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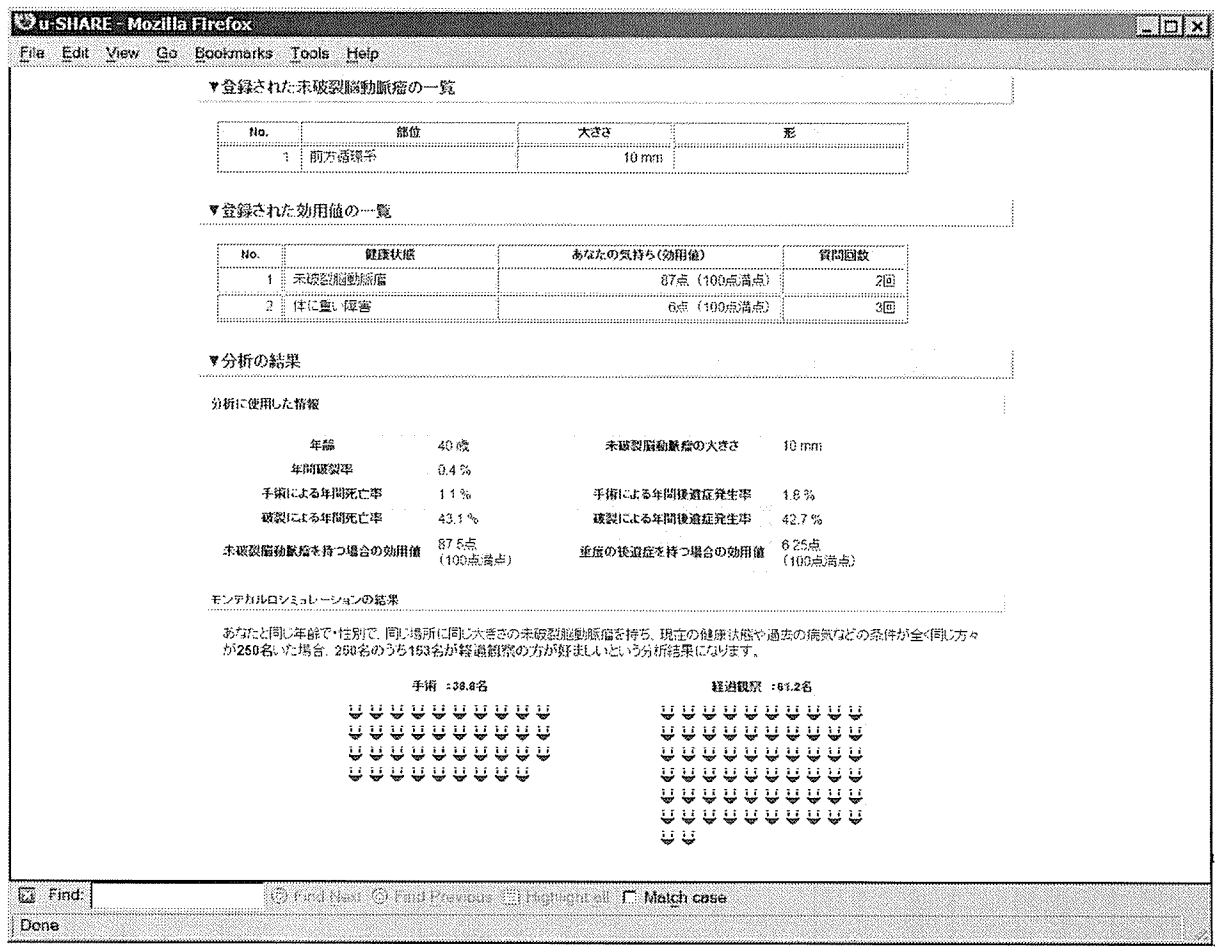

研究成果の刊行に関する一覧表

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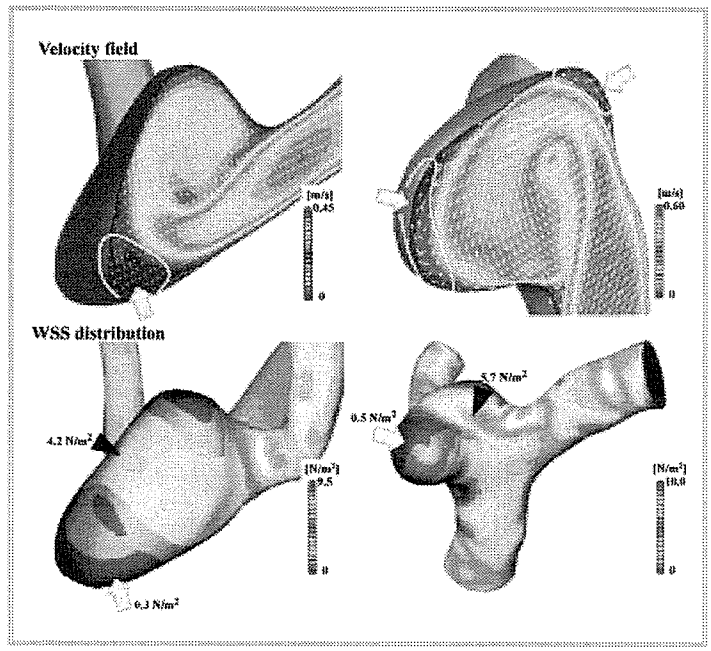

Low Wall Shear Stress May Trigger the Rupture of Cerebral Aneurysms

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Role of the Bloodstream Impacting Force and the Local Pressure Elevation in the Rupture of Cerebral Aneurysms

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Background and Purpose—Inertial force of the bloodstream results in the local elevation of intravascular pressure secondary to flow impact. Previous studies suggest that this "impacting force" and the local pressure elevation at the aneurysm may have a large contribution to the development of cerebral aneurysms. The goal of the present study is to evaluate how the bloodstream impacting force and the local pressure elevation at the aneurysm influences the rupture of cerebral aneurysms.

Methods—A total of 29 aneurysms were created in 26 patient-specific vessel models, and computer simulations were used to calculate pressure distributions around the vessel branching points and the aneurysms.

Results—Direct impact of the parent artery bloodstream resulted in local elevation in pressure at branch points, and bends in arteries (231.2±198.1 Pa; 100 Pa=0.75 mm Hg). The bloodstream entered into the aneurysm with a decreased velocity after it impacted on the branching points or bends. Thus, the flow impact at the aneurysm occurred usually weakly. At the top or the rupture point of the aneurysm, the flow velocity was always delayed. The local pressure elevation at the aneurysm was 119.3±91.2 Pa.

Conclusions—The pressure elevation at the area of flow impact and at the aneurysm constituted only 1% to 2% of the peak intravascular pressure. The results suggest that the bloodstream impacting force and the local pressure elevation at the aneurysm may have less contribution to the rupture of cerebral aneurysms than was expected previously. (***Stroke.* 2005; 36:1933-1938.)**

Key Words: blood pressure ■ computer simulation ■ hemodynamic phenomena ■ intracranial aneurysm ■ stress, mechanical

The development of cerebral aneurysm is promoted by various physical factors associated with blood flow.[1–4] Because cerebral aneurysms usually arise at the vascular branching point or the strong curvature, it is suggested that the physical force generated by blood flow impact may be particularly important.[1–4]

Flow impact results in 2 physical forces different in direction. One is the "impacting force," which results from the inertial force of the bloodstream and acts perpendicular to the vessel wall.[5] The other is the wall shear stress (WSS), the viscous friction of the bloodstream that acts parallel to the vessel wall.[6] The role of the former force is intuitively assumed significant in the pathophysiology of cerebral aneurysms; however, this assumption needs to be proven with scientific evidence because the site of flow impact around the aneurysm and the magnitude of the impacting force has not been obtained yet.

The impacting force of the bloodstream can be considered as the local elevation of pressure at the area of flow impact, as described below.[5,7] The kinetic energy of fluid is converted to pressure when the velocity decreases and vice versa. Thus, it is called "dynamic pressure" in the field of fluid mechanics. At the time of flow impact when the bloodstream changes its direction, the velocity decreases momentarily, and most of the dynamic pressure is converted to the static pressure. This results in the local pressure elevation at the area of flow impact. Previous study[5,8] also states that the complex velocity distribution around the aneurysm results in the pressure elevation at the aneurysm.

Fluid dynamic simulation calculates the spatial distribution of the velocity and the pressure in a mathematical model of vessel, and this method can be applied to study the bloodstream impacting force and the local pressure elevation at the aneurysm. Cerebral arteries of the skull base, where the aneurysm usually occurs, are tortuous and branching, and the spatial pressure distribution in the vessel may come under the profound influence of this geometrical complexity. Thus, the mathematical models of vessel are

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created from the clinical diagnostic images for each case, and the flow phenomena around the aneurysm are simulated in the patient-specific vessel models in this study.

