Impact of Cerebral Microcirculatory Changes on Cerebral Blood Flow During Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

Hiroki Ohkuma, MD; Hiroshi Manabe, MD; Masahiko Tanaka, MD; Shigeharu Suzuki, MD

Background and Purpose—Cerebral microcirculatory changes during cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH) are still controversial and uncertain. The aim of this study was to investigate the changes of cerebral microcirculation during cerebral vasospasm and to clarify the roles of microcirculatory disturbances in cerebral ischemia by measuring cerebral circulation time (CCT) and regional cerebral blood flow (rCBF).

Methods—In 24 cases with aneurysmal SAH, rCBF studies by single-photon emission CT and digital subtraction angiography (DSA) were performed on the same day between 5 and 7 days after SAH and/or within 4 hours after the onset of delayed ischemic neurological deficits. CCT was obtained by analyzing the time-density curve of the contrast media on DSA images and was divided into proximal CCT, which was the circulation time through the extraparenchymal large arteries, and peripheral CCT, which was the circulation time through the intraparenchymal small vessels. They were analyzed in association with rCBF and angiographic vasospasm.

Results—Severe angiographic vasospasm statistically decreased rCBF, and correlation between the degree of angiographic vasospasm and rCBF was seen (\(r = 0.429, P = 0.0006\)). Peripheral CCT showed strong inverse correlation with rCBF (\(r = -0.767, P < 0.0001\)). Even in none/mild or moderate angiographic vasospasm, prolonged peripheral CCT was clearly associated with decreased rCBF.

Conclusions—In addition to the marked luminal narrowing of large arteries detected as severe angiographic vasospasm, microcirculatory changes detected as prolonged peripheral CCT affected cerebral ischemia during cerebral vasospasm. These results suggested that impaired autoregulatory vasodilation or decreased luminal caliber in intraparenchymal vessels may take part in cerebral ischemia during cerebral vasospasm. (Stroke. 2000;31:1621-1627.)

Key Words: cerebral aneurysm • microcirculation • subarachnoid hemorrhage • vasospasm

Cerebral vasospasm associated with aneurysmal subarachnoid hemorrhage (SAH), which is angiographically characterized as the persistent luminal narrowing of the major extraparenchymal cerebral arteries, affects cerebral microcirculation and causes decreased cerebral blood flow (CBF) and delayed ischemic neurological deficits (DIND). Microcirculatory changes after SAH have been investigated, especially in association with autoregulation of CBF. Several reports have indicated that autoregulation is impaired during vasospasm, since autoregulatory response to the changes of PaCO₂ or acetazolamide administration is reduced, and CBF is vulnerable to change by the changes of systemic arterial blood pressure. The weak response to the PaCO₂ or acetazolamide administration has been attributed to maximal dilation in the peripheral arterioles in an attempt to maintain sufficient CBF in the face of decreased cerebral perfusion pressure (CPP) due to vasospasm. Increased cerebral blood volume (CBV) after SAH detected by positron emission tomography (PET) or the radioisotope tracer method could explain this maximal dilation of peripheral arterioles.

Contrary to this, however, recent PET studies have shown decreased CBV during cerebral vasospasm, which suggests that the appropriate vasodilating capacity of distal vessels in response to reductions in local CPP is impaired after SAH. Furthermore, recent histopathological studies have revealed that intraparenchymal small arteries or arterioles show luminal narrowing rather than dilation during cerebral vasospasm after experimental SAH. Therefore, the changes of microcirculation, especially whether microcirculatory vessels dilate or not during vasospasm, are controversial and still uncertain. CBV measured by PET has been used clinically for estimating the changes of microcirculatory blood volume; however, it is difficult to determine which type of peripheral vessels of arterioles, capillaries, and venules plays a main part in the changes of CBV. Furthermore, PET is not feasible for routine clinical use. Therefore, another method for evaluating microcirculatory changes should be introduced. Cerebral microcirculation is regulated by cerebral circulation time (CCT), regional CBV...
(rCBV), and regional CBF (rCBF). Recently, CCT can be easily measured by analyzing the time-density curve of the contrast media on digital subtraction angiography (DSA), and we considered that microcirculatory changes during vasospasm could be estimated by evaluating CCT on DSA images.

