Non-invasive and continuous monitoring of cerebral blood flow as a parameter for neurological deterioration in acute brain injury

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Background: Monitoring the cerebral blood flow (CBF) is crucial when caring for patients in neurological intensive care units (NICU). Changes in CBF, either due to hypo- or hyperperfusion, have been associated with neurological deterioration. By using a non-invasive continuous CBF monitor, we aimed to assess whether cerebral flow index (CFI) fluctuations could correlate with neurological deterioration.

Methods: We prospectively collected data from patients with acute brain injury (subarachnoid hemorrhage [SAH], Moyamoya disease [MMD], and ischemic stroke), who were at a high risk for CBF disturbance between May 2017 and June 2019. Non-invasive CBF measurements were performed in the bilateral prefrontal cortex using a c-FLOW device. Continuous CBF was assessed using CFI. The delta value and percent change in CFI were compared between patients with and without neurological deterioration.

Results: A total of 45 patients (mean age, 51.6 years; male, 48.9%) were included in our analysis (SAH, 13; MMD, 17; ischemic stroke, 15). The mean monitoring duration was approximately 52 hours. Nine patients (20.0%) had neurologic worsening during c-FLOW monitoring in NICU. The delta value (median, 10.4; interquartile range [IQR], 3.9–14.3 vs. median, 3.4; IQR, 2.5–5.6; P=0.008) and percent change in CFI (28.5% vs. 9.0%, P<0.001) was significantly higher in groups with neurological deterioration. In two patients with neurological deterioration, no CFI change was observed because aggravation of cerebral perfusion occurred outside the area of CFI monitoring.

Conclusion: Continuous non-invasive CBF monitoring with c-FLOW may be useful for patients with acute brain injury at high risk for CBF alterations.

Keywords: Acute brain injury; Cerebral blood flow; Cerebral flow index; Monitoring; Neurologic deterioration

INTRODUCTION

Cerebral ischemia is an important cause of secondary neurological deterioration in patients with acute brain injury [1-3]. Therefore, monitoring of the cerebral blood flow (CBF) is crucial in the neurological intensive care units (NICU) [4-9]. CBF can be assessed by perfusion imaging, transcranial Doppler ultrasonography, or direct measurement using an invasive intraparenchymal...
probe [10-13]. Each method has its own limitations. Perfusion imaging can only provide a snapshot of CBF; therefore, continuous monitoring is not possible [14-16]. Transcranial Doppler ultrasound can be continuously monitored, but only measures CBF velocity as a surrogate of CBF [17]. Parenchymal CBF monitoring, such as with Hemedex, is an adequate tool for continuous monitoring [17-21]. However, an intraparenchymal probe must be inserted into the subcortical white matter through the burr hole. Its invasiveness limits its application in patients with brain injury, especially in those with coagulopathy [21-23]. Therefore, there is a growing need for non-invasive but accurate, continuous tools for CBF monitoring [24-28]. The c-FLOW monitor is a non-invasive tool for CBF measurement; it uses optoacoustic effects and provides a surrogate for CBF in the form of a cerebral flow index (CFI) [29]. Recent studies showed that continuous CBF monitoring is possible when using c-FLOW [29,30]. However, whether the CFI is correlated with clinical deterioration among NICU patients due to acute brain injury remains to be elucidated. Therefore, we aimed to investigate whether the absolute value of CFI is linked to neurological deterioration due to perfusion state.

METHODS

Study population
We prospectively enrolled 45 patients with acute brain injury within 7 days of onset between May 2017 and June 2019. Primary diagnoses were as follows: (1) acute ischemic stroke in the anterior circulation with a high risk for CBF deterioration (n = 15); (2) subarachnoid hemorrhage (SAH) with a risk for vasospasm (n = 13); (3) Moyamoya disease (MMD) after bypass surgery between the superficial temporal artery and the cortical branch of the middle cerebral artery (n = 17).

