CLINICAL NOTE


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Paroxysmal sympathetic hyperactivity (PSH) after severe brain injury is detrimental to the recovery of patients. Pharmacologic management of PSH is difficult and efficacy is unpredictable or incomplete. This report presents 6 cases of PSH after extremely severe traumatic brain injury in which hyperbaric oxygen therapy (HBOT) controlled paroxysmal autonomic changes and posturing in the early subacute phase after limited success with conventional medication regimens. Thus, HBOT may present an option for the management of PSH in addition to pharmacologic therapy. Potential mechanisms for these effects are discussed.

Key Words: Case report: Hyperbaric oxygen therapy; Paroxysmal sympathetic hyperactivity; Rehabilitation; Traumatic brain injuries.

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PAROXYSMAL SYMPATHETIC hyperactivity (PSH), sometimes called dysautonomia, is a clinical syndrome that affects a subgroup of survivors of severe brain injury with an estimated incidence of 8% to 33% in moderate and severe traumatic brain injury (TBI). The syndrome consists of paroxysmal autonomic nervous system changes (eg, increased heart rate, respiratory rate, temperature, blood pressure, sweating, papillary dilation) accompanied by various forms of muscular hyperactivity (eg, decerebrate or decorticate posturing, dystonia). PSH typically appears first in the intensive care setting and may persist into the rehabilitation phase, lasting weeks or months after the injury in individuals who remain in a low-response state.

In a prospective cohort study, subjects with PSH had a significantly worse outcome, longer period of hospitalization, and higher estimated costs than survivors of TBI without PSH. It is believed that misdiagnosis and delayed management may contribute to unnecessary morbidity, although it cannot be confirmed whether the worsened neurologic outcome was caused by the PSH.

The use of hyperbaric oxygen therapy (HBOT) in the treatment of TBI has been controversial. Historically, HBOT was considered to have had a role in only decreasing cerebral blood flow and intracranial pressure while increasing oxygen availability to injured brain cells. However, as highly technical equipment has become available in both animal and clinical studies of TBI, HBOT appears to be working at the mitochondrial level to improve cerebral aerobic metabolism after brain injury. Clinically, HBOT has decreased mortality rates and improved functional outcome in patients with severe brain injury. In our department, HBOT has been used for several decades in the rehabilitative treatment of patients with TBI and seems to improve patients’ recovery from the traumatic coma. Recently, we found that symptoms of PSH in 1 patient with severe TBI quickly disappeared after several HBOT treatments, which to our knowledge has not been reported previously. We then consecutively treated 5 other patients with PSH after severe TBI, and all showed positive responses.

METHODS

Subjects
Six patients (5 men, 1 woman; age range, 8–23y) with PSH after severe TBI received HBOT (table 1). Of the 6 cases, 5 resulted from traffic accidents and 1 resulted from a fall. Cranial computed tomographic scans showed diffuse and focal intracranial lesions. Emergency craniotomy for the evacuation of intracranial hematomas was performed in 3 cases. Further treatments were initiated according to guidelines for the management of severe head injury when patients were transferred to the neurosurgical intensive care unit (ICU). HBOT was defined as the simultaneous occurrence of 5 or more of the following features: (1) tachycardia (heart rate >120 beats/min), (2) tachypnea (respiratory rate >30 breaths/min), (3) hyperthermia (temperature >38.0°C), (4) hypertension (blood pressure >160/110 mmHg), (5) increased muscle tone, (6) decerebrate or decorticate posturing, and (7) excessive sweating. A diagnosis of PSH requires at least 1 daily paroxysm that occurs for at least 3 days. Infections or other possible causes of PSH were ruled out. Appropriately drug therapy was administered to patients with PSH, but the therapeutic effect on the paroxysms was incomplete. HBOT was initiated after the patients were...
stabilized. PSH medications were discontinued within 2 weeks when symptoms resolved from the HBOT.

Hyperbaric Oxygen Therapy

After providing full written informed consent, patients received HBOT in a monoplace hyperbaric chamber at the Hyperbaric Oxygen Center of the Second Military Medical University under the supervision of a specialized technician and a physician. Compression with 100% oxygen up to 1.5 atm absolute occurred at a rate of 1 psi/min. Patients were maintained there for 120 minutes and then underwent decompression at a rate of 1 psi/min to ensure adequate decompression. Treatment was provided once daily for 10 days as a full course of treatment; 5 days later, the second course started. Arterial blood pressure, electrocardiograms, and oxygen saturation were monitored routinely within the hyperbaric chamber. Episodes of PSH were recorded during HBOT and during the next year of follow-up. Glasgow Coma Scale scores before and after HBOT also were recorded (Table 2).

