Evaluation of Therapeutically Induced Hypertension in Patients with Delayed Cerebral Vasospasm by Xenon-enhanced Computed Tomography

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Abstract

Serial cerebral blood flow (CBF) measurements were made with stable xenon-enhanced computed tomography in 20 patients with angiographically confirmed ruptured intracranial aneurysms, before and during induced hypertension with continuous infusion of dopamine. All patients showed angiographic vasospasm during their course. Twelve patients without symptomatic vasospasm (Group 1) had the lowest hemispheric CBF on the craniotomy side of 31.6 ± 6.8 ml/100 gm/min on days 4-9 (control value, 40.1 ± 2.0 ml/100 gm/min), while the other eight patients with symptomatic vasospasm (Group 2) had the lowest hemispheric CBF on the craniotomy side of 25.0 ± 7.6 ml/100 gm/min on days 10-14. The critical hemispheric CBF inducing neurological deficits was about 20 ml/100 gm/min in Group 2. Dysautoregulation was usually present in Groups 1 and 2, but therapeutically induced hypertension could reverse the delayed neurological deficits, if begun early at the stage of delayed vasospasm.

Key words: subarachnoid hemorrhage, delayed vasospasm, cerebral blood flow, induced hypertension

Introduction

Cerebral ischemia caused by delayed vasospasm is a major cause of the morbidity and mortality in patients with ruptured intracranial aneurysms. Despite recent improvements in microsurgical techniques, the occurrence of severe vasospasm and its associated neurological deficits lead to unacceptable morbidity and mortality after aneurysm surgery.1,6,11,16,22) The neurological deficits caused by cerebral vasospasm are potentially reversible if adequate blood flow can be restored before permanent infarction occurs.

Intravascular volume expansion and induced hypertension have become commonly used adjunctive treatments for the neurological deficits produced by cerebral vasospasm.3,10,15) These procedures can increase regional cerebral blood flow (rCBF) leading to an improvement of cerebral tissue oxygenation in patients with vasospasm, which seems to be based on the impairment of autoregulation in the ischemic brain.3,8,14,17) Such methods are very useful in reversing neurological deterioration in patients with symptomatic vasospasm. However, some patients with symptomatic vasospasm fail to respond to the treatment and go on to develop permanent neurological deficits, which are thought to occur because rCBF does not increase. In such patients, an increase in local vasogenic edema following induced hypertension may be effective in reducing the local perfusion pressure.

Stable xenon-enhanced computed tomography (Xe\textsuperscript{133} CT) is a useful method for the determination of rCBF that can overcome many of the limitations of other techniques. This method provides direct anatomical correlations to CT findings and moreover has a relatively high resolution. It can give quantitative information even in the deep regions of the brain.5,13,19,24)

This study was undertaken to assess the value of early and serial rCBF measurements in predicting delayed ischemic neurological deficits, as well as in evaluating the indications for and efficacy of
therapeutically induced hypertension.

**Clinical Materials and Methods**

This series included 20 patients, ranging in age from 38 to 87 years, with angiographically confirmed ruptured intracranial aneurysms (Table 1). They were transferred to our institution within 6 hours of the onset. A definitive diagnosis of subarachnoid hemorrhage (SAH) due to ruptured intracranial aneurysm was confirmed by CT and intra-arterial digital subtraction angiography (IA-DSA), as reported previously.25) The severities of SAH on admission and the delayed cerebral vasospasm were assessed and classified according to CT findings.26) All patients were classified as group 3 except one who was in group 4. The ruptured aneurysm was located on the internal carotid artery in 11 patients, on the middle cerebral artery in six, and on the anterior communicating artery in three. All patients underwent aneurysmal neck clipping on the day of admission.

After the operation, each patient underwent Xe CT-CBF studies which involved performing three to five measurements on days 1-3, 4-9, 10-14, 15-24, and/or 25-31 after the hemorrhage. rCBF was assessed before and during induced hypertension with continuous infusion of dopamine (7-15 μg/kg/min). IA-DSA was also performed 1-2 days before or after each Xe CT-CBF study. The Xe CT-CBF studies were performed using a short inhalation of 30% Xe and the curve-fitting method of analysis, as described previously.25) Changes in end-tidal Xe concentration (ET-Xe), blood pressure, and electrocardiography were monitored during each examination. ET-Xe was continuously measured by a thermoconductivity analyzer and the blood pressure was also monitored continuously by cannulating the radial artery with a 23-gauge polyethylene catheter. Blood gas analysis (PaO2 and PaCO2) was also performed at the end of each examination.

