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Perindopril and Simvastatin Attenuate Dilation of the Descending Thoracic Aorta *Via* Down-Regulation of Interleukin-6 in an Experimental Model of $CaCl_2$-Induced Aneurysm Formation

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Research Article

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ABSTRACT

Introduction: Some clinical studies aimed to discover potential pharmaceutical agents that could be used protectively against aneurysmal dilation of the aorta. Our study evaluates the role of perindopril and simvastatin in an experimental model of aortic aneurysm.

Materials and methods: Thirty-nine rabbits were allocated into 4 groups: control group, $CaCl_2$ group, $CaCl_2$+simvastatin group and $CaCl_2$+perindopril group. All animals underwent to left posterolateral thoracotomy and normal or $CaCl_2$ saline application on the wall of their descending thoracic aorta. The following parameters were evaluated: maximum vessel diameter, wall thickness, the presence of atherosclerosis, thickness of the atheromatous plaque and the expression of IL-6 and MMP-9 on the aortic wall.

Results: Aortas treated with $CaCl_2$ presented apparent atherosclerosis in 75% of the cases as opposed to only 20% of the control aortas. Treatment with either simvastatin or perindopril significantly attenuated the effect of $CaCl_2$ (4,145 ± 484 μm; p=0.039, and 4,209 ± 280 μm; p=0.05, respectively, compared with the $CaCl_2$ group). Neither intensity nor extent of MMP-9 expression differed among groups. On the other hand, intensity of IL-6 expression was lower in both the simvastatin and perindopril-treated groups compared with the $CaCl_2$ group (p=0.01). A significant positive correlation between aortic diameter and wall thickness was observed in the $CaCl_2$ group (r=0.7; p=0.023), which was diminished in the simvastatin and perindopril groups (r=0.238; p>0.05, and r=0.05, p>0.05).

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Conclusion: Our study shows the protective role of perindopril and simvastatin against aortic aneurysm formation and progression *via* down-regulation of local inflammation on the aortic wall.

INTRODUCTION

An aortic aneurysm is defined as the dilation of one or more segments of the aorta to greater than 1.5 times normal size [1]. Although usually asymptomatic, it is associated with high mortality and morbidity rates due to the risk of rupture or dissection [1,2]. The pathophysiology of the thoracic aortic aneurysm (TAA) is complex and multifactorial, involving biomechanical, inflammatory, genetic, and environmental factors [2]. Inflammation and remodeling aberrations seem to be the predominant mediators for aneurysm formation and progression [2]. Matrix metallopeptidases (MMPs) and interleukins have been reported to be the major representatives of the implicated pathways [3,4].

Up to date, the gold standard for treatment of a non-ruptured aneurysm is the surgical or endovascular repair [5,6]. Although some clinical studies aimed to discover potential pharmaceutical agents that could be used protectively against aneurysmal dilation of the aorta, there is no enough evidence yet [7-9].

Perindopril is an angiotensin-converting enzyme inhibitor (ACE-i) that is primarily utilized as anti-hypertensive and has been associated with decreased mortality in patients with cardiovascular disease. Its pressure-lowering activity could lead to shear stress normalization and a subsequent down-regulation of the aortic wall inflammation [9]. Simvastatin is a β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitor which is mostly prescribed for dyslipidemias. However, there is substantial evidence that statins exert specific effects other than the lipid-lowering ones, mainly associated with anti-inflammatory properties [10].

Our study aimed to investigate the role of perindopril and simvastatin in an experimental model of TAA and their implication in the inflammatory process and tissue remodeling.

MATERIALS AND METHODS

Animal Model and Study Design

Eight-week-old New Zealand male adult rabbits weighing 3-4 kg were obtained from a certified breeding farm in Greek territory. Animals were housed in single metal cages and had access to tap water and standard balanced rabbit chow ad libitum. Room temperature ranged between 20 and 22°C, relative humidity ranged between 55 and 65%, and the light/dark cycle was 6 a.m./6 p.m. All possible precautions were taken to avoid animal suffering at each stage of the experiment. The experimental protocol was approved by the "Scientific Committee for the approval of protocols using animals for scientific purposes" established in the Laboratory for Experimental Surgery and Surgical Research "N.S. Christeas" of Athens Medical School and by the competent Veterinary Directorate of Attica Region. The protocol complied with EU legislation (Directive 2010/63/EU) regarding the use of animals in biomedical science. Before enrollment in the protocol, animals were acclimatized for three weeks.

