Cardiac Cycle-Related Volume Change in Unruptured Cerebral Aneurysms
A Detailed Volume Quantification Study Using 4-Dimensional CT Angiography

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Background and Purpose—The hemodynamic factors of aneurysms were recently evaluated using computational fluid dynamics in a static vessel model in an effort to understand the mechanisms of initiation and rupture of aneurysms. However, few reports have evaluated the dynamic wall motion of aneurysms due to the cardiac cycle. The objective of this study was to quantify cardiac cycle-related volume changes in aneurysms using 4-dimensional CT angiography.

Methods—Four-dimensional CT angiography was performed in 18 patients. Image data of 1 cardiac cycle were divided into 10 phases and the volume of the aneurysm was then quantified in each phase. These data were also compared with intracranial vessels of normal appearance.

Results—The observed cardiac cycle-related volume changes were in good agreement with the sizes of the aneurysms and normal vessels. The cardiac cycle-related volume changes of the intracranial aneurysms and intracranial normal arteries were 5.40%/H110064.17%/H11006 and 4.20%/H110062.04%/H11006, respectively, but these did not differ statistically (P=0.12).

Conclusions—We successfully quantified the volume change in intracranial aneurysms and intracranial normal arteries in human subjects. The data may indicate that cardiac cycle-related volume changes do not differ between unruptured aneurysms and normal intracranial arteries, suggesting that the global integrity of an unruptured aneurysmal wall is not different from that of normal intracranial arteries. (Stroke. 2012;43:61-66.)

Key Words: 4DCTA ■ intracranial aneurysm ■ quantification of volume change

Incidental discovery of unruptured cerebral aneurysms is now common, partially due to the prevalence of MR angiography for screening intracranial abnormalities in daily clinical settings. The rate of rupture of these aneurysms is reported to be 0.3% to 4.0% per year1–7 and appropriate management is required. Risk assessment of future rupture leading to subarachnoid hemorrhage is important in the decision to intervene with these unruptured aneurysms. To date, the reported risk factors for rupture of cerebral aneurysms are size, location, hypertension, and history of smoking.5,7–9

To further evaluate the risks and theoretical foundations of rupture of unruptured aneurysms, the hemodynamic factors of aneurysms were recently evaluated in detail using computational fluid dynamics and electrocardiographic gated CT angiography. In addition, studies have also examined the use of 4-dimensional CT angiography (4DCTA) to detect aneurysm blebs to predict the rupture point.10–12

However, most previous reports have focused only on the static morphological characteristics of the aneurysm, and few have attempted to evaluate the dynamic shape or volume changes of an aneurysm caused by arterial pulsed pressure caused by the heartbeat. The aneurysm is stretched in each cardiac cycle, and understanding the magnitude of this change is thus crucial to understand the hemodynamics involved in cerebral aneurysms. Thus, we quantified the volume changes caused by the cardiac cycle in unruptured cerebral aneurysms using 320 multidetector 4DCTA.

Materials and Methods

Clinical Materials
Twenty-two unruptured cerebral aneurysms from 18 patients were analyzed by 4DCTA as preoperative assessment. Five aneurysms were located at the internal carotid artery, 8 at the middle cerebral artery, 3 at the anterior communicating artery, 5 at the anterior cerebral artery, and 1 at the basilar artery. The local ethics committee approved the use of the clinical data for research and waived the
Table 1. Patient Profiles

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, Y</th>
<th>Sex</th>
<th>Location</th>
<th>Size, mm</th>
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<tr>
<td>2</td>
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<td>ACOM</td>
<td>3.96×4.64×4.34</td>
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<tr>
<td>3</td>
<td>55</td>
<td>F</td>
<td>ICA</td>
<td>10.71×9.43×7.98</td>
</tr>
<tr>
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<td>70</td>
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<td>MCA</td>
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<tr>
<td>5</td>
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<td>F</td>
<td>ICA</td>
<td>3.23×3.75×3.5</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>F</td>
<td>ACA</td>
<td>7.23×7.60×7.41</td>
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<tr>
<td>7</td>
<td>69</td>
<td>F</td>
<td>ACA</td>
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<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>ACA</td>
<td>16.10×13.58×15.61</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>F</td>
<td>ICA</td>
<td>5.96×4.05×2.83</td>
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<tr>
<td>10</td>
<td>76</td>
<td>F</td>
<td>MCA</td>
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<td>11</td>
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<td>F</td>
<td>ICA</td>
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<tr>
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<td>MCA</td>
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<td>18</td>
<td>62</td>
<td>M</td>
<td>ICA</td>
<td>3.39×3.66×3.88</td>
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</table>

M indicates male; F, female; MCA, middle cerebral artery; ACOM, anterior communicating artery; ICA, internal carotid artery; ACA, anterior cerebral artery; BA, basilar artery.

requirement for written informed consent from patients. Detailed patient data are listed in Table 1.

