that muscle-derived stem cells attenuated the rate of aneurysm formation in elastase-induced aortic aneurysms in rats [40].

The advantages of this model include circumferential aneurysmal degeneration with precise localization and structural stabilization, without proceeding to rupture. However, there are discrepancies in the rate of aneurysm formation related to differences in technique and elastase preparation [41,42]. In addition, the fatality rate is increased because this model requires direct manipulation of the aorta, with the possibility of aortic injury. Injection over a long time period resulted in extensive aortic elastolysis, and was also associated with higher rates of complications, such as lower limb ischemia [43].

### 3) Calcium chloride models

Extraluminal application of calcium chloride ($CaCl_2$) to the aorta induces aneurysm formation. A pathogenic association between calcium deposition and aneurysm formation was first suggested in a study using periarterial application of $CaCl_2$ to rabbit common carotid artery [44]. Calcium is deposited due to its high affinity for elastin, and the calcium-elastin complex destroys the elastin network and weakens the vascular walls to cause an aortic aneurysm; inflammatory responses accelerate due to this complex. This method was then applied to rabbit aortas through placement of a gauze pad soaked in a $CaCl_2$ solution [45]. A mouse model was also successfully produced using the same technique [46].

The abluminal incubation of $CaCl_2$ led to structural disruption of the media elastic network and inflammatory responses, as seen in human aortic aneurysms [47]. Moreover, a number of mechanisms, such as calcification, oxidative stress, neovascularization, and vascular smooth muscle cell apoptosis, may be relevant to the pathogenesis of human aortic aneurysms. Calcification of medial elastin itself has been associated with elastin degradation, vascular smooth muscle cell apoptosis, and inflammation. However, the $CaCl_2$ models had some different features, with an inability to observe thrombus, atherosclerosis, and ruptures, which are seen in human aortic aneurysms.

$CaCl_2$ models can be applied to wild-type mice, making assessment of transgenic rodent models more straightforward and rapid; pathology usually developed in the infrarenal abdominal aorta, the most common location of human aortic aneurysms [47].

### 4) Angiotensin II model

The elastin model, in which pancreatic elastase is injected into the aorta, and the $CaCl_2$ model, in which $CaCl_2$ is applied directly around the aorta, can induce aortic aneurysms with degenerative changes of the aortic wall, in the absence of intravascular hemodynamic force. However, these have disadvantages associated with the need to avulse the artery directly and manipulate it; in addition, aneurysms can be induced only in the infrarenal abdominal aorta, and human aneurysm features, such as thrombus, arterial stenosis, and ruptures, cannot be observed.

The angiotensin II model, which is the most widely known, induces aortic aneurysms in LDL receptor –/– or $ApoE^{-/-}$ mice by injecting angiotensin II with an osmotic pump for 4-6 weeks [31,48]. Angiotensin II contributes to the formation of aneurysms through various effects on the vasculature, in addition to its hypertensive effect. Angiotensin II induces

changes similar to aortic aneurysms in humans, such as degeneration of the medial aortic wall, inflammatory responses, and thrombosis [49]. Aneurysm formation in this model tends to occur in the suprarenal aorta, in contrast to humans, where aneurysms develop in the infrarenal aorta.

Although the majority of angiotensin II infusion models have used hyperlipidemic mice, recently it was reported that aortic aneurysms develop during angiotensin II infusion into wild type C57BL/6 mice, which is the background strain of the hyperlipidemic mice [50]. However, the incidence was much lower in C57BL/6 mice compared with the hyperlipidemic mice. Therefore, although hyperlipidemia is not essential for development of aneurysms, its presence augments the incidence of aneurysm formation.

Recently, aortic aneurysm models have been induced by injecting angiotensin II together with BAPN, which breaks down elastin crosslinks, directly induces degenerative changes in the aortic wall, directly stimulates endothelial cells, and causes the expression of several chemokines and adhesion molecules [51,52]. The combination infusion of angiotensin II and BAPN, which causes the degeneration of elastic lamina, induced both thoracic and abdominal aortic aneurysms in wild-type mice. Although aneurysms can be induced successfully in both the thoracic and abdominal regions, the results differ morphologically and histologically between the regions, and the frequency of ruptures or avulsion is relatively high, suggesting the need for further studies.

The pharmacological manipulation of aneurysm development in this model has been investigated. Hydralazine lowered systolic blood pressure, but had no effect on aneurysm formation in angiotensin II infused $ApoE^{-/-}$ mice, showing that aneurysm formation was independent of blood pressure [53]. On the other hand, doxycycline [54], vitamin E [55], simvastatin [56], and rosiglitazone [57] reduced the incidence and extent of aneurysm formation in angiotensin II treated hyperlipidemic mice.

