

## Original Article

## A Comparative Study of Cerebrovascular Reactivity Using Transcranial Doppler Ultrasonography in Sports-Related Concussion Patients

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**Abstract**

**Objective:** This study aimed to investigate the relationship between changes in cerebrovascular resistance under hyperventilation stress and symptom induction in patients with sports-related concussions (SRCs).

**Subjects and Methods:** This study included 51 patients who visited our hospital between January 2020 and December 2023 (19 with a previous history of SRC, 20 without a previous history of SRC, and 12 control subjects). Using transcranial Doppler (TCD), the resistance index (RI) was calculated from the blood flow in the right middle cerebral artery before and after 1min of hyperventilation stress, and the percentage change in RI ( $\Delta$ RI rate) was determined. The presence or absence of symptoms before and after hyperventilation were assessed.

**Results:** The  $\Delta$ RI rate before and after hyperventilation stress was 0.19 in the "Previous History group," 0.25 in the "No-Previous History group," and 0.29 in the "Control group." Symptom induction rates following hyperventilation stress were 52.6% (10/19) in the "Previous History group," 25% (5/20) in the "No Previous History group," and 0% (0/12) in the "Control group." Significant differences were observed in both RI and symptom induction rates between the Previous History and Control groups.

**Conclusion:** In patients with SRC, particularly those with a history of SRC, reduced cerebrovascular reactivity to hyperventilation stress and pronounced symptom induction were observed. These findings suggest that interventions that consider respiratory changes may be beneficial during stepwise return-to-play protocols following the SRC.

**Keywords:** cerebrovascular reactivity; return to sport; sports-related concussions; transcranial Doppler ultrasonography

**Introduction**

Sports-related concussion (SRC) is a form of mild traumatic brain injury (TBI) that results from either a direct impact on the head or an indirect force transmitted to the body that affects the head. The International Sports Concussion Conference defines SRC as "a complex pathophysiological process involving the brain." From an epidemiological perspective, concussions are highly prevalent, particularly in the context of sports-related trauma [1]. An estimated 1.1 to 1.9 million concussions are reported annually in the United States, approximately 20% of which are sports-related [2]. However, it is possible that a significant number of SRCs remain unreported, and the actual incidence may be higher.

In addition to its high prevalence, SRC is associated with prolonged and symptom exacerbation of symptoms due to re-injury. Effective management of SRC involves a stepwise approach, gradually increasing the exercise load upon return to competition [3]. However, this process may exacerbate symptoms and, potentially delay the athletes return to competition. Prior research has indicated that cerebral blood flow diminishes after concussion [4]. Moreover, fluctuations in carbon dioxide (CO<sub>2</sub>) concentration due to respiratory changes during anaerobic exercise may alter cerebrovascular resistance and, contribute to symptom recurrence [5]. However,

the precise relationship between respiratory changes and cerebrovascular resistance in SRC remains unclear [6,7].

Transcranial Doppler (TCD) ultrasonography is widely used to assess the cerebral blood flow and cerebrovascular resistance [8]. This method is particularly valuable for conditions such as cerebral vasospasm following subarachnoid hemorrhage. This study investigated symptom recurrence in patients with SRC by evaluating the changes in cerebrovascular resistance using (TCD) after induced hyperventilation.

**Material and Methods****Data Sources and Study Population**

This retrospective study analyzed the electronic medical records of patients diagnosed with (SRC). We searched the electronic medical records of patients who visited the Sports Head Trauma Outpatient Clinic of the Department of Neurosurgery at Toho University Medical Center Ohashi Hospital, located in Meguro Ward, Tokyo, between January 2020 and December 2023. Patients aged 13 years or older who were examined within 28 days of injury were included in the study. Patients with structural brain injuries identified using by neuroimaging (brain computed tomography [CT] or magnetic resonance imaging [MRI]) were excluded.

Previous research investigating the impact of SRC history has predominantly compared individuals who have experienced one or more SRCs to those without such experience. Some studies have compared multiple SRC experiences in participants with no prior concussions, which is the approach adopted in this research.

Patients with SRC were categorized into two groups based on their previous SRC history: "Previous History" and "No Previous History" groups. In addition, a Control group was selected from patients diagnosed with non-head trauma during the same period. This study was approved by the Ethics Committee of the Toho University Medical Center Ohashi Hospital (approval number H21095 and H24033).

