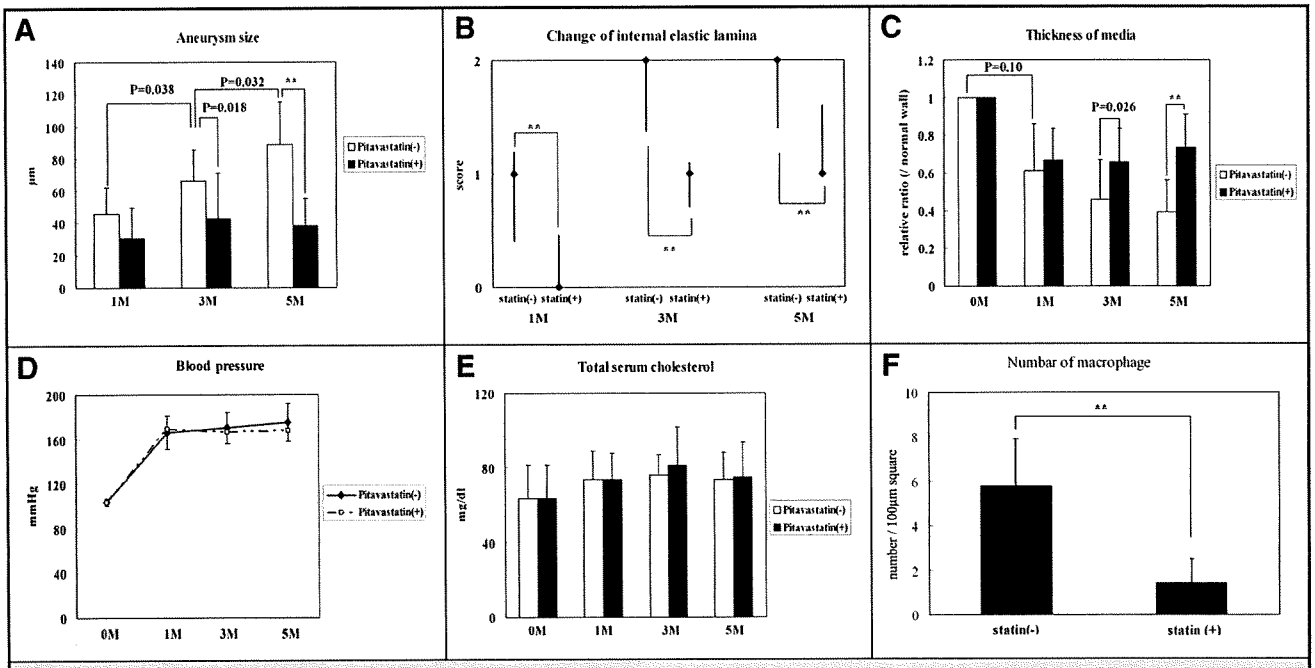

FIGURE 1. *Graphs showing effects of pitavastatin on the formation and progression of CA.* **A,** *aneurysm size in the control and pitavastatin-treated groups. Data were analyzed by Kruskal-Wallis 1-way analysis of variance (ANOVA) on ranks followed by the Tukey-Kramer test.* **B,** *change of internal elastic lamina after aneurysm induction with or without pitavastatin treatment. Data were analyzed by the Siegel-Tukey test.* **C,** *relative media thickness of aneurysmal walls compared with that of surrounding normal arterial walls in the control and pitavastatin-treated groups. Blood pressure* (**D**) *and total serum cholesterol level* (**E**) *of the control and pitavastatin-treated groups. Data were analyzed by Kruskal-Wallis 1-way ANOVA on ranks followed by the Tukey-Kramer test.* **F,** *number of macrophages infiltrating into aneurysmal walls 3 months after aneurysm induction per 100-μm square. Data were analyzed by the Mann-Whitney U test. 0M, before aneurysm induction; 1M, 3M, and 5M, after 1, 3, and 5 months of aneurysm induction, respectively;* **, $P < 0.01$.

ribonucleic acid (RNA) from the entire circle of Willis was isolated using an RNeasy Fibrous Tissue Mini Kit (Qiagen). RNA extraction was carried out according to the manufacturer's instructions. Total RNA was converted into complementary DNA (cDNA) using Sensiscript reverse transcriptase (Qiagen). The conditions for the cDNA synthesis were 1 hour at 37°C, followed by heating at 93°C for 5 minutes.

Quantitative Polymerase Chain Reaction

Constructs for IL-1β, iNOS, VCAM-1, MCP-1, MMP-9, and β-actin were produced by TOPO TA Cloning (Invitrogen, Carlsbad, CA) from cDNA according to the manufacturer's instructions. Quantitative (real-time) polymerase chain reaction (PCR) was performed using a QuantiTect SYBR Green PCR Kit (Qiagen) and LightCycler Quick System 330 (Roche Diagnostics, Basel, Switzerland). β-Actin was used as an internal control. The primer sets used were as follows: forward, 5'-cacctctcaagcagagcacag-3' and reverse, 5'-gggttccatggtgaagtcaac-3' for IL-1β; forward, 5'-ttcaggtatgcggtatttgg-3' and reverse, 5'-gttggaagtgtagcgtttcg-3' for iNOS; forward, 5'-gcgaaggaaactggagaagaca-3' and reverse, 5'-acacattagggaccgtgcagtt-3' for VCAM-1; forward, 5'-cctccaccactatgcaggtctc-3' and reverse, 5'-gcacgtggatgctacaggc-3' for MCP-1; forward, 5'-ttcaaggacggtcggtatt-3' and reverse, 5'-ctctgagcctagaccccaactta-3' for MMP-9; and forward, 5'-aagtccctcaccctcccaaag-3' and reverse, 5'-aagcaatgctgtcaccttccc-3' for β-actin. The conditions for real-time PCR were 42 cycles of 95°C, 20 seconds for denaturation, 53°C, 20 seconds for annealing, and 72°C, 20 seconds for extension. For quantification, the second derivate maximum method was used for crossing point determination using LightCycler Software 3.3 (Roche Diagnostics). The amount of messenger RNA (mRNA) was expressed as the ratio to β-actin mRNA.

Gelatin Zymography

Total protein from the entire circle of Willis was purified by a Bio-Plex cell lysis kit (Bio-Rad, Hercules, CA) according to the manufacturer's instructions. In one experiment, 100 μg of protein was used. Gelatin zymography was performed using a Gelatin Zymo-Electrophoresis Kit (Primary Cell, Sapporo, Japan) according to the manufacturer's instructions.

Effect of Pitavastatin on Preexisting CAs

To examine the effect of pitavastatin on preexisting CAs, pitavastatin administration started 1 month after aneurysm induction. After aneurysm induction, animals in both groups were fed a high-salt diet containing 8% sodium chloride for 1 month. After 1 month of aneurysm induction, a normal diet with 4 mg/kg/d of pitavastatin was given to the pitavastatin-treated group. In the control group, a normal diet was given after 1 month of aneurysm induction. Animals were sacrificed 3 months after aneurysm induction, and the aneurysm size and media thickness were examined as described above.

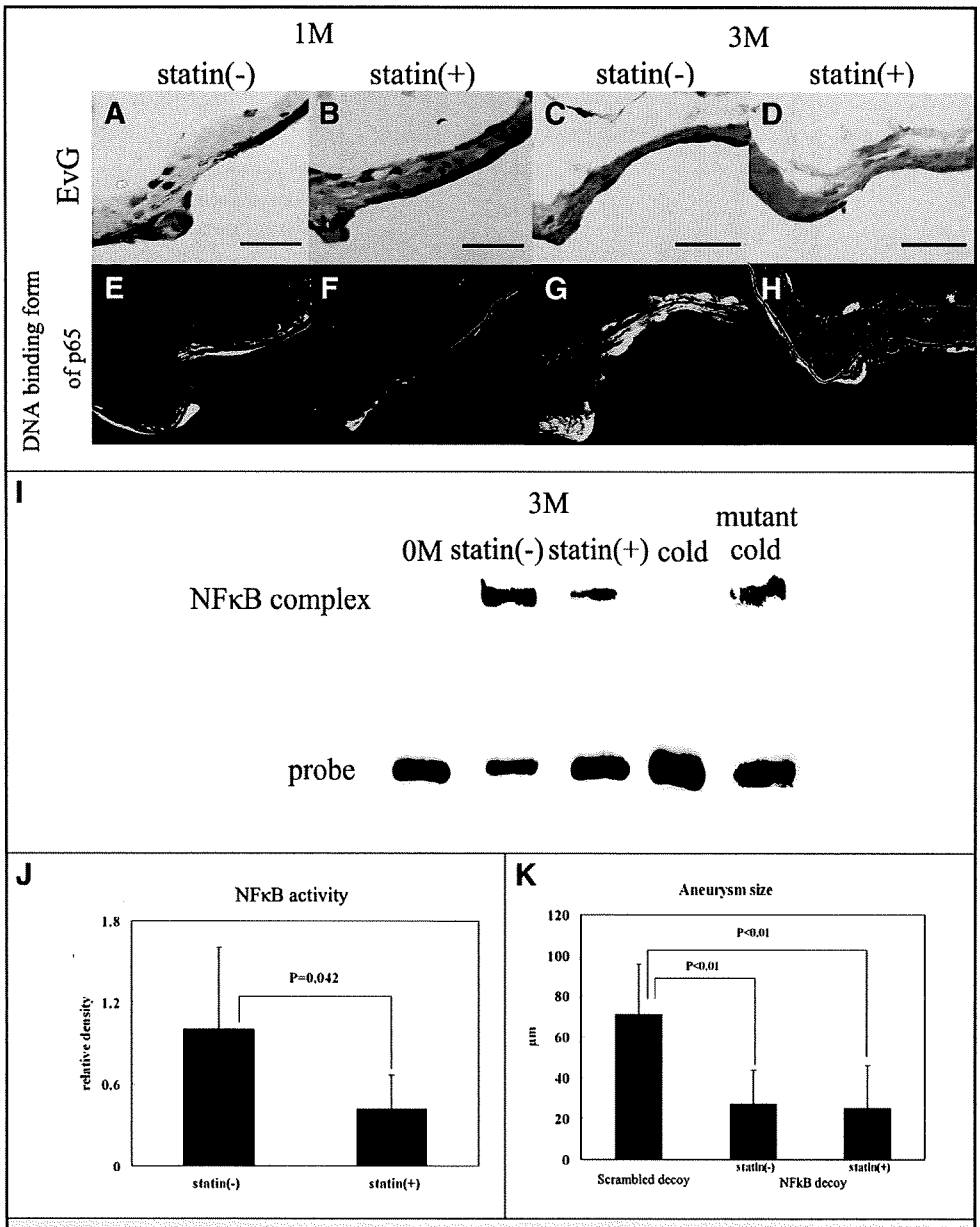

FIGURE 2. *Nuclear factor κB (NF-κB) activation in aneurysmal walls.* **A–H,** *immunohistochemical staining of the deoxyribonucleic acid-binding form of the NF-κB p65 subunit in rats 1 month* (**E** *and* **F**) *and 3 months* (**G** *and* **H**) *after aneurysm induction with* (**F** *and* **H**) *or without* (**E** *and* **G**) *pitavastatin treatment. Elastica van Gieson (EvG) staining of serial sections of* **E** (**A**), **F** (**B**), **G** (**C**), *and* **H** (**D**). *Bar = 30 μm.* **I,** *electrophoretic mobility shift assay (EMSA) for an NF-κB binding site in cerebral arteries of rats before aneurysm induction (0M) and 3 months (3M) after aneurysm induction with or without pitavastatin treatment. The fourth and fifth lanes show competition experiments with a 200-fold excess amount of cold κB oligonucleotide (cold) and of mutated κB oligonucleotide (mutant cold) in cerebral arteries of rats 3 months after aneurysm induction. A representative image of 5 independent experiments is shown.* **J,** *graph showing densitometric analysis of EMSA. Data were analyzed by the Mann-Whitney U test. n = 5 per group.* **K,** *graph showing aneurysm size of NF-κB decoy oligodeoxynucleotide (ODN) or scrambled decoy ODN-treated rats with or without pitavastatin treatment 3 months after aneurysm induction. Data were analyzed by Kruskal-Wallis 1-way analysis of variance on ranks followed by the Tukey-Kramer test.*

