Effect of Vasa Vasorum on Basilar Artery Vasospasm Following Subarachnoid Hemorrhage

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BACKGROUND: **A well-documented association exists between the vasa vasorum and vasopathologies, including atherosclerosis. However, information on the role of the vasa vasorum during vascular degenerative changes of vasospasm after subarachnoid hemorrhage (SAH) is insufficient.**

METHODS: **In this study, 34 rabbits were divided into 3 groups: basal group (N = 8), sham group (N = 8), and SAH group (N = 18). Experimental SAH was formed using a double-injection model. During follow-up, the neurologic status of the rabbits was observed. All rabbits were euthanized after 2 weeks, and the vasopathologic degeneration was categorized as normal, mild, moderate, and severe according to the changes in the basilar arteries. The numbers, locations, and spasms of the vasa vasorum and their relation to the vasodegenerative changes of the basilar artery were investigated.**

RESULTS: **The basilar arteries were graded as normal in the basal and sham groups. In the SAH group, 6 rabbits had mild, 7 had moderate, and 5 had severe degeneration. Neurologic deficits were prominent in the SAH group, and deficit grades correlated with vascular degeneration. The number of the vasa vasorum were significantly higher in the SAH group, and an enhanced formation of the vasa vasorum was noted in which severe degenerative changes were present. Moreover, the vasospasm index of the vasa vasorum, which increased with the aggravation of vascular degenerative changes, was significantly higher in the SAH group.**

CONCLUSIONS: **The vasa vasorum and their vasospasm play a crucial role in the pathogenesis of basilar artery degeneration in the vasospasm following SAH.**

INTRODUCTION

Cerebral vasospasm is a substantial cause of morbidity and mortality after subarachnoid hemorrhage (SAH).[1,2] Basilar artery vasospasm, which causes brainstem hypoperfusion, is a prognostic factor associated with poor outcomes in severe vasospasm after SAH.[3] Degenerative changes noticed in the cerebral arteries after SAH have a significant role in the pathogenesis of vasospasm.[4] Various ultrastructural changes seen in the intima, media, and adventitia layers cause arterial contraction leading to hypoperfusion and ischemia.[5]

The vasa vasorum is a web of microvessels that supply the walls of large vessels.[6] Vasa vasorum, primarily observed in the adventitia layer, is more common in proximal arteries, such as the basilar artery, than distal intracranial arteries.[7] A correlation between the appearance of the vasa vasorum and vasopathologic conditions exists[7,8]; however, there is limited literature regarding the relationship between vasa vasorum and mural degenerative changes in the vasospasm. Therefore, this study aims to clarify this issue using an experimental rabbit model of SAH.

METHODS

The guidelines of the National Institutes of Health were followed during the preparation of work design and animal husbandry. The study design was approved by the Institutional Ethical Committee

Key words
- Basilar artery
- Degeneration
- Subarachnoid hemorrhage
- Vasa vasorum
- Vasospasm

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
H&E: Hematoxylin and eosin
SAH: Subarachnoid hemorrhage
TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling

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of Animal Research of Ataturk University. Thirty-four adult male New Zealand white rabbits (weight 3.95 ± 0.22 kg) were divided into 3 groups: basal group (N = 8), sham group (N = 8), and SAH group (N = 18). The rabbits were maintained in polypropylene cages under 12/12 hours light/dark cycle and controlled temperature (21°C ± 0.5°C) before and during the experiment.

No intervention was done to the basal group, whereas the experimental SAH was induced using the double-injection model.[9] The animals were anesthetized using an intramuscular injection of a mixture of ketamine hydrochloride (25 mg/kg), lidocaine hydrochloride (15 mg/kg), and acepromazine (1 mg/kg). Initially, 1.0 mL of cerebrospinal fluid (CSF) was percutaneously drained from the cisterna magna, and within 1 minute, 2.5 mL of autologous blood derived from the central auricular artery was injected into the cisterna magna. The rabbits were then positioned prone with head tilted down 30° for 30 minutes. The same procedure was repeated after 48 hours. The same procedures were performed in the sham group, but the isotonic saline solution was used instead of autologous blood.

After the second injection, all animals were followed up for 2 weeks as per normal laboratory standards without treatment, and all of them were euthanized at the end of the experiment. Their brains, basilar arteries, and branch complexes were removed and preserved in 10% formalin solution for 7 days. The specimens were embedded in paraffin blocks, and 20 consecutive sections of 5 μm were taken from all preparations for histopathologic examination. Basilar artery preparations were stained using hematoxylin and eosin (H&E) and TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) methods. H&E and TUNEL staining preparations were evaluated by 2 independent pathologists using the Olympus BX51 System Microscope (Olympus Corporation, Tokyo, Japan).