The aim of this study was 2-fold: (1) to investigate microcirculatory changes during cerebral vasospasm by measuring CCT on DSA and comparing it with angiographic vasospasm, rCBF measured on single-photon emission CT (SPECT), and DIND; and (2) to test whether CCT can be a new technique of assessing vasospasm.

Subjects and Methods

Subjects

SAH Patients

During a period of 2 years from April 1994 to March 1996, 78 consecutive patients with aneurysmal SAH, whose diagnosis was confirmed by CT scan and cerebral angiography, were admitted to our institute and underwent aneurysm surgery within 48 hours after the onset of SAH. Five to 7 days after SAH, \[^{123}\text{I}]\text{IMP}\ SPECT and DSA were routinely performed within a 1-hour interval on the same day, as described later, to start prophylactic-induced hypertension on the basis of the angiographic findings before DIND occurred. Prophylactic-induced hypertension was achieved by maintaining mean arterial blood pressure between 105 and 120 mm Hg. In addition to these routine examinations, if DIND occurred, \[^{123}\text{I}]\text{IMP}\ SPECT followed by DSA were performed again within 4 hours after the onset of DIND, and, if necessary, intra-arterial injection of papaverine was performed. In the cases with papaverine infusion, SPECT and angiographic data were collected before papaverine infusion. The patients were considered to have DIND due to vasospasm when a focal neurological deficit or deterioration in level of consciousness was seen and other possible causes of deterioration, such as rebleeding, hydrocephalus, surgical complication, electrolyte disorder, infection, or seizure, were excluded.

Of 78 patients, the 24 patients who fulfilled the following criteria were included as the subjects of this study (Table 1): (1) CT scan on admission showed group 3 in Fisher classification; (2) intracranial pressure was controlled by ventricular drainage or lumbar drainage, which was placed during aneurysm surgery or within 3 days after SAH and was established to allow for cerebrospinal fluid outflow at 10 mm Hg above ear level until 14 days; (3) age was younger than 70 years; (4) no brain damage was caused during aneurysm surgery, and no temporary clipping was used during aneurysm surgery; (5) atherosclerotic stenosis was not seen in either the cervical carotid artery or in the intracranial large arteries on preoperative initial angiography; (6) hematocrit was confirmed to be within normal range on the day of the examination; (7) arterial pH value, partial pressure of oxygen in arterial blood, and PaCO\(_2\) were confirmed to be within the physiological range during the examination; and (8) mean arterial blood pressure during the examination was maintained between 105 and 120 mm Hg. In the cases who underwent prophy-

<table>
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<th>GOS at 3 Months</th>
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<td>ACoA aneurysm</td>
<td>II</td>
<td>+9 (10)</td>
<td>SD</td>
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MCA indicates middle cerebral artery; GOS, Glasgow Outcome Scale; ACoA, anterior communicating artery; ICA, internal carotid artery; R, right; L, left; GR, good recovery; MD, moderately disabled; and SD, severely disabled.
lactic-induced hypertension based on the findings of the routine angiography and received the repeated examination because of the onset of DIND, mean arterial blood pressure was also maintained between 105 and 120 mm Hg during the repeated examination.

In these 24 patients, angiographic vasospasm and CCT measured on DSA and rCBF measured on SPECT were comparatively evaluated, as will be described. In this study, the evaluation was focused on the territory of the middle cerebral artery, since evaluation of CCT in the anterior cerebral artery is difficult because of variable dominance of each side of the internal carotid artery, and evaluation of rCBF in the cortical territory of the anterior cerebral artery is also difficult because of ambiguous distinction of both frontal lobes along interhemispheric fissure on SPECT images. To evaluate the influences of surgery, such as brain retraction, on rCBF, SPECT study in the routine examination was used for comparison of rCBF on the operation side with that on the opposite side in cases with internal carotid artery aneurysm or middle cerebral artery aneurysm, since anterior communicating artery aneurysm was operated by the interhemispheric approach.