A CT scanner with a 512 × 512 matrix and 10-mm collimation (Quantex RX; Yokogawa Medical Systems, Tokyo) was used in this study. It was set for a 3-second scanning time at 120 kVp and 130 mA. Although the smoothing process reduces the resolution of the image obtained, we performed smoothing because the concentration of Xe used was only 30% and the inhalation time was only 4 minutes.

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**Table 1** Summary of 20 patients with ruptured intracranial aneurysms

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical grade**</th>
<th>CT group**</th>
<th>Location of aneurysm</th>
<th>Symptomatic vasospasm</th>
<th>Angiographic vasospasm</th>
<th>Outcome***</th>
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<tr>
<td>1</td>
<td>70</td>
<td>F</td>
<td>II</td>
<td>3</td>
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<td>–</td>
<td>slight</td>
<td>GR</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>II</td>
<td>3</td>
<td>rt ICA-PcomA</td>
<td>+</td>
<td>severe</td>
<td>GR</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>F</td>
<td>III</td>
<td>3</td>
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<td>severe</td>
<td>GR</td>
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<tr>
<td>4</td>
<td>68</td>
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<td>II</td>
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<td>GR</td>
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<td>5</td>
<td>52</td>
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<td>moderate</td>
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<tr>
<td>9</td>
<td>70</td>
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<tr>
<td>10</td>
<td>69</td>
<td>F</td>
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<td>GR</td>
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<td>3</td>
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<td>moderate</td>
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<tr>
<td>12</td>
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<td>II</td>
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<td>GR</td>
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<tr>
<td>14</td>
<td>41</td>
<td>F</td>
<td>II</td>
<td>3</td>
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<td>+</td>
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<td>15</td>
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<td>16</td>
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<td>moderate</td>
<td>GR</td>
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<tr>
<td>17</td>
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<td>mild</td>
<td>GR</td>
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<tr>
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<td>39</td>
<td>M</td>
<td>II</td>
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<td>GR</td>
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<tr>
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<td>M</td>
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<td>severe</td>
<td>MD</td>
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<td>20</td>
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<td>II</td>
<td>3</td>
<td>rt IC-PcomA</td>
<td>–</td>
<td>moderate</td>
<td>GR</td>
</tr>
</tbody>
</table>

Fig. 1 ROIs are set in each cerebral hemisphere. The right and left hemispheric CBF are defined as mean values in ROIs 1 and 2, respectively.

Preanalysis smoothing routines were used to reduce pixel-to-pixel variation, and 13 × 13 pixel smoothing was used. The theoretical background of this method has been described previously.24

We determined each hemispheric CBF value by setting a region of interest (ROI) as shown in Fig. 1. Hemispheric CBF values were taken directly from the data base without normalization for arterial PaCO2, which varied by less than 3 mmHg during the sequential studies performed in each patient.

Pulmonary capillary wedge pressure was raised to 15–18 mmHg with packed red cell transfusion and/or albumin infusion and hypertension was induced [increase in mean arterial blood pressure (ΔMABP), 22.1 ± 2.4 (mean ± SD) mmHg] when symptomatic vasospasm appeared. This therapy was continued for 3–5 days after the onset.

Results

Angiographic vasospasm was demonstrated in all patients during the period of delayed cerebral vasospasm (Table 1). Symptomatic vasospasm with disturbance of consciousness (somnolent state) and focal neurological deficits (hemiparesis and/or aphasia) occurred in eight patients (Cases 2, 3, 5, 11, 14, 15, 18, and 19; Group 2). In Cases 6 and 9, the initial clinical grade (Hunt & Kosnik’s classification7) was IV with thick cisternal blood clots and large intracerebral hematomas, and the clinical outcome was poor, severe disability and vegetative state (Glasgow Outcome Scale9), respectively. The other patients had better outcome.

In the 12 patients without symptomatic cerebral vasospasm (Group 1), induced hypertension significantly increased the hemispheric CBF for the craniotomy side on days 1–3, 4–9, 10–14, and 15–24 (p < 0.05, p < 0.05, p < 0.05, and p < 0.05, respectively) (Table 2). On the contralateral side, induced hypertension significantly increased the hemispheric CBF on days 1–3 and 4–9 (p < 0.05 and p < 0.05, respectively). Minimum CBF value for the craniotomy side was 33.8 ± 5.4 ml/100 gm/min on days 4–9.