The goal of the present study was to evaluate how the bloodstream impacting force and the local pressure elevation at the aneurysm influences the rupture of cerebral aneurysms in the complex geometry of cerebral vasculature.

Subjects and Methods

Patient Population

From June 2001 to March 2003, 109 patients at our institutions were diagnosed with cerebral aneurysms by 3D digital subtraction angiography (DSA). Of these patients, a total of 29 aneurysms (14 aneurysms were diagnosed after the rupture, and 3 of them accompanied an unruptured one, respectively) in 26 patients (10 males, 16 females; mean age 61.9 years) were deemed of adequate quality for the creation of computational mesh and were used to construct computer models. Aneurysm location included the internal carotid artery (ICA; n=14), the middle cerebral artery (MCA; n=14), and the communicating artery of the anterior cerebral artery (ACA; n=1). Nine ICA aneurysms and 1 MCA aneurysm arose from the sidewall of the parent artery (sidewall aneurysm), where no branch, or only a tiny branch, was recognized near the aneurysms. The other 19 aneurysms were recognized at the typical bifurcation (bifurcation aneurysm).

The number, location, and size of the aneurysms are summarized in Table 1. Written informed consent was obtained from each patient or his/her next of kin.

Image Acquisition

A 3D DSA was performed using a clinical C-arm angiography unit (ANGIOSTAR Plus; Siemens A.G.). Angiographic images with matrix size of 512×512 pixels were obtained with a 33-cm field of view, acquiring 50 exposures (70 kilovolt peaks; 400 mA; 10 ms) before and during the injection of contrast medium. Subtracted angiographic images were transferred to a Unix workstation equipped with 3D Virtuoso (Siemens A.G.). Regions for analysis were selected, and the images were reformatted into tomographic images with a pixel size of 0.13 mm and a slice thickness of 0.13 mm.

Modeling of Vessels and Aneurysms

Lumen boundaries were segmented with the threshold scheme, and the surfaces of the vessels and the aneurysms were constructed with a marching cubes algorithm using ImageDesign (Quint Corporation). Surface irregularities resulting from partial volume effects, truncated small arteries, and other noises were automatically corrected with using original software,[9] and additional smoothing of the polygonal surfaces was performed manually. The analysis region included the vessels from the cavernous portion of the ICA to the vessels that were 10 to 15 mm distal to the aneurysm.

Numerical Simulation

Computer simulation of the bloodstream was performed using a commercially available finite-volume solver (SCRYU/Tetra for Windows Version 5; Software Cradle Co). The velocity fields were determined under the governing equations of continuity and Navie-Stokes.[7] Spatial distributions of pressure was determined by solving the Poisson equation of pressure to complement the velocity fields.[7]

Boundary conditions were defined using specific parameters. Blood was assumed to be an incompressible Newtonian fluid with a specific gravity of 1053 kg/m^3 and a viscosity of 4.0×10^{-3} N/m^2 per second.[10,11] The viscoelastic properties of the vessel wall were neglected, and a rigid wall with no-slip condition was assumed.[12] One typical blood velocity waveform of ICA was obtained with transcranial Doppler measurement (0.61 m/s at peak systole, 0.24 m/s at end diastole, and 57 bpm) and used to create the inlet boundary condition for all cases because this study focused mainly on the effect of the patient-specific vascular geometry around the aneurysm. From the blood velocity waveform of ICA, Womersley's velocity profile (ie, a cross-sectional velocity distribution of a developed pulsatile flow) was created for the inlets of each mathematical model as described in the previous literature.[13] Traction-free boundary conditions were applied to all the outlets of the vessels. The width of the time step for the calculation was adjusted by the solver to control the Courant number <1.0. To confirm the numerical stability, calculations were performed for ≥3 cardiac cycles, and the result from the last cycle was used for analysis. This protocol required ≈36 hours to complete the calculation of 1 case using a standard personal computer with a single Pentium 4 processor (3.0 GHz). The average Reynolds and Womersley numbers were 402 and 4.17, respectively, which implies a laminar flow condition.

Data Analysis

The spatial distribution of pressure in the vessel was visualized with colored contours from the computed pressure and analyzed qualitatively. Sites where the pressure elevates locally were recorded, and the flow structures were investigated with streamline visualizations and cross-sectional velocity field visualizations.

The computed pressure by the solver represents the spatial difference of pressure compared with the pressure of the outlet boundary, and thus, it comes under a considerable influence of the positional relationship between the measurement point and the outlet boundary. For quantitative comparison among cases, the "reference plane" that has an identical positional relationship with the measurement point was introduced, and it was defined as a cross-sectional plane perpendicular to the vessel axis located just proximal to the area of the local pressure elevation (Figure 1A). The spatially averaged pressure of this plane was used as a reference pressure, and the pressure difference between the computed pressure by the solver and the reference pressure was recalculated. The magnitude of this recalculated pressure was not affected by variation in the outlet boundary in each case and used for the statistical analysis with nonpaired t test or 1-way ANOVA. WSS distributions were also visualized with colored contours and were compared with the pressure distributions. The calculation of WSS from the velocity field was performed as described previously.[14]

TABLE 1. Site, Size, and Aspect Ratio (AR) of the Aneurysms

Site of Aneurysm	No.	Age	Size (mm)	AR
ICA	14 (7)	61.9	6.29	1.27
MCA	14 (7)	62.7	4.65	1.05
ACA	1 (0)	50	8.28	2.38
Total	29 (14)	61.9	5.59	1.21

Numbers in parentheses indicate the number of ruptured aneurysms. Mean values are shown in age, size, and AR.

Results

Temporal changes of the computed pressure were in synchronization with the pulsatile flow velocity at the inlet section. Spatial differences in the pressure were greater during systole than during diastole. Thus, the pressure was analyzed at peak systole for all subsequent experiments.

Luminal Pressure Elevation

Qualitative analyses of 26 cases revealed 39 sites of the local pressure elevation in the luminal part of the vessel wall (Figure 1), all secondary to the direct impact of the parent artery bloodstream. The magnitude of the pressure elevation averaged among these sites was 231.2±198.1 Pa (mean±SD; 100 Pa [N/m^2]=0.75 mm Hg). Although the local pressure elevation was greater at the branches (242.1±216.9 Pa) than at the bends (194.8±118.6 Pa; P=0.54; t test), it did not