### 5) Deoxycorticosterone acetate and the high salt model

Clinically, there is evidence that systemic hypertension is closely associated with aortic aneurysm formation [58,59]. In an experiment on hypertension using mice, deoxycorticosterone acetate (DOCA), a precursor of aldosterone, was correlated with the occurrence of aortic aneurysms, with some animal specimens showing aortic ruptures. When DOCA was administered with a high salt content, an aortic aneurysm was induced, with features of human aneurysm, such as changes in elastin, infiltration of inflammatory cells, and degeneration of smooth muscle cells [51].

However, when angiotensin II or DOCA were used alone in wild-type mice, reports on incidence rates varied. In cases with high incidence rates, BAPN, an inhibitor of Lox (which induces the formation of elastin-collagen cross-links in the medial aortic wall), was co-administered [60]. Consequently, currently known animal models are not yet well developed, with regard to either the mechanisms underlying the occurrence of aortic aneurysms, or similarities to human aneurysms. In particular, studies on co-administration of angiotensin II and DOCA have not been reported.

## OUR EXPERIENCE ON ANIMAL MODELS OF ANEURYSM RESEARCH

For more productive research, knowing the proper in-

**Table 1.** The incidence of aortic aneurysm formation

| Reference | Substance | Animal | Incidence of aneurysm formation (n/total, %) |
|---|---|---|---|
| Anidjar et al. (1990) [36] | Elastase | Wistar rat | 10/10 (100) |
| Park et al. (2013) [40] | Elastase | SD rat | 5/6 (83) |
| Bi et al. (2013) [61] | Elastase | New Zeland white rabbit | 6/6 (100) |
| Tanaka et al. (2009) [62] | Elastase | SD rat | 2/12 (16.7) |
| | $CaCl_2$ | | 0/9 (0) |
| | Elastase+$CaCl_2$ | | 13/14 (92.7) |
| Isenburg et al. (2007) [63] | $CaCl_2$ | SD rat | 8/12 (66.7) |
| Cassis et al. (2009) [53] | Angiotensin II | $ApoE^{-/-}$ mouse | 13/26 (50) |
| Cao et al. (2010) [64] | Angiotensin II | $ApoE^{-/-}$ mouse | 41/65 (63) |
| Kanematsu et al. (2010) [51] | Angiotensin II+BAPN | C57BL/6J mouse | 22/45 (48.9) |
| | DOCA+BAPN | | 7/10 (70) |
| Liu et al. (2013) [60] | DOCA+salt | C57BL/6J mouse | 28/45 (62) |

SD rat, Sprague-Dawley rat; BAPN, β-aminopropionitrile; DOCA, deoxycorticosterone acetate.

cidence of aneurysm formation in animal model is an essential factor. The incidence of animal models for aortic aneurysm has been reported at different rates according to its causative substances (Table 1) [36,40,51,53,60-64].

We performed a pilot study to overcome the limitations of the previously presented elastase infusion and $CaCl_2$ models, and to increase the incidence of aortic aneurysms in hyperlipidemic mice through co-administration of angiotensin II and DOCA.

Seven-week-old $ApoE^{-/-}$ hyperlipidemic mice (n=10) were purchased from Japan SLC Inc. (Shizuoka, Japan) and subjected to inhalation anesthesia using isoflurane, following an adaptation period of one week. The mice were divided into four groups: control group (n=1), angiotensin II group (n=3), DOCA group (n=3), and angiotensin II+DOCA group (n=3). Angiotensin II was administered for the first 4 weeks through a subcutaneously implanted osmotic-pump (Alzet model 2004, 28-day release; Durect Corporation, Cupertino, CA, USA), and DOCA pellets (50 mg, 21-day release; Innovative Research of America, Sarasota, FL, USA) were also subcutaneously implanted in the dorsal region (Fig. 1). Four weeks later, at the study endpoint, mice were anesthetized for tissue harvesting, and aortas were isolated for pathological and immunological analysis.

In all hyperlipidemic mice, atherosclerotic lesions were seen in abdominal aorta and thoracic aorta. Among them, angiotensin II+DOCA mice showed most prominent atherosclerotic changes on the aorta (Fig. 2) and one of them showed an aneurysmal change on the ascending aorta (Fig. 3).