Baseline characteristics and clinical definition
Patient characteristics, including age, sex, and risk factors, were reviewed using electronic medical records. Clinical information, including admission diagnosis, vascular territory at risk, side of the lesion, and dose of sedative agents during admission, was gathered. Neurological assessment was performed using the National Institute of Health Stroke Scale (NIHSS) and Glasgow coma scale (GCS) during NICU admission. All patients were examined by NICU nurses or neurointensivists at least every 4 hours. Neurological deterioration was defined as having a total NIHSS of ≥ 4 points or GCS ≤ 2, as previously described [31,32]. Patients were categorized into two groups based on the presence or absence of neurological deterioration.

Monitoring of CBF
Non-invasive CBF monitoring was performed using c-FLOW (Ornim Medical) (Fig. 1). c-FLOW is a device that utilizes near-infrared laser light (808 nm) tagged with low-power 1 MHz ultrasound and continuously assesses prefrontal CBF using optoacoustic effects. The device generated CFI values every 2 seconds, which were averaged over the previous 30 seconds [30]. The CFI values range from 0 to 100, with higher values representing higher CBF [29]. CBF monitoring was performed at least 48 hours after ICU admission, and stopped if the neurointensivists on service decided that the patient was neurologically stable and that CBF monitoring was no longer needed [33,34]. When neurological deterioration was identified, CFI data were collected over 4 hours (2 hours before and after deterioration) and averaged over a 10-minute period for comparison [35]. In patients without neurological worsening, the percentage change and delta values were calculated from the baseline (initial CFI when CBF monitoring was initiated) and most deviated CFI values from baseline. Artifacts regarding falsely increased or decreased CFI due to sensing
errors were deleted before and after examining the CFI records and medical reviews.

**Statistical analysis**

Data are presented as mean ± standard deviation or as median with interquartile range (IQR) according to the data distribution. We evaluated the differences with the t-test and the chi-square test. The Mann-Whitney U-test or Student t-test were used for continuous variables; the Fisher’s exact test or Pearson’s test were used for categorical variables between the groups. For all analyses, \( P < 0.05 \) was considered significant. All data were analyzed using IBM SPSS version 23.0 (IBM Corp.).

**RESULTS**

c-FLOW monitoring was performed (median, 52 hours; IQR, 26–96 hours) in the included patients (male, 48.9%; mean age, 51.6 years). MMD (37.8%) was the most common reason for c-FLOW monitoring, followed by ischemic stroke (33.3%). Among them, nine patients (20.0%) experienced neurological deterioration while on c-FLOW monitoring. There were no statistical differences in sex, age, or vascular risk factors between patients with and without neurological deterioration (Table 1). The use of sedatives did not differ between the two groups (Table 1).

Table 2 lists the corresponding CFI values. The average CFI during monitoring was not significantly different in patients with...

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**Table 1. Baseline characteristics according to neurological deterioration**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total patients (n=45)</th>
<th>Neurological deterioration (n=9, 20%)</th>
<th>No neurological deterioration (n=36, 80%)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.6±17.8</td>
<td>50.0±19.0</td>
<td>52.0±17.6</td>
<td>0.777</td>
</tr>
<tr>
<td>Male</td>
<td>22 (48.9)</td>
<td>6 (66.7)</td>
<td>16 (44.4)</td>
<td>0.207</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (46.7)</td>
<td>4 (44.4)</td>
<td>17 (47.2)</td>
<td>0.590</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (26.7)</td>
<td>3 (33.3)</td>
<td>9 (25.0)</td>
<td>0.682</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13 (28.9)</td>
<td>2 (22.2)</td>
<td>11 (30.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (8.9)</td>
<td>1 (11.1)</td>
<td>3 (8.3)</td>
<td>0.605</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>17 (37.8)</td>
<td>4 (44.4)</td>
<td>13 (36.1)</td>
<td>0.711</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (20.0)</td>
<td>2 (22.2)</td>
<td>7 (19.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>CAD</td>
<td>2 (4.4)</td>
<td>0</td>
<td>2 (5.6)</td>
<td>0.636</td>
</tr>
<tr>
<td>Initial NIHSS</td>
<td>2 (0–14.5)</td>
<td>1 (0–2)</td>
<td>3.5 (0–16.25)</td>
<td>0.177</td>
</tr>
<tr>
<td>Initial GCS</td>
<td>15 (3–15)</td>
<td>9 (7–15)</td>
<td>12.5 (3–15)</td>
<td>0.659</td>
</tr>
<tr>
<td>Acute brain injury</td>
<td></td>
<td></td>
<td></td>
<td>0.106</td>
</tr>
<tr>
<td>SAH</td>
<td>13 (28.9)</td>
<td>5 (55.6)</td>
<td>8 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Moyamoya disease</td>
<td>17 (37.8)</td>
<td>3 (33.3)</td>
<td>14 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>15 (33.3)</td>
<td>1 (11.1)</td>
<td>14 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Duration of CFI monitoring (hr)</td>
<td>52 (26–96)</td>
<td>88 (28–106)</td>
<td>45 (24–88)</td>
<td>0.232</td>
</tr>
<tr>
<td>Sedation</td>
<td>3 (6.7)</td>
<td>1 (11.1)</td>
<td>2 (5.6)</td>
<td>0.497</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