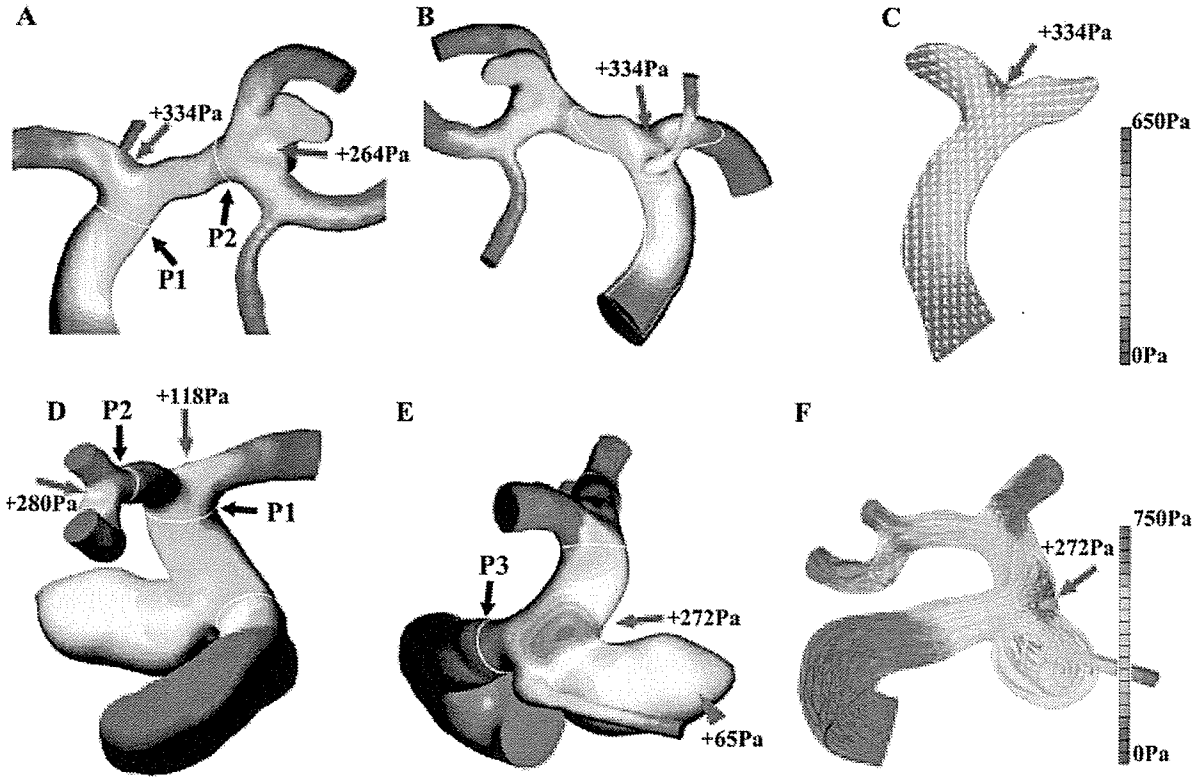

Figure 1. Local pressure elevation in the lumen. Pressure distributions of 2 ruptured aneurysms are presented with colored contour. Bifurcation aneurysm at MCA (A through C) and sidewall aneurysm at ICA posterior communicating artery (D through F). A, Anterior view. Local pressure elevation is easily recognizable at the bifurcation of ICA and MCA (red arrow). The pressure calculated by the solver was subtracted by the spatially averaged pressure of the reference plane (white line; P1and P2). B, Posterior view. White lines indicate the cross-sectional plane in C. C, Cross-sectional view of the intravascular pressure distribution. Flow impact at the bifurcation of ICA results in the local pressure elevation. D, Anterior view. Local pressure elevation at the bifurcation of ICA and MCA. E, Medial view. Local pressure elevation near the aneurysm orifice and at the top of aneurysm (red arrowhead). F, Fusion image of the streamline and the pressure distribution on the vessel wall. Flow impact just proximal to the aneurysm orifice causes the local pressure elevation, and only a portion of the bloodstream enters the aneurysm.

differ when comparing different types of vessels (ICA, MCA, or ACA; P=0.98; ANOVA).

Aneurysmal Pressure Elevation

The local pressure was greater in the aneurysm (119.3±91.2 Pa) than in the adjacent luminal area in all cases (Figure 2; Table 2). The bloodstream entered into the aneurysm with a decreased velocity after it impacted at the branch points or the bends. Thus, the flow impacts at the aneurysm occurred usually weakly. At the top or the rupture point of the aneurysm, the flow velocity was always delayed. The stasis of flow with a weak impact resulted in the local pressure elevation at the aneurysm. There was no significant difference in the degree of the pressure elevation when comparing

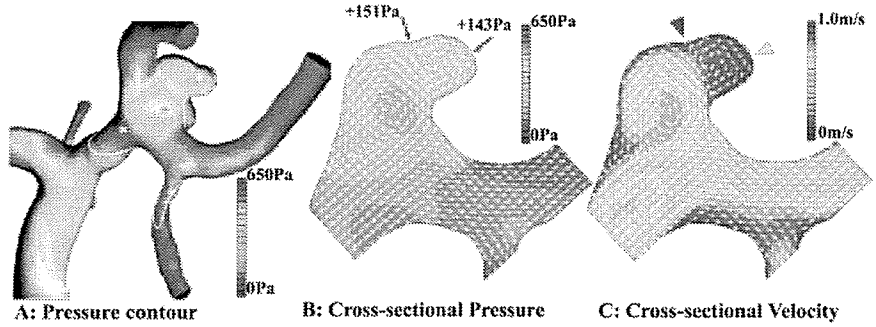

Figure 2. Local pressure elevation in the aneurysm. Same case shown in Figure 1A through 1C. A, Pressure distribution on the vessel wall. The impact of parent artery bloodstream resulted in the local pressure elevation near the orifice of the left MCA aneurysm (red asterisk). Pressure was also high at the aneurysm wall (white asterisk) than at the adjacent lumen (yellow asterisk). White line indicates the cross-sectional plane of B and C. B, Cross-sectional pressure distribution in the aneurysm. Pressure is elevated in the aneurysm compared with the luminal part. C, Cross-sectional velocity distribution in the aneurysm. Flow impact is recognized at the fundus of the aneurysm (red arrowhead). Flow is markedly delayed at the top (blue arrowhead).

TABLE 2. Magnitude of the Local Pressure Elevation at the Aneurysm

Site of Aneurysm	Ruptured	Unruptured	Total
ICA	114.9 (n=7)	117.2 (n=7)	115.9 (n=14)
MCA	117.3 (n=7)	127.1 (n=7)	122.2 (n=14)
ACA	...	123.0 (n=1)	123.0 (n=1)
Total	116.1 (n=14)	122.6 (n=15)	119.3 (n=29)

Mean values are shown in Pascal (N/m^2).

the ruptured (116.1±99.7 Pa) and unruptured aneurysms (122.6±85.6 Pa; P=0.85; t test). The averaged pressure elevation in the sidewall aneurysms was 95.6±90.6 Pa, and that in the bifurcation aneurysms was 132.5±91.4 Pa. The bifurcation aneurysms had a slightly higher pressure (P= 0.31; t test); however, the difference was only 36.9 Pa (0.28 mm Hg) on average.

Aspect Ratio and the Pressure Elevation of the Aneurysm

The aspect ratio of the ruptured aneurysms (1.31±0.33) was higher than that of the unruptured aneurysms (0.97±0.37) in our cases (t test; P=0.03). However, the correlation coefficient between the aspect ratio and the local pressure elevation of the aneurysm was only 0.26 (P=0.24).

Flow Impact Around the Aneurysm

In 27 of 29 aneurysms, the bloodstream of the parent artery did not impact directly on the aneurysm. It impacted on the luminal wall proximal to the aneurysm orifice. After that, a substantial portion of the bloodstream remained and flowed away in the vessel lumen. This phenomenon was observed similarly in the bifurcation aneurysms (Figure 1A) as well as in the sidewall aneurysms (Figure 1E). In the remaining 2 aneurysms (both were the ruptured aneurysms), the aneurysm orifices were so large that the entire bloodstream entered into the aneurysm, and the bloodstream of the parent artery directly impacted the aneurysm wall (Figure 3). The magnitude of the local pressure elevation at the area of flow impact in these 2 aneurysms was 104.1 Pa (0.78 mm Hg) and 298.8 Pa (2.24 mm Hg), respectively. The flow velocity at the top or the rupture point of the aneurysm was always delayed in 29 aneurysms.

Relationship Between Pressure Distributions and WSS Distributions

The local pressure elevation induced by the impact of the bloodstream was always accompanied by high WSS, which occurred adjacently to the site of the local pressure elevation. Further, the high velocity flux at the center in the parent artery shifted toward the outer wall after the branches and the bends of the vessel because of the centrifugal forces that act more intensely on the faster flux. A different cross-sectional velocity field was produced after the impact, resulting in high WSS downstream of the local pressure elevation (Figure 4).

Discussion

Based on the flow simulation of clinically imaged vasculature, the present study demonstrated that flow impact resulted in the local elevation in pressure of 250 Pa (1.88 mm Hg) at branch points and bends of cerebral arteries. However, its magnitude was small compared with the total intravascular pressure, which is nearly equal to the pressure measured at radial artery[15] that averages 128/82 mm Hg in healthy subjects,[16] even when the bloodstream of the parent artery directly impacted on the aneurysm wall. These results suggest that the impacting force of the bloodstream may have a less significant role in the rupture of cerebral aneurysms than is expected intuitively.

Previous studies[5,8] have demonstrated that the pressure of the aneurysm is locally elevated up to 3× higher than that of the luminal part. However, those studies only characterized the pressure fraction that was converted from the dynamic pressure (ie, the kinetic energy of fluid) rather than determining the contribution of the local pressure elevation to the total intravascular pressure. The present study demonstrated that the decreased velocity in the aneurysm leads to the local pressure elevation of 150 Pa (1.13 mm Hg), which only accounts for 1% of the peak intravascular pressure. Further, the magnitude of the pressure elevation in the aneurysm did not differ when comparing ruptured and unruptured aneurysms. Thus, the local pressure elevation at the aneurysm may also have less contribution to the rupture of cerebral aneurysms than is expected previously.

The magnitude of the impacting force and the local pressure elevation at the aneurysm are small compared with the total intravascular pressure; however, they are momen-

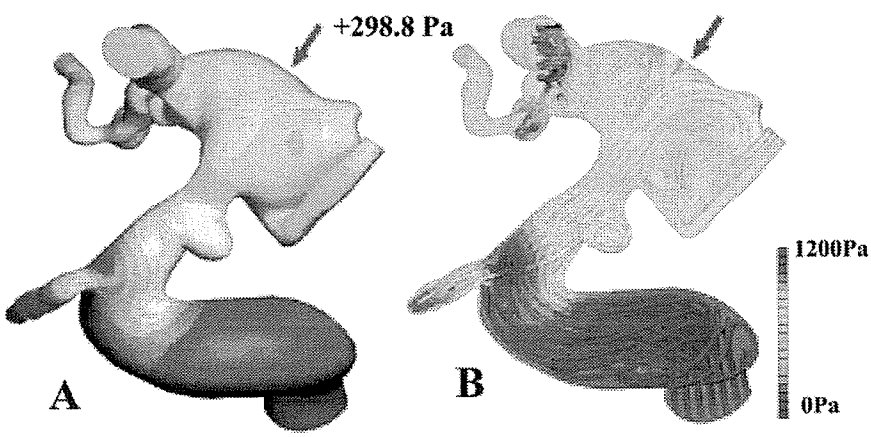

Figure 3. Direct flow impact on the aneurysm. Pressure distribution of right ICA aneurysms are presented with colored contour. The larger aneurysm is ruptured, whereas the smaller aneurysm is unruptured. A, Local pressure at the site of flow impact (red arrow) is 298.8 Pa. B, Fusion image of the streamline and the pressure distribution. Direct flow impact is recognized on the wall of the larger aneurysm.

