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Roles of hypertension in the rupture of intracranial aneurysms

Yoshiteru Tada, MD, PhD, **Kosuke Wada, MD**, **Kenji Shimada, MD, PhD**, **Hiroshi Makino, MD**, **Elena I. Liang, BS**, **Shoko Murakami, MD, PhD**, **Mari Kudo, MD**, **Keiko T. Kitazato, BS**, **Shinji Nagahiro, MD, PhD**, and **Tomoki Hashimoto, MD**
Department of Anesthesia and Perioperative Care (Y.T., K.W., K.S., H.M., E.I.L., S.M., M.K., T.H.), University of California, San Francisco, Calif; Department of Neurosurgery (Y. T., K. T. K, S. N.), School of Medicine, The University of Tokushima, Tokushima City, Japan

Abstract

Background and Purpose—Systemic hypertension has long been considered as a risk factor of aneurysmal rupture. However, a causal link between systemic hypertension and the development of aneurysmal rupture has not been established. In this study, using a mouse model of intracranial aneurysm rupture, we examined the roles of systemic hypertension in the development of aneurysmal rupture.

Methods—Aneurysms were induced by a combination of deoxycorticosterone acetate (DOCA)-salt induced hypertension and a single injection of elastase into the cerebrospinal fluid in mice. Anti-hypertensive treatment was started six days after aneurysm induction. Aneurysmal rupture was detected by neurological symptoms and confirmed by the presence of intracranial aneurysm with subarachnoid hemorrhage. Hydralazine (direct vasodilator) or the discontinuation of the DOCA-salt treatment was used to assess the roles of systemic hypertension. Captopril (angiotensin converting enzyme inhibitor) or losartan (angiotensin II type 1 receptor antagonist) was used to assess the roles of the local renin-angiotensin system in the vascular wall.

Results—Normalization of blood pressure by hydralazine significantly reduced the incidence of ruptured aneurysms and the rupture rate. There was a dose dependent relationship between the reduction of blood pressure and the prevention of aneurysmal rupture. Captopril and losartan were able to reduce the rupture rates without affecting systemic hypertension induced by DOCA-salt treatment.

Conclusions—Normalization of blood pressure after aneurysm formation prevented aneurysmal rupture in mice. In addition, we found that the inhibition of the local renin-angiotensin system independent from the reduction of blood pressure can prevent aneurysmal rupture.

Keywords

Intracranial aneurysm rupture; hypertension; angiotensin; animal model

Introduction

Systemic hypertension has long been considered as a risk factor of aneurysmal rupture.[1, 2] However, findings from clinical studies are conflicting, presumably due to the fact that the

Correspondence to: Tomoki Hashimoto, MD, Department of Anesthesia and Perioperative Care, University of California, San Francisco, 1001 Potrero Avenue, No. 3C-38, San Francisco, CA 94110. hashimotot@anesthesia.ucsf.edu, tel: 415-206-8958, fax: 415-206-8170.
*Y.T. and K.W. contributed equally to the project.

Disclosures
None

majority of patients with a diagnosis of hypertension are treated with anti-hypertensive agents,[3, 4] and as a result, these patients tend to have normal blood pressure at the time of diagnosis of intracranial aneurysm.[5] While experimental studies showed a link between the formation of intracranial aneurysms and systemic hypertension,[6–10] a causal link between systemic hypertension and the development of subarachnoid hemorrhage—aneurysmal rupture— has not been fully established in either experimental or clinical setting.

In patients with systemic hypertension, different types of anti-hypertensive agents with different molecular targets are chosen based on the types of end-organ damages and underlying pathophysiology.[2] However, it is not clear which type of anti-hypertensive agents may be suitable for patients with unruptured aneurysms, or which type of anti-hypertensive agents can reduce aneurysmal subarachnoid hemorrhage.

Hypertension may directly or indirectly contribute to aneurysmal rupture. Hypertension may weaken the aneurysmal wall by directly increasing mechanical stresses. In addition, activation of local renin-angiotensin system by systemic hypertension can cause vascular inflammation and remodeling[11] and may contribute to aneurysmal rupture. Certain polymorphisms in the genes related to renin-angiotensin system are reported to be associated with aneurysmal rupture.[12–14]

Recently, we have developed a mouse model of intracranial aneurysm that morphologically and histologically resemble human intracranial aneurysms.[9, 15] In this model, aneurysmal rupture causes neurological symptoms that can be easily detected by a simple neurological examination.[16, 17] This model provides a unique opportunity to conduct preclinical studies for identifying therapeutic targets for the prevention of aneurysmal rupture. Utilizing this mouse model of intracranial aneurysm, we examined the roles of systemic hypertension and the local renin-angiotensin system in the mechanisms for the rupture of intracranial aneurysms.