4DCTA Acquisition
Electrocardiography-triggered CT angiography was performed on a 320-detector CT system (Aquilion ONE; Toshiba, Nasu, Japan) using the following parameters: 120-kV tube voltage, 270-mA tube current, 350-ms gantry rotation time, 140-mm range, and 1 heartbeat. Contrast medium (Optiray 320 mgI/mL; Comedion Japan, Tokyo, Japan) was injected at a 5-mL/s infusion rate. After the test injection with 15 mL of contrast medium, the actual scanning was started at the appropriate time according to the test injection. For the actual scanning, 50 mL of contrast medium was used. Images for this study were reconstructed using a kernel optimized for intracranial vessel imaging (window center, each 10% of the R-R interval; image matrix, 512×512; pixel interval 0.25 mm or 0.5 mm). Thus, 10 CT volume data sets were created for each patient. All of the CT data sets were transferred to an offline workstation and further analyzed by an in-house program developed using Matlab (MathWorks, Natick, MA) as detailed subsequently (Figure 1A).

Analysis of Cardiac Cycle-Related Volume Changes in Cerebral Aneurysms and Normal Cerebral Vessels
First, the cerebral arteries were identified in the raw CT data by adjusting the window and level values from 110 to 890. For deletion of brain tissues and most of the bone structures at the same time as retaining the signals from the contrast medium, window and level values <110 and >890 were substituted for 0. Next, a value of 1 was substituted for the voxels with vessels or bones, and 0 was substituted for those without. As a result, the original row CT data of each phase was converted into a 512×512×640 or 512×512×570 matrix (Figure 1B). Next, to evaluate the volume change in an aneurysm caused by the heartbeat, the dome of the aneurysm, not including the parent artery, was selected as 3-dimensional voxels of interest (Figures 1C and 2A). The volume of the aneurysm was then estimated in each phase of the cardiac cycle. At the same time, the volumes of normal cerebral arteries were estimated using the same technique for comparison to the aneurysms at the following locations: bifurcation of the middle cerebral artery, the tip of the internal carotid artery, and the tip of the basilar artery. As shown in Figure 1C, the terminal areas of internal carotid artery, middle cerebral artery, and basilar artery, not including the parent artery and vessel trunks, were selected as voxels of interest. Vessels affected by the aneurysms were excluded from analysis. The presented data were obtained by voxel of interest placed by a single operator (J.K.). Interobserver variation was confirmed by analyzing randomly selected 5 aneurysms and 15 normal vessels by an independent operator (M.K.). Interobserver discrepancy was measured to be 11.9±17.6 mm³ in aneurysm and 1.54±3.9 mm³ in normal vessels, which was considered acceptable for further analysis.

Artifact Measurement
Because a rotating x-ray beam can induce artifacts that may impact volume measurement, we measured the volume change in a syringe filled with normal saline as a phantom under the same conditions. We observed a 0.248% volume change during the time equivalent to 1 cardiac cycle (1 second). Therefore, a volume change of <0.248% was considered to indicate an insignificant artifact.

Statistical Analysis
Statistical analysis was performed using Student t test and JMP software (SAS, Cary, NC). One-way analysis of variance was used for 3-group comparison. P<0.05 was considered statistically significant.

Results
The results are summarized in Table 2. The volume changes in an aneurysm and a normal cerebral artery at each phase during 1 cardiac cycle are shown in Figure 2B. Both cases showed waveforms containing 2 peaks resembling an arterial pulse wave.

To quantify the volume change during 1 cardiac cycle, the following parameters were defined. Expansion volume (Ex. volume) was defined as the difference between the maximum and minimum volume of the aneurysm or arterial vessel within the voxel of interest during 1 cardiac cycle. Expansion rate (Ex. rate) was defined as Ex. volume divided by minimum volume, indicating the magnitude of expansion of the aneurysm or the normal arterial vessel.