During follow-up, the rabbits were assessed as per the neurologic deficits scale devised by Endo et al,[10] which classifies no neurologic deficit (normal) as grade 1, minimal or suspected neurologic deficit as grade 2, mild neurologic deficit without abnormal movements as grade 3, and severe neurologic deficit with abnormal movements as grade 4.

A grading scale was devised for the classification of degenerative changes of the basilar artery in the histopathologic samples. The histopathologic changes determined in previous studies were considered during the grading process.[7,11-13] In addition, the level of cell and tissue damage was considered for grading.[14] The changes in the samples were rated as per the degree of damage in the basilar arteries: intimal edema and endothelial swelling (1 point), muscular swelling (2 points), inner elastic membrane convolutions (3 points), endothelial desquamation and apoptosis (4 points), muscular apoptosis and medial myonecrosis (5 points), and medial hemorrhage (6 points); these were accepted as degenerative change criteria for basilar artery. The assessment was based on a total of 28 points, and degeneration was classified into 4 levels according to the total points: (1) no obvious degeneration (normal), 0–6 points; (2) mild degeneration, 7–13 points; (3) moderate degeneration, 14–20 points; and (4) severe degeneration, 21–28 points. Although endothelial and muscular apoptosis were evaluated using the TUNEL assay, other criteria were evaluated using H&E staining.

The numbers and locations of vasa vasorum of the basilar artery and their vasospasm indexes were evaluated. The vasospasm indexes were calculated using the method used in previous studies.[15,16] Wall surface/lumen surface ratio was accepted as the vasospasm value of the vasa vasorum (the wall surface was calculated by subtracting the lumen surface from the total surface). The vasospasm index was calculated as follows: wall surface/lumen surface = $(\pi R^2-\pi r^2)/\pi r^2 = (R^2-r^2)/r^2$, where R^2 is the external diameter and r^2 the internal diameter of arteries. The relationship of vasa vasorum numbers, and their vasospasm indexes with the degeneration scores of basilar arteries were also examined.

Statistical analysis was performed using IBM SPSS version 19 software (IBM Corporation, Armonk, New York, USA). The results for continuous variables were provided as mean ± standard deviation. While testing categorical variables, the χ^2 test was used. Normality of distribution for continuous variables was evaluated using the Kolmogorov–Smirnov test. When the normality assumption was provided for 3 or more groups, one-way analysis of variance test was used with Bonferroni test as a post hoc, otherwise the Kruskal–Wallis test was used. As a post hoc test for pairwise comparisons, the Dunn's test was used. According to the normality of the distribution, either the Pearson's or the Spearman's correlation coefficient was used to evaluate the correlation between measurements. The size of the correlation was evaluated using correlation coefficients (0.00–0.30 is negligible, 0.30–0.50 is low, 0.50–0.70 is moderate, 0.70–0.90 is high, and 0.90–1.00 is very high). A P value of <0.05 was considered statistically significant.

RESULTS

Macroscopic and Microscopic Evaluations

In the basal and sham groups, a macroscopically normal gross anatomic appearance was observed (Figure 1). Microscopic appearance of the basilar artery was within normal limits in both groups (Figure 2). In the SAH group, diffuse bloody appearance, which was prominent in the sulcus basilaris, was observed macroscopically in the ventral surface of the brain (Figure 3). Microscopic examination of the basilar artery revealed varying degrees of degenerative changes with endothelial swelling and desquamation, internal elastic membrane distortions, medial swelling, myonecrosis, and hemorrhage (Figures 4, 5, and 6). The number of vasa vasorum and the vasospasm indexes were noted (Figures 2 and 4). TUNEL staining detected varying degrees of endothelial and muscular apoptosis in the SAH group (Figure 7). In some vasa vasorum, the presence of apoptosis was demonstrated via the TUNEL assay (Figure 8).