Methods

Experiments were conducted in accordance with the guidelines approved by the University of California, San Francisco, Institutional Animal Care and Use Committee. Intracranial aneurysms were induced in 8–10 week-old male mice (C57BL/6J, Jackson Laboratory) as previously described.[9, 1817] We combined induced systemic hypertension and a single injection of elastase into the cerebrospinal fluid at the right basal cistern.[9, 1817] **(Detailed methods are presented in the** online supplements.)

To induce systemic hypertension, we used deoxycorticosterone acetate-salt hypertension (DOCA-salt hypertension).[19] Mice underwent nephrectomy followed by an implantation of DOCA pellet one week later; 1% sodium chloride drinking water was started on the same day as the DOCA pellet implantation.[15, 19] Mice received a single injection of elastase (0.035 units) into the cerebrospinal fluid at the right basal cistern on the same day as DOCA pellet implantation. Aneurysms were defined as a localized outward bulging of the vascular wall, whose diameter was greater than the parent artery diameter.[9, 18]

To detect aneurysmal rupture, two blinded observers performed daily neurological examination as previously described.[17] Neurological symptoms were scored as followings; 0: normal function; 1: reduced eating or drinking activity demonstrated by a weight loss greater than two grams of body weight (approximately 10% weight loss) over 24 hours; 2: flexion of the torso and forelimbs upon lifting of the whole animal by the tail; 3: circling to one side with a normal posture at rest; 4: leaning to one side at rest; 5: no spontaneous activity. We have shown that this neurological testing system is sensitive and specific for

detecting aneurysmal rupture in this model.[17] Mice were sacrificed when they developed neurological symptoms (score 1–5). All asymptomatic mice were sacrificed 28 days after aneurysm induction. The brain samples were perfused with phosphate-buffered saline, followed by a gelatin containing blue dye in order to visualize cerebral arteries. Two blinded observes assessed aneurysm formation and subarachnoid hemorrhage. Rupture rate was defined as the total number of mice with ruptured aneurysms divided by the number of mice with any aneurysms.[17] Figure 1 shows representative mouse with normal cerebral arteries, an unruptured aneurysm from a mouse that was asymptomatic throughout the experimental period, and a ruptured aneurysm with subarachnoid hemorrhage from a mouse that became symptomatic 12 days after aneurysm induction.

Our previous study found that aneurysm formation happens during first 6 days after aneurysm induction and aneurysmal rupture start occurring approximately 7 days after the aneurysm induction in this model.[17] We found that by treating the mice with an experimental agent stating from 6 days after aneurysm induction, we can test whether the experimental agent can reduce the rupture rate.[17] Therefore, in this study, the treatments with anti-hypertensive agents were started 6 days after aneurysm induction and continued for two weeks.

Statistical Analysis

Primary outcomes were the incidence of unruptured intracranial aneurysms and the rupture rate (number of mice with ruptured aneurysm/number of mice with ruptured or unruptured aneurysms). We used Fisher's exact test for the analysis of primary outcomes. As an exploratory analysis, the survival analysis was performed using the Log-rank test. Mice that did not develop aneurysms were excluded in the survival analysis. Blood pressure and body weight were analyzed by ANOVA, followed by the Tukey-Kramer post hoc test. All of the results were expressed as mean ± SD. Statistical significance was considered at $P < 0.05$.

Results

Effect of normalization of blood pressure on the development of aneurysmal rupture

As a first step to examine the contributions of systemic hypertension to aneurysmal rupture, we tested effects of normalization of systemic hypertension after aneurysmal formation on the development of aneurysmal rupture. We used hydralazine to normalize the blood pressure. Hydralazine, a direct vasodilator, can normalize systemic hypertension induced by DOCA-salt hypertension without directly affecting the renin-angiotensin system.[19] The hydralazine treatment (25 or 50 mg/kg/day in drinking water)[19, 20] was started 6 days after aneurysm induction and continued for two weeks (Figure 2A). The control group received drinking water without hydralazine.