In Group 2, CBF values on the craniotomy side significantly increased by the induced hypertension on days 1–3, 4–9, 10–14, and 25–31 (p < 0.05, p < 0.05, p < 0.02, and p < 0.05, respectively) (Table 2). Resting CBF showed the lowest values on days 10–14. CBF values on the contralateral side also increased by the induced hypertension on days 1–3, 4–9, and 10–14 (p < 0.05, p < 0.05, and p < 0.02, respectively). Control value of the hemispheric CBF in the normal volunteers, with ages ranging from 27 to 50 years, was 40.1 ± 2.0 ml/100 gm/min.

Serial CBF changes are demonstrated in Fig. 2. Cases 2, 3, 14, 15, 18, and 19 had symptomatic vasospasm on the craniotomy side, while in Cases 5 and 11 symptomatic vasospasm occurred on the contralateral side. The critical hemispheric CBF, at which neurological deficits developed, was about 20

Table 2 Hemispheric CBF changes before and after induced hypertension (IH) in Groups 1 and 2

<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>craniotomy before IH</td>
<td>36.8 ± 2.4 (12)</td>
<td>31.6 ± 6.8 (9)</td>
<td>40.8 ± 10.4 (12)</td>
<td>36.3 ± 8.4 (4)</td>
<td>37.5 ± 8.3 (11)</td>
</tr>
<tr>
<td></td>
<td>after IH</td>
<td>40.6 ± 3.3* (11)</td>
<td>33.8 ± 5.4* (9)</td>
<td>44.7 ± 11.8* (11)</td>
<td>39.5 ± 7.3* (4)</td>
<td>35.7 ± 6.2 (8)</td>
</tr>
<tr>
<td></td>
<td>contralateral before IH</td>
<td>38.8 ± 3.0 (12)</td>
<td>33.1 ± 4.7 (9)</td>
<td>39.2 ± 6.6 (12)</td>
<td>37.8 ± 8.0 (4)</td>
<td>35.8 ± 2.7 (11)</td>
</tr>
<tr>
<td></td>
<td>after IH</td>
<td>42.1 ± 4.5* (11)</td>
<td>35.3 ± 3.9* (9)</td>
<td>40.1 ± 7.3 (11)</td>
<td>38.8 ± 7.4 (4)</td>
<td>39.9 ± 7.8 (8)</td>
</tr>
<tr>
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<td>craniotomy before IH</td>
<td>38.9 ± 3.6 (8)</td>
<td>37.8 ± 6.4 (7)</td>
<td>25.0 ± 7.6 (8)</td>
<td>36.0 ± 0.8 (2)</td>
<td>37.8 ± 1.2 (8)</td>
</tr>
<tr>
<td></td>
<td>after IH</td>
<td>42.3 ± 2.8* (6)</td>
<td>40.3 ± 9.1* (7)</td>
<td>34.3 ± 9.6** (6)</td>
<td>38.5 ± 0.4 (2)</td>
<td>41.1 ± 3.5* (8)</td>
</tr>
<tr>
<td></td>
<td>contralateral before IH</td>
<td>38.4 ± 1.1 (8)</td>
<td>34.3 ± 3.5 (7)</td>
<td>32.2 ± 5.0 (8)</td>
<td>32.0 ± 1.6 (2)</td>
<td>37.6 ± 2.4 (8)</td>
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<tr>
<td></td>
<td>after IH</td>
<td>42.3 ± 1.0* (6)</td>
<td>39.6 ± 5.9* (7)</td>
<td>36.0 ± 3.0** (6)</td>
<td>35.5 ± 2.0 (2)</td>
<td>38.8 ± 3.9 (8)</td>
</tr>
</tbody>
</table>

Values are means ± SD (ml/100 gm/min). *p < 0.05, **p < 0.02 between before and after IH. ( ) : number of cases studied by CBF measurement.