Thirty-nine rabbits were allocated into 4 groups:

(a) Control group (n=6): Animals were subjected to posterolateral thoracotomy and normal saline application on the wall of their descending thoracic aorta (sham surgery).

(b) $CaCl_2$ group (n=15): Animals underwent posterolateral thoracotomy, and a solution of 0.5 mol/L $CaCl_2$ was applied on the descending thoracic aorta.

(c) Simvastatin group (n=9): Animals were treated with 2.5 mg/kg/day per os in addition to the application of $CaCl_2$ solution.

(d) Perindopril group (n=9): Animals were treated with 0.3 mg/kg/day in addition to the application of $CaCl_2$ solution.

The simvastatin and perindopril groups received the respective regimen for one week before and 12 weeks after the operative procedure.

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Surgical Procedure

Sedation was induced by intramuscular injection of 25 mg/kg ketamine and 5 mg/kg xylazine. The animals were then intubated and connected to a volume-controlled ventilator. Mechanical ventilation was adjusted to 28-30 breaths/min. Anesthesia was maintained by the intravenous administration of 30-50 mg/kg sodium thiopental via an ocular vein. 100 mL of normal saline was administrated in each animal for hydration and blood loss replacement. Left posterolateral thoracotomy was performed through the 4th intercostal space. After entering the pleural cavity, the descending thoracic aorta was exposed from the origin of the left subclavian artery to the diaphragm with the meticulous removal of adjacent tissues. Afterward, a gauze moistened with $CaCl_2$ dilution (0.5 mol/L) was applied to the periadventitial surface of the aorta. The chest wall was closed in layers. A chest tube was not used, as the animals would not tolerate it. The animals were awakened, and extubation followed. After surgery, each animal remained under close observation for one hour and then it was transferred to its cage. Antibiotic prophylaxis consisted of two doses of enrofloxacin (5 mg/kg), administered intra-operatively and on the first post-operative day. No deaths were observed postoperatively, and no animals were excluded from the analysis. Feeding was initiated later during the day of surgery. Pentobarbital was used for euthanasia.

Sham surgery was identical to those above except for the application of normal saline rather than $CaCl_2$ on the aortic wall. Mean operative time was 40 minutes and it was comparable between both surgical procedures.

Histopathological Examination

Following euthanasia, the descending aorta was immediately fixed in 10% formalin at room temperature for 24 h. The tissue was then embedded in paraffin, sectioned and mounted on glass microscope slides. The sections were stained with hematoxylin-eosin and examined using light microscopy by two independent researchers who were blinded to the randomization scheme.

Vascular tissue was studied, and the following parameters were evaluated: maximum vessel diameter, wall thickness, the presence of atherosclerosis, and thickness of the atheromatous plaque.

Immunostaining

Deparaffinization, hydration and regain of antigenicity were achieved by heating of the samples in an automatic machine (Dako) with the use of a low pH solution at 90oC. The samples were then incubated in a solution of hydrogen peroxide for 15 minutes so that the endogenous peroxidase was neutralized. Afterward, they were washed out with PBS buffer, and the samples were incubated overnight at 4°C with anti-MMP-9 antibody in 1:200 dilution. Next day, after washout with PBS buffer, the samples were incubated in Envision Flex-HRP for 30 minutes. After washout, they were incubated in chromogen 3,3′-diaminobenzidine (DAB) (Dako), which recognizes the complex and chemically reacts with it, leading to the “brown” pigmentation of the antigen-antibody complex. Following that, the samples were stained with hematoxylin, they were dehydrated with alcohol, and finally, they were clarified with xylole. The final stage was the evaluation of the immunostaining with the use of optical microscopy. The same procedure was followed in the case of IL-6 with the sole exception that a dilution of 1:50 was used for antigenicity regain.

Statistical Analysis

Data are expressed as mean ± 1 standard deviation for continuous variables and as frequency (% percentage) for qualitative data. The normality of the distributions was assessed with Kolmogorov-Smirnov’s test and graphical methods. Comparisons between more than two groups were performed with Analysis of Variance (ANOVA) using Bonferroni’s post-hoc test. ANOVA was used to test for group differences in all examined variables apart from urea% increase. Mann-Whitney’s U test was utilized as a non-parametric test for group comparisons regarding urea% increase after I/R induction. A false discovery rate of 5% was controlled with a Benjamini-Hochberg p-value correction. Chi-square test was used for analysis of dichotomous variables. All tests were two-sided. Differences were considered as statistically significant if the null hypothesis could be rejected with >95% confidence ($p<0.05$). All statistical analyses were conducted in SPSS (version 21 for Mac OS; SPSS, Inc., Chicago, IL, USA).