**Normal Controls**

Nineteen cases with unruptured cerebral aneurysms aged between 36 and 70 years, who underwent DSA and $^{[123]}$IIMP SPECT and in whom DSA showed no stenotic lesions of either the cervical carotid artery or the intracranial large arteries, were selected as normal controls. CCT and rCBF were measured in the same manner. To evaluate and compare the values obtained in relation to age, the cases were divided by age into 3 groups: age younger than 50 years ($n=7$), age from 51 to 60 years ($n=6$), and age from 61 to 70 years ($n=6$).

The study was approved by the local ethics committee, and all patients in both the SAH group and the control group gave informed and written consent to participate.

**Digital Subtraction Angiography**

A 5F selective catheter was inserted via the femoral artery into each internal carotid artery, and its tip was set at the level of the second cervical vertebra. Six milliliters of the contrast agent was injected into the internal carotid artery at 4 mL/s by autoinjector. Images were obtained at a rate of 6 frames per second with the use of a DSA unit (Advantx, GE Medical Systems) with a pixel matrix of $512 \times 512$, and the DSA images were stored in the computer system (Macintosh, Apple Computer Inc).

The degree of angiographic vasospasm was evaluated by comparing preoperative angiographic lumen caliber with the lumen caliber on postoperative routine angiography or on the angiography taken in the event of onset of DIND. The horizontal portion of the middle cerebral artery ($M_h$) was divided into 4 equal-length portions on the images of anteroposterior projection; the internal carotid artery between the origin of the ophthalmic artery and the internal carotid artery bifurcation was divided into 3 equal-length portions on the images of lateral projection. The diameters at the midpoint of each of these divided portions were measured on the computer with the use of the National Institutes of Health image analysis system. If the diameters of each portion on the preoperative angiography are designated $a$, $b$, $c$, $d$, $e$, $f$, and $g$, and the diameters of the same portion on the following angiography are designated $h$, $i$, $j$, $k$, $l$, $m$, and $n$, the percentage of arterial diameter can be calculated as $(h/a+j/b+j/c+ k/d+l/e+m/f+n/g)/7 \times 100\%$. To test the interobserver variability in the measurement of arterial diameter, 2 observers (H.O. and M.T.) independently measured the arterial diameters in all angiograms available in this study by the same manner as described above, which revealed very strong correlation between 2 measures ($r=0.996$, $P<0.0001$ by the Spearman rank correlation coefficient). The degree of angiographic vasospasm was defined as follows: a reduction in arterial diameter $>50\%$ was categorized as the severe vasospasm group, a reduction between 25% and 50% was categorized as the moderate vasospasm group, and a reduction of $<25\%$ was categorized as the none or mild vasospasm group.

To estimate the CCT, the regions of interest (ROI) were set in the vertical intracavernous portion of the internal carotid artery ($C_i$), the cortical segment of the rolandic artery ($M_r$), and the rolandic vein ($V_r$) on the images of lateral projection. B, Time-density curve of the contrast media in each ROI.

![Figure 1](image)

Figure 1. Measurement of CCT. A, ROIs were set in the vertical intracavernous portion of the internal carotid artery ($C_i$), the cortical segment of the rolandic artery ($M_r$), and the rolandic vein ($V_r$) on the images of lateral projection. B, Time-density curve of the contrast media in each ROI.

[(V_r) on the images of lateral projection (Figure 1A). The time-density curve of the contrast media in each ROI was obtained from the series of DSA images (Figure 1B). The time-density curve was fitted to a gamma variate function by the least-squares method and mean transit time (MTT) in each ROI was determined as $\frac{(0->t)\cdot Cu \cdot (0->t)\cdot C}{(0->t)\cdot Cu \cdot (0->t)\cdot C}$, where $C$ is the quantity of contrast medium remaining at the site and $t$ is the time after the contrast media is injected. Overall CCT was defined as the the difference between MTT in $C_i$ and MTT in $V_r$, and it was divided into proximal CCT, which was the circulation time in the extraparenchymal large arteries and was defined as the difference between MTT in $C_i$ and MTT in $M_r$, and peripheral CCT, which was the circulation time in the intraparenchymal small vessels and was defined as the difference between MTT in $M_r$ and MTT in $V_r$.