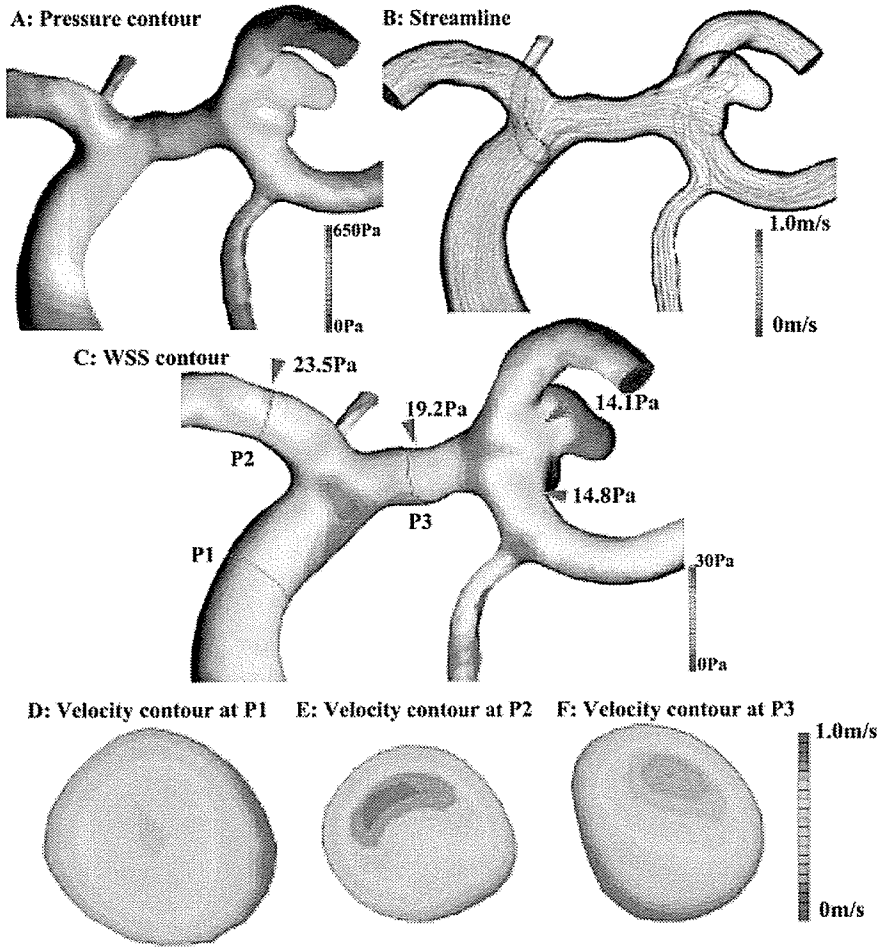

Figure 4. Appearance of local pressure elevation and high WSS after the impact of the bloodstream. Same case shown in Figure 1A through 1C. A, Pressure distribution. B, Streamline colored with the magnitude of velocity. The shift of high-velocity flux outward after the flow impact at the bifurcation of ICA is easily recognized. C, WSS distribution. High WSSs (red arrowhead) appear after the flow impact at separate sites from the local pressure elevation shown in A. D, Cross-sectional velocity contour at the level of ICA (P1). High-velocity flux is located at the center. E and F, Cross-sectional velocity contour after the flow impact (P2 and P3, respectively). High-velocity fluxes are located peripherally.

tarily values. A long-standing effect of these small forces cannot be expected from this study.

The flow dynamics around the aneurysm come under a considerable influence of the positional relationship between the aneurysm and the parent artery.[1] The pressure elevation at the bifurcation aneurysm was slightly higher than that of the sidewall aneurysm; however, the contribution of pressure elevation of both aneurysm types was similarly small. Aspect ratio of the aneurysm, which also has been indicated to have a significant influence on the hemodynamics in aneurysms,[17] also influenced little on the pressure elevation at the aneurysm. The reason why the different flow dynamics do not result in a considerable difference in the local pressure elevation may be that the dynamic pressure is considerably small compared with the energy of the static pressure.

As was shown in Figure 4, the flow impact results in high WSS on the distal side of the local pressure elevation. Although the magnitude of the WSS is as low as 2 Pa in the physiological condition,[6] which is only 1% of the magnitude of the local pressure elevation, the WSS is the only force that acts parallel to the vessel and is related to the formation of cerebral aneurysms.[18] The initial pathological changes of aneurysm formation are observed at distal side of the bifurcation apex.[19] This corresponds to the area of high WSS but not at the area of flow impact and local pressure elevation. As to the rupture of aneurysms, the possible role of the high WSS mixed with low WSS in the aneurysm wall is also reported.[9] Thus, the significance of the impact of the bloodstream in the development of cerebral aneurysms may be mediated by high WSS rather than elevation of the local pressure.

The number of cases analyzed in this study is limited; however, it might be stated from our results that the impacting force, which intuitively seems a potent physical force generated by flow, may have less significance than is expected.

Our simulations are based on the patient-specific vessel models. However, only 1 typical velocity waveform is applied on the inlet boundary, and the viscoelasticity of the vessel, which might differ among the cases, is neglected. More patient-specific simulation will be of benefit to predict the individual rupture risk of the aneurysms diagnosed before bleeding.

Conclusions

Impacting force of the bloodstream and the local pressure elevation at the aneurysm may have less effect on the rupture of cerebral aneurysms than is expected. Computer simulation of the bloodstream may be of utility in advancing our understanding of hemodynamic stress and the pathophysiology of vascular disease.

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Editorial

Comments on the unruptured aneurysm study from Japan; does this study clarify what to do?

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When the neurosurgeon, neurologist, interventional neurosurgeon, or neuroradiologist sees a patient with an unruptured intracranial aneurysm, the patient wants to know two things: 1) What risk does this aneurysm pose to my life and to my quality of life? 2) If it is treated what are the risks of treatment and are those risks higher or lower than the risk of the disease? The patient wants to know what the physician would do if he or she had this aneurysm.

The Risk of Rupture of an Unruptured Aneurysm

To answer the first question about the risk of aneurysm rupture is challenging for any neurosurgeon. If we look at rates quoted from the literature in Tables 2 and 3 in the paper written by Morita, et al., the risks of rupture range from 0.3 to 6.9% per year. Actually in its first report the International Study of Unruptured Intracranial Aneurysms (ISUIA) demonstrated a low rupture rate of 0.05% per year in a retrospective study.[8] This is a 10-fold difference in values according to the paper by Morita, et al., and more than a 100-fold difference if you compare the 6.9% rate with data provided in the first ISUIA study. For the patient the decision process is different if the risk is 0.3% per year or 6.9% per year. Therefore, treating physicians need better data or a better way to screen the data that are reported. How can the treating physician obtain these data?

The Ideal Study

If one were to think of the ideal study necessary to identify the risk of hemorrhage from unruptured intracranial aneurysms, one would want a study in which an unbiased sample of patients was selected from the universe of all patients with unruptured aneurysms to determine the risk of rupture. If one wanted to know what the risks are in patients who display symptoms from their aneurysms, those symptoms would have to be defined and the patient sample would be taken from the universe of symptomatic patients with unruptured aneurysms. For risks in patients whose aneurysms were found incidentally, one would sample the universe of those patients with incidentally found aneurysms. Unfortunately, no studies have been performed in these ways. Therefore, any data that are reported are biased by the referral source or a selection of some kind.

Prominent Studies in the Literature

To me, the best study in the literature is the one conducted by Juvela and colleagues.[11,12] Before 1979 in Finland no patients with unruptured aneurysms were surgically treated; they were observed. These patients came primarily from a population of patients who harbored multiple aneurysms of which one had bled. The other aneurysms were then followed. It is assumed in the study of Juvela and colleagues that multiple aneurysms in the same patient have a rupture rate equal to that of a single unruptured aneurysm in a patient. This selection bias has been criticized. The patients who came to the investigators' institution represented a large sample of the Finnish population and were not selected because aneurysm surgery was not performed at any other institution in Finland. In that study the risk of rupture was 1.4% per year.[11,12]

The ISUIA was divided into two studies, one retrospective and the other prospective, both of which represent severely biased samples of the universe of patients with unruptured aneurysms.[7,8] In the later study (2003) the groups were further subselected in a biased manner to undergo surgery, endovascular treatment, or no treatment. The rupture rate was calculated from data in the no-treatment group after subselection.[7] Data on the rupture rate in both studies are virtually useless to me as a clinician for those reasons. The key question for neurosurgeons regarding the ISUIA studies is: "Is the patient discussed in these studies the patient I am seeing in consultation?" To me the answer is "no" or "I don't know." You can read a more detailed explanation of my criticisms of these studies in other papers.[2,3]

The report from Europe by Rinkel, et al., provides an analysis of the literature and includes one Japanese study.[14] This study is well done. Its discussion section provides a fair evaluation of the results, which indicate a 1.9% rupture rate per year. It must be remembered, however, that this report is also a compilation of selected series.

