Chapter 34
Changes in Cerebral Blood Oxygenation Induced by Active Standing Test in Children with POTS and NMS

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Abstract Orthostatic dysregulation (OD) has been classified into subtypes by heart rate and blood pressure; however, the hemodynamics of brains have not yet been revealed. Therefore, we investigated changes in cerebral blood flow and oxygenation during an active standing test to clarify the pathophysiology of two subtypes: postural tachycardia syndrome (POTS) and neurally mediated syncope (NMS). We studied 31 children (15 boys, 16 girls; mean age, 14.0 ± 1.7 years) who presented with OD at the Department of Pediatrics and Child Health, Nihon University School of Medicine between 2009 and 2011. OD was diagnosed using the Japanese clinical guidelines for juvenile orthostatic dysregulation. After a 10-min resting period in the supine position, patients were asked to quickly stand up and keep upright for 10 min. Cerebral blood flow and cerebral oxygenation were measured using transcranial Doppler sonography and near-infrared spectroscopy. POTS showed a significant decrease of oxy-Hb and resistance index (RI), suggesting transient ischemia with maintainable cerebral autoregulation. NMS showed a decrease of oxy-Hb and an increase of RI, suggesting ischemia and impairment of autoregulation.

Keywords Orthostaticdysregulation • Postural tachycardia syndrome • Neurally mediated syncope • Transcranial Doppler sonography • Near-infrared spectroscopy

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1 Introduction

Orthostatic intolerance, known as orthostatic dysregulation (OD) in Japanese pediatrics, is an autonomic nervous system disorder of children and adolescents. The first OD research meeting in Japan was held in 1959 [1], where an original OD study group and proposed diagnostic criteria were developed. Patients with OD often present with various symptoms including vertigo on standing up, fainting in the standing position, and unspecific symptoms and signs in adolescents. The mechanism of these symptoms seems to be related to an imbalance between sympathetic nerves and parasympathetic nerves. The Task Force of Clinical Guidelines for Child Orthostatic Dysregulation of Japan has recently issued clinical guidelines for juvenile OD (version 1) [2], which advocates new diagnostic criteria including a modified Schellong test to classify the subtype of OD for a general pediatrician. While these diagnostic criteria are useful for speculating the pathophysiology, a more simple method for objectively evaluating hemodynamic changes, in particular, flow of central venous return, is required. In the Japanese clinical guidelines, four subsets of OD were recognized using non-invasive beat-to-beat blood pressure and heart rate monitoring: instantaneous orthostatic hypotension (INOH), postural tachycardia syndrome (POTS), neurally mediated syncope (NMS), and delayed orthostatic hypotension (delayed OH). POTS involves marked tachycardia during upright posture without obvious hypotension. The mechanisms responsible were postulated to involve loss of plasma volume, insufficient venous constriction, or hyperadrenergic response to orthostatic stress. The criteria for defining POTS are an increase in heart rate during standing of 35 beats/min or heart rate during active standing of 115 beats/min. NMS involves sudden onset of fainting/near-fainting associated with VAS depression while standing with or without bradycardia [2]. Recently, cerebral hemodynamics have been studied in orthostatic intolerance using Transcranial Doppler (TCD) sonography [3, 4] or near-infrared spectroscopy (NIRS) [5–8]. However, there are very few reports that examine cerebral circulation changes in these patients. We presumed two or more different hemodynamics of brains in each subtype. Thus, in the present study we investigated changes in cerebral blood flow and oxygenation during active standing test to clarify the pathophysiology of POTS and NMS.

2 Methods

We studied 31 children (15 boys, 16 girls) who presented with OD at the Department of Pediatrics and Child Health, Nihon University School of Medicine, between 2009 and 2011. The subset of OD was determined with the Japanese clinical guidelines for juvenile orthostatic dysregulation [2]. The patients were not treated with any drugs. We tested a conventional Schellong's orthostatic test. After a 10-min resting period in the supine position, patients were asked to quickly stand up and keep upright for 10 min. Figure 34.1 presents an overview of the experimental protocol. Blood pressure was measured with a non-invasive beat-to-beat blood pressure

