Effect of Hyperoxia on Cerebral Blood Flow Velocity and Regional Oxygen Saturation in Patients Operated on for Severe Traumatic Brain Injury—The Influence of Cerebral Blood Flow Autoregulation

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BACKGROUND: The effect of normobaric hyperoxia on brain oxygenation in the presence or absence of intact autoregulation has not been studied previously in acute traumatic brain injury (TBI).

METHODS: In this prospective clinical investigation of 50 patients operated on for severe TBI, cerebral blood flow (CBF) velocity in the middle cerebral artery was measured using transcranial Doppler. Regional cerebral oxygen saturation using near-infrared spectroscopy at 3 different fractions of inspired oxygen (FiO₂) (0.4, 0.6, and 1) was measured in the last 25 of these patients.

RESULTS: There was no difference in the hemodynamic and respiratory variables except for PaO₂, which increased with increasing FiO₂. The CBF velocities and pulsatility indices did not vary at different levels of FiO₂ (0.4, 0.6, and 1) both on the operated and on the nonoperated side. The regional cerebral oxygen saturation as evaluated by bifrontal near-infrared spectroscopy sensors increased with increasing FiO₂ on the operated (pathologic) side with impaired cerebral autoregulation and not with intact autoregulation.

CONCLUSIONS: In severe TBI, middle cerebral artery CBF velocity is not affected by hyperoxia in both the pathologic and the normal side. The cerebral oxygen saturation increased with increasing arterial hyperoxia in the operated cerebral hemisphere and remained within baseline range in the nonoperated hemisphere. Impairment in the cerebral autoregulation in the pathologic hemisphere contributes to this luxury oxygenation.

INTRODUCTION

Recent evidence has shown that monitoring cerebral oxygenation and improving oxygenation to the brain after traumatic brain injury (TBI), especially when cerebral hypoxia exists, may result in improvement in the biochemical milieu and in turn, the neurologic outcome. One of the simplest ways to improve cerebral oxygenation is by producing hyperoxia by increasing the fraction of inspired oxygen (FiO₂) in mechanically ventilated patients. In patients with TBI, this normobaric hyperoxia (NBH) has been shown to improve brain oxidative metabolism and decrease intracranial pressure (ICP). The risk of...
cerebral hypoxia is most acute in the first 24–48 hours after injury. The administration of a high FiO2 (0.6–1.0) in the emergency room may be justifiable until admission to the intensive care unit for the placement of invasive neurocritical care monitoring systems. Thereafter, the FiO2 levels need to be carefully titrated to prevent cerebral hypoxia. In a phase 2 clinical trial, compared with standard care (control treatment) combined hyperbaric oxygen NBH treatments significantly improved markers of oxidative metabolism in relatively uninjured brain as well as pericontusional tissue, reduced intracranial hypertension, and showed improvement in markers of cerebral toxicity. There was a significant reduction in mortality and improved favorable outcome as measured by Glasgow Outcome Scale. The combination of hyperbaric oxygen and NBH therapy appears to have potential therapeutic efficacy compared with the 2 treatments in isolation. On the other hand, hyperoxia within the first 24 hours of hospitalization is associated with worse short-term functional outcomes and higher mortality after TBI. Although the mechanism for this finding has not been completely elucidated, it may involve hyperoxia-induced oxygen-free radical toxicity with or without vasoconstriction. Thus, there seems to be contradictory literature on the usefulness of hyperoxia in TBI.

Cerebral blood flow (CBF) pressure autoregulation is impaired in TBI. How this affects the response of the brain to NBH has not been previously investigated.

The objective of the current study is to evaluate the effect of NBH on CBF velocity as examined by transcranial Doppler (TCD) and on cerebral oxygenation as assessed by near-infrared spectroscopy (NIRS) in operated patients with severe TBI. It is also intended to study the effect of hyperoxia on cerebral oxygenation in the presence of impaired cerebral autoregulation (CAR).