The study by Morita, et al., reported in this issue, was

performed in the same manner as the Rinkel study; they are both detailed reviews of published studies. The study by Morita, et al., however, only included Japanese reports. This study documents a rupture rate of 2.7%, reportedly higher than the rate in the Rinkel report and in others, perhaps, because of racial differences in the rupture rates. This leads us to another question: does all of this information help us decide what to recommend to the patient?

How to Use This Information

Symptomatic Unruptured Aneurysms. There are two circumstances in which the clinician will see a patient with an unruptured intracranial aneurysm. First, the patient will present with symptoms that ultimately can be related to the aneurysm. The patient will complain of persisting or progressively more frequent headaches, double vision (third nerve palsy), or visual loss—symptoms difficult to exclude as not being related to an aneurysm.[5] In these circumstances most likely the clinician will want to treat the aneurysm. According to the paper by Morita, et al., the risk of rupture in symptomatic patients is 7.3%, but there were only 42 patients in that category. In the paper by Rinkel, et al., the risk of rupture in this category is also increased. Among 463 patients the risk of rupture was 6.5%.[14] Using common sense, a category excluded by the statistical method, if one operates on an unruptured aneurysm and sees the blood swirling in the thinned dome of the aneurysm, it does not take much persuasion to know that this aneurysm is dangerous and will rupture sometime. From the Rinkel and Morita reports one has to conclude that there is a significant risk of choosing no treatment for this symptomatic unruptured aneurysm. The risk of rupture in the symptomatic group of patients ranges from 6.5 to 7.3%. Thus, the only choice is whether the risk of treatment is worse than the risk of the disease or of no treatment. I will discuss this subject later in this editorial.

Asymptomatic Unruptured Aneurysms. The second category of patients with unruptured aneurysms only pertains to those patients who were found incidentally to harbor aneurysms. These patients present with symptoms or another reason indicating the need for an imaging study unrelated to the aneurysm. The papers by Juvela and colleagues[11,12] fall into this category. In the paper by Morita, et al., there are 876 cases in this category and the risk of rupture is 1.8%. In the paper by Rinkel, et al., the risk of rupture is reported to be 0.8%.[14] Now the problem with the asymptomatic group is what to recommend. Dickey and Kailasnath[4] reported that the risk of rupture increases exponentially—to the third power—with the diameter of the aneurysm: the larger the aneurysm, the higher the risk of rupture. The Rinkel, Morita, and ISUIA studies all support that general conclusion. In contrast to what Wieber and colleagues[7,8] wrote in 1998 and 2003, that an aneurysm must reach 7 to 10 mm in diameter before it ruptures, these other papers do not dictate any size limitation to aneurysm rupture.[4,14] Juvela, et al.,[11] arrived at the same conclusion in the Finnish study reported in 1993. These researchers also reported that cigarette smoking, size of the unruptured aneurysm, patient age, and female sex carry higher risks of rupture.[10,12] If we assume that the rupture rate for asymptomatic intracranial aneurysms is 1 to 2% per year, the cumulative rupture rate over a 10-year period is 10 to 20%.[12] These factors—aneurysm size, cigarette smoking, age, and female sex—should thus be included when presenting data to the patient. What would you want done if the aneurysm was yours is the key question.

Incidences of Mortality and Morbidity Associated With Surgical Treatment and With No Treatment

Now, what is the risk of treatment of these aneurysms? Let's assume a zero mortality rate, which has been reported and used as a justification for surgery. But death is not the only risk: there is also the risk of morbidity. Here is where the ISUIA provides us with excellent data.[7,8] In the ISUIA, patients were followed up for incidences of mortality and morbidity including cognitive deficits, which were evaluated using neuropsychological studies. Most neurosurgeons perform a cursory examination postoperatively and do not evaluate any cognitive deficits the patient may have. In the ISUIA the combined morbidity and mortality rate was approximately 11 to 15% at 1 year. This is very significant. Cognitive morbidity constituted one third of the combined morbidity–mortality rate and both mortality and morbidity were associated with the surgery.

Incidences of Mortality and Morbidity From Endovascular Treatment

What is the combined mortality–morbidity rate in patients undergoing endovascular treatment? In a superselected group treated endovascularly the ISUIA found a 9.8% mortality–morbidity rate with 3.2% of patients experiencing cognitive disorders after interventional treatment.[7] In a study of 247 unruptured intracranial aneurysms treated with coil embolism Gonzalez, et al., reported 5.5% morbidity and mortality.[6] Investigators in the International Subarachnoid Aneurysm Trial (ISAT) reported a morbidity–mortality rate that was lower than the rate associated with surgery and the difference had statistical significance.[9] There is much criticism of this study by neurosurgeons; yet, the conclusions of the study are valid based on the questions asked.[1] An additional report of the ISAT group should be published in 2005 and will reveal cognitive defects in the surgery and endovascular groups, which were randomly selected. My guess is that the cognitive deficits after coil placement will be much lower than those after surgery.

The Future

In the future we will observe detected unruptured intracranial aneurysms by using magnetic resonance angiography. When the aneurysm enlarges it can be treated.[13] Juvela, et al.,[11] made this observation based on repeated conventional angiography studies obtained during the follow-up period of their study in 1993.

My Answer Concerning What to Do

So, what does the clinician tell the patient with a symptomatic or asymptomatic unruptured intracranial aneurysm about the risks of treatment? Will surgery provide treatment that can be viewed favorably even in light of the 10 to 15% rate of mortality and morbidity to which you will subject the patient if you operate? That is the choice the patient must make given the data. To me the data can be used to argue for treatment. What would I want done if it were my unruptured aneurysm? For me, get me to the most experienced inter-

ventionalist and treat it endovascularly. I do not want any cognitive deficits that may come with surgery. I am convinced that the endovascular approach, if available and excellent, is better. If I am in a situation in which endovascular treatment is not available or is not of excellent quality, I would prefer to have the aneurysm treated surgically because the risk of hemorrhage to me is a risk I would not want to take. Under these conditions I would obtain the services of the best aneurysm surgeon I could find and have the lesion clipped. If the aneurysm is small and regular in shape, it can be followed by imaging every 6 months to see if its size increases. After all the anxiety I may experience over this option, endovascular treatment would eliminate both my concern and the aneurysm.

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RESPONSE: We appreciate Dr. Ausman's comments and agree with his points regarding the dilemma of choosing the best approach to manage an unruptured cerebral aneurysm (UCA). Our report did not set out to answer this specific question. Rather, we wrote it to warn physicians in countries not included in the ISUIA that data compiled by that study might not apply to all populations. The natural course of a UCA and the risk of rupture associated with it can be influenced by many factors, as Dr. Ausman and other authors have indicated. We would like to nominate race as one of these factors. In Japan, because we widely use a brain assessment system (the so-called Brain Dock), we find more asymptomatic aneurysms incidentally than physicians in other countries.[8] We therefore assumed that reviewing Japanese publications might clarify the natural course of UCAs found incidentally. Our data revealed an unexpectedly high rupture rate, which could have been caused by several factors including race and the behavioral backgrounds of the Japanese and any possible bias caused by patient selection or the design of the study. Even considering these biases, however, we can state that our data show that the rupture rate is relatively high among patients admitted to a hospital to undergo a detailed assessment of the UCA. Hence, some of these UCAs may be excluded because their detailed study or even registration as a UCA was not considered appropriate. There may also be subtle nuances among neurosurgeons in selecting cases, and such criteria must be clarified in a scientific way.