## Methods and Observational Items

The Sports Head Trauma Outpatient Clinic routinely performs medical interviews, physical examinations, Sports Concussion Assessment Tool (SCAT) 5, and (TCD) evaluations for all patients. Through a retrospective review of electronic medical records, we extracted four observational items::

1. Patient basic information (age, sex, height, weight, headache history, previous concussion history, sports type, position)
2. SCAT5 subjective symptom scores (total number and severity of symptoms)
3. Cerebral blood flow evaluation using TCD from the right middle cerebral artery (mean flow velocity, peak flow velocity, pulsation index [PI], and , resistance index [RI])
4. RI change rate ( $\Delta$ RI) and symptom presence before and after hyperventilation.

## Instrumentation

The SCAT5 symptom evaluation is an objective measure of symptoms following SRC. It has been found to be sensitive, reliable, and valid in concussed high school and collegiate athletes [25]. The checklist includes 22 symptoms that are graded on a Likert scale from 0 (not present) to 6 (severe). The total scores represents the total number of symptoms checked and the total severity score.

A TCD ultrasound (2 MHz probe, Nicolet® SONARA®Transcranial Doppler System, Natus Neurology, Middleton, Wisconsin, USA) was used to record blood flow velocity at the M1 segment of the right middle cerebral artery at a depth of 45-55 mm. After identifying the vessel and optimizing the signals based on depth, waveform, and velocity, the ultrasound probe was fixed using a head frame(Natus Neurology, Middleton, Wisconsin, USA).

Cerebrovascular reactivity can be measured using various methods. Although CO<sub>2</sub> inhalation methods have higher short and long-term reproducibility than breath-holding techniques, the latter are low-cost, portable, and minimally invasive. Following previously published protocols, cerebrovascular reactivity was measured using breath-holding and hyperventilation techniques.

After standard TCD measurements in the supine, resting state, the participants were instructed to hold their breath for 20s, followed by 40s of normal breathing. The breath-holding protocol was repeated five times. After a 2-minute recovery period, the participants were instructed to breathe at a rate of 36 breaths per minute using a metronome for 20s, followed by 40 s of normal breathing. This procedure was repeated five times.

The primary evaluation items for the cerebrovascular reactivity protocol were the RI before and after breath-holding and hyperventilation, and the RI change rate ( $\Delta$ RI):  $\Delta$ RI = (post-hyperventilation RI - resting RI) / resting RI(Fig . 1).

$$PI = (\text{Peak flow velocity} - \text{Diastolic flow velocity}) / \text{Mean flow velocity}$$

$$RI = (\text{Peak flow velocity} - \text{Diastolic flow velocity}) / \text{Peak flow velocity}$$

$$\Delta RI = (\text{Post-hyperventilation RI} - \text{Resting RI}) / \text{Resting RI}$$

**Figure . 1.** Calculation Formula of PI, RI and  $\Delta$ RI

## Data Analysis

The analysis included age, sex, height, weight, headache history, previous concussion history, sports type, position, SCAT5 subjective symptom score cerebral blood flow evaluation, RI,  $\Delta$ RI rate, and symptom presence. Comparisons were made among the three groups. Statistical analysis was performed using Welch's t-test or the Kruskal--Wallis test, with significance set at  $p < 0.05$ . The statistical software R (version 4.1.2) was used for all analyses.

## Result

### Patient and Injury Characteristics

We reviewed the electronic medical records of 425 patients during the observation period and extracted data from 51 patients (Tables 1 and 2). Patients were excluded if they had incomplete observation items, were under 13 years of age, or had an structural brain injury on head CT or MRI. The 51 patients were categorized into three groups: 19 in the "Previous History" group, 20 in the "No Previous History" group, and 12 in the "Control" group.