Statistical Analysis

Data (mean ± standard deviation) were analyzed by use of the Mann-Whitney *U* test for a 2-group comparison and by the Kruskal-Wallis 1-way analysis of variance on ranks, followed by the Tukey-Kramer test for a multiple comparison. For analysis of the IEL score, the Spiegel-Tukey test was used. Differences were considered statistically significant at a *P* value of less than 0.05.

RESULTS

Effect of Pitavastatin on CA Formation

The serum concentration of pitavastatin measured by high-performance liquid chromatography (60.6 ±37.9 nmol/L, n = 10) reached the value sufficient for inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (half-maximal inhibitory concentration, 6.8 nmol/L).

In the control group, aneurysm size was 45.9 ± 17.9 μm (n = 10) after 1 month, 66.3 ± 19.3 μm (n = 10) after 3 months, and 88.8 ± 26.4 μm (n = 10) after 5 months of aneurysm induction. Aneurysm size was significantly increased from 1 to 3 months ($P = 0.038$) and from 3 to 5 months ($P = 0.032$). In the pitavastatin-treated group, the aneurysm size was 30.7 ± 19.1 μm (n = 10) after 1 month, 42.8 ± 28.5 μm (n = 10) after 3 months, and 38.5 ± 17.1 μm (n = 10) after 5 months. Aneurysm size was significantly smaller than the control after 3 ($P = 0.018$) and 5 months ($P < 0.01$) (Fig. 1A). In the control group, the IEL score (95% confidence interval [CI]) was 0.41 to 1.19 (n = 10) after 1 month, 1.28 to 1.72 (n = 10) after 3 months, and 1.40 to 2.00 (n = 10) after 5 months. Pitavastatin treatment signifi-

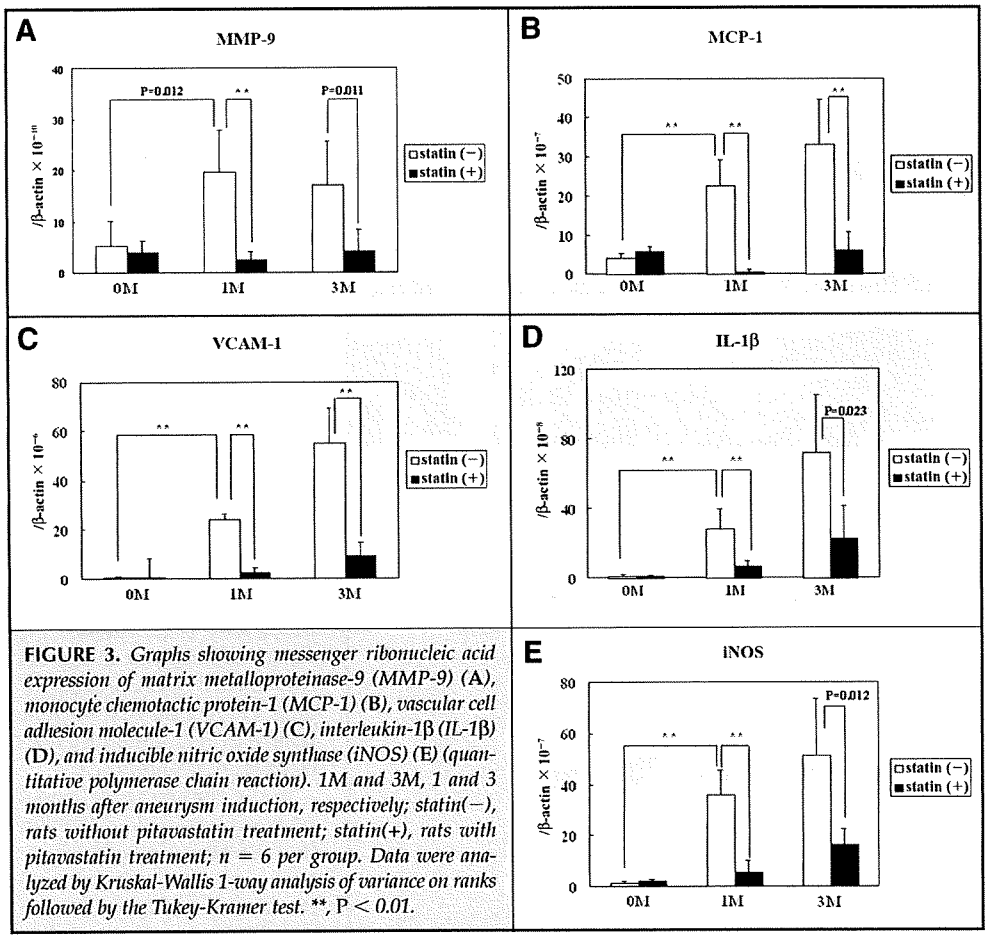

FIGURE 3. *Graphs showing messenger ribonucleic acid expression of matrix metalloproteinase-9 (MMP-9)* (**A**), *monocyte chemotactic protein-1 (MCP-1)* (**B**), *vascular cell adhesion molecule-1 (VCAM-1)* (**C**), *interleukin-1β (IL-1β)* (**D**), *and inducible nitric oxide synthase (iNOS)* (**E**) *(quantitative polymerase chain reaction). 1M and 3M, 1 and 3 months after aneurysm induction, respectively; statin(−), rats without pitavastatin treatment; statin(+), rats with pitavastatin treatment; n = 6 per group. Data were analyzed by Kruskal-Wallis 1-way analysis of variance on ranks followed by the Tukey-Kramer test.* **, $P < 0.01$.

cantly reduced the IEL score after 1 month (95% CI, −0.06–0.46; n = 10; $P < 0.01$), 3 months (95% CI, 0.70–1.10; n = 10; $P < 0.01$), and 5 months (95% CI, 1.00–1.60; n = 10; $P < 0.01$) (Fig. 1B). In the control group, media thickness was 0.61 ± 0.25 (n = 10) after 1 month, 0.46 ± 0.21 (n = 10) after 3 months, and 0.39 ± 0.17 (n = 10) after 5 months of aneurysm induction. In the pitavastatin-treated group, media thickness was 0.66 ± 0.17 (n = 10) after 1 month, 0.66 ± 0.18 (n = 10) after 3 months, and 0.74 ± 0.18 (n = 10) after 5 months. Media was significantly thicker in the pitavastatin-treated group than in the control group after 3 ($P = 0.026$) and 5 months ($P < 0.01$) (Fig. 1C).

In both groups, systemic blood pressure was elevated with time after aneurysm induction, but there was no significant difference between the control group (1 month, 166.2 ± 14.8 mm Hg, n = 10; 3 months, 170.2 ± 14.3 mm Hg, n = 10; 5 months, 175.4 ± 16.9 mm Hg, n = 10) and the pitavastatin-treated group (1 month, 169.4 ± 21.8 mm Hg, n = 10; 3 months, 166.6 ± 15.5 mm Hg, n = 10; and 5 months, 168.0 ± 13.4 mm Hg, n = 10) (Fig. 1D). The serum cholesterol level was not different between the control group (1 month, 73.7 ± 15.4 mg/dL; n = 10; 3 months, 76.4 ± 10.8 mg/dL, n = 10; and 5 months, 73.8 ± 14.7 mg/dL, n = 10) and the pitavastatin-treated group (1 month, 73.9 ± 14.2 mg/dL, n = 10; 3 months, 81.2 ± 20.7 mg/dL, n = 10; 5 months 75.0 ± 18.7 mg/dL, n = 10) (Fig. 1E).

Macrophage Accumulation in Aneurysmal Walls

Macrophages infiltrated into aneurysmal walls with CA progression. Macrophage infiltration after 3 months of aneurysm induction was significantly reduced by pitavastatin treatment (control group, 5.8 ± 1.4 cells/100-μm square, n = 10; pitavastatin-treated group, 2.1 ± 1.1 cells/100-μm square, n = 10; $P < 0.01$) (Fig. 1F).

NF-κB Activation in Aneurysmal Walls

In immunohistochemical analysis for the DNA-binding form of the NF-κB p65 subunit, NF-κB was highly activated in aneurysmal walls of control rats 1 and 3 months after aneurysm induction (Fig. 2, E and G). The number of DNA-binding forms of NF-κB p65 subunit-positive cells was reduced by pitavastatin treatment (Fig. 2, F and H). By electrophoretic mobility shift assay, 1 specific complex band was detected after 3 months of aneurysm induction in the control group (Fig. 2I). This band was completely abolished by competition with the κB oligonucleotide but not with a mutated motif, confirming the specificity of this band for NF-κB (Fig. 2I). DNA binding activity of NF-κB was decreased by pitavastatin treatment (n = 5; $P = 0.042$) (Fig. 2, I and J). NF-κB decoy ODN treatment significantly reduced CA size 3 months after aneurysm induction (scrambled decoy, 70.8 ± 23.8 μm, n = 10; NF-κB decoy, 27.0 ± 16.8 μm, n = 5; $P < 0.01$). Pitavastatin treatment did not show synergistic effects on CA size under NF-κB decoy ODN treatment (25.0 ± 20.8 μm, n = 4) (Fig. 2K).