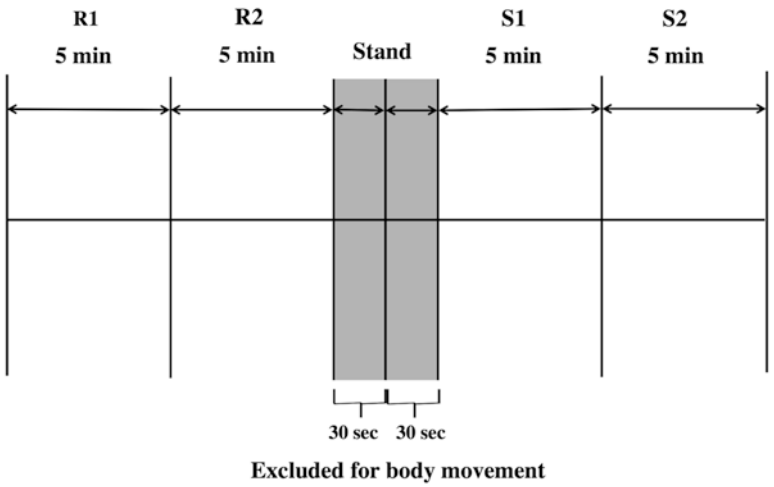

Fig. 34.1 The experimental protocol

monitor (BP-608 Evolution II CS; Omlon Colin Co., Ltd., Tokyo, Japan). Cerebral blood flow was measured by Transcranial Doppler sonography (TCD) (Companion III; Riko Trading Co., Ltd., Tokyo, Japan) and cerebral blood oxygenation was simultaneously measured by near-infrared spectroscopy (NIRS) (TRS20; time-resolved spectroscopy; Hamamatsu Photonicus Co., Ltd., Shizuoka, Japan). Nineteen patients were categorized as POTS, and 12 as NMS. The active standing tests were performed in the same quiet and temperature-regulated room by one physician and one technologist at 9:00 a.m. We terminated the test immediately when standing became impossible, or when patients became hypotensive. In TCD sonography, resistance index (RI) was calculated as a cerebral vascular resistance with the following formula: RI = Vs – Vd/Vs, where Vs and Vd represent systolic flow velocity and diastolic flow velocity, respectively in the middle cerebral artery.

The ethics committee of Nihon University Itabashi Hospital approved this study according to the revised version of the Declaration of Helsinki. Informed consent was obtained from all patients or their parents.

2.1 Statistical Analysis

Data were analyzed with statistical software (JMP8 SAS Institute Inc., Tokyo, Japan). To reduce the influence of body motion, the data for 30 s before and after standing up (for a total of 1 min) were excluded. Data were classified into four groups: R1 (first half of resting time), R2 (second half of resting time), S1 (first half of standing time), and S2 (second half of standing time) as in Fig.34.1. Based on the average value of R2, data were compared using the Dunnett's multiple comparison test. Differences were statistically significant at a P-value ≤ 0.05.

3 Results

3.1 Changes in Cerebral Blood Flow During Standing

RI data are shown in Table 34.1. During standing, RI decreased in 10 patients with POTS and increased in five patients, while RI decreased in three patients with NMS and increased in five patients.

3.2 Changes in Cerebral Blood Oxygenation

Cerebral blood oxygenation data are shown in Table 34.2. During standing, 15 patients with POTS exhibited decreased oxy-Hb, all patients exhibited increased deoxy-Hb, and 18 patients increased total-Hb. During standing, 6 patients with NMS exhibited decreased oxy-Hb, 11 patients increased deoxy-Hb, and 10 patients increased total-Hb. The summary of results is shown in Table 34.3.

Table 34.1 TCD sonography (changes of RI)