**Table 1: Characteristics and result of SCAT5/TCD**

|   | Patient group    |                     |             | P value |
|---|------------------|---------------------|-------------|---------|
|   | Previous History | No Previous History | Control     |         |
|   | (n=19)           | (n=20)              | (n=12)      |         |
| Age, mean (SD), year                          | 21.9(4.3)        | 19.6(4.0)           | 17.0(3.3)   | <0.05   |
| Sex   |                  |                     |             |         |
| Male (%)                                      | 15(78.9)         | 12(60.0)            | 12(100.0)   | <0.05   |
| Female (%)                                    | 4(21.1)          | 8(40.0)             | 0(0.0)      |         |
| Height, mean (SD), cm                         | 172.7(8.7)       | 167.1(9.2)          | 172.8(4.8)  | 0.132   |
| Weight, mean (SD), kg                         | 73.4(13.7)       | 63.3(17.9)          | 66.8(11.0)  | 0.059   |
| Headache history (%)                          | 5(26.3)          | 5(25.0)             | 2(16.7)     | 0.771   |
| Number of prior concussions, mean (SD), times | 4.2(4.9)         | 0(0.0)              | 0.1(0.3)    | <0.05   |
| Sports  |                  |                     |             |         |
| Rugby (%)                                     | 6(31.6)          | 4(20.0)             | 0(0.0)      |         |
| American football (%)                         | 4(21.1)          | 4(20.0)             | 11(92)      |         |
| Soccer (%)                                    | 4(21.1)          | 4(20.0)             | 0           |         |
| Lacrosse (%)                                  | 1(0.1)           | 4(20.0)             | 0           |         |
| Others (%)                                    | 4(21.1)          | 4(20.0)             | 1(0.1)      |         |
| Collision, Rugby+American football (%)        | 10(52.6)         | 8(40.0)             | 11(91.7)    | <0.05   |
| Positiona                                     |                  |                     |             |         |
| Offence (%)                                   | 7(36.8)          | 9(45.0)             | 7(58.3)     | 0.697   |
| Defence (%)                                   | 8(42.1)          | 9(45.0)             | 4(33.3)     |         |
| Others (%)                                    | 4(21.1)          | 2(10.0)             | 1(0.8)      |         |
| SCAT5   |                  |                     |             |         |
| Number of symptoms, mean (SD)                 | 7.8(7.3)         | 6.8(6.6)            | 1.1(1.4)    | <0.05   |
| Symptom severity, mean (SD)                   | 23.6(32.0)       | 14.3(17.0)          | 1.3(1.6)    | <0.05   |
| TCD   |                  |                     |             |         |
| Mean flow velocity, mean (SD), cm/s           | 57.1(7.87)       | 64.1(10.14)         | 58.9(8.38)  | <0.05   |
| Peak flow velocity, mean (SD), cm/s           | 95.1(15.0)       | 99.9(15.3)          | 100.1(12.2) | 0.428   |
| PI, mean (SD)                                 | 0.98(0.15)       | 0.87(0.13)          | 1.02(0.14)  | <0.05   |
| RI, mean (SD)                                 | 0.59(0.05)       | 0.56(0.05)          | 0.60(0.04)  | <0.05   |
| ΔRI, mean (SD)                                | 0.19(0.08)       | 0.25(0.11)          | 0.28(0.12)  | <0.05   |
| Patient of symptom induction (%)              | 10(52.6)         | 5(25.0)             | 0(0.0)      | <0.05   |

**Abbreviations:** SD, standard deviation; SCAT5, sports concussion assessment tool 5; TCD, transcranial Doppler; PI, pulsatility index; RI, resistance index  
 \*a Rugby was not divided into offense and defense; therefore the FW was tentatively placed in offense and the BK in defense.

**Table2: List of all cases**

| No. | Age (year) | Sex  | Height (cm) | Weight (kg) | Sports            | Position | Number of prior concussions | Headache history |
|-----|------------|------|-------------|-------------|-------------------|----------|-----------------------------|------------------|
| 1   | 21         | Male | 183         | 73          | Soccer            | GK       | 2                           | –                |
| 2   | 17         | Male | 180         | 66          | Soccer            | SB       | 0                           | –                |
| 3   | 21         | Male | 175         | 93          | American football | OL       | 1                           | –                |