RESULTS

Aortic Diameter and Wall Thickness

$CaCl_2$ application on the aortas led to an average of 21% increase in diameter compared to the cohort of untreated animals (4,876 ± 617 μm *vs.* 3,856 ± 604 μm, respectively; p=0.014). Treatment with either simvastatin or perindopril significantly attenuated the effect of $CaCl_2$ (4,145 ± 484 μm; p=0.039, and 4,209 ± 280 μm; p=0.05, respectively, compared with the $CaCl_2$ group) **(Figure 1)**. Wall thickness did not differ among groups (p>0.05 in all cases) **(Figure 2)**.

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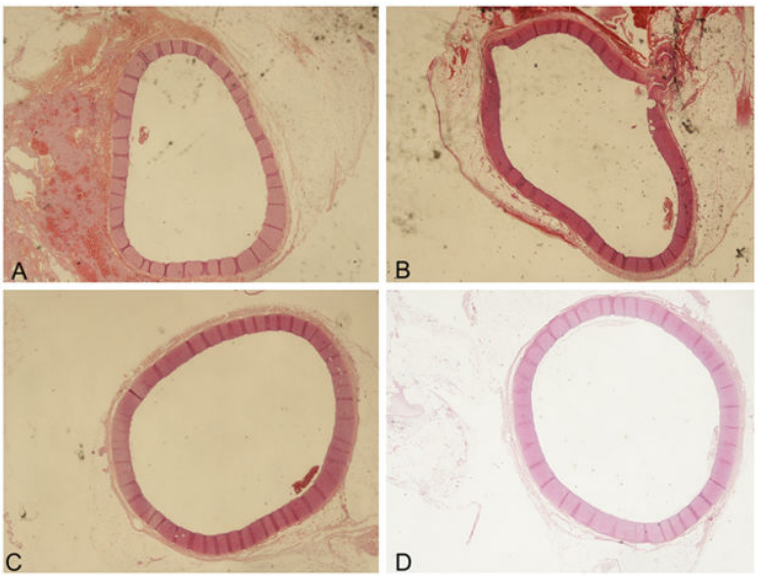

Figure 1. Hematoxylin and eosin (H&E) staining of the descending thoracic aorta. (A) Control group: Normal histological appearance of the aorta. H&E magnification, 40x; (B) $CaCl_2$ group: Increase in aortic diameter. H&E magnification, 40x; (C) Simvastatin group: Attenuation of $CaCl_2$ effect on aortic diameter. H&E magnification, 40x; (D) Perindopril group: Attenuation of $CaCl_2$ effect on aortic diameter. H&E magnification, 40x.

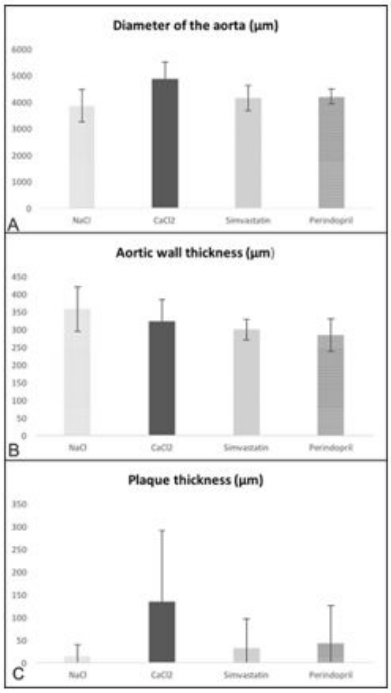

Figure 2. Differences among control, $CaCl_2$, simvastatin and perindopril groups regarding (A) Diameter of the aorta; (B) Aortic wall thickness and (C) Plaque thickness.

Atherosclerosis and Plaque Formation

Aortas treated with $CaCl_2$ presented apparent atherosclerosis in 75% of the cases as opposed to only 20% of the control aortas **(Figure 3)**. Administration of simvastatin to $CaCl_2$ treated rabbits was associated with atherosclerosis progression in only 30% of the cases, whereas this percentage was 20% in the perindopril-treated group **(Figure 3A)**. Mean plaque thickness was higher in the $CaCl_2$ group when compared with the control, simvastatin, and perindopril group (134 ± 157 µm *vs.* 13 ± 26 µm *vs.* 32 ± 64 µm *vs.* 42 ± 83 µm, respectively) **(Figures 3B-3D)**. However, statistical significance was not achieved in the observations above due to the wide range and standard deviation of the distributions **(Figure 4)**.