The Ideal Study

In his description of the "ideal study," designed to clarify the natural course of UCAs and to determine the best treatment strategy, Dr. Ausman summarizes the current status of our knowledge very well. To identify the true natural course of UCAs, we must observe all encountered lesions in this group without intervention for a defined period. The study by Juvela and colleagues[5] partly fulfills this criterion. Their study, however, included patients who presented exclusively with subarachnoid hemorrhage (SAH), and it is difficult to speculate about the natural course of incidentally found UCAs when using these data. In Japan, most UCAs encountered in routine practice are found incidentally in patients with no history of SAH.[8] Is it ethical then to perform a study in which all UCAs are followed, even though some patients request treatment? Furthermore, is it possible to provide patients with unbiased comments about the risk–benefit ratios associated with observation and intervention based on current data? Without conducting such studies, even with some biases, we may be able to identify some data indicating which factors influence the rupture risk. Symptoms, posterior location, and the size of the aneurysm seem to be definitive factors.[3] On the other hand, treatment risks are also worsened by these same factors, making the choice difficult. The issues of treatment risks and selection of the best strategy are beyond the scope of our study. The ISUIA has indeed clarified some of the issues regarding case management risks.[3] Although these risks are very high compared with what we commonly believed to be the case,[1] the ISUIA demonstrated that the risks are significantly influenced by the size and location of the aneurysm and the age of the patient.[3,4] The influence of the hospital's case volume has also been discussed as an important factor.[2]

The Future

Even with extensive current studies, there remains a large

gray area in determining the best treatment for any patient. More than 70% of UCAs are not large and are located in the anterior circulation. What should we do with those cases? We need to conduct randomized controlled trials by selecting specific groups for which previous studies could not clearly determine the best approach. Of course, this should be done in patients who fully agree to participate in a study after a thorough discussion with the investigators and after they have provided informed consent. In the future, the recommended treatment should be determined from the individual risk–benefit ratio. We should have a mathematical model for the assumed rate of rupture for individual aneurysms according to various risk factors such as size, location, presence of blebs, patient age and sex, and smoking or other life-style histories. By comparing the calculated lifelong risks of rupture and outcomes associated with the institution and surgeon, a treatment can be recommended. With improved imaging techniques and flow-dynamics simulation, we are learning about the anatomical fragility,[6] topical wall shear stress, and moments of pressure for individual aneurysms.[7] Such data might also be useful for determining the individual risk of rupture. With these advanced methods of investigation, well-designed prospective studies, and a high-quality database of UCAs, we will be better equipped to determine the best strategy for each patient.

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Editorial

The risk of rupture of unruptured cerebral aneurysms in the Japanese population: a systematic review of the literature from Japan by Morita, et al.

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Morita and colleagues present a very interesting paper about an important topic that may be particularly pertinent in Japan given that some of the highest incidence rates for subarachnoid hemorrhage (SAH) have been cited in reports from that country. There are obviously many challenges inherent in the approach of collating and combining data from several relatively small retrospective reports, as illustrated by this study and substantially acknowledged by the authors. We faced similar challenges in North America and Europe in an attempt to evaluate small retrospective studies, and our inability to provide uniform, robust results while using this approach led to the development of the International Study of Unruptured Intracranial Aneurysms (ISUIA). It is nevertheless interesting that the results of the current study indicating increased rupture risk for large, posterior circulation, and symptomatic unruptured cerebral aneurysms were very similar to the pattern observed in the ISUIA[1,2] (a multivariate analysis performed in the ISUIA indicated that the increased risk associated with symptomatic unruptured aneurysms was related to the increased size of these lesions). Moreover, the overall rupture rate of 2.7% per year reported in the current study would not differ statistically from the overall rupture rates we reported from early small retrospective series from a single institution.[3,4] It is difficult to evaluate the apparent cases of rupture of small aneurysms in the absence of information about which patients had prior SAH and without sufficient follow-up information to allow calculation of rupture rates. Given the substantial differences in patient populations, study design, and follow-up analyses, it is not statistically possible to compare the results of the current metaanalysis with the results of the ISUIA by using traditional probability values.

Notwithstanding the aforementioned points, the results of the study by Morita, et al., are intriguing and provide food for thought as we anticipate the results of the two ongoing prospective studies in Japan that the authors mention in their paper. A difference in risk factors and the behavior of unruptured intracranial aneurysms in substantially different genetic populations cannot be excluded.

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Response: We appreciate Dr. Wiebers' thoughtful comments about our systematic review. As he has emphasized, reviewing and summarizing small series is difficult because the case material, classification, follow-up methods, and study periods differ among series. Because of these difficulties, we asked the authors of each study included in our review to provide their own data reclassified according to our criteria. Most of the authors kindly fulfilled our request, and we particularly appreciate their cooperation. The strength of our study relies on their efforts, which we could request because our report is based on single-nation studies and we know each other very well. Without such a relationship with each author, we might not have been able to obtain uniformly classified data. Nonetheless, as Dr. Wiebers notes, it was still a difficult task to collect such information because some of the authors' data were already lost—some from a change in recording style occurring during software upgrades and some because of computer breakdowns. Furthermore, some of the older raw data had not been obtained with informed consent from patients and we did not collect raw data. To carry out a multivariate analysis regarding risk factors (such as a comparison of the influence of symptomatic and larger aneurysms), we need patients' raw data. Problems such as publication biases be-

come more serious when assessing management results collected from surgical series.[4] With these problems in mind, we strongly recommend that authors who wish to publish their own series of specific diseases obtain informed consent from each patient for a generalized data analysis. Authors should also keep raw data obtained in each patient with their report in a format that will not be lost. Such efforts can contribute tremendously to future scientific study. Furthermore, the method of classification, measures used to evaluate outcomes or events, and other pertinent information should be uniform. We hope that guidelines developed to direct the management of specific diseases also contain recommendations about methods of follow up and other pertinent issues.[1] The two on-going prospective studies in Japan have been constructed to overcome the innate problems of retrospective data collection. The first study is a prospective on-line collection of data from patients with unruptured cerebral aneurysms treated in the involved institutions (Unruptured Cerebral Aneurysm Study in Japan, UCAS Japan).[2] Each patient chose a treatment plan based on the recommendations of the attending physician, and prospective follow-up and management data are being assessed. No results about rupture risk or management outcome have yet been published. The second study is being conducted by a group of neurosurgeons at national hospitals who agreed to observe all patients harboring unruptured aneurysms with a diameter less than 5 mm (Small Unruptured Aneurysm Verification; SUAVe study). The latest publication from this group[3] shows that, even among these small lesions, four aneurysms ruptured and the calculated rupture risk was 0.8% per year (95 confidence interval 0.2–3%). Eighteen aneurysms enlarged, seven of which were surgically treated. A location on the anterior communicating artery and the occurrence of multiple aneurysms in older women were factors affecting the rupture risk. Because the study is limited to a select group and the follow-up period is short, the confidence interval is wide and longer follow-up periods and further case involvement are required to establish acceptable data. Nonetheless, a close follow-up review with reasonable sensitivity to enlargement of the lesion has proved to be a valid method for managing small aneurysms. We hope such efforts to build valid prospective data obtained via uniform measures from multiple institutions will solve some of the mystery surrounding unruptured aneurysms and provide useful information for their appropriate treatment. This cannot be accomplished using the current retrospective analysis of data. These efforts might also be used to identify the reason for the difference in incidence of SAH between patients in Japan and those in Western countries. Nevertheless, there will still be some patients in whom detailed prospective data analysis may not clarify the optimal management strategy and a randomized controlled trial is required. The aforementioned prospective studies may help us define the group of patients best served by randomized controlled trials.

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Risk of rupture associated with intact cerebral aneurysms in the Japanese population: a systematic review of the literature from Japan

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Object. Knowing the rate of rupture associated with unruptured cerebral aneurysms (UCAs) can help surgeons determine a case management strategy in patients harboring these lesions. According to large-scale cohort studies involving populations in North America and Europe, small unruptured aneurysms carry a very low risk of rupture. In Japan, however, there have been sporadic reports of higher rates of rupture. To identify the rupture risk associated with UCAs in the Japanese population, the authors systematically reviewed retrospective studies of the natural course of these lesions.

Methods. The authors searched Medline and the Japan Medical Abstract Society Index for reports of UCAs in Japan. Two of the authors verified the eligibility of the reports and extracted data independently. Additional information was directly obtained from the authors of the original reports.

Thirteen reports covering a total of 3801 patient-years fulfilled the criteria for our study. Subsequent rupture was documented in 104 patients and the annual rupture rate was 2.7% (95% confidence interval 2.2–3.3%). Large, posterior-circulation, and symptomatic aneurysms were associated with significantly higher rates of rupture (relative risks 6.4, 2.3, and 2.1, respectively). The risk of rupture determined by the authors' review was significantly higher than that reported by investigators from international cohort studies.

Conclusions. Although a selection bias of patients may be the cause of the higher rupture risk, untreated UCAs that have been followed in Japanese institutions have a considerably high rate of rupture. The natural course of UCAs should be carefully estimated in countries not included in the international studies.