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ml/100 gm/min. Therapeutically induced hypertension improved the neurological deficits due to delayed cerebral vasospasm in seven patients of Group 2, but in Case 5 motor aphasia persisted in the chronic stage. Left hemiplegia occurred due to delayed cerebral vasospasm in Case 19, but it was markedly improved by the induced hypertension, resulting in mild hemiparesis (4/5). ∆MABP by the induced hypertension in the five periods were $21.0 \pm 2.8, 23.0 \pm 3.2, 22.4 \pm 2.8, 21.1 \pm 2.4$, and $20.5 \pm 2.2$ mmHg, respectively. There were no significant differences.

Representative Cases

Case 2: A 47-year-old male was transferred to our institution with severe headache, which had developed suddenly 30 minutes before admission. CT scans demonstrated SAH with thick cisternal blood and IA-DSA disclosed a right internal carotid-posterior communicating artery aneurysm. Successful clipping of the aneurysm was performed. A Xe\textsuperscript{e} CT-CBF study on the next day showed areas of slightly low blood flow in bilateral frontal and temporal lobes, with preservation of normal flow to the deep nuclei. Induced hypertension increased rCBF in bilateral frontal regions and the right temporal lobe. ∆MABP was 23.0 mmHg.

On day 14, he became somnolent with left hemiparesis. Precontrast CT scans demonstrated widening of the right Sylvian fissure, but an Xe\textsuperscript{e} CT-CBF study performed the same day depicted areas of markedly low blood flow in the right frontoparietal and temporal lobes, with a right hemispheric CBF value of 20.4 ml/100 gm/min. Hypertension was induced, which significantly increased the hemispheric CBF to 44.8 ml/100 gm/min (Fig. 3). Figure 4 shows maps of ∆CBF defined as the difference between CBF before and during induced hypertension. A homogeneous increase in CBF occurred in the right middle cerebral artery territory except the right basal ganglia, where rCBF slightly decreased as shown in Figs. 3 and 4. ∆MABP was 19.3 mmHg on that day. IA-DSA showed severe vasospasm of the right internal carotid and middle cerebral arteries.

He showed marked improvement in his neurological deficits after hypertensive therapy and was discharged without residual deficits on day 43. Case 11: A 50-year-old female was transferred to our institution in a somnolent state with a history of severe headache. CT scans and IA-DSA disclosed severe SAH due to rupture of an anterior communicating artery aneurysm. She was operated on to clip the aneurysm. Postoperatively, her consciousness became clear without neurological deficits.

On day 13, she became drowsy with right hemiparesis and acalculia. An Xe\textsuperscript{e} CT-CBF study showed areas of low flow in the left frontoparietal and temporal lobes. In particular, rCBF in the left parietal lobe was only 18.5 ml/100 gm/min. Therapeutically induced hypertension significantly increased the rCBF in the left parietal lobe to 25 ml/100 gm/min. rCBF in the right temporo-occipital area inversely decreased during induced hypertension (Fig. 5). ∆MABP was 21.3 mmHg.

Her consciousness became clear, and the focal neurological deficits disappeared soon after starting the therapy. She was discharged without neurological deficits on day 43.

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Fig. 3 Case 2. Precontrast and Xe\textsuperscript{e} CT scans on day 14. Precontrast CT scans demonstrated no infarction (left). Xe\textsuperscript{e} CT scans showed markedly low blood flow areas in the right frontoparietal-temporal lobes (center). Induced hypertension significantly increased rCBF homogeneously in those regions except the right basal ganglia, where rCBF decreased during induced hypertension (right).

Fig. 4 Case 2. \(\Delta\)CBF maps on day 14, showing a homogeneous increase in rCBF in the right middle cerebral artery territory except the right basal ganglia.

Discussion

Simple and less invasive methods for the quantitative evaluation of three-dimensional rCBF are necessary for the early diagnosis and treatment of cerebral ischemia in various types of cerebrovascular disease. CBF is decreased in patients with cerebral vasospasm following SAH and delayed ischemic neurological deficits occurring together with severe angiographic vasospasm are associated with a marked reduction in CBF\textsuperscript{4,14,17,18,20,21,26}. In this report, we measured the serial changes in rCBF as well as the mean hemispheric CBF, and evaluated the degree of dysautoregulation. Induced hypertension with intravascular volume expansion has become a common treatment of symptomatic cerebral vasospasm, which is thought to be due to impaired autoregulation in the ischemic brain.