Through this preliminary experiment, we confirmed that administration of angiotensin II and DOCA augmented atherosclerotic lesions on the aorta and that aneurysms occurred in the ascending aorta when angiotensin II and

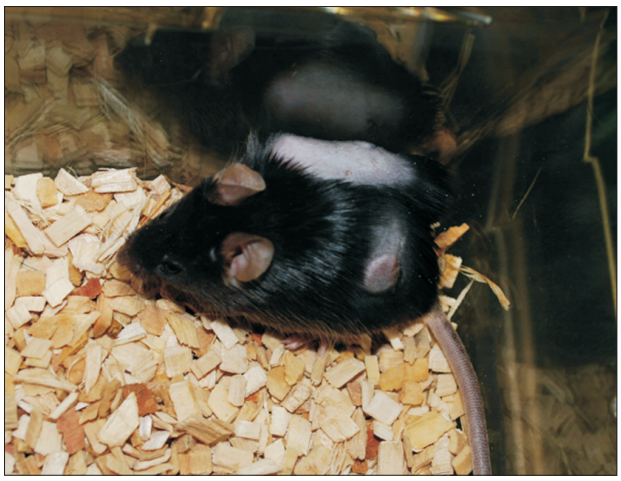

**Fig. 1.** Photography of mouse showing subcutaneously implanted osmotic pump filled with angiotensin II and deoxycorticosterone acetate pellet.

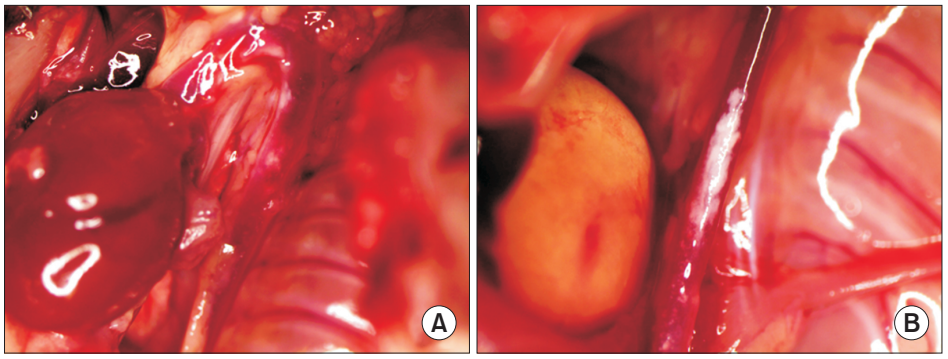


**Fig. 2.** Atherosclerotic lesion on thoracic (A) and abdominal (B) aorta in angiotensin II+deoxycorticosterone acetate mouse.

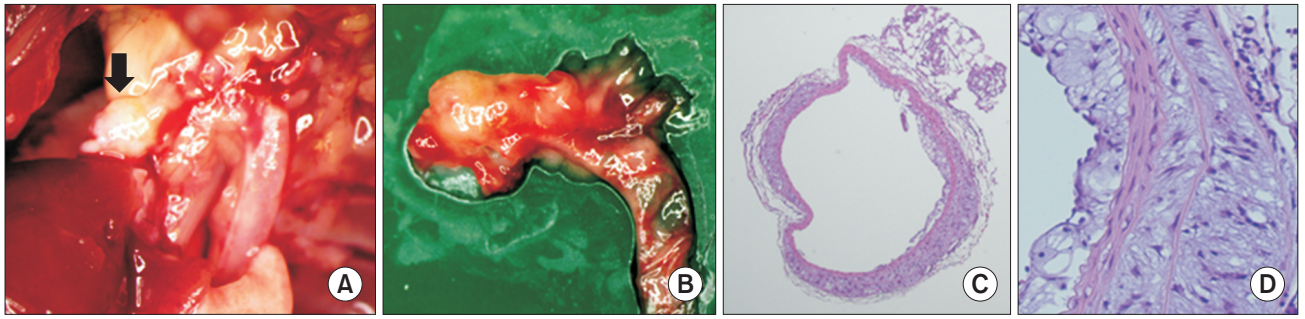


**Fig. 3.** Aneurysm formation on ascending aorta in angiotensin II+deoxycorticosterone acetate mouse. (A, B) Dissected aortic arch showing aneurysmal change (black arrow) on ascending aorta. (C, D) H&E staining of ascending aorta (x5, x20).