CASE REPORTS

Case 1

Case 1 developed severe PSH in the ICU. Treatment with intravenous midazolam could not relieve the syndrome, and intravenous morphine was effective only temporarily, but was not curative. Propranolol therapy was initiated (10 mg 3 times a day, increased to 30 mg 3 times a day) with minimal effect. Treatment with regular oral bromocriptine, titrated to the maximum tolerated dose, was initiated and only partly relieved but did not stop the episodes. Gabapentin was added up to a stable daily dose of 900 mg, which markedly decreased body temperature, blood pressure, and heart rate, but improvement in muscular tension and sweating was not significant. The patient continued to experience PSH episodes, particularly after such stimulation as sputum aspiration. The patient then received HBOT. After 2 treatments, the frequency of episodes markedly decreased, and they completely stopped after 5 treatments. Medications were discontinued within the next 2 weeks, and there was no recurrence during the subsequent year of follow-up.

Case 2

Case 2 experienced increased body temperature, blood pressure, heart rate, and respiration rate with decerebrate posturing and profuse sweating. The patient was treated for traumatic epilepsy at the early stage; however, treatment with phenobarbital, diazepam, carbamazepine, and sodium valproate showed no therapeutic effects, and electroencephalography showed no therapeutic effects, and electroencephalography showed no

Table 1: Demographic Characteristics of Patients With PSH

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Initial GCS Score</th>
<th>Mode of Injury</th>
<th>CT and MRI Findings</th>
<th>Emergency Surgery</th>
<th>Time to PSH (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>19</td>
<td>4</td>
<td>Motor vehicle collision</td>
<td>DAI, hemorrhage in corpus callosum and R basal ganglia, L temporal lobe contusions, diffuse cerebral swelling, SAH</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>21</td>
<td>5</td>
<td>Motor vehicle collision</td>
<td>DAI, B corpus callosum injury, L frontal lobe and thalamus hemorrhage, L temporal bone fracture, SAH</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>8</td>
<td>5</td>
<td>Motor vehicle collision</td>
<td>DAI, B frontal lobe contusions, R frontal bone fracture</td>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>23</td>
<td>4</td>
<td>Motor vehicle collision</td>
<td>DAI, B frontotemporal lobe contusions, SDH with midline shift</td>
<td>IHR, DC</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>21</td>
<td>4</td>
<td>Motor vehicle collision</td>
<td>R frontotemporal SDH with midline shift</td>
<td>IHR, DC</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>17</td>
<td>4</td>
<td>Fall</td>
<td>R frontotemporal SDH with midline shift</td>
<td>IHR, DC</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: B, bilateral; CT, computed tomography; DAI, diffuse axonal injury; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; IHR, intracranial hematoma removal; L, left; MRI, magnetic resonance imaging; R, right; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

Table 2: Features of PSH Before HBOT and Consciousness Changes After Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tachycardia</th>
<th>Tachypnea</th>
<th>Hypertension</th>
<th>Hyperthermia</th>
<th>Increased Sweating</th>
<th>Posturing</th>
<th>Time to HBOT (d)</th>
<th>GCS Score Before HBOT</th>
<th>GCS Score When HBOT Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>48</td>
<td>9</td>
<td>15</td>
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<tr>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>50</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>–</td>
<td>+</td>
<td>+</td>
<td>62</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: –, absence of symptom; +, presence of symptom; GCS, Glasgow Coma Scale.
epileptic waves. PSH subsequently was diagnosed, and mor-
phine was administered intravenously with minimal effect.
Propranolol and bromocriptine therapy were initiated, and
doses gradually were increased to the maximum tolerated, with
insignificant results. Gabapentin was added up to 600mg 3
times a day without effect. HBOT then was introduced with
excellent response. The frequency of episodes significantly
decreased after 3 treatments, and the episodes stopped after 6
treatments. There was no recurrence after drug withdrawal.

Case 3
Case 3 showed dysautonomic paroxysms with decerebrate
posturing and agitation during episodes. Midazolam, propran-
olol, and bromocriptine had limited effects. Intravenous mor-
phine transiently stopped the paroxysms, but did not prevent
their recurrence. HBOT then was initiated with good effect.
The degree of PSH decreased after 3 treatments, the frequency
was markedly decreased after 5 treatments, and paroxysms
completely resolved after 6 treatments.

Case 4
Case 4 showed paroxysms of PSH in the ICU. Episodes were
inducible (when positioned lying on either side), but also
occurred without an obvious stimulus. Propranolol and bro-
mcriptine initially were used with minimal effect. Gabapentin
then was introduced, with a decrease in frequency and severity
of episodes. Hydrocephalus appeared 2 months later, and the
crises worsened, but improved after placement of a ventricu-
loperitoneal shunt. However, the patient continued to experi-
ence the episodes when stimulated, particularly with muscle
stretches and joint range of motion. HBOT then was performed
with good response. The paroxysms stopped after 5 treatments,
and there was no recurrence with drug withdrawal.