Basilar Artery Degeneration

When degeneration scores were evaluated, the mean score in the basal group was 0.75 ± 0.71, and all animals were classified as non-degenerated as per the basilar ischemic degeneration scale. The mean degeneration score was found to be 1.25 ± 1.16 in the sham group. All animals in this group were also classified as non-degenerated. However, the SAH group had a mean degeneration score of 18.12 ± 6.15, with degeneration present in all the animals—mild in 6, moderate in 7, and severe in 5 as per the degeneration scoring scale. Within the SAH group, 3 degeneration

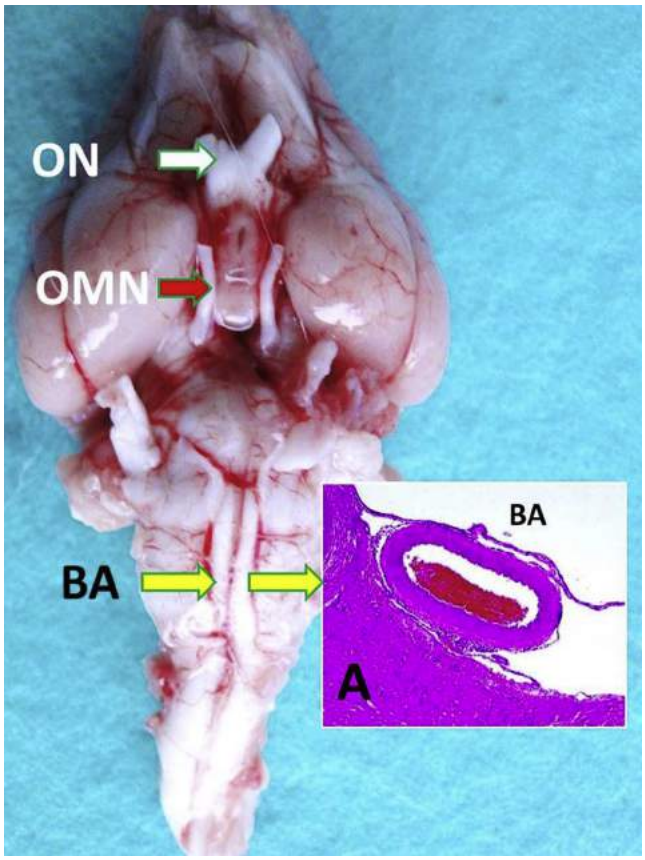

Figure 1. Base: Gross anatomic appearance of the dorsal surface of the rabbit brain from the basal group; basilar artery (BA) at the sulcus basilaris, optic nerve (ON), and oculomotor nerve (OMN). **A**: Histologic appearance of the basilar artery at the pontine level (hematoxylin and eosin ×20).

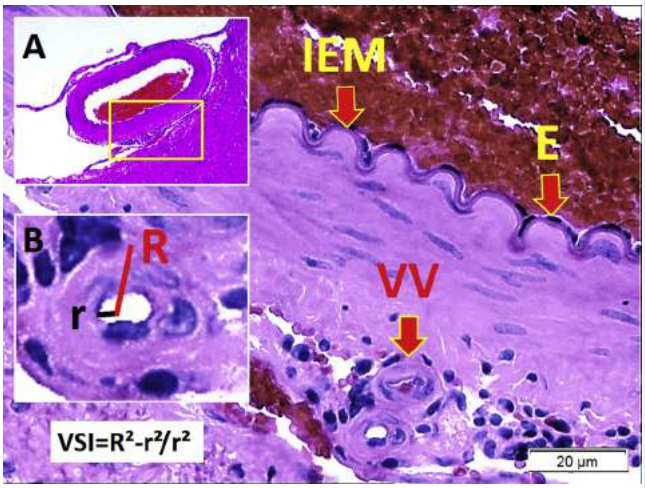

Figure 2. **A**: Microanatomic appearance of the basilar artery of a rabbit from the basal group within normal limits (hematoxylin and eosin ×20). Base: An enlarged view of the rectangle in **A**; histopathologic view of the endothelial cells (E) in the tunica intima, inner elastic membrane (IEM), smooth muscles in the tunica media, and vasa vasorum (VV) in the tunica adventitia within normal limits (hematoxylin and eosin ×100). **B**: The wall surface/lumen surface values were accepted as the vasospasm index (VSI) and formulated as follows: VSI = $(R^2-r^2)/r^2$ (hematoxylin and eosin ×200).

subgroups were formed according to the degeneration grading: mild, moderate, and severe. No difference was observed between the basal and sham groups ($P = 0.686$). A significant statistical difference was observed between the SAH and the other 2 groups ($P < 0.001$).

