Critical Closing Pressure in Subarachnoid Hemorrhage
Effect of Cerebral Vasospasm and Limitations of a Transcranial Doppler-Derived Estimation

Martin Soehle, MD; Marek Czosnyka, PhD; John D. Pickard, MCh, FRCS; Peter J. Kirkpatrick, FRCS(SN)

Background and Purpose—Critical closing pressure (CCP) is thought to be jointly influenced by intracranial pressure and cerebrovascular tone. We examined how CCP is affected by cerebral vasospasm after subarachnoid hemorrhage (SAH).

Methods—In 15 patients with vasospasm of the middle cerebral artery, CCP was calculated using 2 methods previously reported (ad model Aaslid and Michel, indexed CCPAaslid and CCPMichel, respectively) based on data of arterial blood pressure and flow velocity (FV) as assessed by transcranial Doppler.

Results—CCP decreased significantly (P<0.05) during vasospasm (CCPAaslid=6.3±22.9 mm Hg, CCPMichel=14.9±16.5 mm Hg, mean±SD) as compared with baseline (CCPAaslid=24.4±20.3 mm Hg, CCPMichel=27.8±19.4 mm Hg). This was not attributable to ICP, which remained unaffected by vasospasm. In addition, CCP was significantly lower on the side of vasospasm (CCPAaslid=11.9±24.2 mm Hg, CCPMichel=18.4±19.6 mm Hg) as compared with the contralateral nonvasospastic side (CCPAaslid=24.7±22.3 mm Hg, CCPMichel=28.2±18.0 mm Hg).

Conclusions—Assuming that autoregulation-related distal vasodilatation outweighs proximal vasospasm, CCP should decrease. Alternatively, CCP might have increased during vasospasm as the tension of big vessels increase, but the turbulence occurring during vasospasm may have impaired the linear relationship between pressure and FV, thus leading to a marked underestimation of CCP. In conclusion, interpretation of CCP in vasospasm is difficult and may be overshadowed by nonlinear hemodynamic effects. (Stroke. 2004;35:1393-1398.)

Key Words: vasospasm, intracranial ☼ subarachnoid hemorrhage ☼ ultrasonography, Doppler, transcranial

Cerebral vasospasm remains among the leading causes of morbidity and mortality in patients surviving subarachnoid hemorrhage (SAH). A marked increase in vasomotor tone results in vasoconstriction and spasm of affected arteries. Assessment of vasomotor tone would therefore give valuable information on the severity of vasospasm and may guide its therapy.

In 1951, Burton provided the concept of assessing vasomotor tone: He hypothesized that if arterial pressure (ABP) falls below a certain threshold, which he called critical closing pressure (CCP), the vessel will collapse completely even though a certain vasomotor tone remains. He proposed CCP to be a measure of that tone. Dewey and co-workers applied this concept to the cerebral circulation and concluded that CCP does not only consist of vasomotor tone (cerebral artery smooth muscle tone [CAST]), but of intracranial pressure (ICP) as well:

\[
\text{CCP} = \text{ICP} + \text{CAST}
\]

Aaslid presented a noninvasive method to assess CCP by applying transcranial Doppler (TCD). He measured blood flow velocity (FV) instead of blood flow and calculated CCP by linear regression analysis of the pressure–flow velocity relationship. Michel et al recently introduced a different TCD-derived method based on the first harmonics of the pulse waveforms of ABP and FV. Assessment of cerebral CCP in human brain pathology has been applied to neonates but not to subarachnoid hemorrhage so far.

This study was performed to investigate the effect of cerebral vasospasm on CCP and whether any detected changes in CCP are caused by changes in ICP or CAST.

Subjects and Methods
This prospective study was performed at the Addenbrooke’s Hospital with approval of the local ethics committee. Data have been analyzed as part of routine clinical audit.