**$^{[123]}$IIMP SPECT**

The rCBF was estimated by the $^{[123]}$IIMP autoradiographic (ARG) method. We used a rotating-type gamma camera (Starcam...
4000XR/T, GE Medical Systems) with a low-energy and high-resolution type collimator, of which full width at half maximum was 8.1 mm. Thirty minutes after the intravenous injection of 222 MBq [123I]IMP, data acquisition was started for a scan duration of 20 minutes so that the midscan time was 40 minutes. Three milliliters of arterial blood was taken from the brachial artery 10 minutes after IMP administration, and the whole-blood radioactivity was measured with a well counter cross-calibrated with SPECT. Assumed distribution volume of IMP for the ARG method was determined by comparing the rCBF obtained by the table look-up method with that obtained from the midline.

Figure 2. Method of setting ROI on SPECT images. Left, On the DSA images of lateral projection, the portion of the rolandic artery (C) was measured. Right, a ROI consisting of 15×30 mm along the cerebral cortex was drawn around the rolandic artery on the 2 consecutive slices (a and b) 20 to 30 mm above the slice showing the foramina of Monro so that the rolandic artery (C) became the cortical center of this ROI. OM indicates orbitomeatal.

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**Statistical Analysis**

In the SAH group, the Spearman rank correlation coefficient was used to calculate correlation between angiographic vasospasm and CCT, correlation between angiographic vasospasm and rCBF, and correlation between CCT and rCBF. The Mann-Whitney U test was used to calculate (1) comparison of CCT and rCBF among the 3 different age groups in the control group, (2) comparison of CCT and rCBF between the control group and the SAH group, (3) comparison of rCBF between the operation side and the opposite side, (4) comparison of the data among the none/mild vasospasm group, moderate vasospasm group, and severe vasospasm group, and (5) comparison of rCBF in the frontal and the parieto-occipital cortex between patients with symptomatic vasospasm and patients without symptomatic vasospasm. Significance was assigned at \( P<0.05 \).

**Results**

**Control Subjects**

Mean±SD values of proximal CCT, peripheral CCT, and rCBF in the control group are shown in Table 2. There were no statistically significant differences of proximal CCT, peripheral CCT, and rCBF among the 3 different age groups.

**Comparison Between Control Group and SAH Group**

Mean±SD values of proximal CCT, peripheral CCT, and rCBF in the SAH group were 1.22±0.36 seconds, 3.36±0.68 seconds, and 35.3±7.0 mL/100 g per minute. Compared with the control group, statistically significant differences were seen in peripheral CCT and rCBF (\( P<0.05 \)).

**SAH Patients**

In 24 patients with SAH, 8 cases showed symptomatic vasospasm. Of these 8 cases, 7 cases (cases 17 and 19 to 24 in Table 1) showed symptomatic vasospasm 2 to 4 days after the routine examinations and underwent repeated examinations within 4 hours after the onset of symptomatic vasospasm, and 1 case (case 18 in Table 1) showed DIND on day 5 before the routine examination was performed and underwent IMP SPECT and DSA on that day. Therefore, overall, examinations were performed 31 times, and 62 sides were obtained for this study. Of 8 cases with symptomatic vasospasm, 4 cases with severe angiographic vasospasm received intra-arterial papaverine injection during angiography. Mean±SD value of PaCO\(_2\) during the examinations was 39.8±2.6 mm Hg, and that of mean arterial blood pressure during the examinations was 113.4±5.2 mm Hg.

**Influence of Surgery on rCBF**

Mean±SD value of rCBF on the operation side was 35.0±6.9 mL/100 g per minute, and that on the opposite side was 36.4±5.2 mL/100 g per minute. There was no statistically significant difference between them.

**Angiographic Vasospasm and CCT**

Arterial diameter correlated well with proximal CCT (\( r=0.681, P<0.0001 \)) (Figure 3); however, there was no

![Figure 2](http://stroke.ahajournals.org/)

![Figure 3](http://stroke.ahajournals.org/)

**Table 2. Data in Control Group**

<table>
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<th>Age, y</th>
<th>n</th>
<th>Proximal CCT, s</th>
<th>Peripheral CCT, s</th>
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<tr>
<td>Total cases</td>
<td>19</td>
<td>1.36±0.35</td>
<td>2.99±0.51</td>
<td>40.5±7.0</td>
</tr>
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</table>
correlation between arterial diameter and peripheral CCT ($r = -0.310, P = 0.0150$).