Neurologic Assessment

Numerical values of neuro-deficit scale distribution are given in Table 1. No neurologic deficit was observed in the animals of the basal and sham groups. Neurologic status of rabbits in the SAH group was evaluated within subgroups as per the basilar artery degeneration levels. In the subgroup with mild degeneration, 3 animals were detected with grade 2, and 3 animals with grade 3. In the subgroup with moderate degeneration, 4 animals were detected with grade 3, and 3 animals with grade 4. In the subgroup with severe degeneration, all 5 animals were detected with grade 4. A positive strong correlation was observed between the basilar artery degenerative scoring and neurologic deficits grading ($r = 0.93$, $P < 0.001$). In addition, a significant difference was found between the distribution of subgroups in the SAH group ($P = 0.005$).

Vasa Vasorum Location and Number

Histopathologic examination of the basilar arteries revealed that the basilar artery supplying the microarterioles was not detected in 7 (21.2%) of 33 animals. The vasa vasorum was identified in 5 (62.5%) animals of the basal group, 5 (62.5%) animals of the sham group, and 17 (94.4%) animals of the SAH group. No statistical difference was noted between the basal and sham groups regarding the existence of vasa vasorum ($P = 1.0$). However, the rate of detection was statistically higher in the SAH group than in the other 2 groups ($P = 0.044$). Furthermore, vasa vasorum were detected only in the adventitia layer and not in the intima or media layers.

Numerical analysis of the vasa vasorum is given in Table 2. The mean number of detected vasa vasorum was 1.5 ± 1.41 in the basal group, 1.76 ± 1.67 in the sham group, and 6.22 ± 2.72 in the SAH group. No difference was noted between the basal and sham groups ($P = 0.858$) However, a significant increase was observed in the SAH group than in the basal group ($P < 0.001$). The mean numbers in the subgroups of SAH for mild, moderate, and severe degeneration were 4 ± 2.19, 6.57 ± 1.51, and 9.2 ± 2.28, respectively. Nonetheless, no significant difference was noted between the mild and moderate subgroups ($P = 0.072$) and moderate and severe subgroups ($P = 0.091$); however, a significant difference was observed between the mild and severe subgroups ($P = 0.002$).

Vasospasm Indexes of Vasa Vasorum

Analysis of the vasospasm indexes of the vasa vasorum is given in Table 3. The vasospasm indexes were found to be 1.04 ± 0.15 in the basal group, 1.12 ± 0.17 in the sham group, and 6.6 ± 1.68

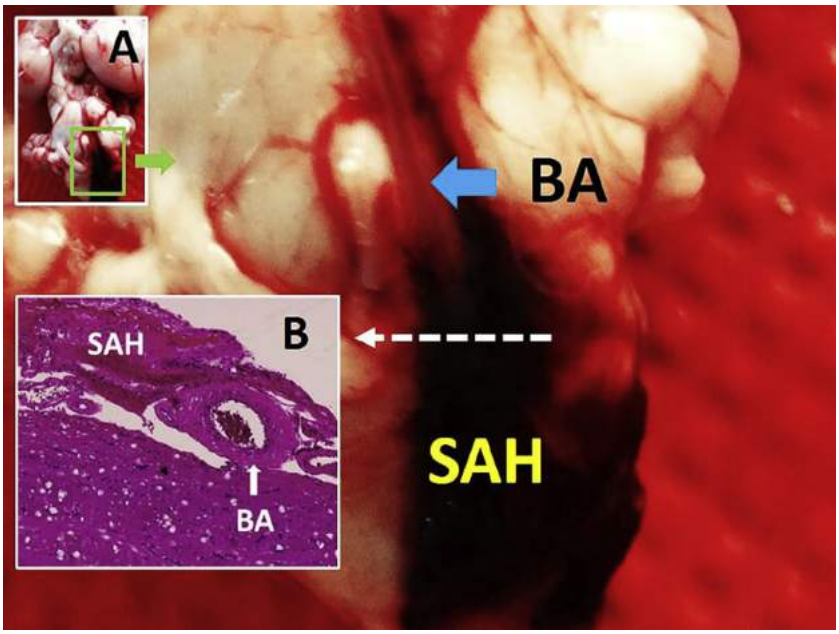

Figure 3. **A**: Gross anatomic view of the dorsal surface of the rabbit brain with experimental subarachnoid hemorrhage. Base: An enlarged view of the rectangle in **A**; gross anatomic appearance of the basilar artery (BA) at the basilar sulcus filled with subarachnoid hemorrhage (SAH). **B**: Histopathologic view of the basilar artery with SAH at the mid-pontine level (hematoxylin and eosin ×20).