Thirty-two patients with a diagnosis of aneurysmal SAH were studied. SAH was confirmed by computed tomography, and aneurysms were identified from cerebral angiography and clipped surgically, except for 2 patients in whom endovascular coiling was performed (Table 1: patients 1 and 18). All patients received intensive care treatment including the routine use of nimodipine (6×60 mg orally).
TABLE 1. Demographic Data, Clinical Data, and Critical Closing Pressure of the 18 Patients With Cerebral Vasospasm

<table>
<thead>
<tr>
<th>N</th>
<th>Gender</th>
<th>Age</th>
<th>WFNS Grade</th>
<th>DID</th>
<th>Baseline (mm Hg)</th>
<th>Vasospasm (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
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<td>4</td>
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<td>2</td>
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<td>3</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
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<td>4</td>
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</tr>
<tr>
<td>8</td>
<td>F</td>
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<td>5</td>
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<td>63.5</td>
<td>16.1</td>
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<tr>
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<td>46</td>
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<td>Hemiparesis</td>
<td>11.6</td>
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<td>Not known</td>
<td>29.1</td>
<td>15.9</td>
</tr>
</tbody>
</table>

The severity of subarachnoid hemorrhage was expressed using the WFNS grading.24 In ventilated patients, delayed ischemic deficits (DID) were referred to as not known, because they might have happened unrecognized. WFNS indicates World Federation of Neurosurgical Societies; F, female; M, male; imp. consc.; impaired consciousness.

CCPMichel indicates critical closing pressure as calculated according to Michel5.

Bilateral examinations of the middle cerebral artery (MCA) and extracranial internal carotid artery (ICA) were performed by transcranial Doppler (Neurogord, 2MHz; Medasonics) every other day. Both MCAs were insonated simultaneously at a depth of 50 mm via bitemporal bone windows using TCD probes that were fixed to a headband to avoid dislocation. The TCD power and amplifier settings were kept constant within each patient and all TCD examinations were performed by the same examiner. Eighteen patients had cerebral vasospasm (Table 1) according to established TCD criteria, which are MCA mean FV exceeding 120 cm/s10 and Lindegaard ratio (FV_MCA/FV_ICA) > 3.11 Those patients received standard triple-H therapy12 until vasospasm had resolved. Ten of the vasospastic patients were sedated and ventilated because of their poor condition. Patients that had no vasospasm were excluded from further analysis.

ICP was measured only in patients requiring ventriculostomy caused by hydrocephalus. ICP readings as obtained via a ventricular catheter were considered reliable if measured at least 30 minutes after closure of the ventricular drainage. Therefore, ICP recordings were performed only if the clinical condition of the patient allowed such transient closure. A radial artery line was placed to assess ABP and to draw arterial blood gas samples.

Simultaneous and continuous recordings of ABP, ICP, and bilateral MCA FV were obtained over a period of 20 minutes every other day from admission until 2 weeks after hemorrhage or until vasospasm had resolved. Data were converted from analog to digital (DT 2814, Data Translation), sampled at 50 Hz by means of an AT laptop computer (Amstrand ALT 386SX) and stored to hard disc. The systolic (ABP_sys, FV_sys), mean (ABP_mean, FV_mean), and diastolic (ABP dia, FV dia) values of ABP and FV, respectively, as well as its first harmonics (A_i, F_i), were calculated using an automated software algorithm designated for recording and analysis of time series. Values were averaged over 5-second intervals to minimize the effect of respiratory waves.

CCP was determined according to Aaslid4 using linear regression of FV on ABP. The intercept of the regression line and the abscissa, which is CCP, was calculated as:

\[ CCP_{Aaslid} = \frac{ABP_{sys} - ABP_{dia}}{FV_{sys} - FV_{dia}} \cdot FV_{sys} \]

In addition, CCP was obtained by applying the formula proposed by Michel5 as:

\[ CCP_{Michel} = \frac{ABP_{mean}}{F_i} \cdot FV_{mean} \]

CAST was calculated according to equation 1. Both CCP and CAST were finally averaged over the monitoring period of 20 minutes.

To investigate the effect of cerebral vasospasm on CCP, 2 analyses were performed. In the first analysis, CCP obtained before vasospasm was compared with CCP assessed during vasospasm to elucidate the temporal effects of vasospasm on CCP. Three patients were excluded from this comparison (Table 1; patients 5 to 7) because they showed vasospasm throughout the entire examination period without the opportunity to analyze CCP during a nonvasospastic period. In a second analysis based on the data of the same 18 vasospastic patients, CCP obtained on the side of vasospasm was compared with CCP obtained from the contralateral, nonvasospastic side to investigate the spatial effects of vasospasm on CCP. In this comparison, 3 patients were excluded (Table 1; patients 8, 10, and 17) in whom vasospasm occurred bilaterally. Hence, analyses consisted of data from 15 of the 18 vasospastic patients.