KEY WORDS • **unruptured aneurysm** • **natural history** • **aneurysm rupture** • **population study**

RECENT reports from large-scale retrospective and prospective cohort studies have concluded that the risk of rupture associated with small UCAs is extremely low. These studies included data primarily from Caucasian populations (> 90% of patients) in North America and Europe.[11,12] The clinical behavior of UCAs is known to vary according to characteristics such as patient sex and age, size and location of the aneurysm, and other factors.[11,13,22] We believe that the genetic background of race should also be incorporated into an analysis of the rupture risk associated with UCAs. Although some investigators have considered variations in the rate of SAH according to race or nation,[1,4,9] few have addressed racial differences in the rupture risk associated with UCAs. Several retrospective series documented a high risk of rupture among UCAs in Japan and Finland;[13,26,27] however, because these studies included only limited numbers of patients, they cannot be compared with large-scale cohort studies. To clarify the rupture risk among untreated UCAs in Japan and to determine whether this risk differs from that shown in international studies, we systematically reviewed the literature on the natural history of UCAs published exclusively by Japanese institutions.

Abbreviations used in this paper: CI = confidence interval; ISUIA = International Study of Unruptured Intracranial Aneurysms; OR = odds ratio; RR = relative risk; SAH = subarachnoid hemorrhage; UCA = unruptured cerebral aneurysm.

Clinical Material and Methods

Inclusion Criteria

To locate studies of the natural course of UCAs published by Japanese institutions from 1980 to 2003, we searched Medline from 1981 onward and the Index of the Japan Medical Abstract Society from 1983 onward. We also searched reference lists of all relevant publications for additional studies. Two authors (A.M. and S.F.) independently evaluated each study to assess its eligibility for this review. The following inclusion criteria were used. 1) The study was performed in a Japanese institution and reported in a peer-reviewed journal in either English or Japanese. 2) Each study included at least 10 patients with unruptured aneurysms, and the exact number of cases and mean follow-up periods were documented. 3) The number of patients presenting with SAH or aneurysm-related symptoms was available. 4) In cases presenting with SAH in which additional aneurysms were present, the ruptured aneurysm had

TABLE 1
*Risk of rupture associated with UCAs in Japan**

Category	No. of Included Studies	No. of Cases	Patient-Years	No. of Ruptures	% Risk of Rupture per 100 Patient-Years (95% CI)	RR (95% CI)	OR of Rupture (95% CI)
overall	13	922	3801	104	2.7 (2.2–3.3)		
patient sex	10						
male†		294	1370	30	2.2 (1.5–3.1)		
female		435	1803	55	3.0 (2.3–4.0)	1.4 (0.9–2.2)	1.3 (0.85–2.22)
patient age (yrs)	11						
<60†		297	1543	35	2.3 (1.6–3.2)		
≥60		520	2077	62	3.0 (2.3–3.8)	1.2 (0.8–1.9)	1.17 (0.74–4.96)
history of SAH	13						
no†		709	2786	62	2.7 (2.1–3.4)		
yes		209	1010	28	2.8 (1.8–4.0)	1.3 (0.85–2.0)	1.06 (0.64–1.74)
symptoms present	13						
no†		876	3657	94	2.6 (2.1–3.1)		
yes		42	137	10	7.3 (3.5–13.4)	2.1 (1.1–3.9)‡	2.20 (0.97–4.96)
aneurysm site	10						
ant†		770	3370	59	1.8 (1.3–2.3)		
pst		127	618	20	3.2 (2.0–5.0)	2.3 (1.4–3.7)‡	2.18 (1.23–3.86)‡
aneurysm size (mm)	11						
<10†		585	2045	31	1.5 (1.0–2.2)		
≥10		100	344	32	9.3 (6.4–13.1)	6.4 (4.0–10.4)‡	8.68 (4.59–16.41)‡

* Ant = aneurysm located in the anterior circle of Willis; pst = aneurysm located in the posterior circle of Willis.
† Referenced category.
‡ Statistically significant RR or rupture rate and OR of rupture were obtained according to the method described by Breslow and Day. In the table the OR represents (odds of rupture in the group)/(OR of rupture of the referenced group).

been obliterated or no other known source of hemorrhage was detected. 5) The UCA was diagnosed using either conventional or digital subtraction angiography, magnetic resonance angiography, three-dimensional computerized tomographic angiography, or a combination of these methods. 6) Documentation of the rupture of the aneurysm (that is, the SAH) could be confirmed with the aid of computerized tomography scanning, lumbar puncture, surgery, or a postmortem examination.

If several publications originated at the same institution, the most recent series or the series including the largest number of cases was selected for review. In studies missing some inclusion criteria,[17,19,20,27,28] we sent requests to the authors and included the study if they could provide the missing data.

Data Extraction and Analysis

Once a study was deemed eligible for review, two of us independently extracted the following data: the total number of cases, the period of follow up, and the number of aneurysm ruptures. We also sent out requests to authors of the studies for additional detailed data not described in the papers. When data were available for stratification, we extracted information concerning patient age (11 studies) and sex (10 studies), the size of the aneurysm (11 studies), the site of the aneurysm (10 studies), any history of SAH (all 13 studies), symptoms caused by the aneurysm (all 13 studies), and incidences of death from SAH (11 studies). If data were available, we also extracted the number of surgeries performed on UCAs during the same period of study at the same institution, and the timing of lesion rupture. The influences of high blood pressure or smoking and their association with the rupture were discussed in very limited series[2,7,17] and were not assessed in this review.

To calculate the risk of aneurysm rupture, we multiplied the total number of patients by the average period of follow up in each study to obtain the total number of patient-years of follow up. The number of patients with subsequent SAH was then divided by the number of patient-years to yield the risk of rupture per 100 patient-years.[22] We used this method to calculate the risk of rupture in all patients and in the various subgroups. We asked the authors of all 13 studies to provide follow-up periods for each subgroup, but only four authors could do so.[17,26–28] Therefore, the other subgroups were analyzed using the average follow-up period of the total number of cases in each study.[3,22]

Analysis of the Review

To identify any variations among the studies in this review, we compared data between factors in the following subgroups: 1) studies including more than and fewer than 50 patients; 2) studies published in English and those in Japanese; and 3) studies from four districts: Touhoku, Kanto, Kinki-Hokuriku, and Chyuugoku-Shikoku.

Comparison With Large-Scale Cohorts and Other Retrospective Reviews

We compared the findings of our review with those of two large-scale international cohort studies (the ISUIA retrospective and prospective cohorts)[11,12] and a systematic review by Rinkel, et al.[22] The review of Rinkel and colleagues incorporated three Japanese series, and we analyzed the data both to include and exclude Japanese cases. We also compared patient characteristics and the overall rupture rate obtained by calculating total patient-years and total cases of rupture.

Statistical Analysis

The chi-square and Fisher exact tests were used to com-

TABLE 2

*Summary of included studies**

Authors & Year	No. of Cases	Patient-Years	No. of Ruptures	% Rupture Rate (95% CI)	No. of Deaths	Location of Institution
Inagawa, et al., 1992	47	240	1	4.0 (0–1.5)	NA	CS
Asari & Ohmoto, 1993	54	197	11	5.6 (2.8–10.0)	10	CS
Mizoi, et al., 1995	49	211	4	1.9 (0.5–4.9)	3	TH
Yasui, et al., 1997	234	1463	34	2.3 (1.6–3.2)	18	TH
Ikawa, et al., 1998†	36	155	7	4.5 (1.8–9.3)	7	CS
Yasui, et al., 1998†	10	25	1	4.0 (0–14.8)	0	KH
Ikeda, et al., 2000†	33	158	11	6.9 (3.5–12.4)	NA	KH
Tsutsumi, et al., 2000	62	267	7	2.6 (1.1–5.4)	6	TH
Murata, et al., 2001†	48	121	4	3.3 (0.9–8.4)	1	KH
Suga, et al., 2002†	100	317	5	1.6 (0.5–3.7)	3	CS
Tsukahara, et al., 2002	110	217	7	3.2 (1.3–6.6)	2	NA
Matsumoto E, et al., 2003	48	158	7	4.4 (1.8–9.1)	7	KT
Matsumoto K, et al., 2003	91	273	5	1.8 (0.6–4.3)	4	KH

* CS = Chyuugoku-Shikoku district; KH = Kinki-Hokuriku district; KT = Kanto district; NA = not available; TH = Touhoku district.
† Published in Japanese.

pare differences between risk factors and the studies. The Mantel–Haenzel method was also used to compare differences in the included series and to obtain RRs and ORs between subgroups.[3] A probability value less than 0.05 was considered significant. Statistical analyses were performed with the aid of a commercially available software program (SAS, version 8; SAS Institute, Inc., Cary, NC).

Results

Rupture Rate of Untreated UCAs in Japanese Institutions

Thirteen studies fulfilled our inclusion criteria.[2,6–8,16,17,19,20,24–28] Of these, eight were reported in English and the other five in Japanese. Twelve authors responded to our requests and nine provided additional information regarding subgroups.[6,8,17,19,20,24,26–28] Five studies included only asymptomatic cases,[7,20,24,26,28] and two studies included only cases without SAH.[24,26] One study included only aneurysms located in the anterior circulation,[17] and one included only patients older than 70 years.[28] We were able to incorporate these studies because the numbers of patients and ruptures were provided. A summary of the studies is shown in Table 1.

