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# Cerebral hemisphere asymmetry in cerebrovascular regulation in ventilated traumatic brain injury

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## Summary

Disturbances in cerebrovascular regulation in the form of diminished cerebral vasoreactivity (CVR) to carbon dioxide and an altered pressure autoregulatory response (PAR) are common after traumatic brain injury (TBI) and correlate with clinical outcome. Daily assessment of the state of cerebrovascular regulation may assist in the clinical management of TBI patients. This study examined 20 ventilated TBI patients. We employed blood flow velocity (BFV) measurement using transcranial Doppler ultrasonography to assess the impact of injury type (focal and diffuse) on cerebral hemisphere asymmetry in cerebrovascular regulation and to examine whether impairment in CVR and PAR correlate with clinical outcomes. Significant hemisphere asymmetries were found in BFV and PAR. Impairment in CVR was associated with unfavorable outcomes and bilateral CVR impairment predicted mortality.

*Keywords:* Blood flow velocity; cerebral vasoreactivity; pressure autoregulatory response; traumatic brain injury.

## Introduction

Cerebrovascular regulation, in the form of cerebral vasoreactivity (CVR) to carbon dioxide and the pressure autoregulatory response (PAR), is affected after traumatic brain injury (TBI). Impairment in regulation is associated with severity of brain injury and correlates with neurological condition and clinical outcome [1, 2]. Knowledge of the state of cerebrovascular regulation is fundamental to understanding the pathophysiology of TBI and its sequelae in individual patients. Daily assessment of CVR and PAR may assist in the clinical management of TBI patients. However, the asymmetry of CVR and PAR between cerebral hemispheres has not been investigated systematically [4].

The aim of this study was to evaluate the cerebral hemisphere asymmetry of CVR and PAR in relation to focal brain injury and to correlate impairment in such regulation with clinical outcome in ventilated TBI patients.

## Materials and methods

Patients aged less than 70 years with moderate to severe TBI, as defined by post-resuscitation Glasgow Coma Scale (GCS), with a score less than or equal to 12, were included in this study. After surgical intervention, all patients were managed in an intensive care unit under a standard protocol including artificial ventilation and sedation.

Physiological parameters including heart rate, arterial blood pressure (ABP), intracranial pressure (ICP), arterial oxygen saturation, end-tidal carbon dioxide concentration ($EtCO_2$), and jugular oxygen saturation were continuously monitored. Blood flow velocities (BFV) in both middle cerebral arteries were determined by transcranial Doppler as soon as possible after surgery.

To determine CVR, the initial $EtCO_2$ was increased by 1 kiloPascal (7.5 mmHg) using moderate hypoventilation. CVR was quantified as the percent change in BFV per unit change in $EtCO_2$, the CVR ratio. Impaired CVR was defined as a less than 1% change in BFV per unit change in $EtCO_2$. To evaluate PAR, blood pressure at normocapnia level was increased to 20 to 25% above the baseline. PAR was measured as the percent change in BFV per unit change in mean ABP, the PAR ratio. There was deemed to be a loss of PAR if there was more than a 1.5% change in velocity per unit change in mean blood pressure [3].

Intracranial lesions were classified according to CT findings as focal (with intracranial hematoma or unilateral contusion with or without brain swelling) or diffuse axonal injury. Clinical outcome was assessed at 6 months after injury using a Glasgow Outcome Score (GOS). Patients were defined as having a favorable outcome if they had GOS grades indicating good recovery or moderate disability.

## Results

Sixty-six CVR and 68 PAR tests were performed on 20 patients (16 males and 4 females; mean age: 39.3 years, range: 2 to 69 years; median GCS score: 6.5).

Table 1. *Side-to-side differences (in relation to pathology) in BFV, CVR ratio, and PAR ratio in focal and diffuse brain injured patients.*

| | Pathology right side (mean ± SD) | Non-pathology left side (mean ± SD) | Difference (mean ± SD) | p-value |
|---|---|---|---|---|
| *Diffuse injury group* | | | | |
| BFV (cm/s) | 91.59 ± 39.22 | 97.53 ± 47.55 | 5.94 ± 32.87 | NS |
| CVR ratio (%/mmHg) | 2.28 ± 2.46 | 2.58 ± 2.29 | 0.30 ± 1.57 | NS |
| PAR ratio (%/mmHg) | 0.79 ± 0.81 | 0.95 ± 0.86 | 0.16 ± 0.58 | NS |
| *Focal injury group* | | | | |
| BFV (cm/s) | 66.08 ± 20.31 | 81.78 ± 24.17 | 15.71 ± 15.17 | <0.0005* |
| CVR ratio (%/mmHg) | 2.75 ± 2.83 | 3.40 ± 2.61 | 0.66 ± 2.27 | NS |
| PAR ratio (%/mmHg) | 1.55 ± 2.00 | 1.02 ± 0.94 | −0.53 ± 1.69 | 0.033* |

*BFV* Blood flow velocity; *CVR* cerebral vasoreactivity; *PAR* pressure autoregulatory response.

