③事後アンケートの実施

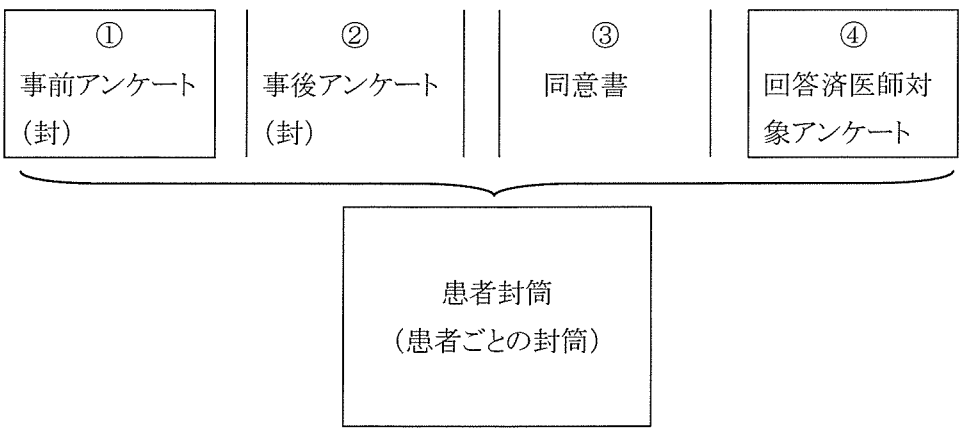
	必要資料
1)事後アンケートを実施する。 ・DVD 終了後すぐその場で、アンケートに回答いただくようにしてください。 ・アンケート前に、DVD に関する質問にはお答えしないようにしてください（アンケート終了後、診察の時にお答えするよう、お伝えください） ・アンケート中、医師やその他の医療スタッフは、もちろん、家族の方も席をはずしていただくようにしてください。 ・時間に制限はありません。回答が終わったら、封筒に入れ、封をしてから、医師または医療スタッフに声をかけるよう、説明してください。 2)診察室へ案内する。 ・封筒に入れた事後アンケートを受け取ってください。	・事後アンケート ・事後アンケート用封筒

④診察

1)診察を行う。 ・基本的には、通常の診察を行ってください。 ・ただし、医師対象アンケートの患者情報の内容については、診察時でご確認ください。 ・DVD 視聴後の感想をお聞きいただき、不明な点や治療に関する不安等がみられましたら、フォローしてください。 ・可能でしたら、気づいた点を医師対象アンケートの最後にお書きください。 **2)図書カードを渡す。** ・最後に、ご協力いただいたお礼とともに、図書カードをお渡しください。	必要資料 医師対象アンケート

⑤医師対象アンケートの回答

1)医師対象アンケートに答える。 ・診察時で確認した患者情報および、診察について、お答えください。 ・このアンケートは患者さんごとにお答えください。 ・可能でしたら、気づいた点を医師対象アンケートの最後にお書きください。 2)患者封筒に入れる。 ・以下の5点の書類をいっしょに患者ごとの「患者封筒」に入れて、封をしてください。 1.回答済事前アンケート（封筒入りのまま） 2.回答済事後アンケート（封筒入りのまま） 3.同意書 （※同意いただけなかった場合も、白紙のままで、返却ください） 4.回答済医師対象アンケート	必要資料 ・医師対象アンケート



注意：同意が得られた後、何らかの理由で研究協力を辞退された場合は、同意書と医師対象アンケートのみご返送ください。そして、医師対象アンケートに、「途中辞退」と明記ください。

⑥研究実施者へ返送

1)患者封筒を返送用封筒に入れる。 ・12 月末までに実施した全ての患者さんのアンケート等をいっしょに返送ください。	必要資料 ・返送用封筒 ・アンケート等が入った患者封筒
2)実施した患者人数等を記入する用紙といっしょを入れる。	・返送用メモ
3)封をして、研究実施者へ返送する。 返送先： 京都大学大学院医学研究科脳統御医科学系専攻 脳病態生理学講座脳神経外科学 〒606-8507 京都市左京区聖護院川原町 54 TEL:075-751-3653　FAX:075-771-6415 担当者：野崎和彦 提出期限：　**2006 年 1 月末　必着**	