|    |    |        |     |     |                   |           |    |   |
|----|----|--------|-----|-----|-------------------|-----------|----|---|
| 4  | 33 | Female | 152 | 46  | Trainer           | -         | 0  | + |
| 5  | 17 | Male   | 160 | 50  | Soccer            | FW        | 0  | - |
| 6  | 20 | Male   | 165 | 74  | American football | RB        | 3  | + |
| 7  | 31 | Male   | 183 | 93  | Rugby             | FB        | 2  | - |
| 8  | 13 | Male   | 165 | 51  | Rugby             | WTB       | 0  | - |
| 9  | 20 | Male   | 168 | 69  | American football | WR        | 1  | - |
| 10 | 21 | Male   | 174 | 72  | Basketball        | GK        | 1  | - |
| 11 | 20 | Male   | 168 | 77  | Rugby             | FL        | 6  | - |
| 12 | 22 | Female | 163 | 51  | Lacrosse          | G         | 0  | - |
| 13 | 22 | Female | 158 | 50  | Lacrosse          | AT        | 0  | - |
| 14 | 19 | Female | 164 | 52  | Lacrosse          | MD        | 0  | + |
| 15 | 19 | Female | 160 | 52  | Cheerleading      | middle    | 0  | - |
| 16 | 17 | Male   | 173 | 74  | Baseball          | inside    | 0  | - |
| 17 | 21 | Male   | 177 | 75  | American football | DB        | 0  | - |
| 18 | 21 | Female | 161 | 54  | Lacrosse          | DF        | 3  | - |
| 19 | 34 | Male   | 183 | 91  | Rugby             | SO        | 14 | - |
| 20 | 21 | Female | 158 | 54  | Karate            | -         | 1  | + |
| 21 | 25 | Male   | 175 | 84  | Rugby             | WTB       | 4  | - |
| 22 | 25 | Female | 169 | 58  | BMX               | freestyle | 20 | + |
| 23 | 14 | Male   | 165 | 42  | Rugby             | WTB       | 0  | - |
| 24 | 25 | Male   | 188 | 87  | Basketball        | G         | 1  | + |
| 25 | 21 | Male   | 174 | 85  | Rugby             | CTB       | 0  | + |
| 26 | 21 | Male   | 171 | 85  | Rugby             | FL        | 5  | - |
| 27 | 17 | Male   | 178 | 70  | Soccer            | CB        | 2  | - |
| 28 | 17 | Male   | 177 | 71  | Soccer            | DF        | 0  | - |
| 29 | 20 | Female | 151 | 48  | Soccer            | MF        | 0  | - |
| 30 | 19 | Male   | 165 | 60  | American football | WR        | 0  | - |
| 31 | 19 | Male   | 184 | 97  | Rugby             | LO        | 0  | - |
| 32 | 19 | Male   | 172 | 70  | Rugby             | FL        | 8  | - |
| 33 | 22 | Male   | 178 | 113 | American football | C         | 0  | + |
| 34 | 21 | Female | 155 | 50  | Soccer            | SB        | 1  | - |
| 35 | 16 | Male   | 175 | 55  | Soccer            | MF        | 3  | + |
| 36 | 18 | Male   | 180 | 85  | American football | DL        | 1  | - |
| 37 | 17 | Male   | 174 | 66  | American football | RB        | 0  | + |
| 38 | 20 | Female | 163 | 56  | Baseball          | Catcher   | 0  | - |
| 39 | 22 | Female | 159 | 60  | Lacrosse          | MF        | 0  | - |
| 40 | 19 | Male   | 174 | 89  | American football | OL        | 0  | - |
| 41 | 15 | Male   | 170 | 49  | American football | TE        | 0  | - |
| 42 | 15 | Female | 172 | 55  | American football | OL        | 0  | + |

|    |    |      |     |    |                   |    |   |   |
|----|----|------|-----|----|-------------------|----|---|---|
| 43 | 15 | Male | 170 | 56 | American football | OL | 0 | - |
| 44 | 15 | Male | 180 | 63 | American football | WR | 0 | - |
| 45 | 13 | Male | 170 | 70 | American football | DB | 0 | - |
| 46 | 18 | Male | 178 | 76 | American football | DB | 0 | - |
| 47 | 26 | Male | 168 | 68 | Wrestling         | -  | 1 | - |
| 48 | 16 | Male | 168 | 72 | American football | DL | 0 | + |
| 49 | 16 | Male | 183 | 70 | American football | WR | 0 | - |
| 50 | 16 | Male | 168 | 56 | American football | TE | 0 | - |
| 51 | 20 | Male | 173 | 78 | American football | S  | 0 | - |