Expression of MMP-9, MCP-1, VCAM-1, IL-1β, and iNOS mRNA in Aneurysmal Walls

With quantitative PCR, expression levels of MMP-9, MCP-1, VCAM-1, IL-1β, and iNOS mRNA were significantly elevated after 1 month of aneurysm induction (MMP-9, $P = 0.012$; MCP-1, $P < 0.01$; VCAM-1, $P < 0.01$; IL-1β, $P < 0.01$; and iNOS, $P < 0.01$; n = 6 per group) (Fig. 3, A–E). In the pitavastatin-treated group, mRNA expression of these genes was significantly

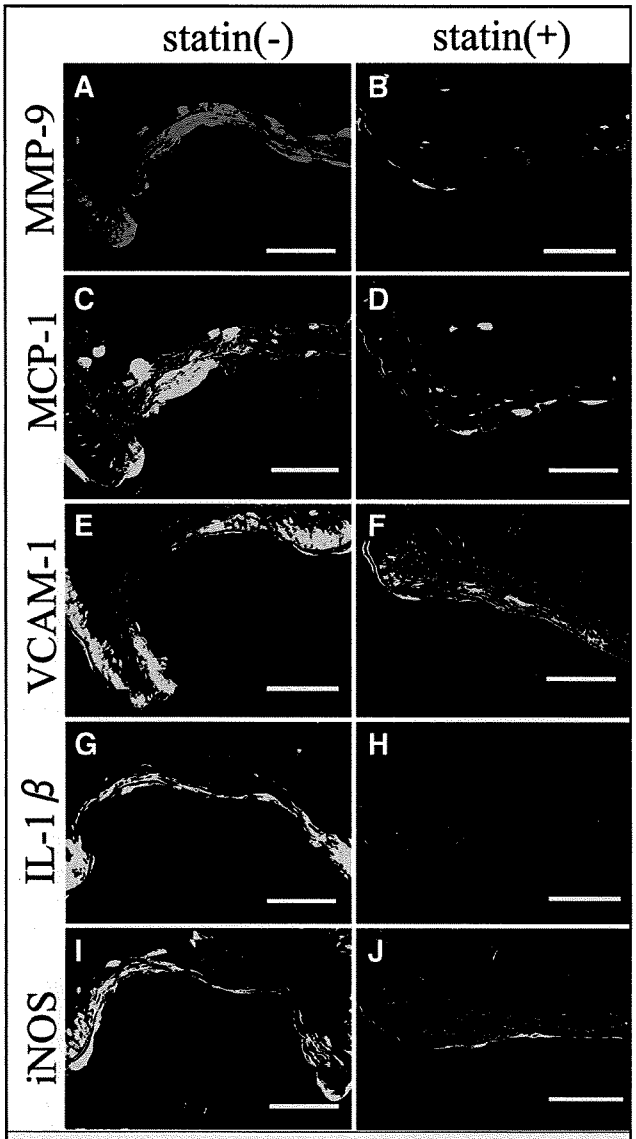

FIGURE 4. *Immunohistochemical analysis for MMP-9 (A and B), MCP-1 (C and D), VCAM-1 (E and F), IL-1β (G and H), and iNOS (I and J) 3 months after aneurysm induction with (B, D, F, H, and J) or without (A, C, E, G, and I) pitavastatin treatment. Bar = 30 μm.*

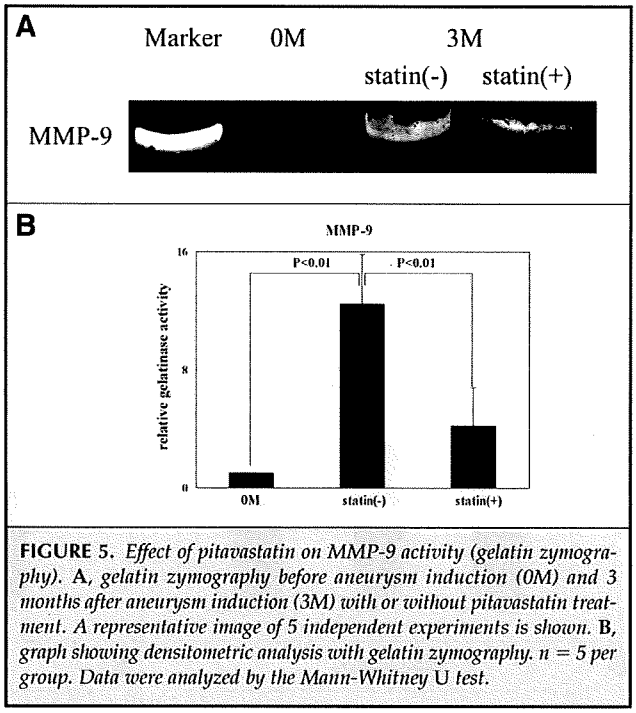

FIGURE 5. *Effect of pitavastatin on MMP-9 activity (gelatin zymography). A, gelatin zymography before aneurysm induction (0M) and 3 months after aneurysm induction (3M) with or without pitavastatin treatment. A representative image of 5 independent experiments is shown. B, graph showing densitometric analysis with gelatin zymography. n = 5 per group. Data were analyzed by the Mann-Whitney U test.*

lower after 1 month (MMP-9, $P < 0.01$; MCP-1, $P < 0.01$; VCAM-1, $P < 0.01$; IL-1β, $P < 0.01$; and iNOS, $P < 0.01$; n = 6 per group) and 3 months (MMP-9, $P = 0.011$; MCP-1, $P < 0.01$; VCAM-1, $P < 0.01$; IL-1β, $P = 0.023$; and iNOS, $P = 0.012$; n = 6 per group) of aneurysm induction (Fig. 3, A–E).

With immunohistochemical analysis, MMP-9, MCP-1, VCAM-1, IL-1β, and iNOS were abundantly expressed in aneurysmal walls 3 months after aneurysm induction in the control group (Fig. 4, A, C, E, G, and I). In the pitavastatin-treated group, expression of these proteins was markedly decreased (Fig. 4, B, D, F, H, and J). Expression of these proteins could not be detected in the contralateral ACA/OA bifurcation of rats with pitavastatin treatment (data not shown).

Activity of MMP-9 in Aneurysmal Walls

With gelatin zymography, gelatinase activity of MMP-9 was increased 3 months after aneurysm induction in the control group ($P < 0.01$, n = 5). In the pitavastatin-treated group, MMP-9 activity in arterial walls was significantly lower than that in the control group ($P < 0.01$, n = 5) (Fig. 5).

Effect of Pitavastatin on Preexisting CAs

In rats without pitavastatin treatment, CAs significantly enlarged in size from 1 month (42.0 ± 17.9 μm, n = 10) to 3 months (64.3 ± 20.3 μm, n = 10) after aneurysm induction ($P = 0.013$). In rats with pitavastatin treatment, aneurysm size after 3 months of aneurysm induction (40.3 ± 27.1 μm, n = 10) was smaller than that of the control ($P = 0.038$) and was not different from that before pitavastatin treatment (Fig. 6B). In rats without pitavastatin treatment, media thickness decreased from 1 (0.57 ± 0.24, n = 10) to 3 months (0.46 ± 0.21, n = 10) after aneurysm induction ($P = 0.24$). In rats with pitavastatin treatment, media thickness was 0.78 ± 0.15 (n = 10) after 3 months of aneurysm induction, which was significantly thicker than that of rats before pitavastatin administration ($P = 0.028$) (Fig. 6C). Systemic blood pressure 3 months after aneurysm induction was not different between rats with (124.1 ± 16.8 mm Hg, n = 10) and without (126.2 ± 15.8 mm Hg,

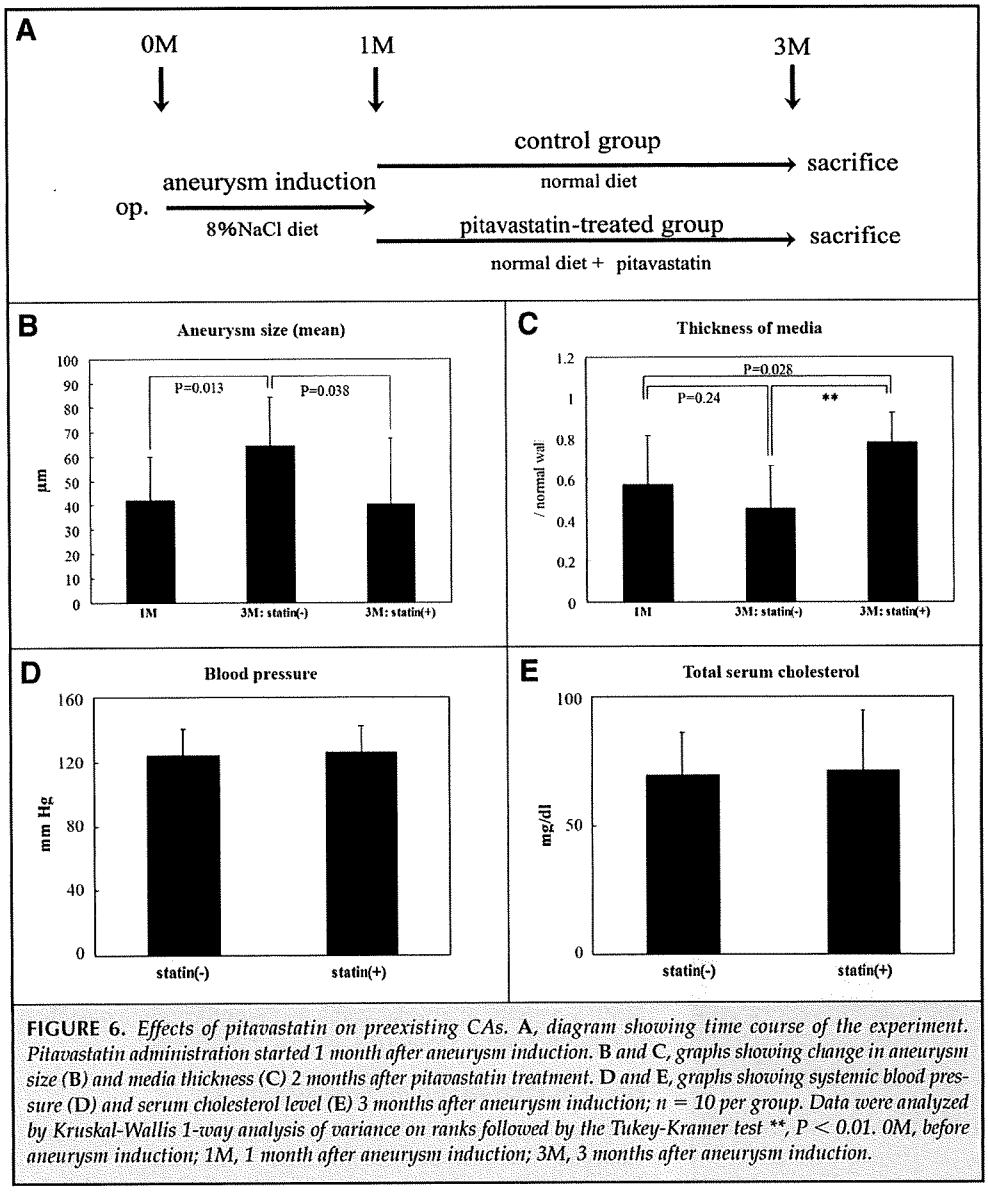

FIGURE 6. *Effects of pitavastatin on preexisting CAs.* **A**, *diagram showing time course of the experiment. Pitavastatin administration started 1 month after aneurysm induction.* **B** *and* **C**, *graphs showing change in aneurysm size* (**B**) *and media thickness* (**C**) *2 months after pitavastatin treatment.* **D** *and* **E**, *graphs showing systemic blood pressure* (**D**) *and serum cholesterol level* (**E**) *3 months after aneurysm induction; n = 10 per group. Data were analyzed by Kruskal-Wallis 1-way analysis of variance on ranks followed by the Tukey-Kramer test* **, $P < 0.01$. *0M, before aneurysm induction; 1M, 1 month after aneurysm induction; 3M, 3 months after aneurysm induction.*

n = 10) pitavastatin treatment (Fig. 6D). Serum cholesterol levels 3 months after aneurysm induction were also not different between rats with (71.5 ± 23.0 mg/dL, n = 10) and without (69.2 ± 17.2 mg/dL, n = 10) pitavastatin treatment (Fig. 6E).