in the SAH group. When the SAH group was subgrouped based on the ischemic degeneration scoring, the indexes were found to be 5.04 ± 1.07 for mild changes, 6.57 ± 0.86 for moderate changes, and 8.25 ± 1.58 for severe changes. However, no statistical difference was noted between the SHAM and basal groups ($P = 0.115$). Vasospasm indexes were significantly higher in the SAH group than in the basal ($P < 0.001$) and the sham groups ($P < 0.001$). Nonetheless, no significant difference was observed between the mild and moderate subgroups ($P = 0.069$) and moderate and severe subgroups ($P = 0.083$); however, a significant difference was observed between the mild and severe subgroups ($P = 0.003$).

DISCUSSION

Histopathologic degenerative changes occur in all 3 layers of the vessel wall in the vasospasm after SAH.[17] Relatively minor changes are observed in the tunica adventitia with edema and inflammatory cell infiltration. However, more prominent changes are seen in the tunica media and intima.[13] The tunica media shows cellular and structural changes, resulting in smooth muscle damage and necrosis.[13,18] Medial hemorrhage may occur with the progression of these disruptions.[7] Changes in the internal elastic membrane include irregularities of the structure and the intermittent loss of continuity.[11,13] The changes seen in the tunica intima include swelling, endothelial damage, and desquamation.[12,17] Cell damage and death occurring in the vasospasm after SAH are similar to other inflammation processes, starting with cell swelling due to intracellular homeostasis disruption and ending with apoptosis and necrosis.[14] The grading scale for degenerative changes in the basilar artery after experimental SAH in this study was based on these well-known features. Therefore, the presence of apoptosis, necrosis, and hemorrhage in the mural structure was given more points than cellular swelling. In addition, owing to the prominence of the changes in the tunica intima and media, these changes were considered during scoring.

The complex pathophysiologic processes after aneurysmal SAH induce ischemia and brain injury, resulting in neurologic deterioration,[19] which may be demonstrated using the grading.[10] The difference in the distribution between the experimental SAH and control groups have been shown in previous studies through neurologic deficits grading,[10,20] with the animals of the SAH group exhibiting neurologically worse conditions. The present study found similar results. In addition, it was observed that the neurologic status of the animals worsened with the increase in degenerative changes in the basilar artery. This finding was supported by another study in which the neurologic deficit grades were noted to decrease when the degenerative changes in the basilar artery after SAH were treated.[20]

The vasa vasorum is a web of microvasculature that plays a vital role in normal vascular mural physiology and pathologic conditions.[21] Under normal physiologic conditions, the diffusion of luminal flow adequately nourishes the inner segments of the vessel wall, whereas the outer parts of the wall are out of this diffusional range and hence need additional nourishment from the vasa vasorum.[6] There is a suggestion of another mechanism