**Abbreviations:** GK, Goal keeper; SB, Side back; OL, Offensive line; FW, Forward; RB, Running back; FB, Full back; WTB, Wing three-quarter back; WR, Wide receiver; G, Guard; FL, Flanker; G, Golie; AT, Attack; MF, Midfielder; DB, Defensive back; DF, Defender; SO, Stand off; CTB, Center three-quarter back; CB, Center back; LO, Lock; C, Center; DL, Defensive line; TE, Tight end; S, Safety

### Patient Demographic Information

No statistically significant differences were observed among the three groups in terms of patient characteristics (height, weight, and history of headache). Mean ages were  $21.9 \pm 4.3$  years for the "Previous History group,  $19.6 \pm 4.0$  years for the "No Previous History group, and  $17.0 \pm 3.3$  years for the "Control group" ( $p < 0.05$ ). Sex composition was as follows: the "Previous History group" consisted of 15 males, the "No Previous History group" had 12 males, and the "Control group" comprised 12 males ( $p < 0.05$ ). The number of previous SRC was  $4.2 \pm 4.9$  in the "Previous History group" ( $p < 0.05$ ). The primary sports were rugby, American football, and soccer, in that order, within the "Previous History group. The "No Previous History" group exhibited a similar representations of rugby, American football, soccer, and lacrosse. American football was the most prevalent sport in the Control group. The percentage of each collision sport (rugby and American football) was 52.6% in the "Previous History established" group, 40.0% in the "No Previous History" group, and 91.7% in the Control group ( $p < 0.05$ ).

### SCAT5 Symptom Score

SCAT5 symptom scores were  $23.6 \pm 32.0$  for the "Previous History group" and  $14.3 \pm 17.0$  for the "No Previous History group, significantly lower at  $1.3 \pm 1.6$  for the "Control group" ( $p < 0.05$ ).

### TCD Cerebral Blood Flow Evaluation

RI of the right middle cerebral artery was measured TCD and was  $0.59 \pm 0.05$  in the "Previous History" group and  $0.56 \pm 0.05$  in the "No Previous History" group, whereas it was  $0.60 \pm 0.04$  in the "Control" group ( $p < 0.05$ ).

### RI Change Rate and Symptom Occurrence during Hyperventilation Challenge

The RI change rate ( $\Delta$ RI) before and after hyperventilation was 0.19 for the "Previous History group, 0.25 for the "No Previous History group, and 0.29 for the "Control group (Fig. 2). Symptom provocation rates during hyperventilation were 52.6% (10/19) for the "Previous History group," 25% (5/20) for the "No Previous History group, and 0% (0/12) for the "Control group (Fig. 3).