DISCUSSION

Recent investigations revealed that the pathophysiology of CA formation and progression is closely linked to vascular inflammation. Various inflammatory cells, especially macrophages, accumulate in aneurysmal walls of human CA samples (6) and experimentally induced CAs in rats (4). One of the earliest events occurring in the arterial wall is NF-κB activation (5). NF-κB has been recognized as one of the major transcription factors influencing key steps in the development of various vascular diseases. In the present study, we demonstrated that pitavastatin inhibited NF-κB activation (Fig. 2) and CA formation (Fig. 1). With inhibition of NF-κB activity by NF-κB decoy ODN, pitavastatin did not show suppressive effects on CA formation (Fig. 2K), suggesting that the inhibitory effect of pitavastatin on CA formation depends on the NF-κB signaling pathway. NF-κB profoundly regulates a variety of proinflammatory genes related to CA progression (5). MCP-1 and VCAM-1, both of which are up-regulated by NF-κB binding to the promoter region (7, 23, 26), are crucial mediators for monocyte recruitment and adhesion to vessel walls (17). Other inflammation-related genes regulated by NF-κB activation in aneurysmal walls include MMP-9, IL-1β, and iNOS (5). MMP-9 degrades the extracellular membrane of CA walls, thereby promoting CA progression (3). IL-1β (18) and iNOS (9, 22) induce apoptotic cell death in medial smooth muscle cells, resulting in the thinning of medial layers in aneurysmal walls and CA progression. Up-regulation of all these genes was also suppressed by pitavastatin treatment in the present study (Figs. 3 and 4), supporting the notion that pitavastatin exerts an inhibitory effect on CA progression through the blockade of NF-κB activation.

Statins have vascular protective effects known as "pleiotropic effects" beyond their cholesterol-lowering effect (16). A large clinical trial demonstrated that statins reduced cardiovascular events, irrespective of serum cholesterol level (13). Because the serum cholesterol level was not affected by pitavastatin treatment in the experimentally induced CA model of rats, the inhibitory effect of pitavastatin on CA formation and progression is likely to be derived from pleiotropic effects. In vitro studies have shown that statins reduced activation of NF-κB in vascular endothelial cells and smooth muscle cells (8, 20).

Activation of NF-κB is involved in endothelial dysfunction, and statins stimulate endothelial production of nitric oxide via the induction and stabilization of IκBα. Improvement of endothelial function via inhibition of NF-κB activation may explain the inhibitory effect of pitavastatin on CA progression. Statins inhibit superoxide production in vascular cells, probably via inhibition of angiotensin II-induced nicotinamide adenine dinucleotide phosphate-oxidase activation (27). We do not know whether CA formation is related to oxidative stress, but the other plausible mechanism of the preventive effect of statins on CA progression is their antioxidant property.

In the present study, we also showed that pitavastatin led to thickening of the media in preexisting CAs (Fig. 6), although simvastatin could cause neither shrinkage of CAs nor thickening of CA walls (2). The fact that only pitavastatin can induce the regression of degenerative changes in the walls of preexisting CAs does not necessarily prove the superiority of pitavastatin over simvastatin because the applied dose of pitavastatin is not comparable to that of simvastatin. Unfortunately, we cannot examine whether statins reduce the incidence of subarachnoid hemorrhage resulting from CA rupture in our model because the rupture rate of CAs is 3% or less in this model. However, there is little doubt that thickening of CA walls results in the prevention of CA rupture. Therefore, statins, especially pitavastatin, may prevent the growth of unruptured CAs and subsequent subarachnoid hemorrhage in a clinical setting. Our data showing CA regression by statins also suggest the repair mechanism in CA walls. It is likely that statins not only inhibit degenerative changes in CA walls but also enhance the repair mechanism in CA walls. Data from animal experiments are not always applicable to human diseases. In our experimentally induced CA model, CAs were induced by renal hypertension augmented by a high-salt diet and excessive hemodynamic stress caused by ligation of the contralateral common carotid artery. Macroscopic and microscopic findings of experimentally induced CAs in rats are similar to those of human CAs (11). Although our model mimics formation and progression of human CAs, clinical studies are essential to demonstrate the preventive effects of statins on CA progression in humans.

We previously reported that simvastatin prevented CA progression in rats (2). The present study provides evidence that pitavastatin, as well as simvastatin, has a preventive effect on CA progression in a cholesterol-lowering independent manner, suggesting that the inhibitory effect on CA progression seems to be a universal effect of statins. Pitavastatin induced the regression of degenerative changes occurring in preexisting CAs, although, in the previous study, simvastatin did not. Another new insight derived from this study is that the primary target of pitavastatin is NF-κB, activation of which causes the inflammatory cascade leading to degenerative changes in CA walls. Statins, especially pitavastatin, will be a promising therapeutic agent for the medical treatment of unruptured CAs.

Disclosure

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COMMENTS

Aoki et al. build on their extensive prior work on the pathogenesis of aneurysms in rats. This work shows that aneurysm progression is limited by treatment with the hydroxy-methylglutaryl-coenzyme A reductase inhibitor, pitavastatin. They previously showed similar benefits with simvastatin, but, in these experiments, they used pitavastatin, which was developed in Japan, undergoes more limited metabolism, and may be associated with fewer drug interactions (1).

These findings add to the literature on beneficial effects of the statins. Existing databases from clinical trials should be examined to determine whether there is any evidence for a reduction in subarachnoid hemorrhage. These drugs were, in some cases, associated with an increased risk of hemorrhagic stroke, which is usually attributed to intracerebral hemorrhage. Since statins are already in widespread use and large studies of their cardiovascular and other health effects have been, and are being, done, what probably needs to be done is to incorporate end points into studies that examine aneurysmal disease. Perhaps this already is being done.

There are some limitations to the present study. Whether the results can be translated from rats to humans are unknown. The investigators were not blinded, and state-of-the-art stereological methods do not appear to have been used. Their unparalleled experience with these studies, however, is reflected in the perfect agreement among the 3 reviewers who graded the changes in the internal elastic lamina.

R. Loch Macdonald
Toronto, Canada

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1. Hayashi T, Yokote K, Saito Y, Iguchi A: Pitavastatin: Efficacy and safety in intensive lipid lowering. **Expert Opin Pharmacother** 8:2315–2327, 2007.

In this article, the authors carefully examine the pathophysiology of aneurysmal development in their rodent model of hypertension-related aneurysm formation. They have previously characterized this model, and, in this study, they follow the size of aneurysms formed, the changing of internal elastic lamina and medial thickness, as well as multiple markers for inflammation in animals that did or did not receive treatment with pitavastatin. This builds on the earlier work with other related agents. In this study, they show that the pitavastatin-treated group demonstrated prevention of progression of aneurysms and a marked decrease in nuclear factor κB (NF-κB) activation in the aneurysmal walls. The findings are coincident with their hypothesis that the NF-κB-activated inflammatory cascade of multiple markers, including matrix metalloproteinase-9, monocyte chemotactic protein-1, and inducible nitric oxide synthase, is inhibited by pitavastatin. Interestingly, not only did preexisting aneurysms not appear to grow, but evidence suggested that the media thickened with this treatment.

The key factors in this effect are the multiple hypotheses: 1) that aneurysmal development involves a significant component of inflammatory response within the vessel wall; 2) that the pleiotropic effects of statins beyond their known cholesterol-lowering effect may be beneficial in multiple aspects of vascular disease; and 3) that the statins' influence not only on cholesterol and oxidation, but also on inflammation, may be important. The authors follow a very logical train of thought to develop their arguments. Of course, other questions arise: first, how well does this model mimic human aneurysm formation? This is a hypotensive model with clear evidence of an inflammatory component. In humans, although the inflammatory component exists, is it equally related to hypertension, and does the inducing agent take place at the same level of development? Furthermore, would other inflammatory agents have the same effect, or do the effects of the statins also involve a relatively less tested antioxidant property? Finally, the authors have caused us to continue to think of these disease processes in a way that is beyond being purely mechanical and to ponder the molecular and genetic triggers at a subcellular level. We must consider the potentially treatable conditions that aggravate these fatal disease processes.

Robert J. Dempsey
Madison, Wisconsin

Building on prior work, the authors have investigated the effect of pitavastatin on NF-κB activation and cerebral aneurysm formation in a rodent experimental model of cerebral aneurysms. They demonstrate that pitavastatin significantly prevented cerebral aneurysm progression and NF-κB activation in aneurysm walls. Furthermore, expression of monocyte chemotactic protein-1, vascular cell adhesion molecule-1, inducible nitric oxide synthase, and matrix metalloproteinase-9 in aneurysmal walls was also inhibited by pitavastatin. Finally, pitavastatin treatment resulted in thickening of the media in preexisting cerebral aneurysms.

Although this study replicates some of the previous work by this group on simvastatin, it does confirm the potential for statins as a candidate therapeutic for the prevention of cerebral aneurysm progression. Furthermore, the present work demonstrates that statins are capable of inducing regression of degenerative changes in preexisting aneurysms and act, at least in part, through inhibition of the NF-κB pathway, which is critical in inflammation.

Collectively, the present work lends credence to the hypothesis that inflammation may be important in the pathogenesis of cerebral aneurysms. Moreover, the present work supports further investigation of statins, with their known pleiotropic effects, for the medical treatment and prevention of cerebral aneurysms.

R. Webster Crowley
Hian K. Yeoh
Aaron S. Dumont
Charlottesville, Virginia

This work may provide another piece in the puzzle of cerebral aneurysm pathogenesis. It is demonstrated here that the formation and progression of experimental rat aneurysms is mediated by NF-κB via downstream effects on chemokines monocyte chemotactic protein-1 and interleukin-1b, inducible nitric oxide synthase, the adhesion molecule vascular cell adhesion molecule-1, and the gelatinase enzyme matrix metalloproteinase-9. These findings are not entirely surprising; the statin agent simvastatin has already been shown to alter NF-κB expression (2), and previous work from this same group has established the therapeutic potential of simvastatin in inhibiting experimental aneurysm growth (1). Still, these findings using the agent pitavastatin strengthen prior results and also suggest that the effect of simvastatin on aneurysms is not unique. They also help clarify the role of NF-κB in this particular experimental model.