**METHODS**

Fifty adult patients aged between 18 and 65 years with TBI were recruited into the study on the basis of convenience sampling, after approval by the institutional ethical committee and written informed consent from the next of the kin. Pregnant women, patients with diffuse brain injury, pediatric patients, and nonavailability of consent were the exclusion criteria for this study. All the patients were managed according to the Brain Trauma Foundation guidelines in a neurointensive care unit. All the patients underwent a craniotomy for evacuation of an extradural hematoma, a subdural hematoma, or a contusion within 24 hours of the injury and the bone flap was replaced at the end of surgery. Postoperatively, mechanical ventilation was facilitated with sedation using morphine or fentanyl. Morphine was used in doses of 8 mg every 4 hours and fentanyl was used as a continuous infusion of 1–2 μg/kg/hour. Ventilator settings were adjusted to maintain an arterial carbon dioxide pressure between 32 and 40 mm Hg. Mean arterial pressure (MAP) was targeted to 90 mm Hg and hypotension caused by intravascular volume depletion and anemia were initially corrected with intravenous fluids and packed red cells, respectively; vasopressor (noradrenaline) was added if required to maintain hemodynamic stability. Hemoglobin concentration was maintained at least at 10 g/dL. Serum sodium level was monitored twice a day and corrected if any abnormality was detected. All patients were managed to achieve euglycemia (140–180 mg/dL). The CBF velocity and TCD examinations were performed on the third to sixth day after surgery. This time window was chosen because the acute changes in the brain blood flow dynamics would have settled by then and the delayed ischemic phase would have commenced.

Examination of the CBF velocity changes with changing FiO2 was performed using a TCD machine (Digi-Lite [Rimed Ltd, Raanana, Israel]). A 2-MHz probe was used to insonate the middle cerebral artery (MCA) on both the operated and nonoperated side. Systolic, diastolic, and mean velocities and pulsatility index (PI) were measured at a baseline FiO2 of 0.4. Then, the FiO2 was increased to 0.6 and 1.0 and the same measurements were repeated after stabilization for 15 minutes at each FiO2. Arterial blood gas was analyzed at each level of FiO2. A transient hyperemic response test was performed on both sides to assess the CAR. To perform this test, the ipsilateral common carotid artery was compressed for 5 seconds while MCA flow velocity was being monitored. The ratio of the peak systolic velocity in the second waveform after the release of compression to the systolic velocity before compression (transient hyperemic response ratio [THRR]) was calculated. If it was >1.1, autoregulation was considered to be intact, and if it was ≤1.0, it was considered as impaired.

In the latter half of the study, when the department had acquired an NIRS machine, regional cerebral oxygen saturation (rSO2) was monitored from the bilateral frontal regions. Two 4-wavelength sensors (EQUANOX Advance Model 8004CA) (Nonin Medical Inc., Plymouth, Minnesota, USA) were applied on the forehead 6–8 cm apart and connected to EQUANOX Model 7600 Regional Oximetry System (Nonin Medical Inc.). At each FiO2 level, rSO2 values were noted both on the operated and on the nonoperated sides. In addition, association of the rSO2 values with the presence or absence of intact autoregulation was verified.

Additional data collected included heart rate (HR), MAP, minute volume (MV), pH, partial pressure of carbon dioxide (PaCO2), and partial pressure of oxygen (PaO2) on arterial blood gas analysis and the demographic data such as age, gender, diagnosis of TBI pathology, type of surgery, and Glasgow Coma Scale score.

**Statistical Analysis**

A repeated measures analysis of variance was used to compare HR, MAP, blood gases, TCD flow velocities, and the rSO2 values at the 3 FiO2 values. A P value <0.05 was considered significant. The data are presented as mean values ± standard deviation. SPSS software version 17.0 (SPSS Inc., Chicago, Illinois, USA) was used for the analysis.

**RESULTS**

Fifty patients were included in the study. Their mean age was 38 ± 13 years. Forty-four were male and 6 were female. Most of the patients had an extradural hematoma (n = 29) on the initial computed tomography scan imaging. This result was followed by a subdural hematoma (n = 13) and a parenchymal contusion (n = 8). The patients’ median Glasgow Coma Scale score was 7 (interquartile range, 5–7). All 50 patients underwent a TCD study to evaluate the CBF velocity. The mean time when the TCD study was performed was 3.8 days (range, 3–6 days) after TBI. Of the 50 patients, 25 also underwent NIRS study at different levels of FiO2.
HR, MAP, MV, pH, and PaO₂ values were comparable at the 3 levels of FiO₂. As expected, PaO₂ values were progressively higher with increasing FiO₂ (Table 1). TCD parameters (systolic velocity, diastolic velocity, mean velocity, and PI) were comparable at the 3 FiO₂ levels. They were also comparable between operated and nonoperated sides (Table 2). The rSO₂ values did not change with increasing FiO₂ on the nonoperated side but there was an increase in rSO₂ at an FiO₂ of 0.6 and 1.0 compared with baseline on the operated side. The rSO₂ at baseline was also higher on the operated side with TBI compared with the nonoperated side, whereas 9/25 (36%) of patients showed impaired CAR on the nonoperated side, whereas 4/16 (25%) of patients showed impaired CAR on the operated side.