**Angiographic Vasospasm and rCBF**

In the severe angiographic vasospasm group, rCBF statistically decreased compared with that in the moderate vasospasm group ($P < 0.05$) and none/mild vasospasm group ($P < 0.01$) (Figure 4A). However, there was no statistical difference between the moderate vasospasm group and none/mild vasospasm group. Overall, there was correlation between arterial diameter and rCBF ($r = 0.429, P = 0.0006$) (Figure 4B).

**CCT and rCBF**

Overall, CCT showed inverse correlation with rCBF ($r = -0.582, P < 0.0001$). In every angiographic vasospasm, overall CCT showed inverse correlation with rCBF ($r = -0.548, P = 0.0019$ in the none/mild vasospasm group, $r = -0.684, P = 0.0003$ in the moderate vasospasm group, and $r = -0.864, P < 0.0182$ in the severe vasospasm group).

Compared with overall CCT, peripheral CCT showed stronger inverse correlation with rCBF ($r = -0.767, P < 0.0001$) (Figure 5A). Every angiographic vasospasm group also showed a strong inverse correlation between peripheral CCT and rCBF ($r = -0.660, P = 0.0002$ in the none/mild vasospasm group, $r = -0.848, P < 0.0001$ in the moderate vasospasm group, and $r = -0.929, P < 0.0229$ in the severe vasospasm group) (Figure 5B through 5D).

**Outcome and rCBF**

In 8 cases with symptomatic vasospasm, 6 cases (cases 17 to 21 and 23 in Table 1) showed clinical improvement. In these 6 cases, no infarction was detected on follow-up CT scan, and mean±SD values of rCBF, proximal CCT, and peripheral CCT on the vasospasm side were $26.3 ± 1.6$ mL/100 g per minute, $0.94 ± 0.15$ seconds, and $4.36 ± 0.34$ seconds, respec-
tively. In the other 2 cases without clinical improvement (cases 22 and 24 in Table 1), infarction at the territory of the middle cerebral artery was detected on the follow-up CT scan, and their prognosis was poor. Their rCBF, proximal CCT, and peripheral CCT on the vasospasm side were 18.0 and 21.2 mL/100 g per minute, 0.87 and 0.67 seconds, and 4.88 and 4.17 seconds, respectively.

rCBF in the Frontal and Parieto-Occipital Cortex
The routine SPECT studies in 23 cases showed that mean±SD value of rCBF in the frontal cortex was 36.4±6.3 mL/100 g per minute, and that in the parieto-occipital cortex was 40.7±7.8 mL/100 g per minute. These rCBF values showed no statistically significant differences compared with rCBF during symptomatic vasospasm, as described below.

The SPECT studies performed in 8 cases during symptomatic vasospasm revealed that mean±SD value of rCBF in the frontal cortex was 35.0±6.8 mL/100 g per minute on the vasospasm side and 36.8±5.7 mL/100 g per minute on the opposite side. Mean±SD value of rCBF in the parieto-occipital cortex was 37.5±7.9 mL/100 g per minute on the vasospasm side and 39.2±5.9 mL/100 g per minute on the opposite side. There were no statistically significant differences between rCBF on the vasospasm side and rCBF on the opposite side.

Discussion
The aim of this study was to investigate the role of microcirculatory changes in cerebral ischemia during cerebral vasospasm after SAH by analyzing CCT and rCBF. CCT has formerly been evaluated by using radioisotope and extracranial counting; however, it was not feasible for routine clinical use. Recently, CCT has been obtained by analyzing the time-density curve on DSA images and has usually been represented as MTT at ROI. In this study, to focus on microcirculation, CCT was divided into the proximal part and the peripheral part. Furthermore, the subjects were strictly selected by excluding cases with possible factors affecting CCT, such as increased intracranial pressure, surgical failure including temporary clip use, intracerebral hemorrhage, and old age. From the results in the control subjects, who were all younger than 70 years, age seemed not to affect CCT and rCBF. rCBF was evaluated by using the IMP-ARG method, which has recently become well established because of its high reproducibility of results in stroke patients and high sensitivity to cerebral hyperperfusion that is consistent with PET studies.