**Table 2. The value of CFI according to neurological deterioration**

<table>
<thead>
<tr>
<th>Value</th>
<th>Neurological deterioration (n=9, 20%)</th>
<th>No Neurological deterioration (n=36, 80%)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total value of CFI during monitoring</td>
<td>38.5±6.4</td>
<td>42.1±7.9</td>
<td>0.055</td>
</tr>
<tr>
<td>Total value of CFI during monitoring in the ipsilateral side</td>
<td>36.0±7.5</td>
<td>40.9±8.8</td>
<td>0.110</td>
</tr>
<tr>
<td>Total value of CFI during monitoring in contralateral side</td>
<td>41.0±4.1</td>
<td>43.2±6.7</td>
<td>0.227</td>
</tr>
<tr>
<td>Delta value of CFI during monitoring</td>
<td>3.7 (0.9–10.4)</td>
<td>2.4 (1.2–4.4)</td>
<td>0.251</td>
</tr>
<tr>
<td>Delta value of CFI during monitoring in the ipsilateral side</td>
<td>10.4 (3.9–14.3)</td>
<td>3.4 (2.5–5.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Delta value of CFI during monitoring in the contralateral side</td>
<td>1.0 (0.5–3.7)</td>
<td>1.1 (0.8–2.3)</td>
<td>0.490</td>
</tr>
<tr>
<td>Percent change of CFI during monitoring (%)</td>
<td>13.2 (1.9–32.8)</td>
<td>6.4 (2.8–10.9)</td>
<td>0.139</td>
</tr>
<tr>
<td>Percent change of CFI during monitoring in the ipsilateral side (%)</td>
<td>28.5 (24.1–60.8)</td>
<td>9.0 (6.8–13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent change of CFI during monitoring in the contralateral side (%)</td>
<td>2.0 (1.1–8.1)</td>
<td>2.7 (2.1–5.2)</td>
<td>0.323</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or median (interquartile range).

CFI, cerebral flow index.
and without neurological deterioration (38.5 ± 6.4 vs. 42.1 ± 7.9, respectively; \( P = 0.055 \)). However, the ipsilateral delta CFI value was significantly higher in patients with neurological deterioration, as compared to those without neurological deterioration (median, 10.4; IQR, 3.9–14.3 vs. median, 3.4; IQR, 2.5–5.6; \( P = 0.008 \)) (Fig. 2A). The delta CFI value on the contralateral side was not different between the patients with and without neurological worsening (median, 1.0; IQR, 0.5–3.7 vs. median, 1.1; IQR, 0.8–2.3; \( P = 0.490 \)) (Fig. 2B). The ipsilateral CFI value decreased by 28.5% (median; IQR, 24.1%–60.8%) at the time of neurological deterioration, as compared to that of 10 minutes before the identification of neurological worsening. The percent changes in the contralateral CFI values did not differ between the groups with and without neurological deterioration (2.0% [1.1–8.1] vs. 2.7% [2.1–5.2], \( P = 0.323 \)).

