Review article

Research progress in traumatic brain penumbra

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Objective  Following traumatic brain injury (TBI), brain tissue that surrounding the regional primary lesion is known as traumatic penumbra; this region may undergo secondary injury and is considered to have the potential to recover. This review aimed to reveal the existence and significance of traumatic penumbra by analyzing all relevant studies concerning basic pathologic changes and brain imaging after TBI.

Data sources  We collected all relevant studies about TBI and traumatic penumbra in Medline (1995 to June 2013) and ISI (1997 to March 2013), evaluated their quality and relevance, then extracted and synthesized the information.

Study selection  We included all relevant studies concerning TBI and traumatic penumbra (there was no limitation of research design and article language) and excluded the duplicated articles.

Results  The crucial pathological changes after TBI include cerebral blood flow change, cerebral edema, blood-brain barrier damage, cell apoptosis and necrosis. Besides, traditional imaging method cannot characterize the consequences of CBF reduction at an early stage and provides limited insights into the underlying pathophysiology. While advanced imaging technique, such as diffusion tensor imaging (DTI) and positron emission tomography (PET), may provide better characterization of such pathophysiology.

Conclusions  The future of traumatic brain lesions depends to a large extent on the evolution of the penumbra. Therefore, understanding the formation and pathophysiologic process of the traumatic penumbra and its imaging research progress is of great significant for early clinical determination and timely brain rescue.

When TBI occurs, there are certain areas surrounding the primary lesions that may develop secondary injury. Similar to the ischemic penumbra, these areas are known as the traumatic penumbra, the retrievable brain tissue around the ischemic core. If there is no timely intervention, the affected brain tissue which could have improved or recovered would become an irreversible injury. Therefore, the key for clinical intervention and treatment is the correct assessment of the penumbra existence at an early stage and the assurance of its progression.

Proposition for traumatic penumbra

The word “penumbra” stems from uranology and is widely used in both basic research and in the clinic, and as an imaging description in the study of ischemic stroke. On radiographic images, ischemic penumbra is defined as the mismatched region of diffusion weighted imaging and perfusion weighted imaging, which reflects the hypoperfusion feature of the infarct core and the surrounding brain tissue. Both stroke and TBI may result in a persistent neuroinflammatory response in the injury penumbra. However, with brain trauma, it is a problem for medical imaging as to whether we can visualize traumatic penumbra with certainty and with good visibility. Regional blood flow studies using xenon-enhanced computed tomography (CT) demonstrated lower-than-ischemic threshold regional cerebral blood flow (CBF) within and around the contused tissues, which raised a question of an ischemic status. This led to the concept of the pericontusional “penumbra”, analogous to the potential salvageable zone surrounding cerebral infarcts.

Stoffel et al proposed the concept of cerebral cortical traumatic penumbra as early as 1997, and tested the excitatory amino acids in the traumatic penumbra of Sprague-Dawley rats with a microdialysis probe. Grande et al found that vasoconstrictor drugs that increase the perfusion pressure may in fact impair oxygenation to the penumbra zones around brain contusions in the treatment of patients with brain trauma. Bell et al found that interstitial brain adenosine, inosine, and hypoxanthine were increased early after controlled cortical impact in rats in both the contusion and penumbra. In later studies of TBI and penumbra, many researchers carried out their studies and experiments from the perspective of basic research and clinical work, meanwhile, imaging studies were also in progress.

Traumatic penumbra refers to the secondary brain injury mainly occurring in the peripheral zone of the primary lesion. In the study, there was a region where diffusion...
weighted imaging and perfusion weighted imaging did not match in the pericontusional area in cats, and they confirmed the existence of traumatic penumbra from the prospective of imaging.16 Other studies reported that there is an evidence for the existence of traumatic penumbra in human traumatic head injury, which defines tissue that is most at risk of secondary ischemic injury and that will be most affected by changes in therapeutic interventions or physiology.17,18

Pathophysiological changes in the penumbra

Cerebral blood flow change
The pericontusional penumbra is known to be an area of low CBF.19 Within 24 hours after TBI, the CBF was half of normal. Low absolute values of CBF were found in both the contusion core and pericontusional parenchyma of patients with head-injuries. By assessing the CBF in and around contusions, it was found that cerebral contusions behave as ischemic lesions with a necrotic core in which the CBF values below the threshold for viability; and a penumbra in which the CBF increases with increasing distance to the core.20 In the study by Depreitere et al,20 CBF values were lowest in the hyperdense/mixed density zones, their absolute values were below 10 ml·100g⁻¹·min⁻¹; the absolute CBF values in the hypodense pericontusional zones varied between 5 and 20 ml·100g⁻¹·min⁻¹; and surrounding normal appearing parenchyma showed a normal or increased CBF.