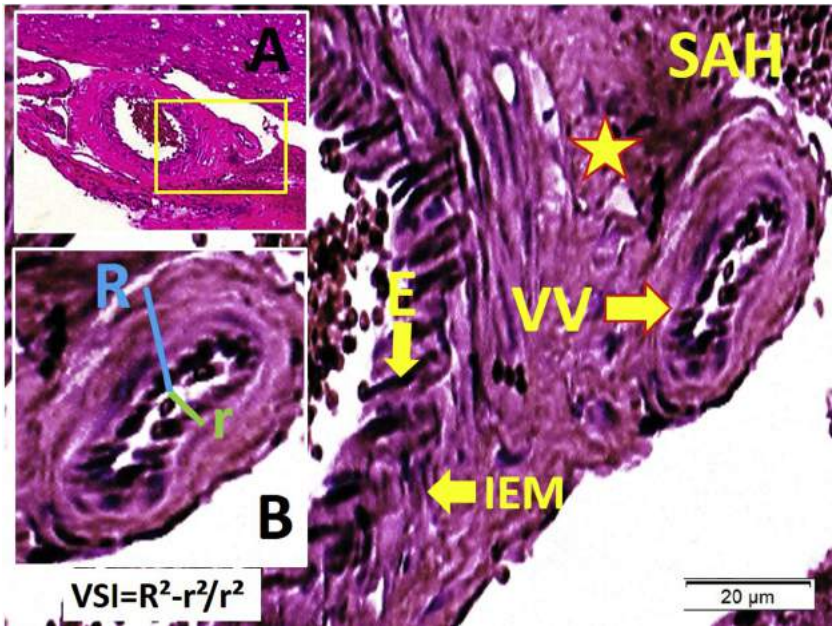

Figure 4. **A**: Histopathologic view of the basilar artery at the sulcus basilaris of a rabbit from the subgroup of severe degeneration (hematoxylin and eosin ×20). Base: The enlarged version of **A**; severe degenerative changes of the basilar artery with endothelial swelling (E), inner elastic membrane convolutions (IEM), medial myonecrosis and medial hemorrhage (Star) and vasospastic vasa vasorum (VV) (hematoxylin and eosin ×100). **B**: The vasospasm index of vasa vasorum is shown (hematoxylin and eosin ×100). SAH, subarachnoid hemorrhage.

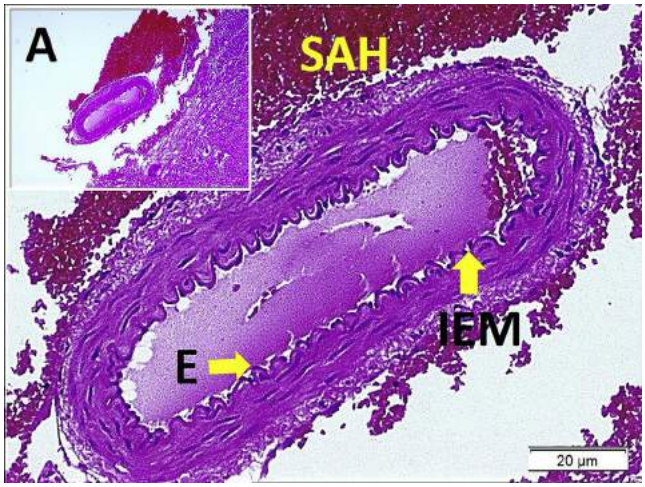

Figure 5. **A**: Microanatomic appearance of the basilar artery at the sulcus basilaris filled with subarachnoid hemorrhage (SAH) (hematoxylin and eosin ×20). Base: The enlarged version of **A**; mild degenerative changes of the basilar artery with endothelial swelling and desquamation (E), inner elastic membrane convolutions (IEM), without vasa vasorum (hematoxylin and eosin ×100).

that nourishes the outer part of the vessel in the intracranial arteries. The intracranial vessels are shown to obtain nourishment from the CSF environment via narrow channels called stomata or rete vasorum,[22,23] which allows the vessel walls to be permeable to the CSF.[22] However, the pathologic conditions of the vessel wall lead to deterioration in diffusion, increasing the need for nutrients and oxygen.[21] Therefore, vasa vasorum formation reportedly increases in intracranial vasopathologic conditions, such as atheroma formation, vascular dissection, vasospasm, and aneurysm.[24,25] In a series of 50 autopsy cases, incidence of the vasa vasorum was 72% with a prominent presence in the proximal arteries, as well as in the existence of atherosclerosis and cerebral disease.[7] Although the vasa vasorum is typically located in the tunica adventitia, it was detected in the tunica media in the event of SAH and medial necrosis.[7]

The enhancement of adventitial vasa vasorum formation was demonstrated at the spastic coronary segment in patients with vasospastic angina.[26] The correlation between the extent of vasa vasorum formation with mural thickening in the vasospasm developed segments was shown via intramural imaging.[26] The present study revealed a significantly increased number of detected vasa vasorum with experimental SAH. Moreover, the number of the vasa vasorum found within the SAH group

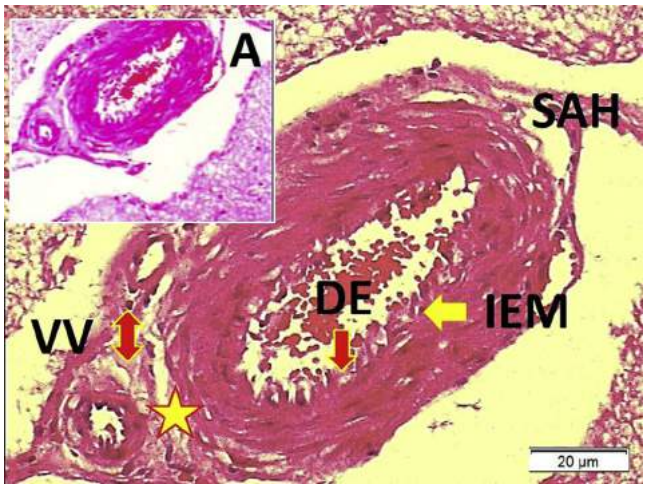

Figure 6. **A**: Microanatomic appearance of the spastic basilar artery with severe degenerative changes at the sulcus basilaris filled with subarachnoid hemorrhage (SAH) (hematoxylin and eosin ×20). Base: The enlarged version of **A**; severe degenerative changes of basilar artery with awful endothelial swelling, degeneration and desquamation (DE), inner elastic membrane destruction and convolutions (IEM), medial hemorrhage (yellow star), and degenerated vasospastic vasa vasorum (VV) (hematoxylin and eosin ×100).