The individual values of CFI changes at the time of neurological deterioration are summarized in Table 3. Among the nine patients, an abrupt drop in CFI values was observed in seven (77.7%). Patient 9 was a 65-year-old male who presented with a ruptured right anterior cerebral artery aneurysm (Fig. 3). After the aneurysm was secured with coil embolization, non-invasive CBF monitoring was initiated on day 1. On hospital day 8, the CFI suddenly decreased from 44.1 to 30.2 at the ipsilateral site, with a concomitant drop in the GCS score from 13 (E3V5M5) to 11 (E2V5M4). Intracranial pressure (ICP) surged from 3 to 18 mmHg, while cerebral perfusion pressure (CPP) dropped from 98 to 79 mmHg, which was regarded as a cause for CFI fluctuation. With a high suspicion for vasospasm, the patient underwent transfemoral cerebral angiography and was administered intra-arterial nimodipine (2 mg), after which the CFI recovered. However, the CFI values did not change in the two patients who experienced neurological deterioration. A 59-year-old man with an anaplastic astrocytoma in the right medial frontal lobe underwent right frontal lobectomy with gross total tumor removal (Table 3,

![Fig. 2](https://doi.org/10.18700/jnc.240016)

**Table 3.** Change of CFI and perfusion state of the patients with neurological deterioration

<table>
<thead>
<tr>
<th>No.</th>
<th>Acute brain injury</th>
<th>Lesion side/perfusion state</th>
<th>Percent change of CFI on neurological deterioration (R/L)</th>
<th>Delta value of CFI on neurological deterioration (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subarachnoid hemorrhage</td>
<td>L/Hypo</td>
<td>7.2/81.8</td>
<td>3.4/14.6</td>
</tr>
<tr>
<td>2</td>
<td>Moyamoya disease</td>
<td>L/Hyper</td>
<td>17.4/23.1</td>
<td>6.4/7.4</td>
</tr>
<tr>
<td>3</td>
<td>Subarachnoid hemorrhage</td>
<td>L/Hypo</td>
<td>9.0/28.5</td>
<td>4.1/10.4</td>
</tr>
<tr>
<td>4</td>
<td>Ischemic stroke</td>
<td>R/Hypo</td>
<td>7.6/1.1</td>
<td>3.0/0.5</td>
</tr>
<tr>
<td>5</td>
<td>Subarachnoid hemorrhage</td>
<td>L/Hypo</td>
<td>2.1/4.8</td>
<td>1.2/2.3</td>
</tr>
<tr>
<td>6</td>
<td>Moyamoya disease</td>
<td>L/Hyper</td>
<td>1.3/73.3</td>
<td>0.47/23.8</td>
</tr>
<tr>
<td>7</td>
<td>Subarachnoid hemorrhage</td>
<td>L/Hypo</td>
<td>1.1/27.9</td>
<td>0.5/4.9</td>
</tr>
<tr>
<td>8</td>
<td>Moyamoya disease</td>
<td>L/Hyper</td>
<td>0.9/25.1</td>
<td>0.4/10.4</td>
</tr>
<tr>
<td>9</td>
<td>Subarachnoid hemorrhage</td>
<td>R/Hypo</td>
<td>46.0/2.5</td>
<td>13.9/1.0</td>
</tr>
</tbody>
</table>

CFI, cerebral flow index; R, right; L, left; Hypo, hypoperfusion; Hyper, hyperperfusion.
Fig. 3. Case of the cerebral flow index (CFI) change during c-FLOW monitoring. (A) CFI values in a patient with neurological deterioration due to vasospasm. CBF values started to decrease and improve after intra-arterial administration of nimodipine. (B) CFI values in a patient with moyamoya disease who underwent left side double barrel bypass surgery. CFI values increased with neurological deterioration, thereby suggesting hyperperfusion. Arterial spin labeling imaging also identified an increase in cerebral blood flow in the left frontal area. (C) CFI values in a patient without neurological deterioration. CFI values did not change during the monitoring period. CT, computed tomography; MRA, magnetic resonance angiography; Rt, right; Lt, left; MRI, magnetic resonance imaging.
case no. 4). On hospital day 7, the patient experienced worsening of the left hemiparesis, with a concomitant drop in the GCS score from 15 to 13. Acute ischemia in the right anterior cerebral artery territory was suspected; however, the CFI values did not change. Brain imaging revealed fluid collection in the right frontal cortex after surgery, which limited the detection of CFI changes, even with the development of ischemia in the right frontal lobe (Fig. 4A). The other patient (case no. 5) was a 52-year-old male who presented with SAH due to a ruptured left middle cerebral artery aneurysm, which was successfully secured on hospital day 0. On hospital day 7, the patient’s mental status had declined from GCS 15 to 12; however, the CFI values did not change. An acute infarc-

