Introduction
Progressive hemorrhagic injury (PHI) is demonstrated to have a high risk of poor outcomes in traumatic brain injury (TBI) patients, including immediate consequences such as death and morbidity, and long-term health disorders.1,2 To date, A series of studies on the mechanisms of PHI have been made, especially in coagulopathy-related ones. Meanwhile, trauma-induced coagulopathy (TIC) has been discussed in many recent studies, which showed some association with PHI.3,4 It is important to make these mechanisms clear to provide possible effective clinical interference and to bring better outcomes. Therefore, we reviewed previous studies and recent advances on PHI and TIC, paying special attention to the connection between them, and discuss possible predictors and therapies.

PHI definition and incidence

PHI definition
Since it was first described by Bollinger and co-workers in 1891, secondary intracranial hematomas after head injuries has been referred to by various terms. These terms include delayed traumatic intracerebral hematoma (DTICH), progressive hemorrhagic injury, hemorrhagic progression of contusion (HPC) and hemorrhage progression (HP).15–9 Each definition focus on different molecular mechanisms and progression process. In this review, we use the term PHI to emphasize and clarify: (1) progressive focus on the progression process of hemorrhage in TBI patients, and (2) the new hemorrhage site which is not continuum to the original contusion.

By far, the definition of PHI has not been unified in different studies. Here we define PHI as the appearance of new lesions or a conspicuous increase in the size of brain injury hemorrhagic lesions, i.e. a 25% increase or more in the follow-up CT scans, during the first 24 h or later after impact.10,11

PHI incidence and harm

Based on previous studies, the incidence of PHI after moderate and severe TBI varies from 10% to 60%.11,12 This may be due to different diagnostic criteria and examinations. In a recent study by Yuan and co-workers,11 the incidence was classified into three groups based on criticality. They set up a scoring system and defined these patients into three risk groups: low risk, intermediate risk and high risk. The PHI rates after TBI for these three groups were 10.3%, 47.3%, and 85.2% in the development cohort, while in the validated cohort, the rates were 10.9%, 47.3% and 86.9%. We recommend this kind of stratified statistics because it
can provide effective interference suggestions to certain groups of patients.

As a secondary brain injury, PHI brings a high risk of deterioration, morbidity and mortality in TBI patients. A study presented that poor outcomes in patients with PHI is nearly five-fold higher at discharge and four-fold higher after one year than those in patients without PHI. Other risk factors that result in deteriorate outcome in TBI patients include elevated D-dimer level, initial brain contusions size, old age, low GCS score, alcoholism, high copeptin level, coagulopathy, midline shift, contrast extravasation on computed tomographic angiography (CTA), male gender, pupillary reflex abnormalities, head injury severity and hypoperfusion. Therefore, studies on the mechanism of PHI may provide effective clinical interference and reduce poor outcomes.

Mechanisms of PHI

Mechanism of PHI development

There are three mechanisms explaining the development of PHI. One is the continuous bleeding of microvessels which ruptured at the time of primary injury, or received kinetic energy from the impact that was not sufficient to rupture them, but enough to activate mechanosensitive molecular processes in microvessels, thereby initiating a series of events that will lead to the delayed catastrophic structural failure of microvessels and PHI. Another one is hypocoagulation state after initial hypercoagulopathy. The third one is activated inflammation induced by the release of excitotoxic substances, blood breakdown products and over-reaction of clearing tissue debris.

Molecular mechanisms

Previous studies have found that PHI might be due to up-regulation and activation of sulfonylurea receptor 1 (SUR1)-regulated NCCa-ATP channels in capillary endothelial cells, predisposing to oncotic death of endothelial cells and catastrophic failure of capillary integrity. After kinetic energy compact on microvessels, the SUR1-regulated NCCa-ATP channel can be activated by Sp1 and NF-kB (a mechanosensitive transcription), then is newly up-regulated in penumbral capillaries in the region of brain injury, and becomes quite prominent 24 h after injury in both the cortex and the underlying structures deep to the cortical site of impact. Meanwhile, the reduced PHI after blocking SUR1 with glibenclamide or Abcc8-AS confirmed this hypothesis. These findings can provide possible targeted therapeutic interference to PHI and bring better outcomes.

TIC definition and mechanisms

Definition and incidence

After severe tissue injury (high injury severity score), there is a traumatic coagulopathy and increased mortality. The definition criteria of TIC varied considerably, which include over 20 different proposed parameters of coagulopathy. These parameters include elevated INR, PT, PTT or D-dimer, decreased fibrinogen or FXIII, higher DIC score, modified DIC score or modified coagulopathy score, lower alpha-2 plasmin inhibitor. Here we cite a table from previous studies which showed various definitions of TIC from 1992 to 2013 (Table 1). The incidence of TIC after TBI ranges widely from 7% to 97.5%, and the mortality of 17%–86%. Mechanisms

To date, there are many studies on the mechanisms of TIC, including tissue factor (TF) hypothesis, hyperfibrinolysis, acute coagulopathy of trauma shock (ACoTs) with protein C pathway, thrombocytopenia, and iatrogenic coagulopathy. The iatrogenic coagulopathy hypothesis was recently termed by Cohen. It focuses on iatrogenic effects of the beneficial resuscitation practices, in which patients with TBI received massive transfusion and presented with hypothermia, dilution and acidosis, and also decompressive craniectomy can result in tamponade effect, etc. These findings are coherent with previous studies. Among these mechanisms, some of them play an important role in the development of PHI.