DVD「未破裂動脈瘤の治療方針」送付とアンケート御協力のお願い

日本脳神経外科学会教育訓練施設長殿

拝啓

初春の候、各先生方におかれましては御清栄のことと存じます。さて、平成16年度より、厚生労働科学研究費補助金循環器疾患等総合研究事業からの援助をいただき、「未破裂脳動脈瘤の要因、治療法選択におけるリスク・コミュニケーションに関する研究」を行なっております。本研究では、未破裂動脈瘤の患者と医療者の間で情報を共有した上で治療方針を決定するShared decision makingを目指し、意思決定に役立つ意思決定支援ツールの開発を目指しています。その成果の1つとしてDVD「未破裂脳動脈瘤の治療方針」を作成させていただきました。このDVDは、これから未破裂脳動脈瘤の治療を考える患者のための情報提供として、1)未破裂動脈瘤の説明、2)未破裂動脈瘤の治療法の説明（開頭術、血管内手術、経過観察）、3)症例を掲載しております（全体で約18分）。

今後、このDVDについて意思決定支援ツールとしての検証を行っていきたいと考えております。この研究事業のために先生方のご意見をお聞かせいただきたいと存じます。お忙しいとは存じますが、是非、同封のDVDをご御覧いただき、アンケートに御協力いただき、FAX（075-771-6415）にて御返送いただければ幸甚でございます。なおDVDは貴院に寄贈させていただきますので、宜しければ臨床にお役立てください。また、追加購入を希望される場合は原価にて配付させていただきます。

先生方の忌憚のないご意見をお待ちしております。アンケートは、できましたら2月末までに御返送いただければ有難く存じます。何卒よろしくお願い致します。

敬具

平成19年1月吉日

厚生労働科学研究費補助金循環器疾患等総合研究事業
「未破裂脳動脈瘤の要因、治療法選択における
リスク・コミュニケーションに関する研究」
主任研究者　橋本信夫

問合せ先：
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担当者：野崎和彦（E-mail:noz@kuhp.kyoto-u.ac.jp）

DVD「未破裂動脈瘤の治療方針」についてのアンケート

①最初から最後まで通して見た
②通してではないが、チャプターごと全て見た
③あるチャプターだけ見た（チャプター名　　）

1. DVD の映像は全てご覧になりましたか。

2. もし、この DVD を患者に見ていただくとすると、どのような患者でしょうか。

①初めて診察する前の患者（DVD の中の患者と同じシチュエーション）
②既に通院している、ある程度説明を行なった患者
③その他
〔　　〕

3. DVD の内容を患者はどれぐらい理解できると思いましたか。

①DVD の説明で十分わかる
②わかると思うが、視聴後、わからないところはなかったか、フォローする方がいいと思う
③わかりにくい点が多い
〔わかりにくい点：　　〕

4. もし、この DVD を患者に見せるとすると、どのような状況で見せますか。

①診察前に見てもらう（待合室や家で）
②診察室でいっしょに見る
③その他（　　）

5. その他、この DVD を患者に見せる場合に関して、注意点などご意見をお聞かせください。

6．追加 DVD 購入希望

なし　　あり　（　　枚）（申し訳ございませんが単価は実費分 500 円です）

さしつかえなければ御記入ください。
貴施設名：　　御本人氏名：
連絡先　：

アンケートの返信先：　FAX　075-771-6415（京都大学医学部脳神経外科）

研究成果の刊行に関する一覧表

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Volume 35, Number 11, November 2004
ISSN 0039-2499
http://stroke.ahajournals.org