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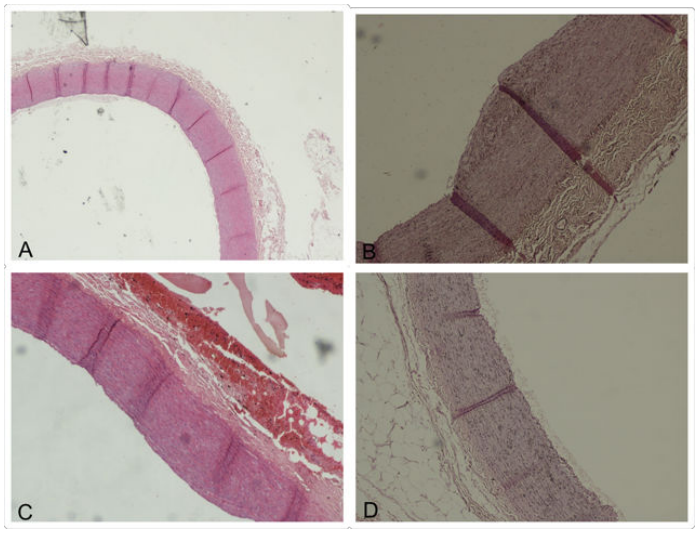

Figure 3. Hematoxylin and eosin (H&E) staining of the aortic wall. (A) Control group: Normal histological appearance of the aortic wall. H&E magnification, 120x; (B) $CaCl_2$ group: Increase in aortic wall thickness, accompanied by the atherosclerotic lesions. H&E magnification, 120x; (C) Simvastatin group: Diminished effect of $CaCl_2$ on aortic wall thickness and atherosclerotic lesions. H&E magnification, 120x; (D) Perindopril group: Diminished effect of $CaCl_2$ on aortic wall thickness and atherosclerotic lesions. H&E magnification, 120x.

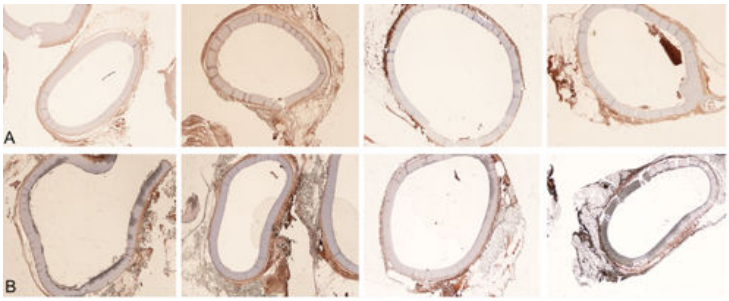

Figure 4. Immunostaining for IL-6 (4A), a sensitive marker for inflammation and MMP-9 (4B), a marker for tissue remodeling. Each picture is representative of each of the following groups: Control, $CaCl_2$, Simvastatin and Perindopril. Magnification, 120x.

IL-6 and MMP-9 Expression

The expression of IL-6 and MMP-9 on the aortic wall was evaluated with immunostaining of the aortic segments **(Figure 4)** respectively. Neither intensity nor extent of MMP-9 expression differed among groups **(Figures 5A and 5B)** respectively. On the other hand, intensity of IL-6 expression was lower in both the simvastatin **(Figure 5C)** and perindopril-treated **(Figure 5D)** groups compared with the $CaCl_2$ group (p=0.01 in both cases).

Correlation of Aortic Diameter and Wall Thickness

A significant positive correlation between aortic diameter and wall thickness was observed in the $CaCl_2$ group (r=0.7; p=0.023), which was diminished in the simvastatin and perindopril groups (r=0.238; p>0.05, and r=0.05, p>0.05) **(Figure 6).** Apart from the lack of statistical significance, it is also intriguing that the correlation coefficient was decreased in the treatment groups suggesting diameter lowering effect independent of the impact of either regimen on the aortic wall thickness.