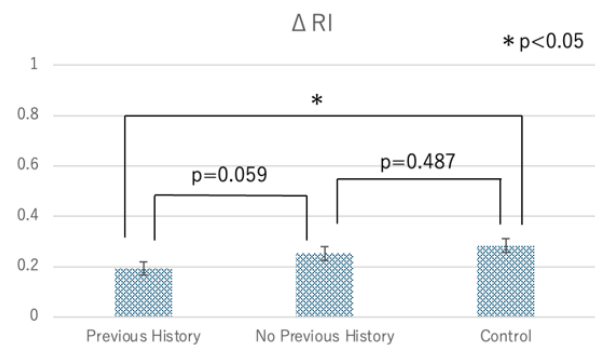


Figure 2. Result of  $\Delta$ RI

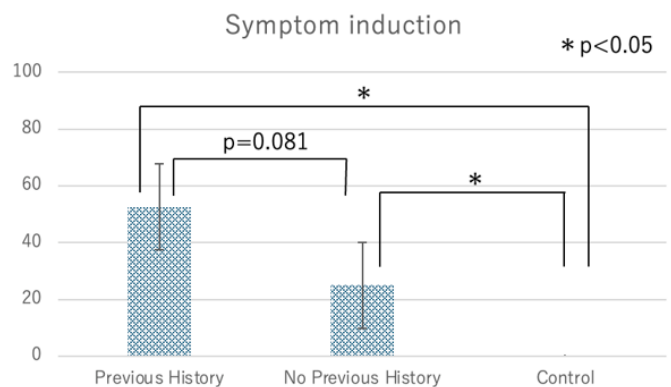


Figure 3. Result of symptom induction

## Discussion

The present study employed a hyperventilation load in patients with SRC. This study aimed to examine the relationship between changes in cerebrovascular reactivity changes and symptom induction. The results demonstrated that in a cohort of patients with a history of SRC, hyperventilatory stress resulted in reduced cerebrovascular reactivity and symptom exacerbation [9-11]. Transient cerebral blood flow changes associated with SRC have been shown to vary across studies, and the detailed pathophysiological mechanisms have remained unclear ([12]). Recently, it has been reported that patients with SRC show differences in cerebrovascular reactivity rather than in cerebral blood flow [13]. In the present study, physiological changes were induced by a hyperventilation load, which allowed for a more detailed visualization of cerebrovascular dysfunction and symptom exacerbation in patients with SRC.

The results of this study revealed that patients with SRC exhibit reduced cerebrovascular responsiveness to arterial CO<sub>2</sub> reduction. Symptoms are elicited when patients are subjected to exercise, leading to ventilatory thresholds.

During mild-to-moderate exercise, hypercapnia causes a decrease in pH and, vasodilation, and an increase in CBF (Cerebral blood flow) [14, 15]. As exercise intensity approaches the ventilatory threshold, arterial blood CO<sub>2</sub> levels decrease due to ventilatory incompatibility [16-18].

Conventional angiographic studies have demonstrated that the diameters of the major cerebral vessels, including the internal carotid artery and the main trunk of the middle cerebral artery, remain unaltered [19]. It was previously thought that changes in contrast media or blood CO<sub>2</sub> concentrations did not cause significant changes unless cerebral vasospasm occurred. Yoshii et al [20], examined the changes in blood CO<sub>2</sub> concentration due to hyper ventilation. They compared patients with minor head trauma and healthy individuals, and demonstrated that the decrease in cerebral blood flow was smaller in the minor head trauma group. This finding suggests that cerebrovascular regulation is impaired in patients with SRC.

The present study evaluated the cerebrovascular effects of hyperventilation using TCD. Similarly, there are reports supporting the potential of TCD in assessing cerebrovascular damage due to SRC [8]. Several studies have reported impaired cerebrovascular reactivity, neurovascular coupling, and dynamic cerebral autoregulation [21-23]. Particularly, an inadequate response to hyper ventilation has been reported [24]. It has also been suggested that cerebrovascular dysfunction may persist even after resolution of clinical symptoms. These results demonstrate altered cerebrovascular function in patients with SRC, and support our findings.

Previous studies have evaluated cerebrovascular reactivity using high CO<sub>2</sub> stimulation. The present study examined cerebrovascular reactivity and symptom induction symptoms during a reduction in CO<sub>2</sub> levels at the ventilatory threshold. This finding is highly beneficial for the development of rehabilitation strategies for SRC. The effects of exercise vary considerably between individuals. A dose-response relationship was observed. Identifying the optimal intensity and frequency of exercise for an individual has the potential to enhance the outcomes after SRC. It is crucial to note that SRC symptoms can manifest or worsen with exercise or exertion, even when the symptoms are not evident at rest [25-28]. The decision to resume competition is typically based on symptom resolution and tolerance to aerobic exercise. In the future, it will be essential to comprehend objective markers of symptom exacerbation and optimize the amount of exercise (intensity, frequency, and duration).

The academic significance of this study lies in its demonstration of the potential for a more objective and comprehensive assessment of patho-

physiology in SRC practice through a combination of physiological indices, such as cerebrovascular reactivity, with conventional neurological findings. In light of these results, it may be advisable to consider therapeutic approaches, such as pharmacotherapy, which can promote functional compensations after brain injury and support environmental adaptation through cognitive rehabilitation. The present study was limited by the small number of cases, lack of blood CO<sub>2</sub> measurements during hyperventilation, and evaluation only during the acute phase. To gain a more comprehensive understanding of SRC pathogenesis, future studies should aim to increase the number of cases, conduct long-term follow-up, and explore more effective therapeutic interventions. The findings of this study have implications in rehabilitation medicine, patient management, and potential treatment strategies.

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## Conflicts of interest

We declare no conflict of interest in the preparation of this document.

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