The 13 studies included 922 patients with UCAs who were followed up for a total of 3801 patient-years. There were 104 subsequent ruptures among the entire patient population (11%), constituting an annual rupture rate of 2.7% (95% CI 2.2–3.3%). The risk of rupture was significantly higher for large aneurysms (RR 6.4, 95% CI 4.0–10.4), aneurysms located in the posterior circulation (RR 2.3, 95% CI 1.4–3.7), and symptomatic aneurysms (RR 2.1, 95% CI 1.1–3.9) compared with each referenced category. Unruptured cerebral aneurysms tended to burst more often in patients presenting with SAH, in women, and in patients older than 60 years, but the differences between these groups were not significant. Because our rupture risks were calculated on the basis of an estimated average follow-up period in some series, we also obtained the OR for the net number of all cases of ruptured aneurysms/all cases of unruptured aneurysms in each subgroup, which would not be affected by the follow-up period. The OR of ruptured lesions in the subgroups also showed a similar tendency for a high rupture risk in large aneurysms, posterior-circulation lesions, and aneurysms with symptomatic presentation (ORs 8.68, 2.18, and 2.20, respectively).

In eight reports the authors discussed the risk of rupture of small aneurysms (< 5 mm); seven of 40 ruptured aneurysms in these studies were smaller than 5 mm.[6,8,17,19,20,24–26] Among patients with aneurysms measuring 5 or 6 mm, an additional four of 40 lesions ruptured; hence, 27.5% (11 aneurysms) of the ruptured aneurysms were smaller than 7 mm. Because of the low number of small aneurysms and the lack of details about the follow-up period, we could not calculate the rupture rate for this group.

Data on this incidence of death caused by SAH from 11 studies showed that 61 (66%) of 92 patients died of SAH.

Eleven reports provided data about surgery during the same period as the studies.[2,7,8,16,17,19,20,25–28] In these 11 studies, surgery was performed in 1601 patients, compared with 787 who were only observed.

The timing of rupture was documented in 11 series, but the total number of ruptures in each year could be obtained from only eight series.[2,6–8,20,24,26,28] Among 47 cases of subsequent rupture, 19 lesions ruptured within 1 year, nine ruptured within the 2nd year, and the remaining 19 aneurysms ruptured after the 2nd year. When we included three additional series that provided Kaplan–Meier life tables showing the timing of rupture,[16,17,27] we noted no acute increase in the rupture rate in any specific year.

Variations Among the Included Studies

A summary of the included studies appears in Table 2 and Fig. 1. The series reported by Ikeda and colleagues[7] and Inagawa, et al.,[8] demonstrated statistically significant differences when they were compared with other studies regarding the rupture rate ($p = 0.0068$). Excluding these two studies from the analysis did not alter the results of our review. Although the overall rupture rate was higher in studies written in Japanese and in those studies including fewer than 50 patients, no significant difference was noted between groups. Geographic location, which can influence the patient's living environment, did not influence the risk of rupture.

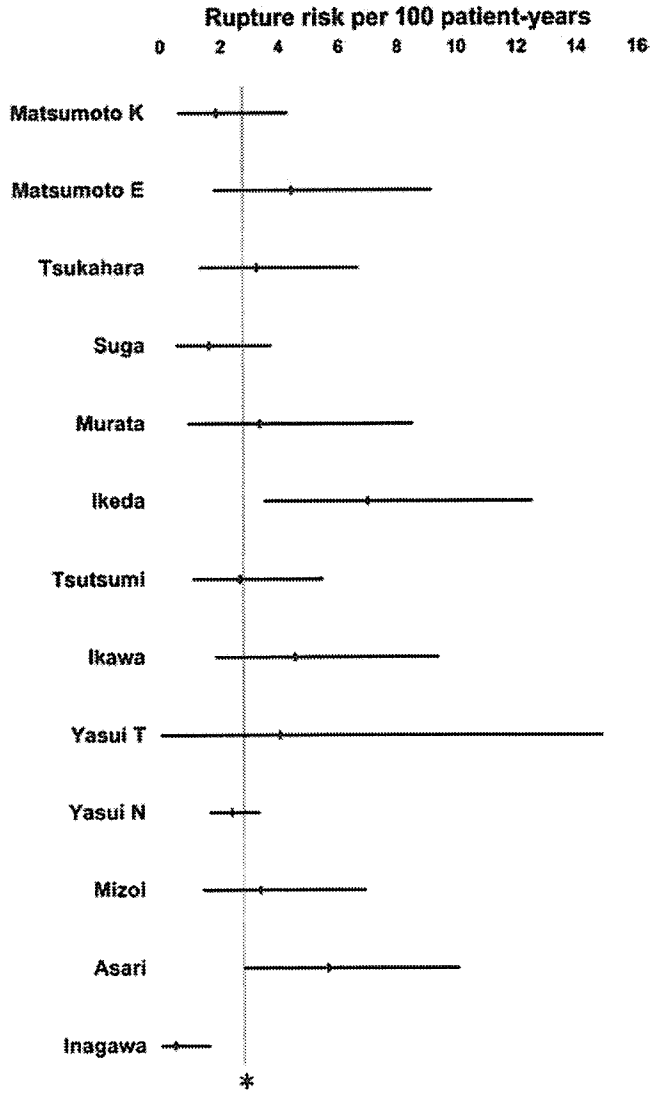

FIG. 1. Chart showing the risk of rupture associated with UCAs in the included studies. The *asterisked line* indicates the average rupture rate of all cases.

Comparison With International Studies

Table 3 offers a comparison of our findings and those of the ISUIA[11,12] and the systematic review from Europe by Rinkel and colleagues.[22] The ISUIA retrospective and prospective cohorts included significantly more female patients, symptomatic aneurysms, and lesions presenting with SAH than our review did. The retrospective cohort included significantly more cases of large aneurysms but fewer cases in which the lesion was located in the posterior circulation. Compared with our study, the prospective group did not show any differences in these subgroups. The ages of patients who were included could not be compared. The overall rupture rate in the 13 studies we reviewed was significantly higher compared with the rates of both the prospective and retrospective ISUIA cohorts. Our review also showed a higher risk of rupture compared with the review by Rinkel, et al.,[22] whereas the significance was less ($p = 0.02$). Excluding Japanese series from the European study did not change our findings. The European review included more cases of anteriorly located lesions, symptomatic aneurysms, and lesions with SAH.

Discussion

Rupture Rate Associated With UCAs

This systematic review shows that the rupture risk of UCAs observed over time in Japanese institutions is relatively high. Eleven percent of all patients who were included in the articles we reviewed experienced rupture of the aneurysm and the average annual rupture rate was 2.7% (95% CI 2.2–3.3%). An analysis of subgroups by RRs of rupture per 100 patient-years and the OR of cases of rupture versus those of nonrupture showed that significant factors influencing the rupture risk include the size, location, and symptomatic presentation of the aneurysm. Patient sex and age and a history of SAH also affected the risk, but these factors did not reach statistical significance. Papers published in Japanese and papers including fewer cases documented a slightly higher risk of rupture, but no significant difference was recognized. Multiple trials have failed to identify any influence of climate, physical stress, or emotional stress on the rate of SAH.[23] To determine whether there was any influence of climate or environmental stress on the rupture risk of UCAs among Japanese patients, in addition to the geographical location of the institution, we compared studies according to average yearly temperature, the largest difference in the average temperature within a year in the territory of each institution (data extracted from the database of the Japan Meteorological Society, http://www.jma.go.jp/JMA_HP/jma/indexe.html), and the population data (data obtained from the database of the Japan Statistics Bureau, http://www.stat.go.jp/english/index.htm). Japanese people usually seek medical care close to their homes, and thus we assumed that the statistics and climate information of a particular institute reflect the patient's living environment. Our comparison of 12 studies (the 13th was a multicenter study that could not be confined to a single area) revealed no apparent differences in climate or population subgroups. In this review, we could not assess other previously documented risk factors associated with the rupture rate, such as hypertension or smoking. Of note, the prevalence of hypertension or smoking in Japanese adults is not higher than that of the US population.[5,18,21]

By systematically collecting data from case series, we determined the number of patient-years and used that number in our analysis of the data. Although our review showed that there were fewer female patients and fewer patients with SAH or symptomatic aneurysms, overall these characteristics did not significantly differ from those of large cohort studies. The rupture rate documented in our review, however, was significantly higher.[11,12] A comparison with the systemic review by Rinkel, et al.,[22] also showed a difference, but this difference was smaller ($p = 0.02$). Even in the patient group with the least risk (patients with aneurysms < 10 cm), the calculated rupture rate was 1.5% per year in our review (95% CI 1.0–2.15%). In addition, rupture was reported in 11 cases in which the aneurysm was smaller than 7 mm (27.5% of all ruptured cases in the pertinent series).

Race or Bias

To explain the high rupture rate documented in our re-