The results of this study showed that a major factor affecting cerebral ischemia during cerebral vasospasm was the luminal narrowing of the large extraparenchymal arteries, which was detected as angiographic vasospasm. Severe angiographic vasospasm, which was defined as >50% narrowing, induced statistically significant reduced rCBF; however, there was no statistically significant difference between rCBF in the none/mild vasospasm group and that in the moderate vasospasm group. These results are consistent with the results of experimental and clinical studies showing that rCBF was significantly reduced only when vessel caliber decreased <50%. However, even in the none/mild or moderate angiographic vasospasm groups, some of the cases showed decreased rCBF and/or DIND, which indicated that factors other than angiographic vasospasm might affect cerebral ischemia.

Microcirculatory changes, detected as prolonged peripheral CCT, are thought to be another factor inducing cerebral ischemia during cerebral vasospasm, since rCBF decreased in statistically significant correlation with prolonged peripheral CCT in any of the angiographic vasospasm groups. Overall, CCT also showed statistically significant correlation with rCBF; however, a correlation between peripheral CCT and rCBF was stronger. This is thought to be due to the influence of proximal CCT, which was shortened in association with angiographic vasospasm. Prolonged CCT has been thought to reflect microvascular rarefaction or increased small-vessel resistance. Indicated that prolonged CCT during cerebral vasospasm was improved by injecting sodium papaverine and suggested that the dilation of small arteries induced by papaverine administration was attributable to shortening of prolonged CCT. Therefore, prolonged peripheral CCT seen in this study is thought to represent increased small-vessel resistance or narrowing of small-vessel caliber.

Regarding microcirculatory changes after SAH, previous clinical studies have yielded conflicting results. Statistically significant increase of CBV in patients with vasospasm has been detected by PET or the radioisotope tracer method. The increased CBV has been thought to be due to maximally dilated peripheral arterioles, and the weak response to vasodilating stimuli such as hypercapnia or acetazolamide has been thought to be attributable to the maximal dilation of intraparenchymal small vessels. However, recent PET studies have shown contradictory findings. showed statistically significant reduced CBV in patients with vasospasm compared with normal volunteers and concluded that severe vasospasm caused the parenchymal vessels to have reduced capacity for autoregulatory vasodilatation, which resulted in decreased CBV. Regarding the discrepancy between their results and the results showing increased CBV, they explained that the multiprobe radiation detection system used by Grubb et al was not targeted on the intraparenchymal vessels but on the pial vessels and that vasospasm was less severe in the report of Hino et al, since increased regional oxygen extraction fraction was not observed. Recent histopathological studies have indicated that intraparenchymal arterioles and small arteries show vasoconstriction and decreased luminal diameter after SAH. Prolonged peripheral CCT seen in this study seems to correspond to the findings showing impaired autoregulatory vasodilatation or decreased luminal diameter in intraparenchymal vessels.

The theory of impaired autoregulatory vasodilatation or vasoconstriction in the intraparenchymal vessels could explain several clinical findings. Some CBF studies indicated that decreased CBF was seen during cerebral vasospasm without restriction to the area of vasospasm in the major arteries. Angiographic vasospasm does not always correlate with decreased CBF. These discrepancies between angiographic vasospasm and CBF might be based on the microcirculatory disturbance. The weak response to acetazolamide or hypercapnia, which was thought to be attributable
to maximal dilation of intraparenchymal vessels, might be
due to the refractoriness of narrowed small vessels to those
vasodilating stimuli.

The therapy for cerebral vasospasm should be reconsidered
by taking into account the microcirculatory changes. Induced
hypertension and hypervolemia might improve rCBF by
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ious factors we have discussed here, further studies will be
needed in which all available methods are used.

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Impact of Cerebral Microcirculatory Changes on Cerebral Blood Flow During Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

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