Although medical treatment of unruptured aneurysms to arrest growth or even lead to vascular healing and aneurysm regression is an appealing notion, interventions in the complex molecular cascades involved in vascular injury and inflammation remain empiric. But by carefully working out the exact molecular mechanisms of aneurysm formation and growth, we may someday arrive at efficacious interventions directed at specific targets in the molecular mechanisms of aneurysm development and growth.

Tim Darsaut
J. Max Findlay
Edmonton, Canada

1. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Hashimoto N: Simvastatin suppresses the progression of experimentally induced cerebral aneurysms in rats. **Stroke** 39:1276–1285, 2008.
2. Sironi L, Banfi C, Brioschi M, Gelosa P, Guerrini U, Nobili E, Gianella A, Paoletti R, Tremoli E, Cimino M: Activation of NF-κB and ERK1/2 after permanent focal ischemia is abolished by simvastatin treatment. **Neurobiol Dis** 22:445–451, 2006.

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特集　急性期破裂脳動脈瘤の治療選択

急性期破裂脳動脈瘤の治療選択の現状(第一報)
—2005年前向き集計—

塩川　芳昭[1]，栗田　浩樹[1]，藤井　清孝[2]，集計参加施設

Prospective SAH Study in Japan, 2005

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Summary: To clarify current treatment status of ruptured cerebral aneurysms in Japan, a prospective multicenter observational study on the treatment results for aneurysmal subarachnoid hemorrhage was conducted over calendar year 2005 and final 1-year outcomes were collected. Studied centers were selected from among institutes of committee member of Japanese stroke surgery organization or symposium of vasospasm in Japan. A total of 927 patients were enrolled in this study and treatment policies were left to each institution according to the patients' background and aneurysmal characteristics. The observational protocol was similar to those of ISAT, especially the categorization of aneurysms, follow-up timing at 2 months and 1 year, patient outcome evaluation and recording of incomplete treatment results.

Finally, 770 patients were treated, and clipping was performed on 79% of them. Coil embolization was preferred in aged or vertebro-basilar artery aneurysm patients, and the 2-month outcome was identical in both the clipping and coil-treated groups. The 1-year outcome was better in the clipping group, but the initial patient condition in the clipping group was definitely better. The completeness of treatment was better in clipping, but post-treatment bleeding, hydrocephalus and epilepsy were identical in each group.

Evaluation of overall management outcome is mandatory to elucidate the contribution of endovascular treatment on the treatment result for ruptured cerebral aneurysms.

Key words:
- aneurysm
- clip
- coil
- subarachnoid hemorrhage

Surg Cereb Stroke (Jpn) 37: 1-6, 2009

はじめに

血管内治療の発展により現在の脳神経外科は破裂脳動脈瘤に対して2つの治療手技を有する状況となった．脳動脈瘤クリッピング術(以下clip)が半世紀近い歴史を有しているのに対して，コイル塞栓術(以下coil)が実施されているのは約15年に過ぎず，現在なおその根治性に限界があることは一般に知られた事実である[1-3]．しかしながら2002年に，主として欧州で行われた破裂脳動脈瘤のprospective randomized studyであるinternational subarachnoid aneurysm trial (ISAT)が発表され[4)5)]，症例を選択すれば血管内治療に優位性のあることが示された．この論文は破裂脳動脈瘤の治療選択に大きな影響を与えたが，患者選択のバイアスによる影響なども考慮すべきであるとの批判も

[1]杏林大学　脳神経外科，[2]北里大学　脳神経外科(受稿日 2008.8.25)(脱稿日 2008.9.17)〔連絡先：〒181-8611 東京都三鷹市新川6-20-2 杏林大学 脳神経外科　塩川芳昭〕[Address correspondence: Yoshiaki SHIOKAWA, M.D., Department of Neurosurgery, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan]

Table 1 Patient population and outcome in each treatment modality

	Clip n=606	Coil n=164	P-value
Average age (y.o.)	58.9	61.8	NS
WFNS I, II, III	68.2%	59.1%	p<0.05
Small aneurysm	89.2%	86.4%	NS
VB aneurysms	7.1%	36.7%	p<0.001
GR + MD (2M)	74%	72%	NS
GR + MD (12M)	77%	69%	p<0.05

abbreviations; clip; patients treated by direct surgery, coil; patients treated by endovascular surgery

WFNS I, II, III; percentage of patients categorized World Federation of Neurological Surgery grade I, II and III.

less than 10 mm; percentage of patients with aneurysms smaller than 10 mm in diameter.

VB aneurysms; percentage of patients with VB; vertebro-basilar artery aneurysms.

GR + MD (2M); percentage of patients categorized good recovery and moderately disabled of Glasgow outcome scale at 2 months after their onset.

多い[6)7)9)10)]．そこで，第35回日本脳卒中の外科学会と
22回スパズムシンポジウム合同でISAT類似のstu
designで前向き集計を行い，本邦の破裂脳動脈瘤の治
選択の現状を明らかとすることとした．

方　法

2005年1年間の破裂動脈瘤症例について，日本脳卒
の外科学会およびスパズムシンポジウム運営委員在籍施
のうち，趣旨に賛同の得られた30施設(別に記載)を対
として表記2学会主催でISAT類似のstudy designで前
き集計(観察研究，悉皆集計)を行った．集計項目は以下
通りである．

患者情報：年齢，性，入院日，入院時間，入院day，入
時H-K grade，入院時WFNS grade，全身合
症，

画像情報：CT分類(Fisher)，診断手技，破裂瘤局在
dome径(mm)，neck径(mm)，bleb有無，

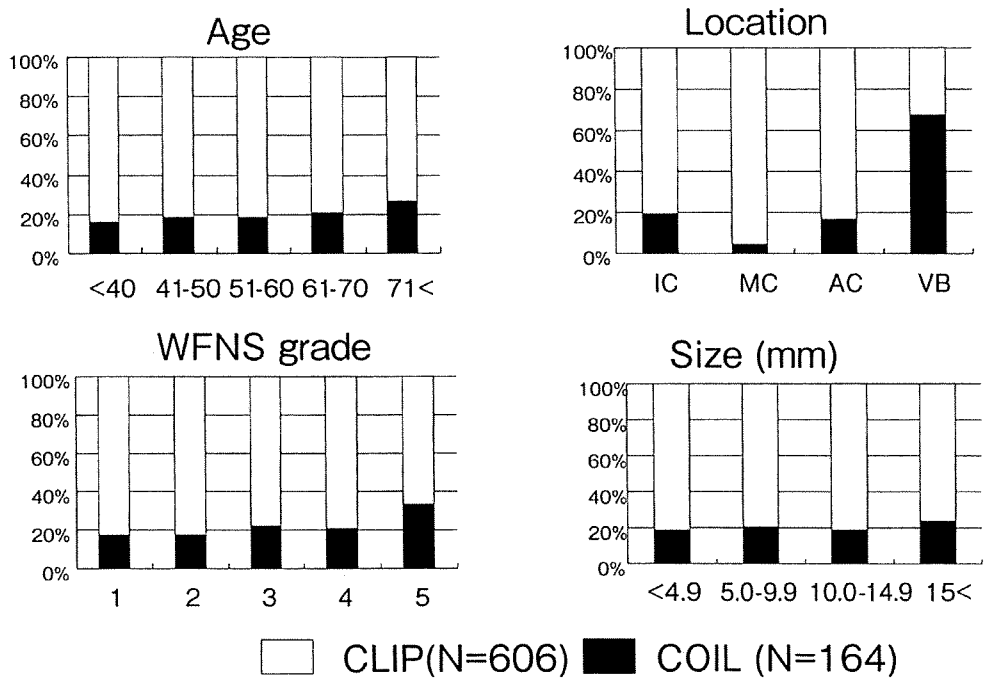

Fig. 1 Selection of treatment modality: Each bar graphs show ratio of patients treated by clipping (white) or coil embolization (black).
upper left: Selection of treatment modality in age. Coil embolization increased in the treatment of elder patients group.
upper right: Selection of treatment modality in aneurysm location. IC; internal carotid artery aneurysms. MC; middle cerebral artery aneurysms, AC; anterior cerebral and anterior communicating artery aneurysms, VB; vertebral and basilar artery aneurysms. Clipping is preferred in MC patients and coil embolization in VB patients.
lower left: Selection of treatment modality in WFNS grade. Coil embolization increased in the treatment of moribund patients group.
lower right: Selection of treatment modality in aneurysm size.

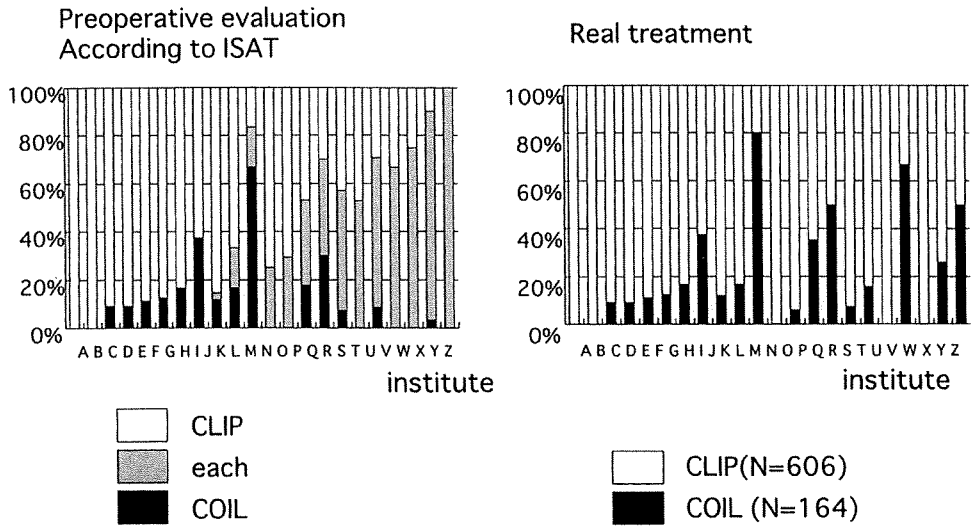

Fig. 2 Selection of treatment modality in each institute.
Each bar graphs show ratio of patients appropriate for or treated in real by clipping (white), coil embolization (black) and each treatment modality was preoperatively considered to be available (gray).
left: Selection of preoperatively assigned treatment modality in each institute. Each institute is indicated in alphabet.
right: Selection of treatment modality in real. The alphabet is identical to left bar graph.