POTS					NMS				
	RI					RI			
Patients	R2	S1	S2		Patients	R2	S1	S2	
7	0.64±0.04	0.59±0.04**	0.61±0.04**	↓	22	0.58±0.02	0.54±0.03**	0.55±0.04**	↓
9	0.56±0.02	0.49±0.03**	0.50±0.04**	↓	25	0.59±0.04	0.57±0.09**	0.57±0.05**	↓
10	0.57±0.03	0.53±0.09**	0.50±0.08**	↓	31	0.50±0.04	0.48±0.13	0.50±0.06**	↓
12	0.55±0.03	0.49±0.03**	0.49±0.03**	↓	23	0.37±0.04	0.40±0.05**	0.56±0.11**	↑
13	0.60±0.04	0.58±0.04**	0.55±0.04**	↓	24	0.48±0.06	0.52±0.05**	0.61±0.11**	↑
14	0.51±0.09	0.44±0.03**	0.44±0.04**	↓	20	0.53±0.03	0.54±0.06	0.59±0.08**	↑
16	0.50±0.05	0.43±0.03**	0.42±0.03**	↓	26	0.51±0.09	0.53±0.04	0.59±0.10**	↑
8	0.44±0.04	0.43±0.04**	0.45±0.04	↓	27	0.44±0.05	0.44±0.04	0.46±0.08**	↑
11	0.52±0.05	0.51±0.07*	0.51±0.08	↓	21	0.50±0.04	0.48±0.04**	0.55±0.01**	↓↑
15	0.56±0.05	0.55±0.10	0.52±0.05**	↓	28	0.60±0.02	0.61±0.022	0.60±0.18	–
1	0.49±0.03	0.76±0.03**	0.63±0.02**	↑	29	0.57±0.05	0.56±0.04	–	–
2	0.53±0.03	0.54±0.02**	0.55±0.02**	↑	30	0.56±0.04	0.57±0.03	0.55±0.05	–
17	0.49±0.04	0.50±0.05**	0.54±0.05**	↑	–	–	–	–	–
18	0.53±0.04	0.93±0.14**	0.69±0.18**	↑	–	–	–	–	–
3	0.51±0.05	0.51±0.04	0.56±0.05**	↑	–	–	–	–	–
4	0.60±0.08	0.67±0.02**	0.56±0.01**	↑↓	–	–	–	–	–
19	0.49±0.04	0.50±0.03**	0.47±0.04**	↑↓	–	–	–	–	–
5	0.53±0.06	0.49±0.04	0.52±0.05	–	–	–	–	–	–
6	0.48±0.06	0.48±0.09	0.48±0.06	–	–	–	–	–	–