As shown in Figure 2A, systemic hypertension was successfully induced in the mice receiving the DOCA-salt treatment. The hydralazine at 50 mg/kg/day that was started 6 days after aneurysm induction effectively normalized blood pressure. The lower dose of hydralazine (25 mg/kg/day) partially normalized blood pressure. Normalization of blood pressure by hydralazine did not significantly affect the formation of aneurysms, as demonstrated by no difference in the total incidence of aneurysms (i.e., the incidence of both ruptured and unruptured aneurysms) between two groups (75 vs. 60%, $P = 0.46$) (Figure 2B). However, normalization of blood pressure by hydralazine (50 mg/kg/day) significantly reduced the incidence of ruptured aneurysms and the rupture rate (incidence of ruptured aneurysms: 56 vs. 13%, $P < 0.05$; rupture rate: 75 vs. 22%, $P < 0.05$) (Figures 2B and 2C). There was a trend for partial normalization of blood pressure by the lower dose of hydralazine (25 mg/kg/day) to reduce the rupture rate (incidence of ruptured aneurysms: 56

vs. 30 %, P = 0.25; rupture rate: 75 vs. 38 %, P = 0.17). Taken together, there was a dose dependent effect of the blood pressure reduction on the development of aneurysmal rupture. For the purpose of exploratory analysis, a symptom-free curve (Kaplan-Meier analysis curve) was plotted after excluding mice that did not have aneurysms (Figure 2D). A log-rank test revealed a significant reduction of aneurysmal rupture with the normalization of blood pressure by hydralazine ($P < 0.05$).

As a next step to further confirm the critical role of hypertension in the development of aneurysmal rupture, we tested whether a reduction of blood pressure by the discontinuation of DOCA-salt treatment reduces aneurysmal rupture. For the discontinuation of DOCA-salt treatment, we removed the DOCA pellet and switched the drinking water with water without salt at 6 days after aneurysm induction (Figure 3A). The control group received the standard DOCA-salt treatment throughout the experimental period.

As shown in Figure 3A, in the mice whose DOCA-salt treatment was discontinued 6 days after aneurysm induction, there was a gradual reduction of blood pressure. However, the discontinuation of DOCA-salt treatment did not completely normalize the blood pressure over the course of 2 weeks, possibility reflecting the residual effects of the DOCA-pellet or salt treatment. There was no difference in the total incidence of aneurysms (72 vs. 58%, P = 0.38) (Figure 3B). The discontinuation of the DOCA-salt treatment significantly reduced the incidence of ruptured aneurysms ($P < 0.05$) (Figure 3B). However, there was only a trend for the discontinuation of the DOCA-salt treatment to reduce the rupture rate ($P = 0.07$) (Figure 3C), probably reflecting the failure of normalization of blood pressure in this group. The improvement of survival by the discontinuation of the DOCA-salt treatment was not statistically significant (Figure 3D).

Local renin-angiotensin II system was up-regulated in aneurysmal walls

Since systemic hypertension can affect the local-renin angiotensin system in the vascular wall,[19] we examined the expression of angiotensin II and angiotensin type 1 receptor (AT_1 receptor) in the normal cerebral artery and intracranial aneurysms in mice. Three representative samples were used. While there was weak expression of angiotensin II and AT_1 receptor in the normal cerebral artery, both angiotensin II and AT_1 receptor were abundant in the mouse model of intracranial aneurysm (Figure 4).

Roles of the local renin-angiotensin system in the development of aneurysmal rupture

To test roles of local renin-angiotensin system in the formation of aneurysms, we utilized captopril (angiotensin converting enzyme inhibitor) and losartan (AT_1 antagonist) in mice with DOCA-salt hypertension. We took advantage of the ability of these agents to block the local renin-angiotensin system without affecting systemic hypertension induced by DOCA-salt hypertension.[15, 19] These agents were previously used to assess the roles of the activation of the local renin-angiotensin system in the vasculature in animals that were rendered hypertensive by the DOCA-salt treatment.[15, 19] The captopril and losartan doses were chosen based on the previous studies.[15, 19, 21–23]

The treatment with captopril (6mg/kg/day in PBS, AK Scientific) or vehicle through an implanted osmotic pump was started 6 days after aneurysm induction and continued for two weeks (Figure 5A). As expected, captopril did not affect the systemic hypertension induced by DOCA-salt treatment. While the captopril treatment started 6 days after aneurysm induction did not affect the overall incidence of aneurysms, it significantly reduced the incidence of ruptured aneurysms and the rupture rate (incidence of ruptured aneurysms: 63 vs. 24%, $P < 0.05$; rupture rate: 91 vs. 36%, $P < 0.05$) (Figure 5B and Figure 5C). The

survival analysis using those mice that had aneurysms revealed a significant improvement of the survival by captopril treatment ($P < 0.05$) (Figure 5D).