Fourteen patients had focal brain injury. Mortality in this group of moderate to severe brain-injured patients was 40%. Seven patients achieved a favorable outcome at 6 months after TBI.

During the CVR tests, moderate hypoventilation ($EtCO_2$: before vs. after: 30.3 ± 3.5 vs. 38.2 ± 4.0 mmHg, $p < 0.0005$) resulted in raised ICP (16.7 ± 9.3 vs. 22.4 ± 11.2 mmHg, $p < 0.0005$) while ABP remained constant (mean ABP: 84.6 ± 16.7 vs. 86.8 ± 17.4 mmHg, $p > 0.05$). During the PAR tests at normocapnia ($EtCO_2$: 34.2 ± 3.4 vs. 34.4 ± 3.8 mmHg, $p > 0.05$), the induced increase in ABP (mean ABP: 80.9 ± 14.7 vs. 101.6 ± 16.5 mmHg, $p < 0.0005$) did not alter ICP (21.3 ± 11.8 vs. 19.7 ± 12.2 mmHg, $p > 0.05$).

In relation to pathology, significant side-to-side differences were found in BFV (lesion side vs. non-lesion side: 73.8 ± 29.5 vs. 86.5 ± 33.4 cm/s, $p < 0.0005$) and CVR ratio (2.6 ± 2.7 vs. 3.2 ± 2.5%/mmHg, $p = 0.035$) but not in PAR ratio (1.3 ± 1.8 vs. 1.0 ± 0.9%/mmHg, $p > 0.05$). Data were stratified into diffuse and focal brain injury groups (Table 1). In the focal injury group, side-to-side differences were found in BFV and PAR. Although CVR ratio was lower on the lesion side, this did not reach statistical significance. No side-to-side differences were found in the diffuse injury group.

Regarding clinical outcome at 6 months after injury, the mean CVR ratios at different GOS were different ($p = 0.001$), and the CVR ratio of non-survivors was significantly lower ($p < 0.005$). No differences were found in the mean PAR ratio in relation to GOS. Further analysis of the dichotomized CVR and PAR ratios (Table 2) indicated a significant correlation between CVR and clinical outcome and mortality whereas there was no such correlation with PAR.

Table 2. *Correlation between CVR and PAR ratios with clinical outcome and mortality (all measurements).*

| *CVR ratio* | *Preserved* | *Impaired* | *p-value* |
|---|---|---|---|
| Outcome: favorable | 15/42 | 0/24 | 0.002* |
| Mortality: death | 1/42 | 13/24 | <0.0005* |
| *PAR ratio* | *Intact* | *Impaired* | *p-value* |
| Outcome: favorable | 11/51 | 4/17 | NS |
| Mortality: death | 12/51 | 4/17 | NS |

*CVR* Cerebral vasoreactivity; *PAR* pressure autoregulatory response.

Table 3. *Association of impaired CVR and PAR with clinical outcome and mortality. CVR and PAR were determined by TCD within 24 hours of admission.*

| *CVR ratio* | *Preserved* | *Impaired* | | *p-value* |
|---|---|---|---|---|
| | | *One side* | *Both sides* | |
| Outcome: favorable | 7/9 | 0/3 | 0/6 | 0.003* |
| Mortality: death | 2/9 | 2/3 | 6/6 | 0.003* |
| *PAR ratio* | *Intact* | *Impaired* | | *p-value* |
| | | *One side* | *Both sides* | |
| Outcome: favorable | 1/10 | 1/4 | 2/3 | NS |
| Mortality: death | 3/10 | 2/4 | 1/3 | NS |

*CVR* Cerebral vasoreactivity; *PAR* pressure autoregulatory response; *TCD* transcranial Doppler.

CVR and PAR tests were performed within 24 hours of admission in 18 and 17 patients, respectively. Impairment in CVR was significantly associated with worse clinical outcome and mortality (Table 3). All 6 patients with bilateral CVR impairment were non-survivors. Such an association was absent for the PAR tests.

## Discussion

CVR to carbon dioxide and the pressure autoregulation response are mediated through different mechanisms. The PAR is very sensitive to brain damage whereas CVR is more resistant. An asymmetry in the PAR was found in the present study and this is consistent with a previous study [4]. However, no association between PAR impairment and unfavorable outcome was found. The fact that some patients with impaired PAR can be treated may explain the dissociation between PAR impairment and unfavorable outcome. Patients with diminished CVR during the first days after TBI were more likely to have a worse outcome than patients with preserved reactivity. In our group of patients, the CVR ratio of non-survivors was lower and all of them had bilateral CVR impairment.

In conclusion, this study supports the utility of BFV measurement using transcranial Doppler coupled with $CO_2$ and blood pressure challenge in the assessment of cerebrovascular regulation. Cerebral hemisphere asymmetry in cerebrovascular regulation was demonstrated and CVR impairment correlated with unfavorable outcome. In contrast, PAR impairment did not necessarily mean a poor prognosis. Daily assessment of the state of CVR and PAR may help in the clinical management and outcome prediction in moderate-to-severe TBI patients.

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