**P<0.01; *P<0.05; ↑ significantly increased; ↓ significantly decreased due to the Dunnett's multiple comparison test

Table 34.2 Change of oxy-Hb, deoxy-Hb and total-Hb

	Oxy-Hb (mean ± SD: μmol/l)				Deoxy-Hb (mean ± SD: μmol/l)				Total-Hb (mean ± SD: μmol/l)			
Patients	R2	S1	S2		R2	S1	S2		R2	S1	S2	
POTS												
1	222.3 ± 12.3	207.2 ± 13.5**	197.0 ± 11.9**	↓	84.7 ± 9.2	96.7 ± 9.6**	96.8 ± 10.4**	↑	307.0 ± 6.5	304.3 ± 2.0	303.8 ± 0	–
2	84.5 ± 2.3	82.1 ± 2.0**	82.5 ± 2.5**	↓	34.1 ± 1.3	37.4 ± 1.5**	38.4 ± 1.8**	↑	118.6 ± 1.6	119.5 ± 1.6*	120.9 ± 1.2**	↑
3	76.6 ± 1.7	74.5 ± 2.0**	73.6 ± 2.2**	↓	29.3 ± 1.2	34.1 ± 1.6**	36.3 ± 2.0**	↑	105.9 ± 1.0	108.5 ± 1.0**	109.9 ± 1.0**	↑
4	78.1 ± 3.2	74.1 ± 2.8**	69.9 ± 2.4**	↓	34.6 ± 1.9	39.5 ± 2.4**	44.8 ± 2.3**	↑	92.3 ± 1.3	96.0 ± 1.4*	97.3 ± 0.8**	↑
5	75.0 ± 2.8	73.2 ± 1.9**	73.1 ± 2.6**	↓	37.4 ± 1.7	45.2 ± 2.0**	47.4 ± 2.5**	↑	435.7 ± 127.2	627.3 ± 40.3**	638.6 ± 31.9**	↑
6	50.8 ± 12	47.0 ± 1.4**	48.6 ± 1.0**	↓	22.5 ± 0.7	28.5 ± 1.7**	30.0 ± 0.7**	↑	60.6 ± 4.3	72.9 ± 3.8**	72.9 ± 6.9**	↑
7	66.4 ± 1.1	62.8 ± 1.4**	64.7 ± 1.4**	↓	28.7 ± 0.9	32.6 ± 1.8**	33.3 ± 1.0**	↑	112.7 ± 1.8	113.6 ± 1.2**	114.7 ± 1,3**	↑
8	91.8 ± 2.4	89.9 ± 3.5**	89.2 ± 2.6**	↓	35.8 ± 1.7	41.4 ± 3.1**	44.7 ± 2.0**	↑	112.4 ± 2.0	118.4 ± 1.2**	120.5 ± 1.6**	↑
9	55.3 ± 0.9	53.5 ± 1.2**	54.4 ± 1.1**	↓	21.0 ± 0.6	22.8 ± 0.8**	23.9 ± 0.7**	↑	73.3 ± 0.6	75.5 ± 1.3	78.6 ± 0.7**	↑
10	65.6 ± 1.4	63.2 ± 1.6**	64.5 ± 1.8**	↓	35.2 ± 1.2	41.5 ± 1.7**	42.6 ± 1.5**	↑	95.2 ± 0.6	95.4 ± 1.3**	98.0 ± 0.8**	↑
11	86.0 ± 82.2	82.3 ± 2.7**	85.2 ± 4.3	↓	31.4 ± 2.3	38.8 ± 2.9**	40.1 ± 3.1**	↑	127.5 ± 1.4	131.3 ± 1.7**	133.9 ± 2.2**	↑
12	59.9 ± 1.2	59.0 ± 1.5*	60.2 ± 1.4	↓	24.3 ± 0.7	27.5 ± 1.0**	27.9 ± 1.0**	↑	76.3 ± 0.7	76.3 ± 1.0**	78.3 ± 1.0**	↑
13	66.3 ± 1.4	65.4 ± 1.4*	66.4 ± 1.5	↓	28.1 ± 0.9	32.6 ± 1.4**	34.2 ± 1.0**	↑	100.8 ± 1.4	104.7 ± 1.6**	107.1 ± 0.8**	↑
14	87.5 ± 4.1	83.2 ± 3.3**	86.0 ± 3.8	↓	50.5 ± 2.5	58.3 ± 3.1**	60.1 ± 3.0**	↑	117.4 ± 3.0	121.1 ± 2.8**	125.3 ± 2.6**	↑
15	92.2 ± 2.0	90.2 ± 1.8**	92.8 ± 2.0	↓	40.2 ± 1.1	45.0 ± 1.8**	45.7 ± 1.0**	↑	84.2 ± 0.7	86.6 ± 1.1**	88.1 ± 0.8**	↑
16	49.2 ± 1.6	49.1 ± 1.7	49.6 ± 1.5	–	31.0 ± 1.1	34.2 ± 1.9**	36.0 ± 1.4**	↑	94.4 ± 0.8	98.0 ± 1.1**	100.6 ± 1.0**	↑
17	59.1 ± 1.6	59.8 ± 1.5	59.8 ± 1.4	–	33.2 ± 0.9	35.9 ± 1.3**	37.5 ± 1.2**	↑	138.0 ± 2.3	141.5 ± 1.7**	146.1 ± 1.8**	↑
18	289.4 ± 84.2	450.4 ± 67.4**	388.6 ± 48.7**	↑	146.3 ± 63.0	177.0 ± 42.8*	250.0 ± 45.9**	↑	132.3 ± 1.4	135.2 ± 1.8**	138.6 ± 1.5**	↑
19	39.3 ± 3.7	47.2 ± 6.3**	48.4 ± 7.4**	↑	21.3 ± 2.8	25.6 ± 3.6**	24.5 ± 3.9**	↑	80.3 ± 0.8	83.2 ± 1.1**	85.6 ± 0.9**	↑

(continued)

Table 34.2 (continued)