As a next step, we tested the effect of losartan that blocks AT1 that is the downstream from captopril's target. The treatment with losartan (30mg/kg/day, AK Scientific) or vehicle was started 6 days after aneurysm induction. Losartan did not affect the systemic hypertension induced by the DOCA-salt treatment (Figure 6A). Similarly to the captopril treatment, the losartan treatment significantly reduced the incidence of ruptured aneurysms and the rupture rate (incidence of ruptured aneurysms: 54 vs. 24%, $P < 0.05$; rupture rate: 71 vs. 33%, $P < 0.05$) without affecting the total incidence of aneurysms (Figure 6B and 6C). The survival analysis using those mice that had aneurysms revealed a significant improvement of the survival by losartan treatment ($P < 0.05$) (Figure 6D).

The inhibition of the local renin-angiotensin system by captopril or losartan without affecting systemic hypertension reduced aneurysmal rupture, suggesting a potential contribution of the activation of the local renin-angiotensin system to the development of aneurysmal rupture.

Discussion

In this study, we found that the normalization of blood pressure after aneurysm formation prevents aneurysmal rupture in mice and that there is a dose-dependent relationship between blood pressure and aneurysmal rupture, establishing the causal relationship between the normalization of blood pressure and the prevention of aneurysmal rupture for the first time. In addition, we found that the inhibition of the local renin-angiotensin system independent from the reduction of blood pressure can prevent aneurysmal rupture. These observations suggest that the activation of the local renin-angiotensin system in the aneurysmal wall presumably by systemic hypertension can induce aneurysmal rupture, at least, in a mouse model of intracranial aneurysm.

Recently, an increasing number of unruptured intracranial aneurysms have been diagnosed, primarily due to the increased use of non-invasive brain imaging techniques.[24–26] Unruptured aneurysms are asymptomatic until they rupture. The 30-day mortality rate after aneurysmal subarachnoid hemorrhage is as high as 45%.[27] Surgical clipping or endovascular coiling can be offered to patients with unruptured aneurysms for the prevention of aneurysmal rupture. Significant technical advancements and refinements have been made in these invasive treatments. However, the mortality and morbidity resulting from the clipping and coiling of unruptured aneurysms are not negligible.[3] The one-year adverse outcome rate, including mortality and significant morbidity, can be as high as 20%.[28, 29] In addition, these invasive therapies are technically intensive and costly. Therefore, the pharmacological prevention of aneurysmal rupture is an attractive alternative approach in patients with unruptured aneurysms.

Previous studies performed by our group and others have focused on the mechanisms involved in the formation of aneurysms. These efforts were based on the assumption that the processes of aneurysmal formation, growth, and rupture share similar mechanisms.[8, 30] however, the mechanisms of aneurysmal rupture may be fundamentally different from those of formation and growth. In the mouse model that was used in this study, spontaneous aneurysmal rupture occurs with a predictable time course, and the aneurysmal rupture can be easily detected by assessing neurological symptoms, as presented in our recently published paper.[17] This model provides us with a unique opportunity to study the mechanisms of aneurysmal rupture as well as pharmacological prevention.

In patients with hypertension, the normalization of blood pressure has been clinically proved to be effective in preventing ischemic stroke, intracerebral hemorrhage, and cardiac events. While the anti-hypertensive treatment is generally recommended for hypertensive patients with unruptured intracranial aneurysm, whether the normalization of blood pressure confers the protection against the development of aneurysmal rupture is not known. It would be practically impossible to test such question in clinical setting, as not treating hypertension is not an ethical option. However, it may be possible to test which class of anti-hypertensive agent is suitable for those hypertensive patients with unruptured aneurysms.

Systemic hypertension can affect the tissue remodeling and inflammation of the aneurysmal wall. In addition to exerting abnormal hemodynamic stresses, hypertension can activate local renin-angiotensin system that exists in the vascular wall.[19] Local renin-angiotensin system can control vascular remodeling by affecting smooth muscle migration and proliferation,[31] the processes that can potentially lead to the destabilization of the aneurysmal wall. In addition, it can mediate vascular inflammation through the activation of NF-kappa B which can further promote the inflammation inside the aneurysmal wall.[30] Gene polymorphisms in angiotensin converting enzymes are associated with the rupture of intracranial aneurysms,[12–14] suggesting a link between renin-angiotensin system and aneurysmal rupture. Taken together with our findings, the local renin-angiotensin system can be a therapeutic target for the prevention of aneurysmal rupture. There are many clinically available anti-hypertensive agents that can inhibit different steps of the local renin-angiotensin system. Anti-hypertensive agents that possess the inhibitory effects on the local renin-angiotensin system may contribute to the prevention of aneurysmal rupture not only through the normalization of blood pressure by also through the inhibition of the local renin-angiotensin system.