内血栓有無，個数，

治療情報：手術日，手術時間，手術 day，手術前 H-K grade，手術前 WFNS grade，再出血有無，ISAT区分，非手術の理由，治療内容，治療完成度，治療合併症，術中破裂，遮断時間〔分〕，治療後再出血，治療後血管撮影所見，

術後経過：DINDの有無，梗塞の有無，drainage手術，shunt手術，てんかん，全身合併症，予後GOS(2M)，予後mRS(2M)，予後GOS(12M)，予後mRS(12M)，予後不良理由

ここで，入院day，手術dayは発症日をday 0とした．重症度のH-KはHunt and Kosnik grade，WFNSはWorld Federation of Neurological Surgery分類の略であり，SAHのCT分類はFisherらのものを用いた．またblebは動脈瘤domeにみられる直径1mm以上の突出と定義した．DINDはdelayed neurological deficits，GOS(2M)は発症2カ月後のGlasgow outcome scale，mRS(2M)は発症2カ月後のmodified Rankin scaleを，GOS(12M)，mRS(12M)はそれぞれ発症12カ月後の予後の略である．これらの項目を，非治療例も含めたすべてのくも膜下出血にて前向き集計し，患者個人情報を含めない内容で事務局(杏林大学脳神経外科)にて集計した．

統計処理は2群間の比較をカイ二乗検定で行い，$p < 0.05$を有意とした．

結　果

ISATと同じ1年後の予後が判明した症例は927例(女性/男性＝2.1，平均年齢60.8歳)であり，全体の来院時WFNS grade I–IIIは59%，テント上動脈瘤は87%であった．このうち治療が行われた770例の詳細を**Table 1**に示す．coilが実施された164例(治療例の21%，瘤内塞栓術141，親血管閉塞23)は，clipが実施された606例(治療例の79%，クリップによる頸部閉塞590，バイパスなど16)と比較して年齢や動脈瘤の大きさには差がなかったが，有意に軽症例が少なく，かつ椎骨脳底動脈系の動脈瘤が多かった．発症2カ月後のGOSでGR＋MDの比率はoverallで59%，治療例全体で68%であったが，重症，テント下症例の多いcoilの治療成績はclipと変わらなかった．しかしながら12カ月後の予後は，患者重症度を反映したためかclip症例の予後が有意($p < 0.05$)に良好であった．

clipとcoilの選択の実際について年齢，重症度，動脈瘤の局在，大きさについて層別解析を行った結果を**Fig. 1**に示す．高齢者ないし重症例でcoilが選択される傾向にあった．局在についてみると，内頸動脈(IC)，前交通動脈ないし前大脳動脈(AC)と比較して，有意にMCではclip，VBではcoilが選択されていた．動脈瘤の大きさについてみると，有意ではないが大型病変でcoilがやや選択されている傾向が認められた．

Table 2 Peri-treatment events and durability in each treatment modality

	Clip n=606	Coil n=164	P-value
Days to Tx (Day)	1.8	3.6	p<0.01
Pre Tx SAH	8.4%	6.4%	NS
Peri Tx SAH (major/minor)	7%-10%	0%-4%	
Tx Durability			
complete	92%	65%	p<0.001
neck remnant	6%	25%	
dome remnant	2%	10%	
Post Tx SAH	2.3%	3.6%	NS

abbreviations; clip; patients treated by direct surgery, coil; patients treated by endovascular surgery, Tx; treatment, Day; day of subarachnoid hemorrhage was defined as Day 0, SAH; subarachnoid hemorrhage

Pre Tx SAH; percentage of patients with second SAH before treatment.

Peri Tx SAH; percentage of patients with second SAH during treatment.

Tx Durability; percentage of patients with morphologically incomplete treatment.

Post Tx SAH; percentage of patients with second SAH after treatment.

Table 3 Frequency of DIND, NPH and epilepsy in each treatment modality

	Clip n=606	Coil n=164	P-value
Fisher group 3	64%	65%	NS
DIND	21.7%	17.9%	NS
LDA on CT	22.6%	24.7%	NS
LDA on CT in DIND	15.6%	9.7%	p<0.05
LDA on CT in non-DIND	6.8%	11.2%	p<0.05
NPH at 2M	28.1%	22.2%	p<0.05
NPH at 12M	22.6%	18.6%	NS
epilepsy at 2M	1.7%	1.1%	NS
epilepsy at 12M	2.3%	2.0%	NS

abbreviations; DIND;delayed neurological deficits, NPH; normal pressure hydrocephalus, Fisher; Fisher grouping of CT findings of SAH

Fisher group 3; percentage of patients categorized Fisher group 3.

DIND; percentage of patients presenting DIND.

LDA on CT; percentage of patients who showed low density area on their final CT.

LDA on CT in DIND; percentage of patients who showed low density area on their final CT among patients presenting DIND. This sub-group is supposed to harbor severe vasospasm.

LDA on CT in non-DIND; percentage of patients who showed low density area on their final CT among patients without presenting DIND This sub-group is supposed to harbor treatment complications.

NPH at 2M; percentage of patients demonstrating NPH at 2 months.

epilepsy at 2M; percentage of patients demonstrating epilepsy at 2 months.

治療方針は各施設の判断に委ねられていたが，破裂脳動脈瘤について，各施設ごとにその動脈瘤がclip向きか，coil向きか，いずれも可能かとしたISATに準じた動脈瘤のカテゴリーに分けた各施設の判断を集計したところ，全体ではclip向き61%，coil向き13%，両者可能26%であった(治療の実際は，前述のごとくclipが79%，coilは21%であった)．各施設ごとにISATに準じた動脈瘤のカテゴリーと実際の治療を提示したものが**Fig. 2**である．質問が正確に理解されなかった可能性はあるが施設間の判断のばらつきは非常に大きく，ISATで検討対象となった「両者の治療いずれもが可能」と判断される比率は，皆無である施設から全数に及ぶものまでさまざまであった．仮に両者可能な症例のすべてが血管内治療を選択された場合に，グラフ全体の左下から右上への対角線の下がすべてcoil(黒)となるはずであるが，数施設を除いてclip firstで治療方針が決定されていることがわかる．また実際にcoilを実施する率の多い(coil優先と考えられる)施設ほど，術前の判断でcoil向きの動脈瘤が多いとする傾向が認められた(Fig. 2右)．

両治療群における周術期の治療合併症と治療の完成度について**Table 2**にまとめた．治療時期はclip 1.8日，coil 3.6日($p < 0.01$)とcoilで有意に遅かったが，治療前の再出血はclip 8.4%，coil 6.4%と差は認められなかった．発症2カ月の時点で不完全治療の割合はclip 8%，coil 35%と有意($p < 0.001$)に血管内治療で多かったが，治療動脈瘤からの再出血はclip 3.0%，coil 5.2%で両者に差を認めなかった．

両治療群における慢性期の脳血管攣縮と正常圧水頭症，てんかんの頻度について**Table 3**に記す．CT上の血腫量に差は認められず，症候性脳血管攣縮を示唆するDINDの頻度と，退院時CT上の梗塞巣の出現率も有意差はみられなかった．重症脳血管攣縮を反映する可能性がある「DINDを呈し，かつ退院時CT上の梗塞巣を有した頻度」は有意($p < 0.05$)にcoilで少なかったが，治療に伴う虚血性合併症の可能性がある「DINDを呈さなかったが，退院時CT上の梗塞巣を有した頻度」は有意($p < 0.05$)にcoilで多かった．正常圧水頭症の頻度はcoilで少ない傾向にあり，特に発症2カ月の時点では有意差が認められた．てんかんの頻度については，両治療群間で差を認めなかった．

考　察

2002年のISAT以降[4)5)]，破裂脳動脈瘤の治療選択についての論議が絶えないが，欧米とは診療環境や治療水準が同一とはいえない本邦における，2005年の時点での治療の現状を明らかとすることを目的として，第35回日本脳卒中の外科学会と第22回スパズムシンポジウム合同で

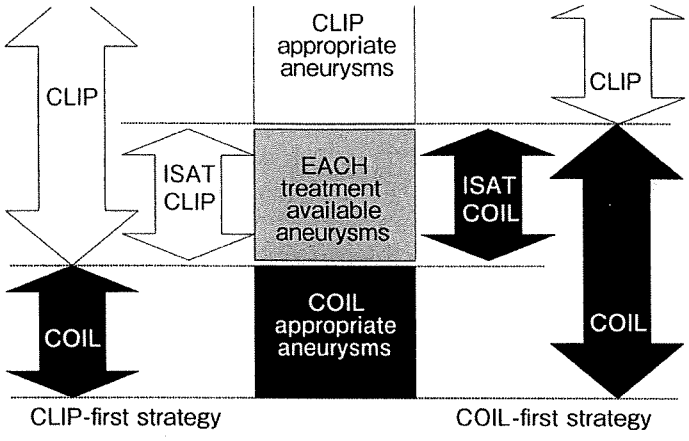

Fig. 3 Schematic drawing of comparison of patient population in clip-first and coil-first strategy.
All aneurysms can be theoretically classified into 3 categories according to ISAT; clip appropriate aneurysms, coil appropriate aneurysms and each treatment available aneurysms. In clip-first strategy, clip appropriate aneurysms (white column) and each treatment available aneurysms (gray column) are treated in real by clipping (white arrow) and only coil appropriate aneurysms (black column) is treated by coil embolization (black arrow). In coil-first strategy, only clip appropriate aneurysms (white column) is treated by clip and each treatment available aneurysms (gray column) and coil appropriate aneurysms (black column) are treated by coil embolization (black arrow). In ISAT study, only each treatment available aneurysms (gray column) is enrolled and allocated.

向き集計を行った．結果として，coilへのアクセスの悪さや治療根治性の低さは現時点で確かに存在するが，少なくとも高齢者，重症例，椎骨脳底動脈系動脈瘤にcoilが選択される傾向が明らかとされた．

本研究では実際に行われた治療内容ごとの比較(コホート研究)を行ったが，患者選択のバイアスに影響されるため，治療内容の優劣を論議することは困難であった[8]．しかしながらこのようなバイアスを考慮しても，重症脳血管攣縮や水頭症がcoilで少なくなっている可能性があり，治療自身による虚血損傷を差し引いても，coilの低侵襲性が現れた結果とも考えられる．

ISATと類似のプロトコールで観察研究を行って明らかとなった点は，ISATのentry criteriaである「clipとcoilのいずれもが可能」とする判断の不確実性である．ここで観念的に動脈瘤をclip向き，coil向き，いずれも可能の3群に分類可能と仮定すると，clip優先の施設ではclip向きといずれも可能の2群にclipを行い，逆にcoil優先の施設ではcoil向きといずれも可能の2群にcoilを行うことになる(Fig. 3)．本研究でも採用した，ある基準で両者の治療がふりわけられたコホート間(図中の白矢印と黒矢印)の比較では，どのような条件を設定しても対象母集団の相違に由来する選択バイアスの影響から免れることはできないのは明らかであり，ISATの着眼点が優れているのは「両者可能」な動脈瘤のみを検討対象としたそのstudy designにある．しかしながら，本研究でも明らかなように，この「両者可能」とする判断に大きなばらつきがあり，ISATでもこの判断の標準化はなされていない．すなわち従来から血管内治療がさかんに行われてきた欧州で「両者可能」と判断された集団が本邦で同様に想定される集団とは大きく異なっている可能性があるのである．それぞれの治療方法の優劣や，さらにはcoilの破裂動脈瘤治療全体に対する貢献などを検討するためには，このような母集団のバイアスを排除し，すべての動脈瘤をまとめて評価するoverall management outcomeの概念に戻る必要があり，第二報にて検討を加える[8)11)]．