American Stroke Association
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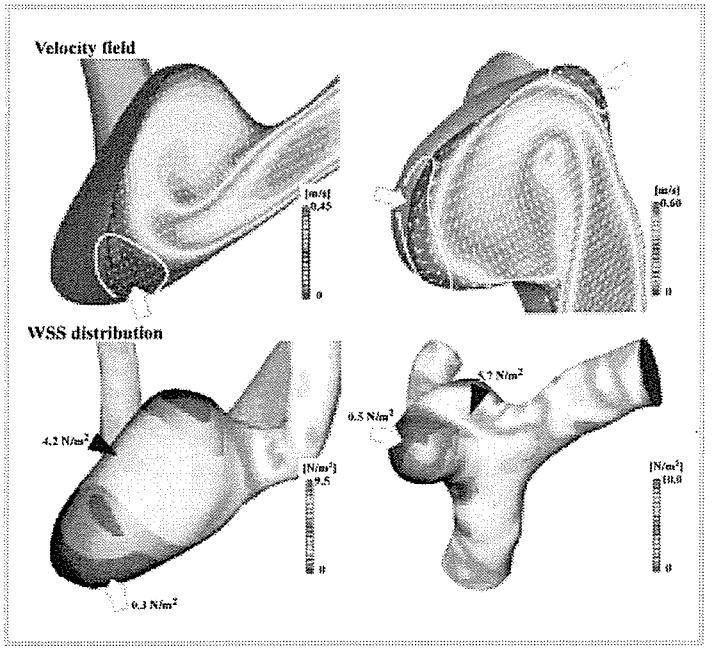

Low Wall Shear Stress May Trigger the Rupture of Cerebral Aneurysms

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

Masaaki Shojima, MD; Marie Oshima, PhD; Kiyoshi Takagi, MD, PhD; Ryo Torii, PhD; Kazuya Nagata, MD, PhD; Ichiro Shirouzu, MD, PhD; Akio Morita, MD, PhD; Takaaki Kirino, MD, PhD

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

Received April 10, 2005; accepted June 28, 2005.

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***Stroke* is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000177877.88925.06**

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 $\approx$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