First we investigated volume changes in normal intracranial arteries due to the cardiac cycle. The minimum volume at each arterial location did not differ (Figure 3A). Moreover, the Ex. rates did not differ significantly between different locations for normal arterial vessels (Figure 3B), confirming our previous findings.

Next, unruptured cerebral aneurysms were analyzed. The Ex. volume of an aneurysm and normal arterial vessel were plotted as a function of minimum volume in Figure 4A, which shows that Ex. volume is in good agreement with the volume of both the aneurysm and the normal arterial vessel itself (R²=0.89 and 0.41, respectively). Bifurcation aneurysms, dilating coaxially against the blood flow of parent arteries, were 13, and side-wall aneurysms, dilating parallel to the blood flow of parent arteries, were 9 among 22 aneurysms. Ex. volume of bifurcation aneurysms and side-wall aneu-
Aneurysms were 30.5±75.2 mm³ and 24.0±18.6 mm³, respectively. There was no significant difference between these 2 groups (P=0.81). Ex. rate of bifurcation aneurysms and side-wall aneurysms were 5.6±3.7% and 5.1±4.5%, respectively, and also not significantly different (P=0.76).

An attempt was made to numerically compare the extent of expansion between aneurysms and normal arterial vessels. As shown in Table 2, Ex. volume of aneurysms and normal vessels were 27.87±60.53 mm³ and 3.10±1.81 mm³, respectively. It was significantly different between aneurysms and normal arterial vessels (P=0.003). However, the mean Ex. rates of aneurysms and normal arteries were 5.40%±4.07% and 4.20%±2.51%, respectively, and were not significantly different (P=0.12; Table 2; Figure 4B). Overall, these results indicate that cardiac cycle-related volume changes do not differ between unruptured aneurysms and normal intracranial arteries.

Discussion

Elucidating the mechanism(s) involved in the initiation, enlargement, and rupture of cerebral aneurysms is crucial for understanding the nature of unruptured cerebral aneurysms. Although the rupture rate of unruptured cerebral aneurysms is reported to be quite low,¹⁻⁷ rupture results in subarachnoid hemorrhage with potentially devastating consequences. In addition to etiologic surveys,²⁻⁷⁻⁹⁻¹⁷ computational simulation of the flow at and around an aneurysm has generated extensive interest as a means to discovering the underlying hemodynamic mechanism(s) that cause physical stress to the aneurysmal wall, possibly resulting in aneurysmal rupture.¹⁸⁻²⁰ Moreover, several studies have evaluated the extent of wall motion of cerebral aneurysms and normal arteries as related to the cardiac cycle.¹⁰⁻¹²⁻¹⁴⁻¹⁶⁻¹⁸⁻²¹⁻²³

After the development of 4DCTA, some studies have performed radiological visualization of the cardiac cycle-related
However, in most of these studies, no quantification of the motion was performed. We previously reported for the first time that quantification of cardiac cycle-related vessel volume change and vessel motion is indeed possible using 4DCTA, a finding confirmed by others. In the present report, we attempted to quantify cardiac cycle-related volume change in normal intracranial arteries and unruptured aneurysms.

Because volume change directly correlates with the extent of wall motion of the object of interest, we speculated that the cardiac cycle-related volume change assessment would approximate the wall motion assessment. As shown in Figure 4B, we did not observe a difference in cardiac cycle-related volume changes rates between unruptured cerebral aneurysms and normal intracranial arteries. On the other hand, Oubel et al reported that the extent of wall motion of ruptured aneurysms has a higher value than that of unruptured aneu-

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**Figure 2.** VOI selection and volume change quantification of case No. 6, a basilar artery aneurysm. A. The VOI for aneurysm analysis is illustrated. The aneurysmal dome, not including the parent artery, was identified by axial, sagittal, and coronal images and chosen as the VOI for analysis. B. Volume changes in the aneurysm (basilar artery aneurysm) and the normal artery (the tip of the left ICA) during 1 cardiac cycle are presented (Patient 6). Both waveforms resemble an arterial pulse wave. Most of the cases presented a similar wave pattern, suggesting that volume changes in both aneurysms and normal arterial vessels are governed by the cardiac cycle. VOI indicates voxel of interest; ICA, internal carotid artery.
rysms, an estimation made using digital subtraction angiography. However, the values used for comparison in their report did not take into consideration the volume of the aneurysm itself. As can be seen in Figure 4A, the volume of both the aneurysm and normal arterial vessel strictly governs the amount of cardiac cycle-related volume change. This observation suggests the need to compensate the cardiac cycle-related volume change or wall motion by the actual volume of the object of interest. The observed slight difference in the correlation of the volume and the amount of cardiac cycle-related volume change between normal vessels and aneurysm should be mentioned (Figure 4A). One possible explanation could be that large aneurysms were compressed by the surrounding tissue such as the brain, leading to a relatively smaller amount of cardiac cycle-related volume change considering its minimum volume.