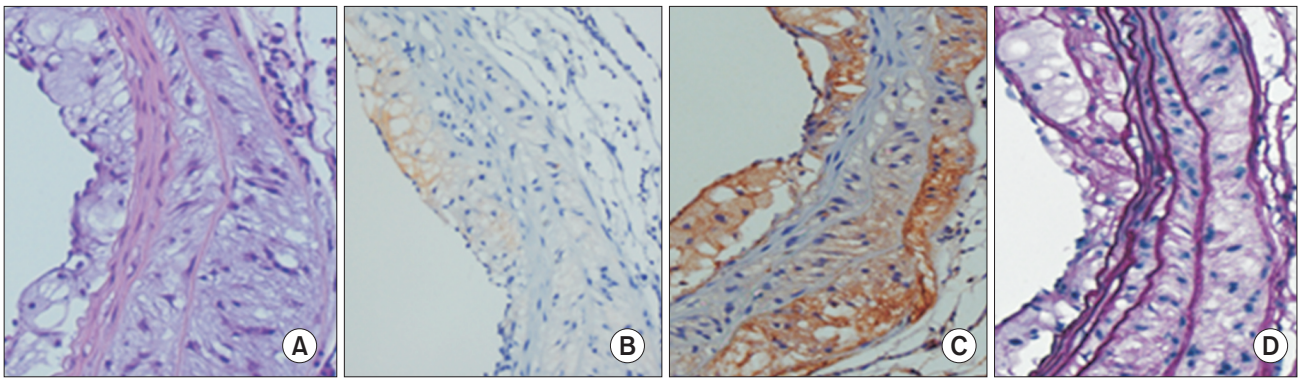


**Fig. 4.** (A) H&E staining and immunohistochemical staining for (B) matrix metalloproteinase (MMP)-2, (C) MMP-9, and (D) Elastica von Gieson on aneurysmal portion in angiotensin II+deoxycorticosterone acetate mouse (A-D: ×20).

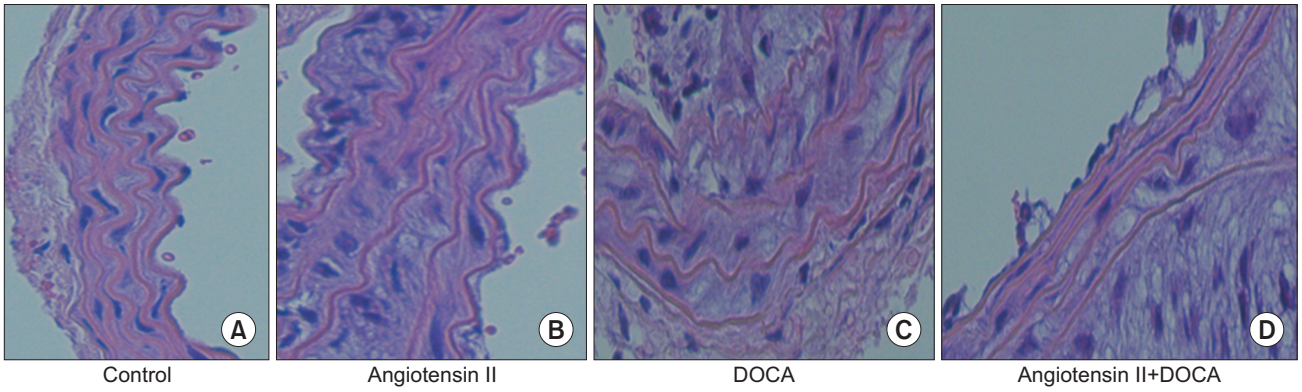


**Fig. 5.** H&E staining of thoracic aorta in (A) control, (B) angiotensin II, (C) deoxycorticosterone acetate (DOCA) and (D) angiotensin II+DOCA mouse (A-D: x40).

DOCA were co-administered to hyperlipidemic mice. This was confirmed by histological testing of the expanded regions of the aorta, showing degeneration of the medial wall, accumulation of extracellular matrix, and infiltration of inflammatory cells (Fig. 3). Moreover, the results of immunohistochemical staining showed expression of MMP-2 and MMP-9, and Elastica von Gieson (EVG) staining results showed changes in the elastic lamina (Fig. 4).

In mice given either angiotensin II or DOCA alone, no visible morphological changes in the aortic aneurysm were observed. However, on histological examination, medial degeneration was much more defined in these mice than in the control group, with the co-administration group showing the most severe degeneration (Fig. 5). MMP-9 expression was distinct in the angiotensin II and co-administration groups (Fig. 6A). EVG staining results showed that, in comparison with the control group, the angiotensin II and DOCA groups showed medial degeneration and thickening; the co-administration group showed medial degeneration and accumulation of extracellular matrix (Fig. 6B).

Although it is difficult to draw conclusions because of the small number of specimens, changes occurring in the course of aortic aneurysm formation were observed in both the angiotensin II and DOCA groups. When animal models were created by administering a mixture of drugs, synergism between the two was believed to improve the incidence rate and reproduce the characteristics of the aortic aneurysm induced by the two drugs.