There are a number of limitations of this study. First, the study design of our study depended on the pharmacological approach. While the utilization of clinically available anti-hypertensive agents makes our findings readily translatable, the anti-hypertensive agents chosen for our study may not be specific to their designed targets (i.e., vascular calcium channel, angiotensin II type 1 receptor, angiotensin converting enzyme and others). These anti-hypertensive agents possess non-hemodynamic effects that can potentially affect the processes that lead to aneurysmal rupture. Another major limitation of this study is that we did not directly assess the activity of the local renin-angiotensin system. Although our immunohistochemistry data suggested the activation of the renin-angiotensin system, we were not able to measure its activity. As it was previously recognized by others, currently there is no reliable way to directly quantify the activation of the local renin angiotensin system.[19]

Summary

Using the mouse model of intracranial aneurysms, we revealed critical roles of systemic hypertension and the local renin-angiotensin system in the development of aneurysmal rupture. Our study may be a basis for the clinical study to find the optimal choice of anti-hypertensive agents for patients with unruptured intracranial aneurysms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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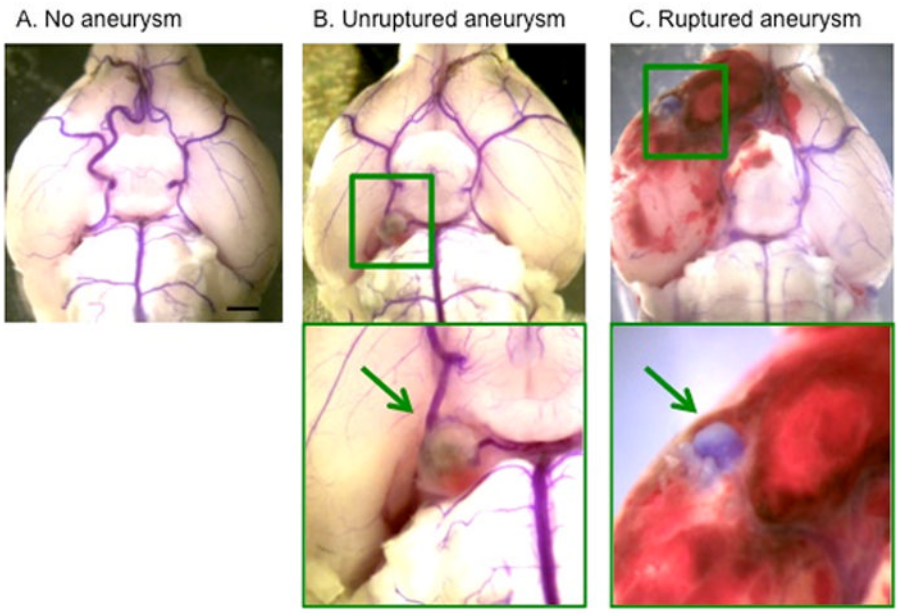

Figure 1. Representative intracranial aneurysms

A: Normal cerebral arteries. B: Unruptured aneurysm in the posterior cerebral artery. C: Ruptured aneurysm with subarachnoid hemorrhage. Cerebral arteries were visualized by blue dyes dissolved in gelatin. Arrows indicate aneurysms.