The pathophysiological mechanism of regional cerebral blood flow change is mainly the microvascular damage in the pericontusional area, leading to ultrastructural arterial occlusion. Furthermore, the decreased CBF and hypoperfusion status in the penumbra may lead to the reduction of oxygen and glucose metabolism which is greatest immediately adjacent to the contusion core. Wu et al demonstrate that there are concurrent changes of CBF and oxygen extraction fraction, CBF and cerebral metabolic rate of oxygen, and CBF and cerebral metabolic rate of glucose.21 This shows that there is a radial diminution of metabolic perturbation from the contusional region. A lower oxygen-glucose ratio is consistently seen in the pericontusional region suggesting the presence of anaerobic metabolism. As an explanation of increased glucose utilization, the increased glucose consumption by infiltrating inflammatory cells and the increased glycogen synthesis by reactive astrocytes have been proposed.22-24 The pathophysiology of the metabolic deterioration is not ischemic in nature. There are probably multiple etiologies responsible for the spatial and dynamic metabolic derangements.

It was discovered in the ischemic penumbra that astrocyte foot processes, which are attached to the outer wall of the blood vessels in the normal physiological state, are swollen under the condition of ischemia. This resulted from decreasing CBF, leading to luminal stenosis of feeding arteries of certain zones. Furthermore, the increased glucose consumption may signify the hypertrophy of the astrocytes under the circumstance of the traumatic event, which would result in vascular compression and the decreasing CBF and finally initiate a positive feedback cycle.25

Cerebral edema and blood-brain barrier damage
The majority of patients who die from TBI develop cerebral edema, a crucial event that can affect the prognosis. Of the complicated pathophysiological changes in traumatic penumbra, there is always obvious blood brain barrier (BBB) leakage.26 After BBB compromise, unwanted cells, debris, and water transmigrate across and infiltrate the BBB, which finally leads to edema.18 In a study,27 BBB permeability changes earlier than the occurrence of cerebral edema in traumatic penumbra in rats. To date, however, cerebral edema has not been well understood due to its complicated mechanism.

The causes of BBB leakage include cerebral ischemia, inflammation, and redox imbalance in the traumatic penumbra. Khan et al19 found that alternations in vascular functions due to endothelial dysfunction and reduced nitric oxide (NO) bioavailability can lead to oxidative exacerbations and BBB leakage. Decreased levels of NO have been reported in plasma and brain tissue from stroke patients and in animal models, indicating an abnormality of NO metabolism after acute injury. Therefore, the decreased NO level may be responsible for the BBB leakage and decreased CBF as well as cell death. Besides, the recruitment and invasion of inflammatory cells were associated with the regions experiencing concomitant BBB damage and neuronal degeneration.21

Cell apoptosis and necrosis
The mechanisms underlying the secondary cell death following TBI are poorly understood, but substantial evidence suggest an important role for apoptosis in delayed cell death.2,18,28 Hypoxia is an important factor which can induce delayed neuronal death. Just as Leker et al29 proposed, cerebral ischemia and trauma have similar pathogenic mechanisms. Studies have shown that hypoxia can cause neuronal apoptosis and necrosis and increase the degree of apoptosis.2,30 In the study by Vlodavsky et al,2 rats exposed to hypoxia demonstrated a significant increase in apoptosis in the traumatic penumbra. Compared with non-hypoxemic animals, the ones exposed to hypoxia demonstrated a higher expression of the pro-apoptotic protein Bax and a lower expression of the anti-apoptotic proteins Bcl-2 and Bcl-xL.