	Oxy-Hb (mean ± SD: μmol/l)				Deoxy-Hb (mean ± SD: μmol/l)				Total-Hb (mean ± SD: μmol/l)			
Patients	R2	S1	S2		R2	S1	S2		R2	S1	S2	
NMS												
20	135.0 ± 41.1	198.4 ± 22.7**	152.0 ± 30.7	↑	48.0 ± 11.7	91.5 ± 22.5**	102.3 ± 16.4**	↑	183.1 ± 37.1	289.8 ± 7.9**	254.3 ± 36.9**	↑
21	50.4 ± 1.2	51.6 ± 1.0**	52.9 ± 2.4**	↑	24.8 ± 0.8	28.1 ± 1.0**	27.8 ± 1.3**	↑	75.2 ± 0.7	79.7 ± 0.8**	80.7 ± 1.7**	↑
22	83.1 ± 2.1	82.0 ± 2.1	84.6 ± 2.4**	↑	40.3 ± 1.4	47.2 ± 2.4**	48.7 ± 1.5**	↑	123.4 ± 1.2	129.3 ± 1.4**	133.3 ± 1.7**	↑
23	68.1 ± 13.5	67.7 ± 9.8	74.3 ± 6.0	–	28.8 ± 5.1	36.3 ± 7.5**	38.2 ± 6.2**	↑	96.9 ± 14.6	104.0 ± 10.1	112.5 ± 3.5**	↑
24	75.1 ± 2.3	74.0 ± 1.8	74.5 ± 1.6	–	32.2 ± 1.5	36.6 ± 1.4**	36.2 ± 1.5**	↑	107.3 ± 1.3	110.6 ± 1.4**	110.7 ± 1.2**	↑
25	68.7 ± 13.6	74.5 ± 12.2	63.1 ± 11.3	–	37.3 ± 7.1	45.9 ± 7.7**	40.5 ± 6.7	↑	106.1 ± 15.8	120.3 ± 13.3**	103.6 ± 10.3	↑
26	93.9 ± 14.7	74.3 ± 11.7**	64.6 ± 11.9**	↓	53.6 ± 13.5	64.1 ± 14.4	70.5 ± 13.2*	↑	147.6 ± 7.2	138.4 ± 7.4*	135.0 ± 7.5**	↓
27	64.7 ± 3.4	64.0 ± 4.2	61.1 ± 5.6**	↓	24.4 ± 2.6	27.3 ± 3.1**	30.4 ± 3.9**	↑	89.1 ± 2.1	91.3 ± 2.4**	91.5 ± 3.0**	↑
28	58.9 ± 22.0	10.8 ± 17.3**	44.5 ± 17.8**	↓	26.6 ± 9.3	9.0 ± 8.2**	27.9 ± 10.4	↓	85.6 ± 30.5	19.8 ± 22.6**	72.4 ± 26.3	↓
29	99.0 ± 2.5	91.4 ± 2.4**	91.1 ± 2.6**	↓	42.2 ± 1.4	50.2 ± 2.8**	52.9 ± 2.0**	↑	141.2 ± 1.6	141.6 ± 1.8	144.0 ± 2.5**	↑
30	81.3 ± 2.4	80.7 ± 3.9	76.7 ± 2.6**	↓	34.7 ± 1.7	40.7 ± 3.8**	45.2 ± 2.1**	↑	116.0 ± 1.2	121.4 ± 1.4**	121.9 ± 1.5**	↑
31	83.7 ± 1.8	82.1 ± 2.4**	84.7 ± 2.4	↓	34.6 ± 1.4	38.5 ± 2.2**	39.8 ± 1.9**	↑	118.4 ± 1.0	120.6 ± 2.1**	124.6 ± 1.4**	↑

**P < 0.01; *P < 0.05; ↑ significantly increased; ↓ significantly decreased due to the Dunnett's multiple comparison test

Table 34.3 Summary of results

	Oxy-Hb	Deoxy-Hb	Total-Hb	RI
POTS				
Number of increase	2	19	18	5
Number of decrease	15	0	0	10
Not significant	2	0	1	2
Others	0	0	0	2
NMS				
Number of increase	3	11	10	5
Number of decrease	6	1	2	3
Not significant	3	0	0	2
Others	0	0	0	2

The numbers denotes the difference between average values over S1 and R1

4 Discussion

POTS showed a significant decrease of oxy-Hb and resistance index (RI) and NMS showed a decrease of oxy-Hb and an increase of RI.