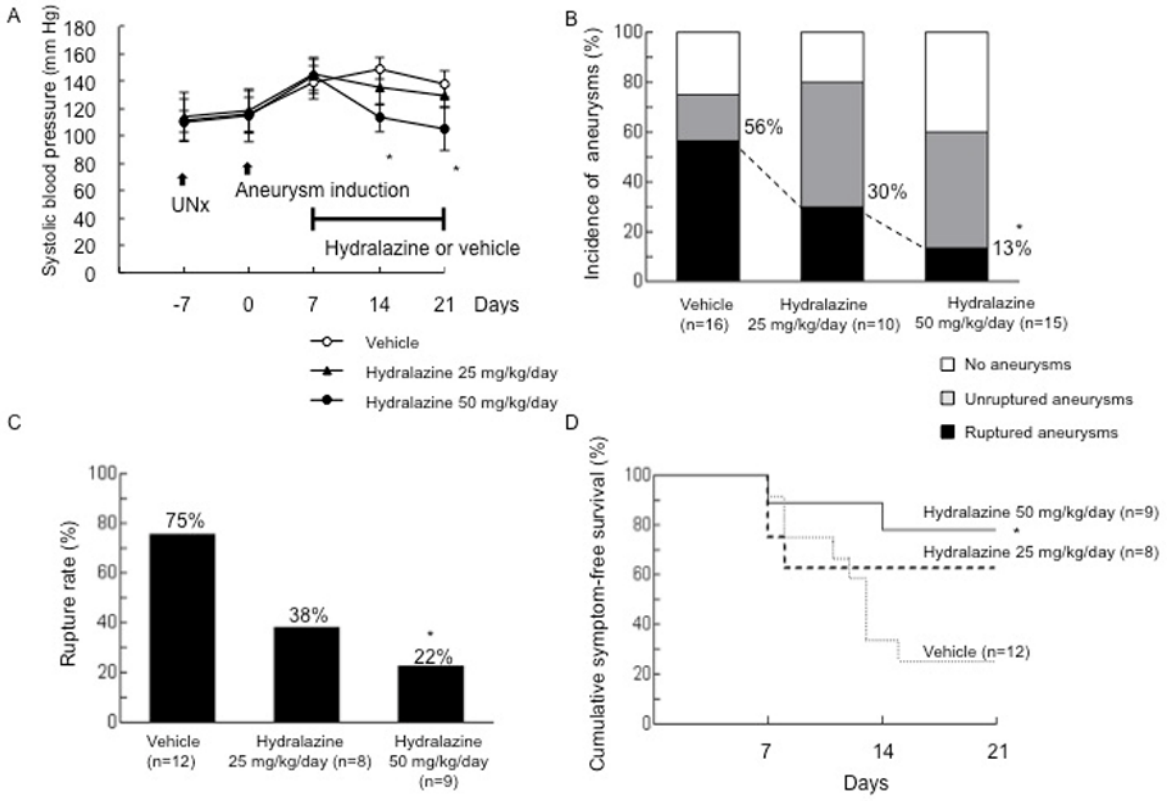

Figure 2. Normalization of blood pressure by hydralazine reduced the incidence of ruptured aneurysms and the rupture rates

A: Blood pressure. B: Incidence of ruptured and unruptured aneurysms. C: Rupture rate. D. Survival curve. Survival curves were constructed after excluding those mice that did not have aneurysms so that the curves mimic clinical settings.