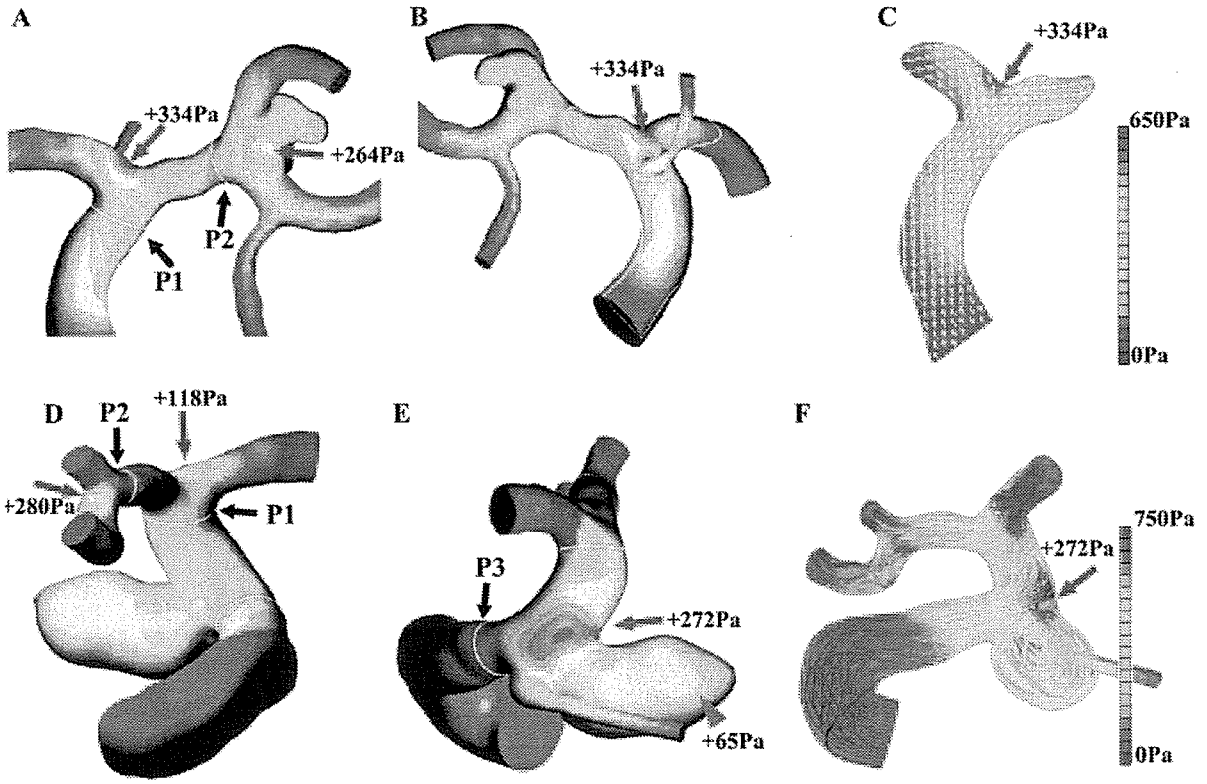

Figure 1. Local pressure elevation in the lumen. Pressure distributions of 2 ruptured aneurysms are presented with colored contour. Bifurcation aneurysm at MCA (A through C) and sidewall aneurysm at ICA posterior communicating artery (D through F). A, Anterior view. Local pressure elevation is easily 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

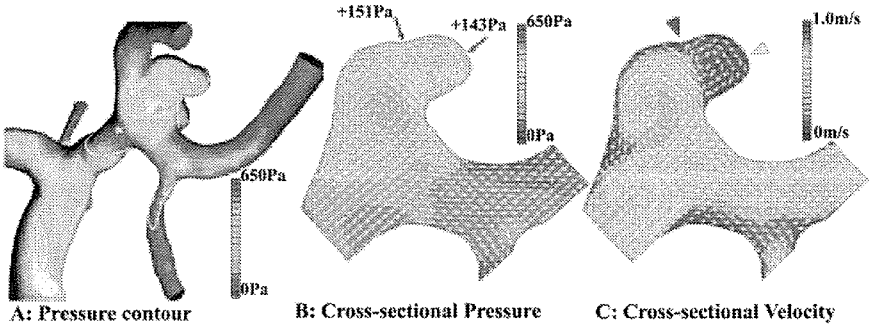

Figure 2. Local pressure elevation in the aneurysm. Same case shown in Figure 1A through 1C. A, Pressure distribution on the vessel wall. The impact of parent artery bloodstream resulted in the local pressure elevation near the orifice of the left MCA aneurysm (red asterisk). Pressure was also high at 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-

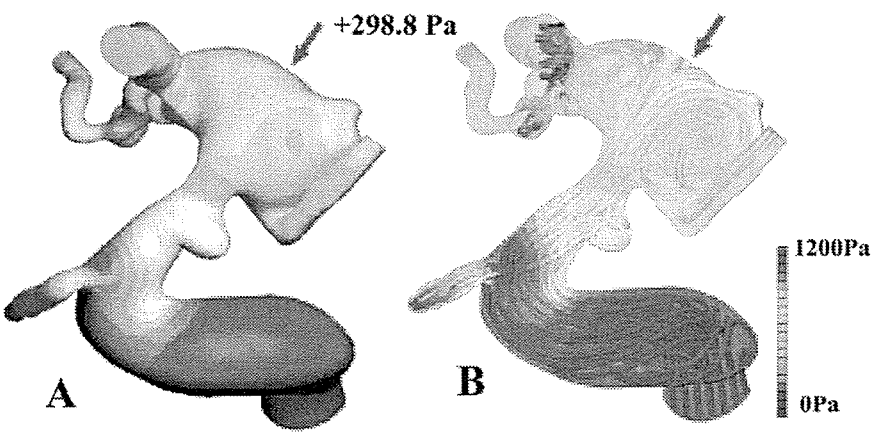

Figure 3. Direct flow impact on the aneurysm. Pressure distribution of right ICA aneurysms are presented with colored contour. The larger aneurysm is ruptured, whereas the smaller aneurysm is unruptured. A, Local pressure at the site of flow impact (red arrow) is 298.8 Pa. B, Fusion image of the streamline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