In many cases, TBI will produce a necrotic area in the original traumatic zone, and the area of necrosis usually expands gradually. The pathophysiology behind the volume expansion is not yet completely understood. However, it is generally believed that TBI is not confined to the contusion core. Excitatory amino acids and inflammatory cytokines can diffuse from the core into the perilesional area. Consequently, there are pathological cascades in the contusion core that are also activated in the pericontusional area. Secondary necrosis of brain parenchyma in the
penumbra is one of the major manifestations of secondary brain damage. Studies based on an experimental trauma model have shown that the size of focal cortical necrosis is increasing over time, and the necrotic area can range up to 130%–400% of the initial lesion within 24 hours after trauma. Stoffel et al. had found a biphasic time course of the necrotic expansion, the first growth phase occurring within 3 hours after trauma and the second growth phase between 12 and 24 hours. The area of the cortical lesion at the outset was (4.60±0.20)% of the area of the ipsilateral hemisphere. The necrotic area expanded to (5.30±0.30)% at 4 hours and (5.90±0.30)% at 24 hours after trauma corresponding to 14% at 4 hours and 26% at 24 hours compared with the primary necrosis. A study has proven that a transient increase of NO or its stable end products (nitrate, nitrite) might be responsible for the first phase of necrosis expansion within minutes after trauma.21

Apoptosis and necrosis also occur in spinal cord injury, most neurons and glial cells may later die by apoptosis after the onset of secondary injury in the spinal cord injury lesion and adjacent areas. Ray et al. reported that calpain is involved in the apoptosis of neurons and glial cells in rats. Animal experiments have suggested that calpain inhibitors can provide effective neuronal protection. Calpain mediated cell death is observed in TBI as well.

Some studies 32-34 report that patchy penumbra also exists in the perihematomal area in hypertensive intracerebral hemorrhage patients. Similar to traumatic penumbra, its pathophysiological alternations includes regional cerebral blood flow change, brain edema, inflammation, apoptosis and the toxic effect of thrombin. It is reported that the perihematomatous tissue injury occurs earlier, whereas the regional CBF only decreases three days after hemorrhage and does not reach the threshold of penumbra. Astrup in 1977 found that when the CBF was reduced to 15 ml·100g⁻¹·min⁻¹, partial brain tissue could recover if the regional CBF increased. If the CBF decreased to 6 ml·100g⁻¹·min⁻¹, it is difficult to restore the brain function, and this area is called the penumbra whose CBF is 6–15 ml·100g⁻¹·min⁻¹. Thus, some scholars believe that it is debatable to define a perihemorrhagic lesion as penumbra. 34,35

The imaging definition of traumatic penumbra

Ischemia penumbra can be defined through the diffusion weighted imaging and perfusion weighted imaging mismatch region. The abnormal CBF caused by regional edema, hemorrhage, and intracranial pressure increase in the traumatic penumbra after TBI can lead to ion pump dysfunction and finally cell death. In addition, neuron death can also develop under conditions of radical formation, protein decomposition, and lipid peroxidation. In this respect, the pathophysiologic mechanism is much more complex than that of ischemia.18,28

However, when differentiating traumatic penumbra from the ischemic core applying the method developed by Wintermark et al. for ischemic stroke patients (ischemic core defined by cerebral blood volume < 2ml/100g and penumbra defined by mean transit time > 150% of normal and cerebral blood volume > 2ml/100g), both the contusion and most of the hypodense pericontusional area were included in the ischemic core and the penumbra was limited to a thin rim surrounding the core. A possible explanation is that the pathophysiologic changes in the areas of TBI and of ischemic stroke are different, and the criteria for defining ischemic penumbra are not suitable for the determination of traumatic penumbra.

The pericontusional low CBF area is expanded with the expansion of the traumatic core, tissues that appear normal on the initial CT scans evolve to hypodensity on later scans, but the CBF values measured before the expansion are not reduced.37 It would be logical to speculate that CT-evolution of contusions is a manifestation of progressive necrosis and resultant hemorrhage. The CBF is reduced inside the contusions and somewhat less dramatically in the hypodense pericontusional areas. This is in keeping with the studies by Von Oettingen et al.37 indicating that perfusion CT is a practical method for assessing the pericontusional ischemia.