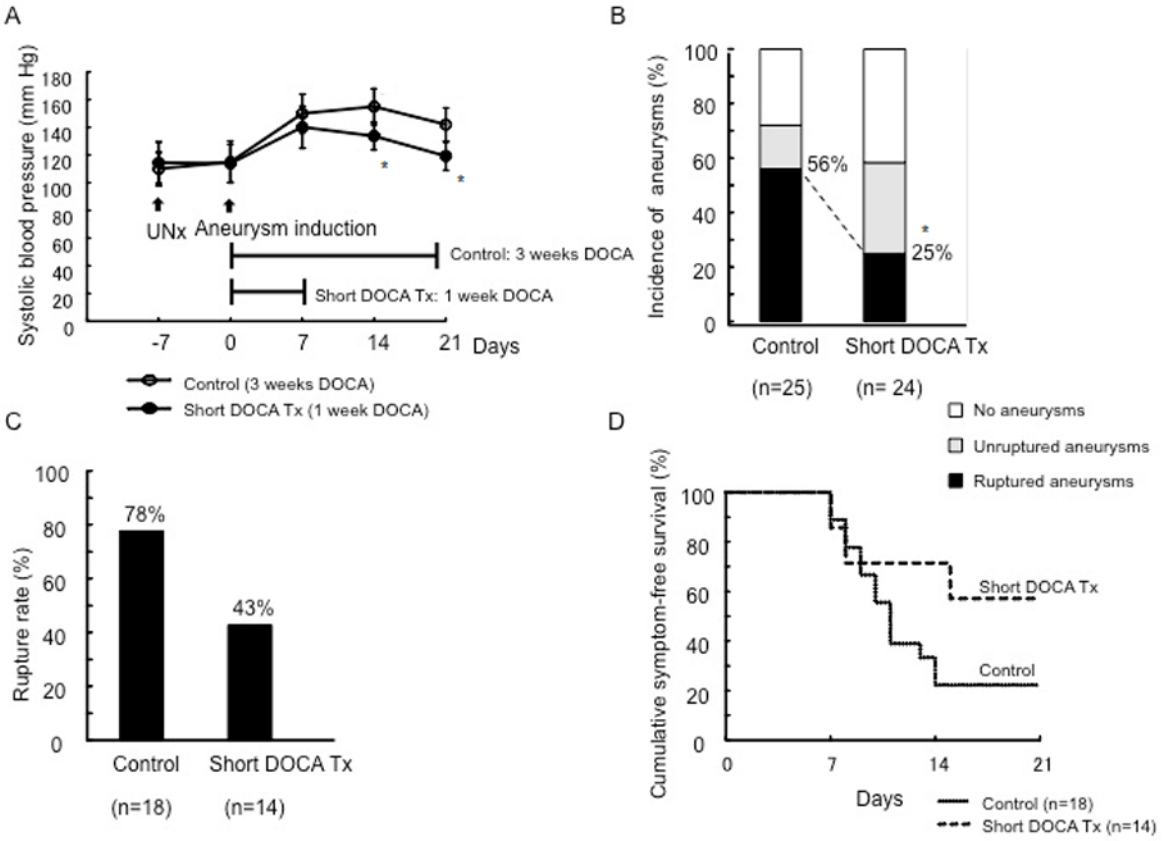

Figure 3. Effects of the discontinuation of DOCA-salt treatment one week after aneurysm induction

A: Blood pressure. B: Incidence of ruptured and unruptured aneurysms. C: Rupture rate. D. Survival curve.

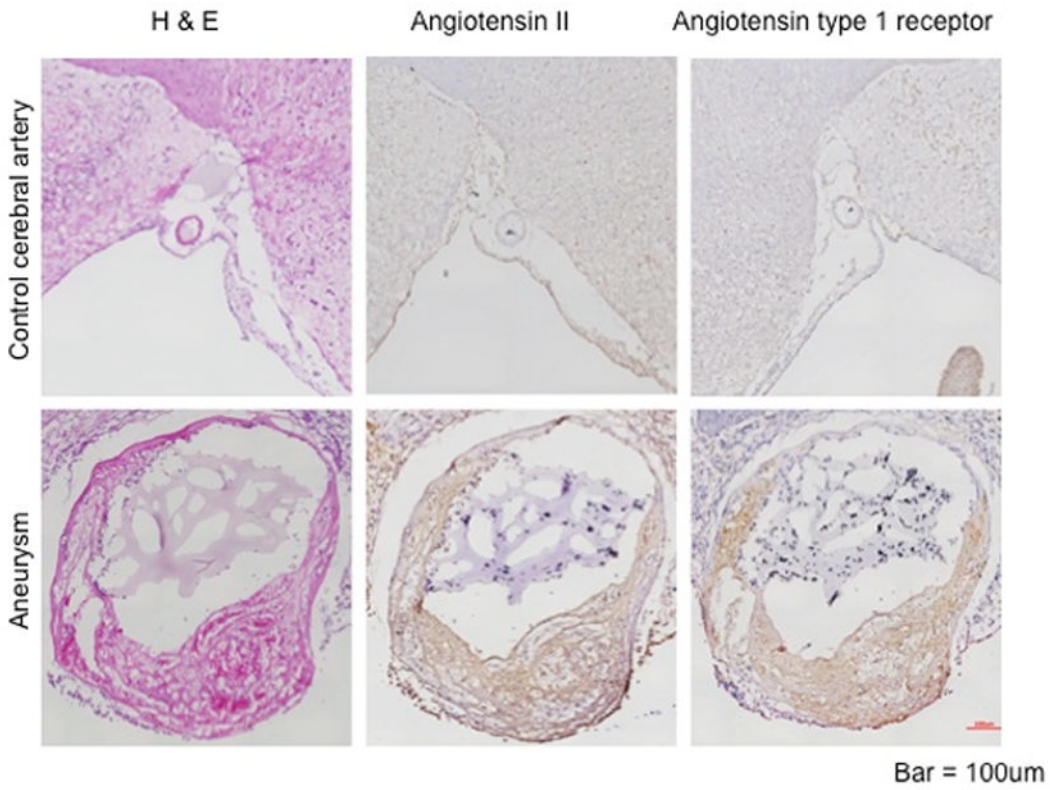

Figure 4.
Expression of angiotensin II and angiotensin II type 1 receptor.