Several TCD examinations and hence CCP values were obtained in each patient during baseline and vasospastic period as well as of the side of vasospasm and its contralateral side. For statistical analysis, data assessed within the same time period of the same side were averaged in each patient. Subsequently, temporal or spatial differences in CCP were analyzed by applying a paired Student t-test after values were evaluated for normal distribution. Pearson product moment correlation was calculated for correlation between FV and CCP. Statistical significance was assumed at P<0.05. All statistical tests were performed using Sigma Stat software (Jandel Scientific). Data are shown as mean±standard deviation.

**Results**

Demographic data, clinical data, and CCP_{Michel} of the 18 patients who had vasospasm are shown in Table 1. The gender ratio was equal for both analyses.

**Critical Closing Pressure During Baseline and Vasospasm**

Between baseline and vasospasm, no statistical differences existed in arterial paCO_2 (35.2±4.2 mm Hg and 36.9±4.5 mm Hg, respectively), paO_2, and pH. However, during cerebral vasospasm, mean ABP was significantly elevated (100±12.6 mm Hg, P=0.007) as compared with baseline (93.4±14.5 mm Hg, Table 2). This difference is presumably caused by ABP support as performed by triple-H therapy during vasospasm. CCP_{Aaslid} decreased significantly (P=0.036) during vasospasm (6.3±22.9 mm Hg, Figure 1) as compared with baseline (24.4±20.3 mm Hg). A significant (P=0.026) reduction in CCP_{Michel} was observed during vasospasm (CCP_{Michel}=14.9±16.5 mm Hg) as compared with baseline (CCP_{Michel}=27.8±19.4 mm Hg, Figure 1), as well. During vasospasm, we found a significant inverse correlation.
However, FV is during vasospasm presumably because of triple-H therapy. ABP is slightly shifted upwards relationship in a SAH patient obtained at baseline and how it is influenced by vasospasm. CCP, determined by the 2 different methods of Aaslid and Michel, respectively, decreased significantly during vasospasm.

**TABLE 2. Comparison of Parameters Between Baseline and Cerebral Vasospasm**

<table>
<thead>
<tr>
<th>Group</th>
<th>Entire Group</th>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>paCO₂ (mm Hg)</td>
</tr>
<tr>
<td>Baseline</td>
<td>15</td>
<td>35.2±4.2</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>15</td>
<td>36.9±4.5</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>0.007</td>
</tr>
</tbody>
</table>

N indicates number of patients; paCO₂, arterial partial pressure of carbon dioxide; MABP, mean arterial blood pressure; CCP, critical closing pressure as calculated according to Aaslid (CCP_{Aaslid}) and Michel (CCP_{Michel}), respectively; ICP, intracranial pressure; CAST, cerebral artery smooth muscle tone (CCP–ICP); NS, not significant.

P = result of paired t test.

Although all 15 patients were included for analysis shown in the left part of the Table (Entire Group), only those 9 patients in whom ICP was measured were analyzed in the right part of the Table (Subgroup).

Between FV and CCP_{Aaslid} (r= -0.53, P=0.04) or CCP_{Michel} (r= -0.61, P=0.02), respectively. In contrast, no such correlation existed between ABP and CCP.

A subgroup analysis of 9 patients, in which ICP was measured, revealed that no statistical difference (P=0.65) existed in ICP between baseline (15.2±4.6 mm Hg) and vasospasm (15.5±5.9 mm Hg, Table 2). CAST was found at baseline to be 8.0±20 mm Hg and 11.2±18.5 mm Hg according to Aaslid and Michel, respectively. CAST decreased during vasospasm and even reached negative values of −13.6±18.0 mm Hg and −5.0±6.8 mm Hg based on CCP_{Aaslid} and CCP_{Michel}, respectively (Table 2).

Figure 2a shows an example of a pressure–flow velocity relationship in a SAH patient obtained at baseline and how it is influenced by vasospasm. ABP is slightly shifted upwards during vasospasm presumably because of triple-H therapy. However, FV is ≈3-fold as compared with baseline. The regression slope was steeper but the line was shifted upwards, which decreased CCP.