This study showed a mild postoperative decrease in blood flow in some areas on the contralateral side.
as well as the craniotomy side, since the contralateral hemispheric CBF decreased to the same extent as on the craniotomy side in Groups 1 and 2. Moreover, dysautoregulation occurred on days 1-3 even in Group 1. In this group, the hemispheric CBF on both sides tended to be lowest (31.6 ml/100 gm/min) on days 4-9, and increased again after this period. In contrast, the hemispheric CBF in Group 2 was lowest (25.0 ml/100 gm/min) on days 10-14. The hemispheric CBF after induction of hypertension during the same period in Group 2 markedly increased to 34.3 ml/100 gm/min, followed by neurological improvement. The lowest hemispheric CBF in Case 2 was 20.4 ml/100 gm/min, while in Case 10 without symptomatic vasospasm it was 19.8 ml/100 gm/min. Figure 2 shows the critical hemispheric CBF producing neurological impairments to be about 20 ml/100 gm/min (about 50% of the control value).

In the absence of significant collateral flow, an acute decrease in the caliber of arterial vessels produced a decrease in perfusion pressure distal to these vessels. When a cerebral artery is narrowed in the subarachnoid space, intraparenchymal arterioles distal to the spastic vessels dilate decreasing their vascular resistance to maintain a normal blood flow in those regions. When those arteriolar vasodilation become maximum, any further decrease in the perfusion pressure will decrease CBF in those regions. Mild decrease in CBF may be tolerated, but further decrease in the perfusion pressure beyond the vasodilatory reserve will produce ischemic symptoms (critical flow level).

Critical rCBF levels for adequate cerebral function during the occurrence of delayed vasospasm have been suggested by several clinical studies. Kawase et al. observed that neurological deficits might develop at a mean rCBF below 55% of the normal value and that levels below 35-40% could produce cerebral infarction. Yonas et al. recently reported that follow-up CT scans showed cerebral infarction in patients with rCBF values below 15 ml/100 gm/min, while cortical regions where rCBF remained at or above 18 ml/100 gm/min did not progress to CT-
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References


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defined infarction and were commonly associated with the clinical resolution of neurological deficits. In our Cases 5 and 11, the delayed neurological deficits appeared contralateral to the craniotomy side, and the minimum hemispheric CBF was more than 25 ml/100 gm/min, greater than in other cases with symptomatic vasospasm. The reason for this discrepancy is thought to be that rCBF on the contralateral side decreased heterogeneously, so that the minimum CBF was not so markedly reduced.

Dysautoregulation of varying severity also occurs in the acute stage after the rupture of an intracranial aneurysm and induced hypertension can improve clinical deficits and/or cerebral circulation. Precise and serial information on the changes in the rCBF before and during induced hypertension and/or hypotension have not been reported, although serial changes in total CBF before, during, and after the procedures have been calculated from the difference in oxygen content between arterial and jugular venous blood. This report demonstrated that dysautoregulation was present and that induced hypertension could not consistently increase rCBF. The rCBF showed various changes, for example, no change (autoregulation or pseudoautoregulation) or a paradoxical decrease at the stage of the most advanced cerebral vasospasm. This phenomenon was thought to result from induced hypertension increasing local brain edema and so causing a decrease in the local perfusion pressure. Neurological deficits are difficult to reverse in this situation by increasing ΔMABP. Moreover, when the rCBF is decreased during induced hypertension, neurological deficits may be aggravated by the procedure. Kassell et al. reported that complications experienced during this type of therapy included pulmonary edema, dilutional hyponatremia, aneurysmal rebleeding, coagulopathy, hemotherax, and myocardial infarction. Also, if hypertension is induced at the stage of improvement of vasospasm or is continued from the stage of symptomatic vasospasm to improvement, hemorrhagic infarction due to the breakthrough phenomenon will occur.

In our series, dysautoregulation was noted just after aneurysm surgery and persisted to the chronic stage in some cases, and induced hypertension did not aggravate the neurological symptoms in any patients. In Case 5, induction of hypertension reversed both the hemiparesis and the disturbance of consciousness but the motor aphasia showed no improvement and remained as a permanent deficit. Thus, induced hypertension therapy may have some limitations in reversing symptomatic vasospasm. Serial measurements of rCBF with the Xe CT-CBF technique are very important for evaluating the resting flow to predict symptomatic vasospasm and to assess the degree of dysautoregulation, as well as following induced hypertension for the management of symptomatic vasospasm.


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