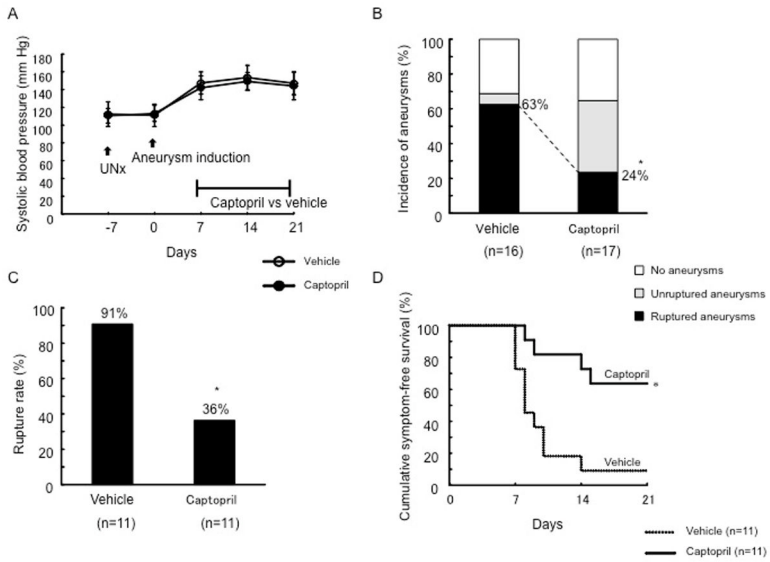

Figure 5. Inhibition of the local renin-angiotensin system by captopril prevented aneurysmal rupture without affecting systemic hypertension

A: Blood pressure. B: Incidence of ruptured and unruptured aneurysms. C: Rupture rate. D. Survival curve.

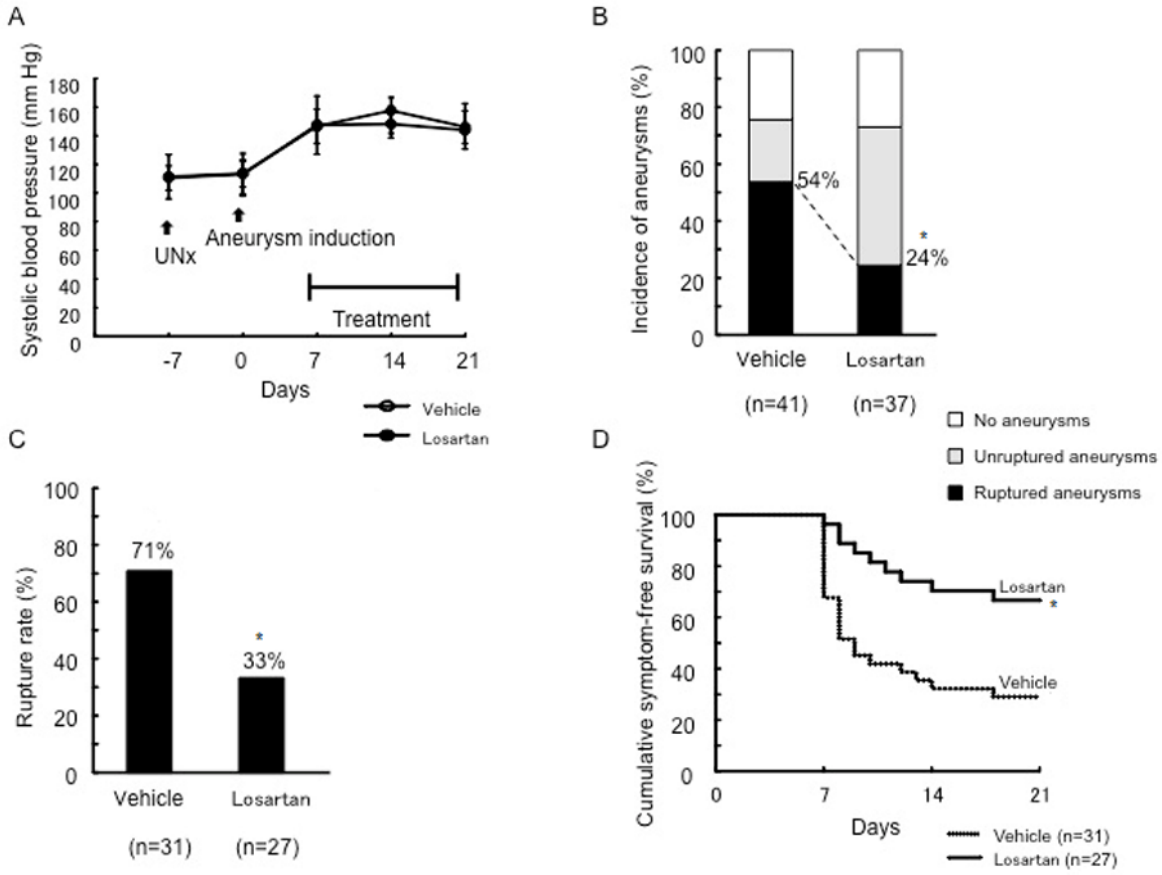

Figure 6. Inhibition of the local renin-angiotensin system by losartan prevented aneurysmal rupture without affecting systemic hypertension

A: Blood pressure. B: Incidence of ruptured and unruptured aneurysms. C: Rupture rate. D. Survival curve.