**Critical Closing Pressure on the Contralateral and Ipsilateral Side of Vasospasm**

CCP was significantly (P_{Aaslid}=0.011, P_{Michel}=0.022) lower on the side of vasospasm (CCP_{Aaslid}=11.9±24.2 mm Hg, CCP_{Michel}=18.4±19.6 mm Hg) as compared with the contralateral side (CCP_{Aaslid}=24.7±22.3 mm Hg, CCP_{Michel}=28.2±18.0 mm Hg; Figure 3). A mean paCO₂ of 37.4±5.6 mm Hg and a mean ABP of 98.9±13.2 mm Hg were revealed in this group.

Figure 2b demonstrates an example concerning the spatial effect of vasospasm on the pressure–flow velocity relationship in a patient with SAH. FV as obtained on the side of vasospasm was ≈30 cm/s higher as compared with the contralateral, nonvasospastic side. The related ABP data were the same, because they correspond to both sides of MCA. The linear regression line was upward shifted and slightly steeper on the side of vasospasm, resulting in a decrease of CCP.

**Discussion**

We measured a significant decrease in CCP during vasospasm as verified by 2 different settings (temporal versus spatial effect) and 2 different methods to calculate CCP. However, if we assumed that cerebral vasospasm causes an increase in vasomotor tone, we would have expected an increase in CCP. Alternatively, CCP might truly have decreased during vasospasm because of a vasodilatation distal to the spastic vessel. The third option was that CCP might have increased as expected but was markedly underestimated because of a nonlinearity of the pressure–flow relationship.

**Decrease in CCP Caused by Changes in ICP**

As a result of equation 1, a decrease in CCP during vasospasm would occur when ICP decreases more pronounced than CAST increases. However, ICP remained unchanged and CAST even decreased in our study when comparing baseline and vasospasm. If we assume that ICP is equal in both hemispheres (Monro–Kellie doctrine), it does not contribute to the observed changes in CCP when comparing the side of vasospasm with its contralateral nonvasospastic side within the same patients. In addition, Weyland et al described in TBI patients that cerebrovascular tone rather than ICP determines CCP in the absence of intracranial hypertension. Moreover, equation 1 expresses the influence of ICP and CAST on CCP as 2 independent factors, although it is obvious that change in ICP may influence vascular tone and, perhaps, vascular tone may influence ICP through the regulation of arterial blood volume. This may be a source of another misinterpretation of changes in CCP.
Decrease in CCP Because of Vasodilatation Distal to Vasospasm

Cerebral autoregulation is thought to affect mainly parenchymal and pial arterioles far distal to major cerebral arteries. MCA vasospasm will result in a marked pressure decrease within the spastic segment and the decreased pressure distal to it will cause vasodilatation of the arteriolar resistance vessels as an autoregulatory response. This would decrease CCP if we assume that CCP refers to the arteriolar level. However, if CCP would characterize vasomotor tone of the regional cerebral vasculature, then the distal vasodilatation would need to outweigh the effect of proximal stenosis to decrease CCP. Until now, it is unclear whether CCP represents vasomotor tone rather of the insonated vessel, the resistance arterioles, or the entire cerebral vasculature.

Underestimation of CCP Because of Nonlinearity of Pressure–Flow Velocity Relationship

According to the Hagen–Poiseuille law, flow \( F \) of a fluid with viscosity \( \mu \) through a channel of length \( L \) and radius \( r \) is related to pressure \( P \) and vessel resistance \( R \):

\[
F = \frac{\Delta P - \pi r^4}{8 \mu L} = \frac{\Delta P}{R}
\]

Cross-sectional averaged flow velocity \( V \) is related to flow \( F \) by the cross-sectional area \( A = \pi r^2 \):

\[
V = \frac{F}{A} = \frac{F}{\pi r^2} = \frac{\Delta P}{8 \mu L} r^2
\]

Therefore, there is a linear relationship between flow velocity and perfusion pressure under the assumption that vessel radius and fluid viscosity are constant during a heart cycle and presumably during the 20-minute monitoring period. As a consequence, CCP is calculated by linear regression of velocity and pressure as described by Aaslid’s formula (equation 2). However, Hagen–Poiseuille law holds true only for a steady, laminar flow of a Newtonian fluid through long, straight vessels with rigid walls. In contrast, blood is a non-Newtonian fluid flowing in a pulsatile fashion through a branched, curved, and tapering vasculature with distensible blood vessels. During cerebral vasospasm, high flow velocities, and hence turbulence occur, which result in a loss of kinetic energy and requires the application of the Bernoulli equation: \( p = \text{fluid density} \)

\[
V = \sqrt{\frac{2 \Delta P}{\rho}}
\]