DISCUSSION

TAA is an insidious disease which can often be left undiagnosed due to the lack of symptoms. Most commonly it is diagnosed in screening ultrasonographic examination or after its rupture, which is associated with high mortality and morbidity rates [11]. Prevention or hindrance to its progress is the critical component of keeping the aneurysm-related mortality low

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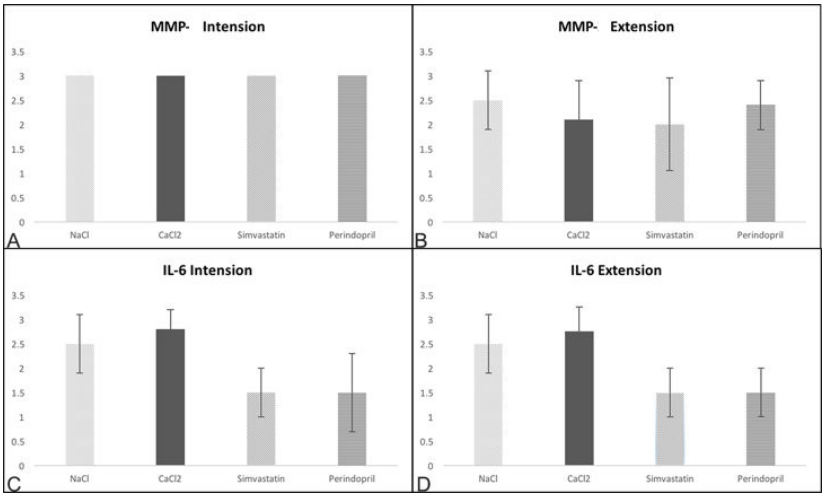

Figure 5. Intension and extension of MMP-9 (A and B) and IL-6 (C and D) expression among groups.

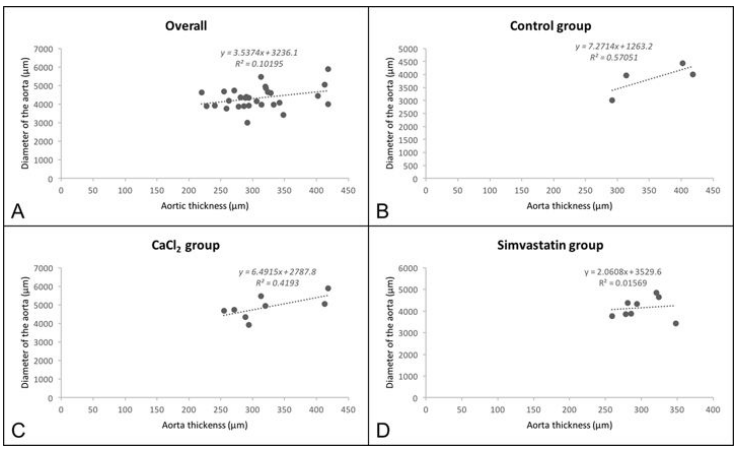

Figure 6. Correlation between diameter of thoracic aorta and aortic wall thickness for the groups altogether and for Control, $CaCl_2$, Simvastatin and Perindopril groups separately.

The correlation between TAA and hypertension is well-established as well as its association with specific genetic and environmental factors [2]. The pathophysiology of TAA formation and progression is closely related to the inflammation and abnormal shear stress on the aortic wall [2]. Thus said, we aimed to investigate the effect of (a) a pressure-lowering agent and (b) of a statin, i.e., a drug with potent anti-inflammatory properties.

Our findings suggest the protective role of both perindopril and simvastatin against TAA formation associated with the down-regulation of IL-6 expression on the thoracic aortic wall. A secondary outcome is the absence of correlation between aortic wall thickness and aortic diameter in the treated groups compared with the $CaCl_2$ group in which a substantial correlation was observed. Moreover, it is pointed out that a $CaCl_2$-induced TAA model in rabbits has never been reported before.

Rabbits as an Optimal Experimental Model

A variety of animal models and interventions has been utilized for the induction of experimental TAA [12-14]. However, rabbits present certain advantages. Firstly, the size of their aorta is large enough for the facile periaortic appliance of dilutions directly to the aortic wall and provides the possibility for obtaining multiple segments for analysis. The similarity of their cardiovascular system to the human one supports the clinical significance of our results [15]. Furthermore, albeit bigger than rodents, rabbits are much smaller than pigs or calves; thus, the use of a large-animal model with low reproductive rate could be avoided. As far as the utilization of $CaCl_2$ is concerned, the high affinity of calcium for elastin results into calcium-elastic tissue complex which in turn weakens the vessel wall and leads to the development of an aneurysm [16].