Postural change from supine to upright causes reduction of perfusion pressure in the cerebral artery due to negative hydrostatic pressure. An autoregulatory mechanism (autoregulation) maintains cerebral blood flow at constant levels over a blood pressure range of 60–150 mmHg. Tanaka et al. measured heart rate and blood pressure in healthy children and the parameters returned to the same level as before measurement within 20 s of standing [2]. RI and oxy-Hb are expected to recover to the same (or nearly the same) level. We did not compare RI and oxy-Hb between patients with OD and healthy children. Kim et al. [9] suggest that children in OD had impaired autoregulation of cerebral circulation during the orthostatic stress, and that this dysfunction was not directly affected by decreased systemic arterial pressure. In patients with POTS and NMS, sympathetic hyperactivity may also alter mechanisms responsible for controlling cerebral vascular resistance. TCD sonography has been used to study cerebral hemodynamics during orthostatic testing, and different patterns of cerebrovascular blood flow (CBF) velocity have been described. In POTS, patients experience cerebral hypoperfusion and excessive catecholamine effects when they stand up, which are associated with excessive reductions in systolic CBF velocity, despite maintenance of arterial blood pressure [10, 11]. Measurement of CBF velocity by means of TCD sonography has emerged as a reliable technique for assessing both blood flow and cerebral vasoreactivity [12, 13]. Therefore, in the present study we used TCD sonography to assess cerebral blood flow velocity during active standing test in patients with POTS.

Miyagawa et al. [14] performed an active standing test in 22 patients with OD and 17 normal children, and used TCD sonography to measure flow velocity of the middle cerebral artery (MCA) and anterior cerebral artery (ACA), and to calculate the pulsatility index (PI). In normal children, PI decreased during 1 min after standing, after which the decrease in PI became stabilized at approximately 10 % of the baseline in the supine position. In the patients with OD, PI increased at 15 s after

standing, and then decreased. Therefore, subjects were not classified to the subtype of OD at that time. In the present study, we calculated the RI as a measure of cerebral vascular resistance. RI decreased in 10 patients with POTS and increased in 5 patients, while RI decreased in 3 patients with NMS and increased in 5 patients. These data suggest that cerebral autoregulation was comparatively well maintained in patients with decreased RI (mainly POTS). In contrast, cerebral autoregulation will be difficult to maintain in patients with increased RI (mainly NMS), and will likely result in decreased cerebral blood flow.

The NIRS technique, which is based on the relative transparency of human tissue to near-infrared light with a modified Lambert-Beer law [15], detects changes in oxygenated Hb (oxy-Hb) and deoxygenated Hb (deoxy-Hb) in brain tissue [16, 17]. Tanaka et al. [18] previously reported impaired cerebral circulation in children with chronic fatigue syndrome using NIRS monitoring with qualitative analysis. Further, they quantified precise changes of cerebral hemodynamics during orthostatic stress in school children using NIRS. Kim et al. [9] suggested that impaired cerebral circulation associated with orthostatic intolerance may be caused by failure of autoregulation in the cerebral vessels, and that the use of NIRS during orthostatic test is a potential diagnostic tool for orthostatic intolerance. Hoshi et al. [19] assessed changes in cerebral blood volume (CBV) with NIRS during an active standing test in 17 patients with OD and 16 normal children, and reported that CBV increased in all normal children, but decreased in 10 patients (58.8 %) with OD. In contrast, Soga et al. [20] used NIRS to examine 19 patients with OD, and found that changes of cerebral circulation did not correlate with the change in systemic circulation. In brain ischemia, both cerebral arterial inflow and oxy-Hb decrease. Owing to the increase in cerebral oxygen demand, deoxy-Hb increases. Further, as cerebral blood flow decreases, total-Hb decreases.

There were very few reports that measured quantitative cerebral blood oxygenation; however, our study using TRS20 developed a quantitative study in patients with OD during an active standing test. In the present study, 15 patients with POTS exhibited decreased oxy-Hb, all patients exhibited increased deoxy-Hb, and 18 patients exhibited increased total-Hb. In contrast, 6 patients with NMS exhibited decreased oxy-Hb, 11 patients exhibited increased deoxy-Hb, and 10 patients exhibited increased total-Hb. These data suggest that transient ischemia is a likely pathophysiological mechanism of OD, while irreversible brain ischemia, which decreases total-Hb, is less likely to be so.

In summary, we investigated changes in cerebral blood flow and oxygenation during active standing test to clarify the pathophysiology of POTS and NMS. POTS patients showed significantly decreased oxy-Hb and RI, suggesting transient ischemia although maintained cerebral autoregulation. In contrast, NMS patients exhibited decreased oxy-Hb and increased RI, suggesting ischemia and impairment of autoregulation.

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