It should also be noted that this is the first study attempting to accurately quantify cardiac cycle-related volume changes in cerebral aneurysms or normal cerebral arteries. Meyers et al previously reported the quantification of aneurysm volume changes with phase-contrast MR angiography. In their report, the ruptured and unruptured intracranial aneurysms demonstrated a 51%±10% and 17.6%±8.9% increase in volume during 1 cardiac cycle, which is markedly different from the present result (5.40%±4.07%). One of the major reasons for this difference is that they estimated the volume of the aneurysm using 2-dimensional images assuming a spherical shape for the aneurysm, although an aneurysm has an irregular shape in situ. Another reason for the discrepancy between the 2 findings is the different modalities used in the 2 studies. In phase-contrast MR angiography, the complex pulsatile flow into the aneurysm causes absence of signal, possibly resulting in overestimation.

Our investigation failing to find a difference in cardiac cycle-related volume changes between aneurysms and normal arterial vessels may suggest that the global integrity of the aneurysmal wall is not different from that of normal vessels. If aneurysmal walls are compromised by stretching forces, then the expansion rate would be larger than that of normal vessels. However, the presented analysis was unable to reflect microlevel wall motion differences, and thus visualization or quantification of aneurysmal wall motion at a more detailed level is required to identify locations at risk of future aneurysmal rupture. For instance, it is necessary to conduct long-term follow-ups for those aneurysms presenting a high Ex. rate in Figure 4B to elucidate if high Ex. rate would indicate high risk for future rupture. Moreover, further analysis of ruptured aneurysms is required to examine the comprehensiveness of our findings. Finally, incorporation of the cardiac cycle-related volume changes in aneurysms into

<table>
<thead>
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<th>Table 2. Expansion Volume and Rate</th>
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<td>Aneurysm</td>
</tr>
<tr>
<td>No. of lesions analyzed</td>
</tr>
<tr>
<td>Expansion volume, mm³</td>
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<tr>
<td>Expansion rate, %</td>
</tr>
</tbody>
</table>

Data are presented as mean±standard deviation.

Figure 4. Relationship between the expansion volume and the minimum volume of the cerebral aneurysms and the normal cerebral arteries. A, The R value of the aneurysms and normal arteries were 0.89 and 0.41, respectively. B, Expansion rates of aneurysms and normal vessels are presented. Data represent mean±SD. The difference was not statistically significant.
computational fluid dynamics is necessary to understand the impact of cardiac cycle-related wall motion in the physics of the fluid dynamics of aneurysms.

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Disclosures
None.

References
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背景および目的: 動脈瘤の発生および破裂の機序を理解する努力の中で, 静的血管モデルで数値流体力学を用いた動脈瘤の血行力学的要因の評価が最近行われている。しかし, 心周期に起因する動脈瘤の動的壁運動を評価した報告はほとんどない。本研究の目的は, 四次元 CT 血管造影法を用いて心周期に関連した動脈瘤の容積変化を定量することである。

方法: 18 例の患者を対象として四次元 CT 血管造影を行った。1 心周期の画像データを 10 相に分割し, 各相の動脈瘤の容積を定量化した。また, これらのデータを正常な外見をもつ頭蓋内血管と比較した。

結果: 観察された心周期に関連した容積変化は, 动脈瘤および正常血管のサイズとよく一致していた。頭蓋内動脈瘤および頭蓋内正常動脈の心周期に関連した容積変化はそれぞれ 5.40 ± 4.17%および 4.20 ± 2.04%であったが, これらに統計学的有意差は認められなかった (p = 0.12)。

結論: ヒト被験者における頭蓋内動脈瘤および頭蓋内正常動脈の容積変化の定量に成功した。データは, 未破裂の動脈瘤と正常な頭蓋内動脈の間で心周期に関連した容積変化に差はないことを示していると思われ, 未破裂動脈瘤壁の全体的な健全性は正常な頭蓋内動脈と差がないことが示唆される。

Stroke 2012; 43: 61-66