Under circumstance of turbulence, flow velocity \( V \) is not proportional to pressure \( \Delta P \), as described by Hagen–Poiseuille, but instead to the square root of pressure. The pressure–flow velocity relationship is hence not linear during vasospasm and (erroneous) application of linear regression (equation 2) will result in a marked underestimation of CCP and might explain the decrease in CCP we found. To yield a meaningful relationship between flow and pressure during vasospasm, both Hagen–Poiseuille and Bernoulli’s equation
need to be applied. By doing so, Aaslid\textsuperscript{17} obtained a close fit between theoretical and experimental data.

**Limitations of the TCD Technique**

The correlation between increased FV (TCD-derived vasospasm), reduction of artery caliber (angiographic vasospasm), and delayed neurological deficits (symptomatic or clinical vasospasm) is discussed controversially\textsuperscript{10,18–21}. Even if we assume that TCD is valid in assessing angiographic vasospasm,\textsuperscript{10,18,20} some authors describe a close relation between TCD-derived and symptomatic vasospasm,\textsuperscript{20,21} whereas others doubt that a close connection exists.\textsuperscript{18,19} Therefore, the results of our study, which were assessed with respect to TCD-derived vasospasm, may not be applicable to angiographic or symptomatic vasospasm. It remains unknown whether CCP correlates with neurological deficits in our patients, because the majority was ventilated resulting in too few neurologically assessable patients to perform a statistical analysis.

Application of TCD enables a noninvasive measurement of CCP\textsuperscript{1–6} but increases concerns because FV, instead of cerebral blood flow, is measured. However, the relationship between CBF and FV is linear as shown in equation 5 as long as vessel diameter remains unchanged, which is likely to be the case during the daily 20-minute TCD insonation period. In addition, because zero blood flow will cause zero FV,\textsuperscript{4} both will occur at the same pressure, which is CCP by definition.

However, technical reasons prevent TCD to assess very low or even zero FV, which would be necessary to fulfill Burton’s concept of zero flow pressure. High-pass filtering of the FV signal is necessary to eliminate artifacts from arterial wall movements; however, it results in poor quality of the spectral outline at low FV. During ventricular fibrillation induced for defibrillator testing, Aaslid\textsuperscript{22} was able to assess FV as low as 6 cm/s but had to estimate zero FV using the described techniques, as well.

As in other studies, we measured ABP in the radial artery instead of the MCA, which may lead to a distortion of the ABP waveform. Because of methodological reasons, CCP\textsubscript{Michel} is less influenced by such potential errors than CCP\textsubscript{Aaslid}.\textsuperscript{22} Differences in the ABP curves between the arteries might add an error to the absolute value of CCP; however, a systematic error will not affect the comparison between baseline and vasospasm or the side of vasospasm and its contralateral side, respectively.

**Assessment of CCP According to Aaslid Versus Michel**

We found CCP calculated according to Michel\textsuperscript{3} slightly higher as compared with the method proposed by Aaslid.\textsuperscript{4} This is in accordance with results obtained in TBI patients\textsuperscript{7} and during ventricular fibrillation.\textsuperscript{22} The method proposed by Michel\textsuperscript{3} is computational costly because it requires fast Fourier transformation; however, it takes into account the frequency-dependent properties of cerebrovascular impedance\textsuperscript{3} and is independent of the insonation angle.\textsuperscript{5} In addition, CCP\textsubscript{Michel} is less contaminated by peripheral ABP waveform distortion\textsuperscript{23} therefore, it is the recommended technique for future studies.\textsuperscript{22}

**Conclusions**

Unexpectedly, we observed a significant decrease in CCP during cerebral vasospasm after SAH. Application and interpretation of a TCD-derived assessment of CCP is particularly difficult in SAH, mainly because of 2 reasons. First, proximal vasoconstriction caused by vasospasm and distal vasodilatation caused by autoregulatory response will influence CCP in opposite ways, and it is unclear which of these effects will prevail. Second, vasospasm causes vortices and turbulence in blood flow, which will impair or even abolish the linear relationship between pressure and FV, thus leading to an underestimation of CCP.

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**References**


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