Perfusion imaging in human TBI shows reductions in CBF around contusions and conventional magnetic resonance imaging can show the growth of such lesions. However, conventional imaging by both CT and magnetic resonance imaging cannot characterize the consequences of CBF reduction at an early stage and provides limited insights into the underlying pathophysiology, while diffusion tensor imaging may provide better characterization of such pathophysiology. 34,38 In the study of Newcombe et al.,13 contusions within the first few days of injury showed a core of restricted diffusion, surrounded by an area of raised apparent diffusion coefficient (ADC). Apart from these two regions, a thinner rim of reduced ADC was observed surrounding the region. It is widely believed that ischemic cytotoxic edema is associated with restricted diffusion (low intensity on ADC maps), while vasogenic edema is associated with increased diffusion (high intensity on ADC maps). The rim of ADC hypointensity was subsumed into the high ADC region as the contusion enlarged a few days later, which indicates that the cytotoxic region that presents as a decreased ADC value seen in the pericontusional zone, may represent a potentially salvageable tissue, “traumatic penumbra”. This finding is consistent with microdialysis studies, which have identified an area of metabolically compromised tissue surrounding the contusion; the rim of cytotoxic edema may represent tissue experiencing microvascular failure.39

Wu et al. utilized F18fluorodeoxyglucose and triple-oxygen positron emission tomography to examine the pericontusional penumbra to assess the oxygen extraction fraction, anaerobic metabolism, and tissue viability of the traumatic lesion. This study indicates that the cerebral
The metabolic rate of the oxygen threshold for irreversible tissue damage is about 36.7 μmol·min⁻¹·g⁻¹. Low CBF, oxygen extraction fraction, and the cerebral metabolic rate of oxygen in the pericontusional hypodense regions are most likely progressing toward necrosis after TBI. Although the pericontusional region appears normal at an early stage on CT and magnetic resonance imaging, the metabolic information at the time, as studied by positron emission tomography, reveals that this region shows evidence of progressive and centrifugal compromise.

**Intervention and treatment for traumatic penumbra**

The time-dependent progression has provided a window of opportunity to take interventional action and reduce secondary injury after TBI. Timely clinical treatment can effectively rescue the tissue which has the potential to recover and hinder the progression of secondary injury.

**Hyperbaric oxygen therapy**

Hypoxia plays an important role in apoptosis and necrosis of neurons. Increasing attention has been attached to hyperbaric oxygen treatment after TBI. In the study by Vlodavsky et al., increased Bcl-2 and Bcl-xL and decreased Bax expression were observed after hyperbaric oxygen treatment. In addition, Voigt et al. found that hyperbaric oxygen treatment had the ability to prohibit the progression of the contusion; hyperbaric oxygen treatment one hour after injury can provide long term neuronal protection for contusions and surrounding penumbra.

**NO modifier**

There is ischemia, inflammation, and redox imbalance in the penumbra and countermeasures to these adverse factors are the key to treat TBI. Khan et al. found that a NO modifier such as S-nitrosoglutathione can not only maintain the redox balance but also improve neuronal function, reduce cell apoptosis, inflammation, BBB leakage and edema, indicating the NO conditioning system has a promising future as a treatment target for TBI therapy. In animal studies, Terpolilli et al. found NO inhalation could significantly improve CBF and reduce intracranial pressure after TBI in male C57 Bl/6 mice. Long-term application (24 hours of NO inhalation) brought about reduced lesion volume, reduced brain edema and less blood–brain barrier disruption, as well as improved neurological function. The outcome of TBI relies on cell death process in the penumbra and effective neuronal protection, thus timely and effective intervention is very important for the rescue of at risk brain tissue.

**Conclusion**

TBI has high mortality. The pathophysiological changes in the traumatic penumbra are dynamic processes, the development and outcome of TBI depends greatly on the progression of tissue damage in the traumatic penumbra. In this paper we review the occurrence, development, imaging confirmation, and clinical treatment of traumatic penumbra in order to provide a reference for early intervention, prohibition of the progression of secondary injury and to maximize protection of injured brain tissue.

**REFERENCES**


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