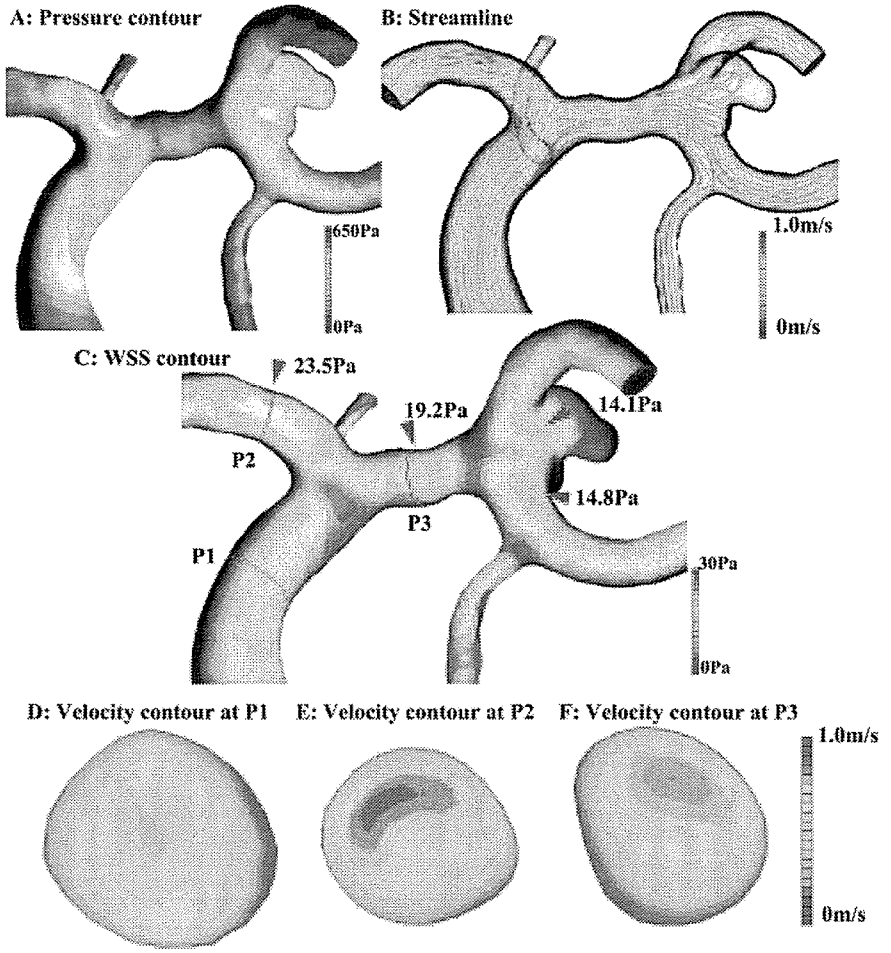

Figure 4. Appearance of local pressure elevation and high WSS after the impact of the bloodstream. Same case shown in Figure 1A through 1C. A, Pressure distribution. B, Streamline colored with the magnitude of velocity. The shift of high-velocity flux outward after the flow impact at the bifurcation 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.

Acknowledgments

The authors thank Chikayuki Ochiai MD, PhD, director of Kanto Medical Center NTT EC, for his constructive criticisms and helpful advice on the accomplishment of this article.

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See the corresponding article in this issue, pp 601–606.

J Neurosurg 102:593–596, 2005

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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See the corresponding article in this issue, pp 601–606.

J Neurosurg 102:597–598, 2005

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-