Case 5
Case 5 presented with typical symptoms of PSH, which were
aggravated further after external noxious stimuli. Propranolol
was administered, but soon was discontinued because of severe
bradycardia and hypotension. Bromocriptine and gabapentin
subsequently were introduced with only a partially positive
response; the excessive sweating and dystonia did not clearly
improve. HBOT then was performed with significant effect.
Symptoms were alleviated markedly after 3 treatments and
completely disappeared after 5 treatments.

Case 6
Case 6 presented with hyperthermia, hypertension, tachycar-
dia, tachypnea, excessive sweating, and dystonia. Antibiotics
were prescribed for microbiologically confirmed pneumonia.
These symptoms persisted after the lung infection was con-
trolled, and PSH subsequently was diagnosed. Propranolol and
bromocriptine were administered with minimal effect. Gabapen-
tin was added, and the symptoms were alleviated, but did
not completely resolve. HBOT then was performed with great
effect. Symptoms improved markedly after 3 treatments and
completely resolved after 6 treatments. There was no recur-
rence after drug withdrawal during the next year of follow-up.

DISCUSSION
Pharmacologic management of PSH is difficult, and insuf-
cient data are available to guide such therapy. A limited
number of drugs have been used individually or in combination
to alleviate PSH, such as morphine, midazolam, propranolol,
bromocriptine, baclofen, and gabapentin.14,15 No clear evi-
dence suggests that 1 medication regimen is superior to an-
other, and some drugs seem to work well for some patients, but
not others. In 3 of our cases, narcotic analgesia produced good
immediate responses, but did not prevent PSH episodes. A
combination of bromocriptine and propranolol also showed
limited effect. Propranolol resulted in severe bradycardia and
hypotension in 1 of the 6 cases. Only some patients responded
to gabapentin therapy, which also could not completely stop
PSH and was almost ineffective in alleviating dystonia and
profuse sweating.

To our knowledge, successful application of HBOT under
such conditions has not been reported. We consecutively
reversed 2 patients, and all responded well to the therapy. These
symptoms resolved after 3 to 10 treatments. There was no
recurrence after drug withdrawal in the subsequent year of
follow-up. Numerous studies have provided a large bulk of
evidence supporting the neuroprotective effect of HBOT in
various models of brain injury.16-18

The mortality of patients with severe TBI could be decreased
significantly by using HBOT, although there still is controversy
surrounding long-term prognosis.12,19 Whether HBOT has
therapeutic effects on chronic brain injury (CBI) is unknown.
Those who support HBOT in managing CBI believe there are
inactive cells that have the potential to recover in many types
of brain injuries, and HBOT possibly could activate such
processes. In clinical practice, we find that many patients with
brain injury progress spontaneously from coma to conscious-
ness and show possible recovery of certain cognitive functions.
This phenomenon of spontaneous recovery from brain injury
suggests that some brain cells that have lost function can regain
it, even after long periods. Recent studies have shown that
HBOT could facilitate functional recovery of patients with
CBI.20-22 Consistent with our clinical observations, and sug-
gests that HBOT may stimulate inactive cells to resume normal
function.

The occurrence of PSH after TBI closely correlated with
central autonomic neuron injury, including the hypothalamus,
thalamus, or mesencephalon.23 Damage to these structures was
accompanied by severe disturbances in consciousness. Clinical
observations show that PSH will stop spontaneously with re-
covery of consciousness in some cases, suggesting that inacti-
ved neurons, which have functional restorative potential, may
exist in these key sites. Activating functions of devitalized
neurons through various methods may improve patients’ per-
formance and relieve PSH. In our cases, HBOT showed good
therapeutic effect in these 6 patients with refractory PSH,
suggesting that HBOT is a therapeutic option in addition to
medication. After HBOT, consciousness improved to various
degrees, suggesting that the therapeutic effect of HBOT on
PSH closely correlated with its effect on neuronal functional
recovery.

Study Limitations
The main limitation of this series is that we could not
exclude all patient changes caused by spontaneous recovery.
Further clinical trials are required to validate the therapeutic
effect of HBOT in patients with PSH and explore its underlying
mechanism.

CONCLUSIONS
Pharmacologic management of PSH is difficult, and efficacy
is unpredictable or incomplete. HBOT may have therapeutic
effects on patients with PSH, with improvement in conscious-
ness to various degrees. The mechanism of these effects may
be that HBOT has a positive role in stimulating restoration of
normal function in inactive neurons. HBOT may represent an
option for PSH management in addition to pharmacologic therapy.

References

Supplier
a. Shanghai Yangyuan Medical Hyperbaric Oxygen Chamber Manufacture, 600 Gugao Rd, Pudong New District, Shanghai, China 201208.