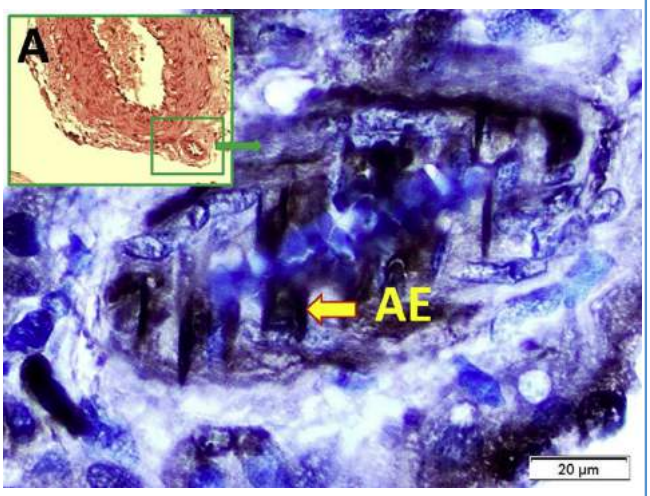

Figure 8. **A**: Histopathologic view of the basilar artery and its vasa vasorum at the sulcus basilaris filled with subarachnoid hemorrhage (hematoxylin and eosin ×20). Base: An enlarged view of the rectangle in **A** with TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) staining; vasa vasorum with significant apoptosis of the endothelial cells (AE) and narrowed lumen (TUNEL staining ×200).

correlated with the basilar artery degeneration rate. This increase in the number of the vasa vasorum in the vasospasm after SAH can be explained based on 2 mechanisms. One potential cause may be the decreased diffusion to the outer sections of the vessel, owing to increased vascular wall thickness after degenerative changes in the intima and media layers after vasospasm.[13,24] The other factor may be the impairment in the nourishment from the CSF because of disruption or occlusion of the stomata with blood and other breakdown products.[27] Therefore, malnourishment caused by these mechanisms probably increases the vasoplastic activity in the vessel wall; this proliferative effect may signal the potential precursor cells to form the vasa vasorum structures.

The possibility of vasospasm after SAH is associated with the degree of SAH.[28,29] Notably, SAH-related blood breakdown products stimulate vasospasm.[30,31] The inflammatory process and oxidative stress initiated by these metabolic products cause

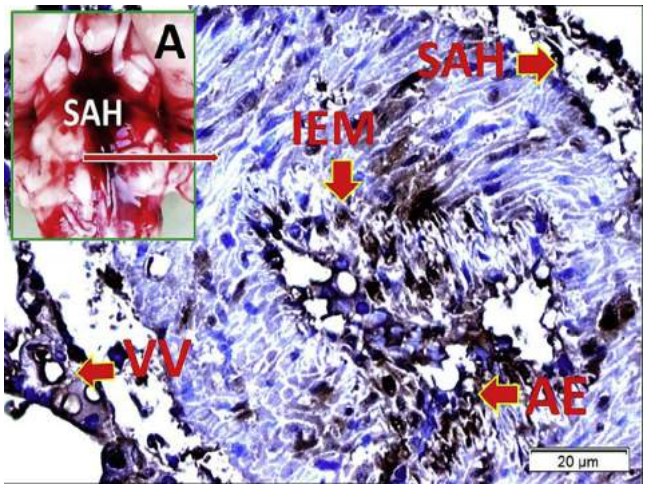

Figure 7. **A**: Gross anatomic view of the basilar artery at the sulcus basilaris filled with subarachnoid hemorrhage (SAH). Base: Histopathologic view of the basilar artery with degenerative changes; swelling and apoptosis of the endothelial cells (AE), inner elastic membrane convolutions (IEM), medial apoptosis, and vasa vasorum (VV) (TUNEL [terminal deoxynucleotidyl transferase dUTP nick end labeling] staining ×40).