結　論

本邦の破裂脳動脈瘤の治療選択の現状を明らかとすることを目的として，2005年1年間の治療成績を30施設の参加を得て前向き集計を行った．血管内治療は治療例の21%に実施されており，治療選択の背景として，患者年齢や動脈瘤の大きさには差がなかったが，重症例や椎骨脳底動脈系動脈瘤でcoilが選択される傾向にあった．それぞれの治療群ごとの予後は，発症2カ月では差を認めず，1年後は

clip症例の予後が良好であったが，患者重症度を反映した可能性があり，異なる治療方法で選択された集団に対するコホート研究の限界と思われた．

clipとcoilの併用時代にはいり，高齢者，重症症例，椎骨脳底動脈系動脈瘤への治療適応が広がっており，破裂動脈瘤の治療成績全体を比較検討する必要があると思われた．

本研究は，以下に記す集計参加施設(順不同)のご協力により遂行されたものであり，この場を借りて深甚なる謝意を表するものである．

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脳卒中の外科 37: 7～11, 2009

特集　急性期破裂脳動脈瘤の治療選択

急性期破裂脳動脈瘤の治療選択の現状(第二報)
—2005年前向き集計と1994年前向き集計との比較—

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Prospective SAH Study in Japan. Comparison Between 2005 Study and 1994 Study

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Summary: To elucidate the contribution of endovascular treatment to the overall management outcome of ruptured cerebral aneurysms, prospective multicenter observational studies conducted over calendar years 1994 and 2005 are compared. The study in 2005 (Study 05) enrolled a total of 927 patients from 30 centers selected from among institutes of committee member of Japanese stroke surgery organization or symposium of vasospasm. Treatment modalities were left to each institute and finally 770 patients were treated. Clipping and coil embolization were performed on 79% and 21% of the patients, respectively. The study in 1994 (Study 94) enrolled 785 patients obtained from 11 institutes, and all the 525 patients were treated by clipping. Patient outcomes were evaluated 3 months (Study 94) and 1 year (Study 05) after onset and treatment, and overall management outcomes were evaluated. Patients' background such as age, aneurysm location and World Federation of Neurological Surgery (WFNS) grade were not significantly different in the 2 studies. As a result, favorable treatment outcomes were obtained in 74.5% of the cases in Study 94 and 75.6% in Study 05. However, overall favorable management outcomes including non-treated cases were obtained in 58.5% of the cases in Study 94 and 64.4% in Study 05, a significant improvement ($p<0.01$). A subgroup analysis demonstrated improvement of treatment outcomes in poor-grade (WFNS IV and V) patients and increased ratio of treated patients in poor grade, aged (>70 years old) and vertebrobasilar aneurysm patients. Compared with Study 05 to Study 94, treatment of ruptured cerebral aneurysm by either clipping or coil embolization improved, not treatment outcome, but overall management outcome than those treated clipping only.

Key words:
- aneurysm
- clip
- coil
- overall outcome
- subarachnoid hemorrhage

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はじめに

血管内治療(coil)の発展により，現在の脳神経外科は破裂脳動脈瘤に対して直達手術(clip)に加えて2つの治療手技を有する状況となった．しかしながらその選択についてはコンセンサスの得られた合理的指針は得られておらず，臨床現場においては症例ごとに治療時点で動員可能な医療資源なども考慮した個別的対応がとられているのが現状で

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Table 1 Comparrison of treatment outcome between Study 94 and Study 05

	Study 94	Study 05	
No. of patients	N=525	N=770	
Average age	57.7	60.8	
WFNS grade I, II, III	70.4%	67.8%	
GR + MD	74.5% (3M)	75.6% (1Y)	ns
D	12.2%	9.7%	ns
	% of GR + MD	% of GR + MD	
Aged	54%	54%	ns
WFNS IV and V	49%	52%	ns
VB	78%	71%	ns
Large	66%	58%	ns

abbreviations; WFNS I, II, III; percentage of patients categorized World Federation of Neurological Surgery (WFNS) grade I, II and III.

GR + MD; percentage of patients categorized good recovery and moderately disabled of Glasgow outcome scale at 3 months (Study 94) and 1 year (Study 05). D; percentage of patients who died at 3 months (Study 94) and 1 year (Study 05).

% of GR+MD; percentage of patients categorized good recovery and moderately disabled among patients who underwent treatments in each sub-group.

Aged; patients subgroup who were older than 70 years old.

WFNS IV and V; patients subgroup with WFNS grade IV and V.

VB; patients subgroup whose ruptured aneurysms located on vertebro-basilar artery.

Large; patients subgroup whose ruptured aneurysms was bigger than 10 mm.

Table 2 Comparrison of overall management outcome betwe Study 94 and Study 05

	Study 94		Study 05	
No. of patients	N=785		N=927	
Average age	58.9		60.8	
WFNS grade I, II, III	59.7%		58.8%	
GR + MD	58.5% (3M)		64.4% (1Y) (p<0.0	
D	30.2%		21.8%	
	% of Tx,	% of GR+MD	% of Tx,	% of GR+M
Aged	59% *1	38%	72% *1	41%
WFNS IV and V	50% *2	26% *3	66% *2	35% *3
VB	73% *4	58%	86% *4	62%
Large	87%	59%	89%	54%

abbreviations; WFNS I, II, III; percentage of patients categoriz World Federation of Neurological Surgery (WFNS) grade I, II and I

GR + MD; percentage of patients categorized good recovery a moderately disabled of Glasgow outcome scale at 3 months (Stu 94) and 1 year (Study 05). D; percentage of patients who died at months (Study 94) and 1 year (Study 05).

% of Tx; percentage of patients who underwent treatments in each s group.

% of GR+MD; percentage of patients categorized good recov and moderately disabled among patients who underwent treatments each sub-group.

Aged; patients subgroup who were older than 70 years old.

WFNS IV and V; patients subgroup with WFNS grade IV and V.

VB; patients subgroup whose ruptured aneurysms located verteb basilar artery.

Large ; patients subgroup whose ruptured aneurysms was bigger th 10 mm in diameter.

*4: p<0.05, *1, *3: p<0.01, *2: p<0.001

ある[1-3)5)]．このようなclipとcoilの併用時代にはいり，個別の治療手技ごとの成績の比較は多数行われているが，はたしてcoilが臨床応用されるようになってから全体として破裂脳動脈瘤の治療成績は向上しているのか否かは明らかではない[6)8)]．そこで，本研究では2005年に日本脳卒中の外科学会およびスパズムシンポジウムで行われた現状調査(Study 05)[7)]と，動脈瘤治療がclipのみであった1995年の日本脳卒中の外科研究会(会長；杏林大学脳神経外科斎藤　勇)において行われた前向き集計(Study 94)[8)]とを比較し，coilが現時点で破裂動脈瘤の治療全体にどのように影響しているかを検討した．

方　法

Study 05は，2005年1年間の破裂動脈瘤症例について，日本脳卒中の外科学会およびスパズムシンポジウム運営委員在籍施設のうち，趣旨に賛同の得られた30施設を対象として行った前向き集計(観察研究，悉皆集計)である．clipかcoilかの治療選択は各施設の判断にゆだねられたが，治療時期はほとんどが急性期(発症2日以内)に行われており，患者予後は発症1年後のGlasgow outcome scale (GOS)で評価した．非治療例も含めたすべてのSAH症例について，患者個人情報を含まない匿名化させた内容を事務局(杏林大学脳神経外科)にて集計した．結果の概要は論文の第一報として別に報告した[8)]．

Study 94も，11施設の参加で行われた前向き集計(観察研究，悉皆集計)で，同様に非治療例も含めたすべてのSAH症例について事務局(杏林大学脳神経外科)にて集計した．当時の動脈瘤根治術は原則的にclipのみで，1施設を除き急性期治療が行われていた．患者予後は発症3カ月後のGOSで評価した[7)]．

統計処理は2群間の比較をカイ二乗検定で行い，p<0.05を有意とした．

結　果

2つの集計について全体(overall)の平均年齢と重症度(軽症例の比率)，および治療された症例の平均年齢と重症度，治療内容をみると，Study 94は785例(男性：女性

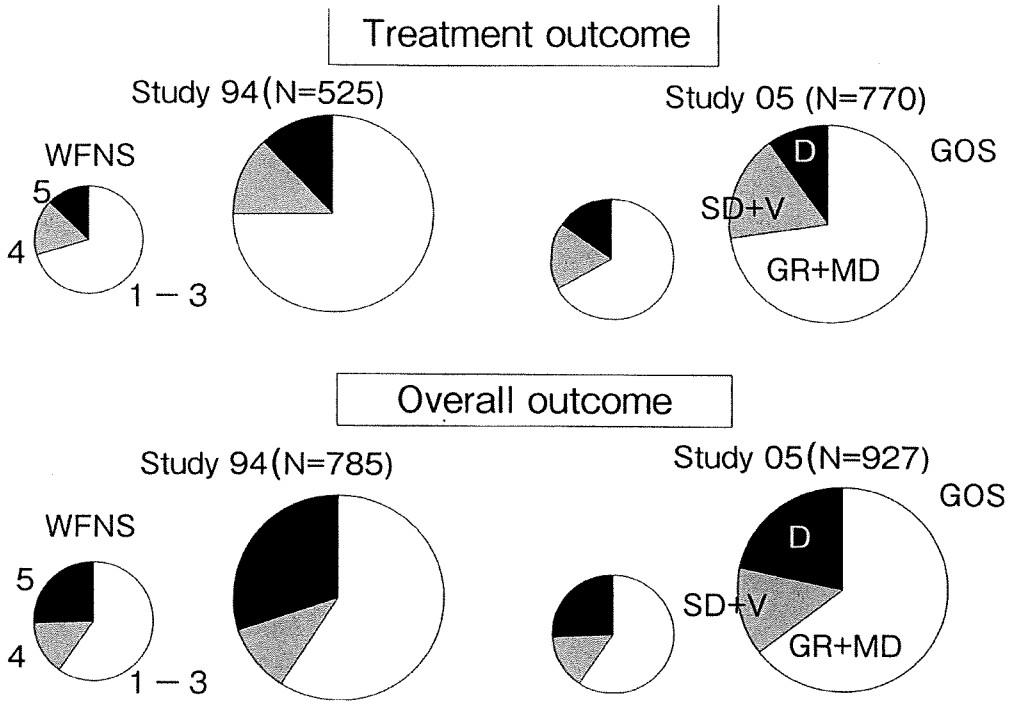

Fig. 1 Comparison of treatment and overall outcome in Study 94 and Study 05: Each small pie graphs on the left show ratio of World Federation of Neurological Surgery (WFNS) grade on admission. WFNS grade 1 to 3; white, grade 4; gray, grade 5; black. Each large pie graphs on the right show ratio of Glasgow outcome scale (GOS). GR+MD is good recovery and moderate disability; white, SD+V is severely disabled and vegetative state; gray, D is dead; black.
upper left: Admission WFNS grade and GOS at 3 months of treated cases in Study 94.
upper right: Admission WFNS grade and GOS at 1 year of treated cases in Study 05. Treatment outcome of Study 94 and Study 05 is identical.
lower left: Admission WFNS grade and GOS at 3 months of all cases including untreated in Study 94.
lower right: Admission WFNS grade and GOS at 1 year of all cases including untreated in Study 05. Management outcome of Study 05 is significantly better than that of Study 94.