### DISCUSSION

In this study, we did not observe any change in the CBF velocities with increasing FiO₂ on both the operated and the nonoperated sides. Increase in the FiO₂ resulted in increase in the rSO₂ in the operated side, whereas this effect was not seen on the nonoperated side. When the relationship between CAR and rSO₂ was analyzed, an increase in the rSO₂ with increasing FiO₂ was observed only in patients with impaired CAR.

We used rSO₂ to measure cerebral oxygenation in this study. The advantages of rSO₂ include that it offers a noninvasive and continuous measurement of cerebral oxygenation. It is a trend monitor and bilateral measurement is possible, which is useful in patients with unilateral injury, in whom the contralateral side acts as control. It has a good correlation with other brain oxygen monitors. The disadvantage of rSO₂ is that it is an evolving technology. The exact portion of the brain from where the measurement is made is difficult to predict. The presence of pneumocephalus (postoperative), blood clot (postoperative), and scalp edema might give erroneous readings.

In contrast, the brain tissue oxygen tension (PbtO₂) monitor has the advantage of being a direct measure of the PbtO₂ but it is invasive, measures very focal area, and bilateral measurement is not possible unless 2 separate probes are placed. A comparative study with computed tomography angiography—based findings (CBF, relative cerebral blood volume, mean transit time) will

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**Table 1. Hemodynamic and Respiratory Variables During the Study Period in 50 Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FiO₂ = 0.4</th>
<th>FiO₂ = 0.6</th>
<th>FiO₂ = 1.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per minute</td>
<td>87.5 ± 18.8</td>
<td>88.6 ± 16.4</td>
<td>86.7 ± 17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>93.7 ± 14</td>
<td>93.9 ± 13</td>
<td>94.4 ± 12.5</td>
<td>NS</td>
</tr>
<tr>
<td>Minute volume, L/minute</td>
<td>6.3 ± 1.3</td>
<td>6.3 ± 1.4</td>
<td>6.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.07</td>
<td>7.42 ± 0.06</td>
<td>7.42 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>34.5 ± 4.5</td>
<td>34.7 ± 4.4</td>
<td>34.8 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>146 ± 38</td>
<td>229 ± 62</td>
<td>414 ± 68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are given ± standard deviation. NS, not significant.

**Table 2. Transcranial Doppler Flow Velocities in the Middle Cerebral Arteries on the Nonoperated and Operated Sides During the Study in 50 Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FiO₂ = 0.4</th>
<th>FiO₂ = 0.6</th>
<th>FiO₂ = 1.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonoperated side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vs, cm/second</td>
<td>96 ± 26</td>
<td>98 ± 25</td>
<td>96 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>Vd, cm/second</td>
<td>42 ± 14</td>
<td>42 ± 15</td>
<td>43 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Vm, cm/second</td>
<td>60 ± 18</td>
<td>59 ± 15</td>
<td>59 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>PI</td>
<td>0.93 ± 0.29</td>
<td>0.96 ± 0.34</td>
<td>0.91 ± 0.27</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Operated side                 |            |            |            |         |
| Vs, cm/second                 | 86 ± 23    | 86 ± 18    | 86 ± 21    | NS      |
| Vd, cm/second                 | 36 ± 13    | 37 ± 13    | 37 ± 15    | NS      |
| Vm, cm/second                 | 51 ± 14    | 52 ± 13    | 52 ± 15    | NS      |
| PI                            | 1.04 ± 0.53| 1.00 ± 0.49| 0.99 ± 0.40| NS      |

Values are given ± standard deviation. Vs, systolic velocity; NS, not significant; Vd, diastolic velocity; Vm, mean velocity; PI, pulsatility index.

**Table 3. Regional Cerebral Oxygen Saturation Values on the Operated and Nonoperated Sides at Different Inspired Oxygen Levels in 25 Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FiO₂ = 0.4</th>
<th>FiO₂ = 0.6</th>
<th>FiO₂ = 1.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonoperated side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rSO₂, %</td>
<td>68 ± 8</td>
<td>69 ± 9</td>
<td>70 ± 8</td>
<td>Not significant</td>
</tr>
<tr>
<td>Operated side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rSO₂, %</td>
<td>76 ± 10</td>
<td>80 ± 12</td>
<td>81 ± 14</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are given ± standard deviation.

**Table 4. Changes in the Regional Cerebral Oxygen Saturation Values with Changes in the Inspired Oxygen Levels on the Operated Side in Patients with Impaired and Intact Cerebral Autoregulation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FiO₂ = 0.4</th>
<th>FiO₂ = 0.6</th>
<th>FiO₂ = 1.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral autoregulation impaired (n = 9), %</td>
<td>87.0 ± 2.1</td>
<td>93.9 ± 3.5</td>
<td>98.5 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral autoregulation intact (n = 16), %</td>
<td>71.1 ± 8.3</td>
<td>72.6 ± 7.8</td>
<td>72.5 ± 8.6</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Values are given ± standard deviation.
throw more light into understanding the impact of hyperoxia in head injury. However, in this preliminary study, we chose to use rSO2 as a measure of cerebral oxygenation.