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Perindopril and Aortic Dilation

Perindopril is a first-line anti-hypertensive agent used widely in patients with cardiovascular disease. Even though a negative correlation between perindopril and TAA progression could be anticipated as a result of its pressure-lowering effects, a retrospective study of 141 patients indicated that there was no benefit for ascending aortic dilation in patients treated with ACE-inhibitors [9]. On the other hand, it has been suggested that ACE inhibitors exhibit anti-inflammatory properties and lead to attenuation of aortic dilation by suppressing the expression of MMP-9. In our study, even though MMP-9 levels did not differ among groups, IL-6 was significantly downregulated, providing evidence for the potent vascular anti-inflammatory effects of perindopril [17,18]. It has been reported that ACE inhibitors can lead to attenuation of the inflammatory cascade by upregulating peroxisome proliferator receptors alpha (PPAR-α) and gamma (PPAR-γ) independently from its pressure-lowering properties and the blockage of renin-angiotensin-aldosterone axis [18]. Although perindopril is not well-known for robust anti-inflammatory activity, we can speculate that suppression of the inflammation at least on a local level may be the central mechanism for its beneficial role in TAA formation considering that IL-6 is one of the primary pro-inflammatory cytokines.

Simvastatin and Thoracic Aortic Aneurysm Formation

Simvastatin is a statin, i.e., a class of drugs not only known for their lipid-lowering action but also for their pleiotropic effects, which are independent of cholesterol metabolism and relevant to the inflammatory cascade [7]. Our results advocate the anti-inflammatory properties of simvastatin as the mediator to diminishing TAA progression. Specifically, treatment with simvastatin was associated with decreased IL-6 expression in the aortic wall and significantly lower aortic diameter compared to the $CaCl_2$ treated group. This finding is in accordance with the existing literature that suggests an inverse correlation between statin treatment and aneurysm progression in patients with diagnosed aneurysmal disease [7,8,19]. Importantly, all available studies attribute this observation to the anti-inflammatory effects of statins [8]. Statins interfere with numerous stages of the inflammatory cascade, namely tumor necrosis factor alpha (TNF-α), nuclear factor kappa B (NF-κB), monocyte chemoattractant protein 1 (MCP-1) and PPAR-α [20-22]. IL-6 shares common pathways with the cytokines above, a fact that presumably can explain our findings [23].

The MMP-9 Paradox

The pathogenesis of TAA is closely related to an abnormal remodeling process of the extracellular matrix, a disequilibrium between matrix synthesis and degradation, partially mediated by proteolysis [8]. Still, downregulation of MMP-9 was not found in our study. This is also reported by other studies demonstrating alternations in the levels of other members of MMP family but not MMP-9 [13]. Although the existing knowledge is scarce regarding the mechanism of the effect of perindopril on MMP-9 levels, there is a small piece of evidence in the case of simvastatin. *In vitro* experiments advocate that animal macrophages and smooth muscle cells produce less active MMP-2 and MMP-9 in response to simvastatin treatment [13]. *In vivo*, though, lymphocytes outnumber macrophages in the aortic wall, and smooth muscle cells are strongly diminished due to apoptosis indicating low levels of MMP-9 regardless of simvastatin administration [13].

Correlation between Aortic Diameter and Wall Thickness

Apart from the evident effects of perindopril and simvastatin in the pathophysiology of TAA, another aspect of our results that merits consideration is the lack of correlation between aortic diameter and wall thickness in the treatment groups. Although both control and $CaCl_2$ groups exhibited a strong correlation between these two parameters, this was not observed in either perindopril or simvastatin group. This finding can be interpreted as an anti-aneurysmal effect of both drugs which is not restricted to their direct impact on the aortic wall thickness. On this ground, speculations for potential activities on a systemic level or solely to the endothelium of the aorta can be made. Given that the existing literature entails evidence for both focal and systemic effects of these drugs, a combined and synergistic effect may be considered [9,17,19,24].

CONCLUSION

The primary outcomes of our study are the protective role of perindopril and simvastatin against TAA formation and progression via down-regulation of local inflammation on the aortic wall. Secondary outcomes include:

- The feasibility and efficacy of $CaCl_2$ periaortic application in the descending thoracic aorta of rabbits as an experimental model of aneurysm formation.
- The loss of association between aortic diameter and wall thickness in the drug-treated groups. Yet, this is an experimental study, and further translational and basic research studies are required to verify our findings.

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LIMITATIONS

Albeit its promising results, this study has specific limitations that should not be neglected, i.e., the small sample size and the absence of measurements in the peripheral blood. Moreover, experimental model of TAA was used, and these findings should be confirmed in different animal models of TAA.

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