1：2.0，平均年齢58.9歳)が登録され，その来院時WFNS grade I-IIIは59.7%であった．治療されたのは全体の66.9%にあたる525例(平均年齢57.7歳)で，その来院時WFNS grade I-IIIは70.4%であり，ほぼ全例がclip(動脈瘤頸部閉塞が93%)であった．一方，Study 05には927例(男性：女性＝1：2.1，平均年齢60.8歳)が登録され，その来院時WFNS grade I-IIIは58.8%であった．治療されたのは全体の83.1%にあたる770例(平均年齢60.8歳)で，その来院時WFNS grade I-IIIは67.8%であった．治療内容は，606例(79%)がclip(動脈瘤頸部97%，バイパス術3%)，164例(21%)がcoil(瘤内塞栓86%，親血管治療的閉塞17%)であった(Table 1, 2)．すなわち2つの集計において，全体および治療例の平均年齢と重症度には差がみられなかった．

治療例の予後はStudy 94で発症3カ月後，Study 05で発症1年後に評価されていた．評価時のGOSでgood recovery (GR)とmoderately disabled (MD)であった予後良好例はStudy 94で74.5%，Study 05で75.6%，死亡例もそれぞれ12.2%，9.7%と差を認めなかった．subgroup別にみた予後良好例の比率も，高齢者(70歳以上)，重症例，後頭蓋窩動脈瘤(VB)，大型病変(直径10 mm以上)のそれぞれの症例群において，Study 94とStudy 05の間には差を認めなかった(**Table 1**)．

これに対して非治療例も含めた全症例の予後(overall management outcome)は，評価時のGOSでGRとMDであった予後良好例はStudy 94で58.5%，Study 05で64.4%，死亡例もそれぞれ30.2%，21.8%と有意($p<0.01$)に改善していた(**Table 2**)．その理由として治療適応の広さを反映

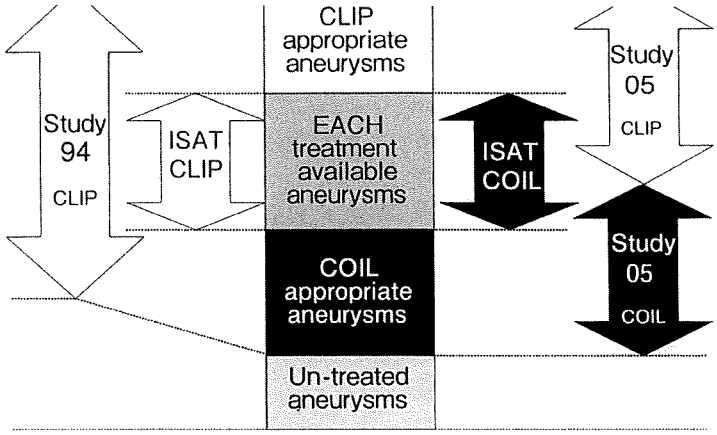

Fig. 2 Schematic drawing of comparison of patient population in Study 94 and Study 05.
All aneurysms can be theoretically classified into 3 categories according to international subarachnoid aneurysm trial (ISAT); clip appropriate aneurysms, coil appropriate aneurysms and each treatment available aneurysms. In Study 94, all the aneurysms are treated in real by clipping (white arrow). In Study 05, clip appropriate aneurysms (white column) and some of the clip available aneurysm (some of the gray column) are treated by clip (white arrow) and some of the coil available aneurysms (gray column) and coil appropriate aneurysms (black column) are treated by coil embolization (black arrow). Note that suspected number of untreated aneurysms is more in Study 94 than in Study 05. In ISAT study, only each treatment available aneurysms (gray column) is enrolled and allocated.

すると考えられるsubgroupにおける治療率(%)は高齢者，重症，VBといずれも有意に増加しており，また重症例の予後良好例は26%から35%へと有意に改善していた(Table 2)．

以上の結果を，Study 94とStudy 05の治療例と全症例について来院時WFNS gradeと評価時GOSを円グラフで表示したものがFig. 1である．上段の治療例においては，近似した重症度の母集団に対して治療結果だけみると差を認めないが，下段の全症例の予後をみると，近似した重症度の母集団に対して予後良好例の増加と死亡例の減少が把握できる．

考　　察

本研究は，clipとcoilの併用時代にはいり，はたしてclipのみの時代と比較して破裂脳動脈瘤の治療成績は向上しているのかを作業仮説として，その検証を試みたものである．比較しているStudy 94とStudy 05の参加施設が同一でないことや評価時期が異なるなど，study designに厳密さを欠くところはあるが，年齢と重症度において近似した母集団に対して，治療された症例群のみに着目した予後(treatment outcome)の比較では両集計間で差を認めていない．しかしながら経過観察となった症例も含む全症例の予後(overall management outcome)は，年齢と重症度において近似した母集団であるにもかかわらず，Study 05で有意に改善していた．その理由として高齢者，VBでは治療成績不変だが治療適応が拡大しており，重症例では治療適応が拡大し，かつ治療成績が向上したためであることが明らかとなった．

日常臨床の場において，clipとcoilの長所を活かした治療選択を重症例や高齢者に行えるようになってきたが，治療例についてのみ比較してみても，成績向上が実感できなかった．この問題を克服するには，破裂動脈瘤により生じたくも膜下出血は発症後の時間経過により病態が変化し，かつ治療対象から脱落する傾向にあることを想起する必要がある．すなわち非治療例も含めたすべての患者集団を評価するoverall management outcomeの観点から検討することが重要なのである．この手法は，かつて破裂動脈瘤の治療時期が論議されていた80年代に，選択された患者集団に対する慢性期手術の良好な成績では患者管理全体の指標にはならない，とした批判に端を発して提唱されたものである[9]．早期治療が一般化した今日においても，clipとcoilの治療選択の際に，両者の治療が可能になったことに

より従来は治療対象から脱落していた症例群の治療成績こそが問題であり，その部分の改善が本研究で示されたともいうことができる．

ここで観念的に動脈瘤を international subarachnoid aneurysm trial (ISAT)に準じてclip向き，coil向き，いずれも可能の3群に分類可能と仮定すると，clipのみが治療手段であった時期は，coilであれば治療可能な病変は治療対象外であった[4]．clipとcoilの両者が可能となったことにより，治療対象が拡大したことと，一部の症例では予後の改善が得られたことが本研究で明らかとなった．(実際には手術手技やモニタリング手法の進歩による治療対象の拡大と予後の改善は想定されるが)仮にclipが10年前と比較してまったく進歩していないとしても，図で示したStudy 94の白矢印はStudy 05で治療対象となっている動脈瘤全体より小さいことになる(**Fig. 2**)．逆の言い方をすれば，治療に至らなかった症例(実際には病院に到着しないさらに多くの症例がある)はStudy 94においてはStudy 05よりも多かった．これらの症例を考慮に入れたoverall management outcomeの考え方によれば，ある基準で両者の治療がふりわけられたコホート間(図中の白矢印と黒矢印)の比較では，どのような条件を設定しても対象母集団の相違に由来する選択バイアスの影響から免れることはできないのは明らかであり，ISATの着眼点が優れているのは「両者可能」な動脈瘤のみを検討対象としたそのstudy designにある．これからの脳神経外科においては，clipとcoilを対峙させる考え方ではなく，両者の利点を生かした治療方針決定(combined decision making)が必須となるであろう．

結　論

血管内治療併用の時代にはいり，破裂動脈瘤の治療例にのみ着眼した検討ではその成績に改善はみられないが，非治療例も含めたoverall management outcomeは有意に改善していた．その理由として高齢者，VBでは治療成績不変だが治療適応が拡大しており，重症例では治療適応が拡大し，かつ治療成績が向上したためであることが明らかとなった．clipとcoilを対峙させるのではなく，両者の利点を生かした治療方針決定が重要である．

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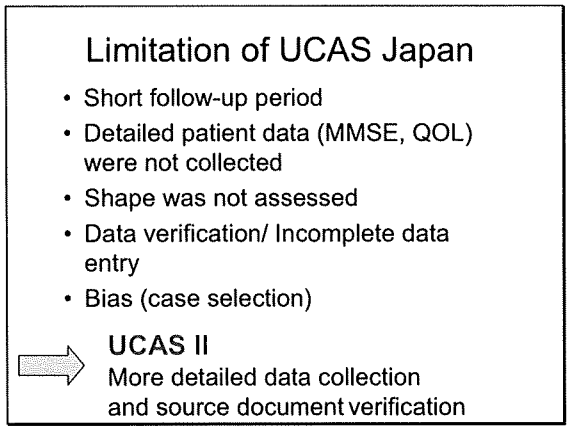
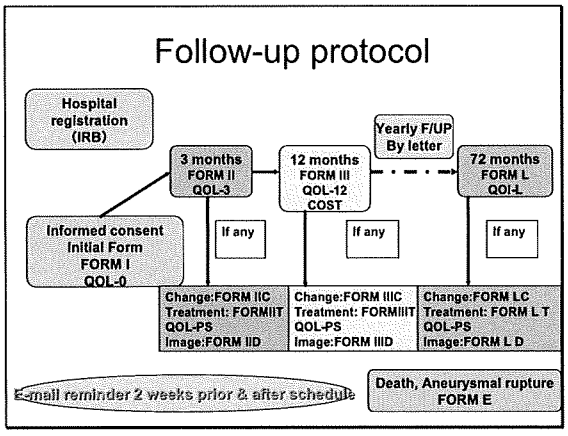
第 34 回日本脳卒中学会総会 シンポジウム大規模臨床試験の現状 2009March 松江

UCAS II 研究の中間経過を発表する。

UCAS Japan では、未破裂脳動脈瘤の自然歴は大きさ、部位に大きく影響されることがあきらかとなっている。しかし本研究の課題として、経過観察期間が短いこと、大規模調査であるため術前後の高次機能や生活の質など患者の細かいデータは集積できなかった。また瘤の因子として形状が重要な因子と考えられているが定義の標準化が難しく評価に加えられなかった。またデータの整合性を全例で検討できてはいない。そこで UCAS II ではさらに詳細なデータを集積するプロトコールを構築し調査を開始した。



UCAS II の目的は未破裂脳動脈瘤が発見されることまた治療によりどのように生活の質や高次機能に影響を与えるかを明らかとすること。未破裂脳動脈瘤の長期経過を検討すること。脳動脈瘤の 3 次元画像情報討し、形状の予後に関与する影響を解析すること。未破裂脳動脈瘤治療の費用効果を検証することである。



経過観察のプロトコールは UCAS Japan に準じ IC を得た後 新規症例を登録、その後 3 ヶ月、12 ヶ月、6 年後の経過を登録する。