**Effect of Hyperoxia on CBF as Assessed by TCD**

In the current study, in patients operated on for severe TBI, we did not find any changes in the MCA CBF velocity with increasing FiO2 on days 3–6. Similar findings were noted in a previous study using positron emission tomography. The investigators did not observe any change in the CBF and cerebral metabolic rate of oxygen (CMRO2) with hyperoxia on the first day after TBI. In contrast, Menzel et al. observed an inverse relationship between CBF as assessed by xenon computed tomography and FiO2 within 96 hours of injury. The potential effect of xenon on the cerebrovascular reactivity by itself and its influence on hyperoxia-induced reduction in CBF could not be excluded. Similarly, a small reduction in CBF velocity in the MCA along with decrease in ICP was seen with hyperoxia (FiO2 = 1) in a large study involving 186 patients. However, the study sample was mixed, with both operated and nonoperated patients being included in the study. Our sample consisted of patients with severe TBI and all the patients had undergone surgery. The PI, a surrogate measure of ICP, was similar across various FiO2 levels, indicating minimal change in the ICP with hyperoxia in our study.

The timing of investigation in our patients (3–6 days after surgical decompression) is chosen in such a way that the beneficial effects of surgical decompression have more or less stabilized. After decompressive craniectomy, a study found a significant reduction of the ICP directly after craniectomy, from 36.4 mm Hg (range, 18–80 mm Hg) to 12.6 mm Hg (range, 2–51 mm Hg). During the following 72 hours, the investigators observed an increase in ICP during the first 8–12 hours after craniectomy, reaching approximately 20 mm Hg, and later leveling out at approximately 25 mm Hg. Thus, the effect of surgical decompression on intracranial dynamics is stabilized and the results seen are the effect of administration of higher concentration of oxygen.

**Effect of Hyperoxia on rSO2**

Studies examining the effect of hyperoxia on cerebral metabolism have shown variable results in patients with TBI. Both improvements in CMRO2 in at-risk brain tissue and no change in CMRO2 have been documented. Rockswold et al. compared the effects of hyperbaric hyperoxia (HBH), NBH, and standard care on PbtO2, metabolism, and ICP in patients with severe TBI. Both HBH and NBH resulted in increase in PbtO2 and decrease in lactate levels on microdialysis but HBH had a more robust effect. A similar increase in SpO2 (jugular venous oxygen saturation) and PbtO2 after hyperoxia (FiO2 = 1) compared with baseline (FiO2 = 0.3–0.5) was seen in a larger population of TBI.

None of these studies examined the influence of CAR on the results of hyperoxia on rSO2. Alterations in CAR are common in the first 4–5 days after TBI and not only contribute to the pathophysiology of TBI but also have a bearing on the outcome. In this study, we examined whether presence or absence of CAR, as assessed by THHR on TCD, influences the response to hyperoxia and found that an increase in rSO2 from normal levels is seen in patients only when CAR is impaired. This finding suggests that on the nonoperated side, after focal TBI, arterial hyperoxia does not lead to an increase in cerebral oxygenation, when autoregulation is intact. Although the nonoperated side may not be totally normal, the minimal diffuse injury might have preserved the normal physiologic response in terms of autoregulation. This physiologic response (cerebrovascular reactivity to oxygen) is hampered when CAR is impaired, so that the rSO2 increased passively with increasing PaO2. Our hypothesis for this differential response is that intact autoregulation causes vasodilatation in response to hyperoxia on the normal side, whereas on the side with impaired autoregulation, hyperoxia does not change the vascular resistance. A study that looked at the effect of hyperoxia reported that NBH increased PaO2 and PbtO2 and significantly decreased lactate pyruvate ratio in patients in whom baseline brain lactate levels were increased, suggesting that NBH improved the brain redox state.

The relationship between CAR, CBF (velocity), and oxygenation is nonlinear. Theoretically, if autoregulation is intact, increase in FiO2 should result in corresponding reduction in CBF (velocity). On the operated side, we postulate absence of autoregulation as a mechanism for increase in cerebral oxygenation with failure of reduction in blood flow corresponding to increase in oxygenation. Hence, TCD flow velocity remains the same but oxygenation increased.