## CONCLUSION

Animal models have been important in increasing our understanding of the pathophysiology of aortic aneurysms, and continue to be valuable and indispensable tools for basic research on pharmacotherapy. Each animal model has features that are remarkably similar to clinical disease in humans, but no one model faithfully recreates the human condition in its entirety. Understanding of specific features and limitations inherent in each model is necessary for interpreting the significance and potential generalizability of results obtained from any one model. The advances

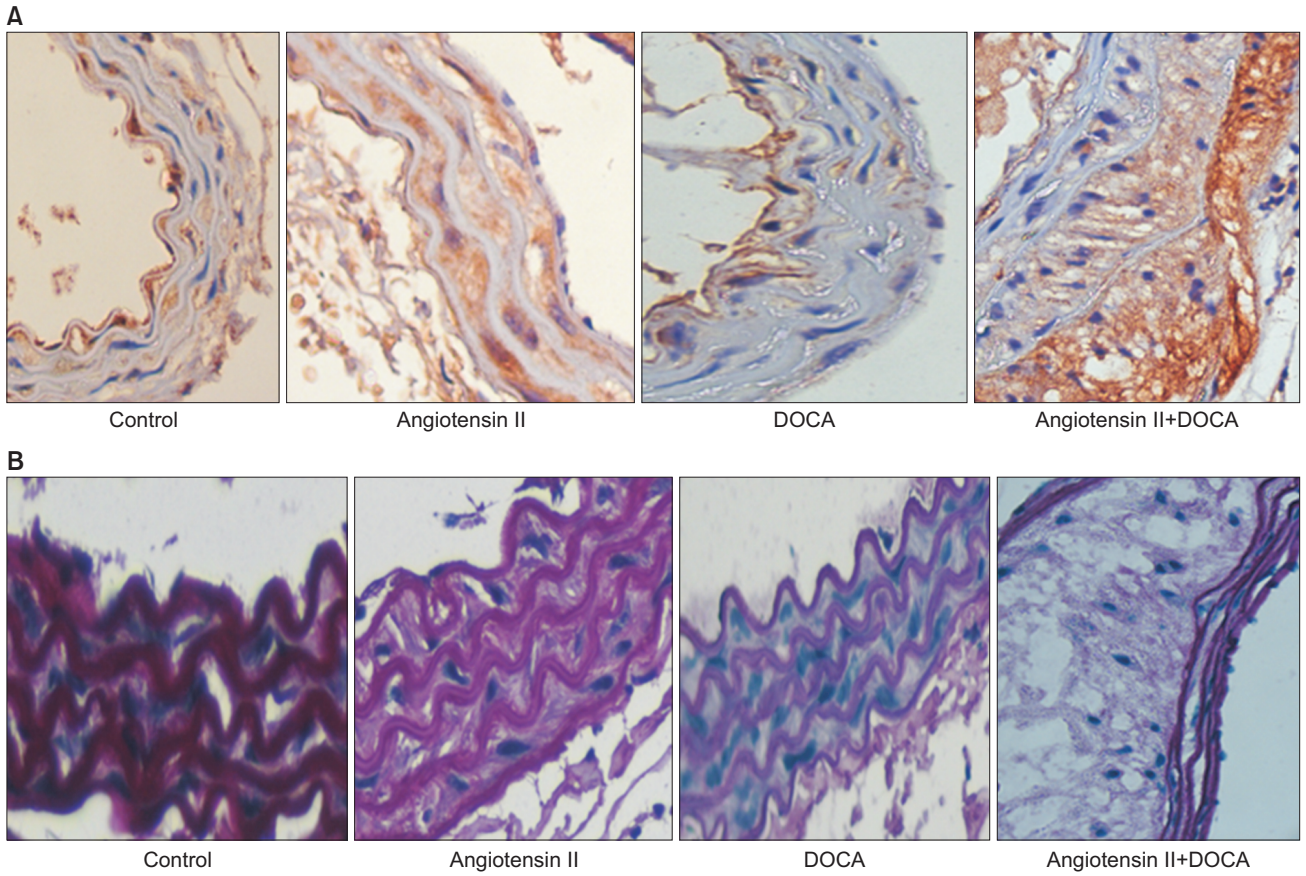


**Fig. 6.** Immunohistochemical staining of thoracic aorta for matrix metalloproteinase-9 (A) and Elastica von Gieson (B) in each group (×40). DOCA, deoxycorticosterone acetate.

in these animal models will provide an understanding of signaling systems at the cellular and molecular levels that are associated with the occurrence of human aortic aneurysms, along with predictions for the risk of rupture.

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