Table 1. Distribution of 33 Rabbits into Neurologic Deficit Grades According to Endo et al.[10]

	Neurologic Deficit Grading				
Groups	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	***P* Scores**
Basal group	8	0	0	0	**<0.001***
Sham group	8	0	0	0	
SAH group					
Mild	0	3	3	0	**0.005†**
Moderete	0	0	4	3	
Severe	0	0	0	5	

Bold values denote statistical significance ($P < 0.05$).
SAH, subarachnoid hemorrhage.
*Positive strong correlation between degenerative scoring and neurologic deficit grading.
†Difference between distribution of subgroups of SAH group.

Table 2. Mean Number of Detected Vasa Vasorum of Groups and Subgroups

Groups	Vasa Vasorum	*P* Scores Between Groups and Subgroups	
Basal group	1.5 ± 1.41	Basal—Sham	0.858
Sham group	1.76 ± 1.67	Basal—SAH	**<0.001**
SAH group			
Mild	4 ± 2.19	Mild—Moderete	0.072
Moderete	6.57 ± 1.51	Moderete—Severe	0.091
Severe	9.2 ± 2.28	Mild—Severe	**0.002**

Numbers vasa vasorum of the groups and subgroups were given as median ±standard deviation.
Bold values denote statistical significance ($P < 0.05$).
SAH, subarachnoid hemorrhage.

Table 3. Vasa Vasorum Vasospasm Indexes of Groups and Subgroups

Groups	Vasospasm Indexes	*P* Scores Between Groups and Subgroups	
Basal group	4.16 ± 0.60	Basal—Sham	0.732
Sham group	4.48 ± 0.68	Basal—SAH	**<0.001**
SAH group			
Mild	20.16 ± 4.28	Mild—Moderete	0.069
Moderete	26.28 ± 3.44	Moderete—Severe	0.083
Severe	33.01 ± 6.32	Mild—Severe	**0.003**

Vasa vasorum vasospasm indexes of the groups and subgroups were given as median ±standard deviation.
Bold values denote statistical significance ($P < 0.05$).
SAH, subarachnoid hemorrhage.

pathologic changes in the vascular mural structure, resulting in vasospasm.[31] The process that causes changes in the vessel structure may cause similar changes in its vasa vasorum. The present study supports this idea. When the vasospasm indexes were calculated based on the wall surface/lumen surface ratio, a significant increase was observed in the SAH group than that in the basal group. Furthermore, the vasospasm index of the vasa vasorum was found to correlate with the grade of basilar artery degeneration. This correlation is presumably caused by 2 mechanisms. One, the blood breakdown products may cause similar changes in the vessel and its subadventitial microvascular web. Two, obstruction in microarterial circulation owing to vasospasm of the vasa vasorum may disrupt the nourishment of the basilar artery, thereby increasing the degenerative event.[32]

There is no study that clearly describes the vasa vasorum in the rabbit basilar artery. However, in a previous study on the rabbit carotid artery, vasa vasorum was defined.[33] Microvessel structures are observed to arise from the artery lumen and originate from the arterial branching regions. The microvascular distribution of the web formed for nourishment is confined to the tunica adventitia and does not penetrate the tunica media.[33] The present study observed similar results, in which the vasa vasorum was only present in the tunica adventitia and did not penetrate the tunica media. In contrast, Takaba et al.[7] have shown that the vasa vasorum penetrate the tunica media in the event of medial hemorrhage and myonecrosis after SAH in a study performed on human cadavers with large arterial structures.

The present study has some limitations. Our experimental cisterna magna double-injection SAH model is somewhat different from the human model. Delayed vasospasm and early brain injury after aneurysmal SAH have been considered the crucial factors of brain damage in the human model. Double-injection model mimics later effects of SAH and is less convenient to examine the acute phase of SAH, including early brain injury. In addition, vasopathologic changes in the aneurysmal wall of the human model cannot be investigated in the double-injection model.

CONCLUSIONS

The present study reveals that the grade of degenerative changes in the basilar artery after SAH, which causes clinical deterioration, was found to correlate with the number of vasa vasorum and their severity of vasospasm. According to these results, the existence of vasa vasorum in the basilar arteries and their functional spasm play crucial roles in the vasospasm pathogenesis and in the degenerative changes of the basilar artery following SAH. The present study may provide foresight for future studies focusing on the treatment modalities for vasa vasorum obstacles in the vasospasm.

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