There are controversial data on the beneficial effects of hyperoxic therapy on the outcome of TBI. NBH in patients with severe TBI improves the indices of brain oxidative metabolism. A recent study has shown that oxygen therapy by mechanical ventilator in the first 6 hours after injury can improve the final Glasgow Outcome Scale score, Barthel index, and modified Rankin Scale score. It could also improve long-term outcomes and enhance rehabilitation and the quality of life. In a diffusion tensor imaging study, the investigators identified a rim of perilesional cytotoxic edema and hyperoxia that resulted in an increase in the apparent diffusion coefficient toward normal (P = 0.02). They reported that hyperoxia may result in benefit within the perilesional rim of cytotoxic edema. Hyperoxia in combination with 50% decrease in MV showed pronounced increase in partial brain oxygen tension (pbrO2) and decrease in brain lactate. Acute hyperoxia significantly improves pressure autoregulation. The vasconstriction induced by acute hyperoxia may allow the cerebral vessels to respond better to transient hypotension.

In contrast, in various subsets of critically ill patients, arterial hyperoxia was associated with poor hospital outcome. Hyperoxia was associated with increased mortality in patients after cardiac arrest, stroke, and TBI. The data from 1 study suggest that supranormal oxygen may aggravate secondary brain damage after severe TBI. In ventilated patients with TBI admitted to the intensive care unit, arterial hyperoxia was independently associated with higher in-hospital case fatality. The investigators suggest that unnecessary oxygen delivery should be avoided in critically ill ventilated patients with TBI. Another study suggested that the baseline metabolic state should be taken into account when applying NBH to patients with TBI. Hyperoxia increased PbtO2 and significantly decreased lactate pyruvate ratio only in patients in whom baseline brain lactate levels were increased. In patients with normal baseline brain lactate levels, no significant changes were found. In a pediatric TBI study, the
magnitudes of the PbtO2 response was correlated with Pao2 and Cao2 (oxygen concentration, arterial). The PbtO2/Pao2 ratio (oxygen reactivity) varied between patients, was related to the baseline PbtO2, and was inversely related to outcome. A greater response appears to be associated with worse outcome. These results are similar to the results of our study in that the response to hyperoxia was better in the patients in whom CBF autoregulation is impaired. Autoregulatory impairment prognosticates poorer outcome.

**Limitations and Strengths**

Acute changes after TBI are maximally seen in the first 72 hours. Our study was performed between days 3 and 6, and therefore the changes in MCA flow velocities and cerebral oxygenation are different from those observed in the initial 72 hours. This period was selected to minimize the confounding effects of hemodynamic instability, anemia, and effect of postoperative edema affecting the TCD and oxygenation measurements.

We selected THRR to assess CAR because this test is noninvasive and repeatable and has been validated as a measure of testing CAR. However, THR may be inappropriate in patients with carotid artery disease, in whom alternative methods should be used. THR is useful to test only the lower limit of CAR. Compression of the carotid body may occasionally cause bradycardia. All our patients were young with no positive history of cerebrovascular disease and no patient developed bradycardia during the test. There are other tests of static autoregulation too. One method is through changing the systemic arterial pressure by injecting a vasopressor and measuring MCA flow velocities using a TCD at 2 different MAP values. However, this technique involves injection of a vasoactive drug systemically with its attendant risks. One more method of assessing autoregulation is by measuring the pressure reactivity index. This technique requires ICP monitoring and a specialized software to draw a correlation between MAP and ICP.

Assuming that the contralateral side is normal may not be totally true. Although grossly the brain looked normal on the contralateral side on a computed tomography scan, there might be diffuse injury of varying degree. However, the fact that CAR was intact on the normal side suggests that the injury to the brain may not be significant.

Our study population belonged to a homogeneous group of operated patients with TBI whereas earlier studies had a heterogeneous mix of operated and nonoperated patients with both focal and diffuse lesions. More importantly, unlike previous studies evaluating the effect of hyperoxia on cerebral oxygenation, this study evaluated the influence of CAR on the rSO2 response to hyperoxia.

A particular problem with NIRS is that one is never sure how much of the measured value may be contributed to by the extracranial vasculature. This might be a particular problem on the operated side because of local swelling and possibly hyperemia of the scalp secondary to the surgical wound. Therefore, the values in this study may be taken as trend indicators rather than absolute. However, we chose NIRS because it is noninvasive and can continuously and bilaterally monitor oxygenation compared with the more invasive brain tissue oxygen and jugular oxygen monitoring techniques, which provide only focal or unilateral information.

**CONCLUSIONS**

NBH failed to increase rSO2 in patients with intact CAR but significantly increased rSO2 in patients with impaired CAR.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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