**Fig. 4.** Cases of detection failure during c-FLOW monitoring of neurological deterioration. (A) The brain imaging showed a postoperative fluid collection in the right frontal cortex. Although the patient experienced an ischemia in the right anterior cerebral artery territory, right cerebral flow index (CFI) values did not change. (B) The brain image indicated that it was difficult to detect the change in CFI due to the brain’s deep structure at the probe’s detection position. There has been no change in CFI values (blue and black lines) among patients with neurological deterioration. CT, computed tomography; FLAIR, fluid attenuated inversion recovery; DWI, diffusion weighted imaging; TFCA, transfemoral cerebral angiography; Lt, left; Rt, right.
tion was identified in the left posterior cerebral artery, which was outside the range of c-FLOW monitoring (Fig. 4B).

**DISCUSSION**

In this study, we showed that fluctuations in CFI, a surrogate for CBF, were correlated with the development of neurological deterioration in patients with acute brain injury. Indeed, the ipsilateral CFI values decreased by 28.5% at the time of neurological deterioration compared to that of 10 mins before the neurological worsening. Similarly, the delta value was significantly higher in patients with neurological deterioration than in those without, especially for ipsilateral brain lesions.

An abrupt decrease in CBF is associated with high morbidity, mortality, and poor neurological outcomes [2,36,37]. Therefore, adequate CBF must be maintained during acute and critical periods. Continuous CBF monitoring may be useful for determining the range of optimal CPP in individual patients based on their autoregulation status [38,39]. Various methods for CBF monitoring have been tried [40-42]. However, most of the experimental studies failed to show a correlation between CBF and neurological deterioration [30,31]. The surrogate CBFs were ICP values or the partial pressure of brain tissue oxygen, which had a limitation in accurately representing the CBF [17,18,24,43].

We used a c-FLOW device to continuously measure CBF. In this study, we showed that a drop in CFI values by 30%, as compared to the immediate previous CFI, was meaningful for identifying neurological deterioration in patients with acute brain injury. A fluctuation of < 10% in CFI values, as compared to the previous values, was common and not associated with neurological worsening.

However, this study has several limitations. First, this was a single-center study with a limited number of patients. Therefore, this needs to be validated in a large number of patients with different diagnoses. Second, the baseline CFI values varied for each patient. Therefore, the CFI must be interpreted as a relative change when compared to the baseline value. Although CFI is a surrogate for CBF, absolute CFI values should not be used as a tool for comparing the perfusion status in other patients. Third, inadequate probe placement may have led to abnormally low or high CFI values. Therefore, we repeatedly checked probe placement in each round. If there was a sudden drop in the CFI, we double-checked the probe placement and ruled out false drops in the CFI owing to probe placement errors. Finally, c-FLOW did not show any neurological worsening in two patients. As mentioned above, CFI did not detect changes in the CBF in the posterior circulation or brain tissues underneath the fluid collection.

In conclusion, our study suggests that a significant decrease in CFI could be a sign of neurological deterioration in patients with acute brain injury. Further studies should confirm the clinical utility of the CFI in a large number of patients.

**ARTICLE INFORMATION**

**Ethics statement**

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. 1704-135-848). Informed consent was obtained from family members or healthcare proxies of unconscious patients.

**Conflict of interest**

Tae Jung Kim is an editor-in-chief, and Soo-Hyun Park and Sang-Bae Ko are editorial board members of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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