Relation of TIC to PHI

As mentioned above, TIC is associated with PHI and increases the rates of disability and mortality. Yang and co-workers found a high rate (about 55.6%) of TIC among PHI patients. Vice versa, PHI is a major outcome of TIC patients. A study showed 80% of TIC patients developed PHI. Based on many previous studies, we conclude that the main mechanism in relation of TIC to PHI is hypocoagulability. Here we discuss three mechanisms in TIC which is of great importance in the development of PHI. To make it clear, we use Fig. 1 to present these relations.

Tissue factor (TF) hypothesis

TF (abundant in the brain) is released into the circulation after patients suffering from TBI, then it activate extrinsic pathway and secondary consumption coagulopathy, resulting in hypocoagulability bleeding disorders such as PHI. This process can be represented by the elevation of tissue plasminogenemia activator (tPA), fibrin degradation products, and decrease of depletion of a-2 plasmin inhibitor. However, this hypothesis is challenged by a recent study, which showed similar TF levels in all study groups regardless of the presence of coagulopathy.

Protein C pathway

Protein C can cleave factors Va and VIIa after being activated, and is important for TBI patients survival. ACoTs is defined as APTT and/or INR followed by trauma, shock, and tissue hypoperfusion. Triggered by hypoperfusion and endothelium damage, protein C pathway is over-activated, which then inhibits co-factors Va and VIIa, decreases plasminogen activator inhibitor (PAI-1) levels, increases tPA, leads hyperfibrinolysis and increases D-dimer level. These consecutive reactions can decrease coagulability and further may cause PHI.

Thrombocytopenia

Platelet count <175,000 mm$^3$ was thought to cause a high risk of PHI, while this is proved to have no statistical significance in a recent study. Platelets dysfunction has been shown to be present after TBI, which could contribute to hemorrhagic complications. Therefore, both quantity and quality defects of platelets in TIC can give rise to the development of PHI.

Other coagulopathy parameters

TIC can be recognized by some laboratory tests, which can also indicate possible development of PHI.
Decreased platelet count. An excellent previous review found no statistical difference in initial platelet count between groups of patients that would or would not exhibit PHI. In a finding of up to 50% of patients who will develop PHI may not present with abnormalities in platelet count. In some recent studies, a certain degree of decreased platelet count is considered to be a significant risk factor for PHI. Juratli and co-workers observed that a low platelet count <100 x 10^9/L in the emergency room (ER) is associated with five-fold higher odds of cerebral contusions progression. While Yuan and co-workers suggested platelet count <100 x 10^9/L, or platelet count ≥100 but <150 x 10^9/L to be a part of a PHI prognostic model, which was developed in 468 patients and validated in 114 patients. Thus, thrombocytopenia remains to be a controversial factor in PHI.

Elevated aPTT/PT/INR. Different previous studies have shown inconsistent results on these factors. The incidence of an elevated aPTT or PT or INR in TBI varies widely, from 1% to 31%, mostly inconsistent results on these factors. The incidence of an elevated aPTT/PT/INR. Different previous studies have shown inconsistent results on these factors. The incidence of an elevated aPTT or PT or INR in TBI varies widely, from 1% to 31%, mostly inconsistent results on these factors. The incidence of an elevated aPTT or PT or INR in TBI varies widely, from 1% to 31%, mostly inconsistent results on these factors. The incidence of an elevated aPTT or PT or INR in TBI varies widely, from 1% to 31%, mostly inconsistent results on these factors.

Increased D-dimer. D-dimer, as a coagulation end product in plasma, can be a marker of coagulation and fibrinolysis pathways. Increased D-dimer in peripheral blood can reflect the activation of coagulation. Meanwhile, D-dimer can trigger some deleterious actions directly such as the stimulation of monocyte synthesis and release of proinflammatory cytokines, which can then lead to the development of edema and hematoma enlargement. In TBI patients, these may result in greater intracranial hematoma volume or early hemorrhagic growth, such as PHI. Tian and co-workers studied on 194 patients and observed that 84 of them had a D-dimer level higher than 5.00 mg/L; PHI was seen in 71.4% of patients with increased D-dimer while in 19.1% of patients with normal D-dimer level, which showed a significant difference. They also found a reliable operating point for the D-dimer level of 5.0 mg/L, with a sensitivity of 72.8% and a specificity of 78.8%. Moreover, increased D-dimer can be a prognostic factor related to poor clinical outcome. It has been described in another study that patients with D-dimer ≥10,000 lg/L had a sensitivity of 78.8% and a specificity of 72.8%.

High pathological fibrinogen. It has been shown that when a pathological fibrinogen level is <2 g/L, a hemorrhage progression is three-fold more likely to occur. And patients with PHI have a higher rate of pathological fibrinogen in comparison to patients without PHI. This factor has not been well studied, but it may be a potential factor if further studies are carried out.

Besides what we have discussed above, there may be other factors, but no agreement has been reached so far. The connection between these coagulopathy factors and PHI remains to be revealed by further studies. The tests of these factors can give instructions on therapeutic interventions and the monitor of therapeutic effects.

**How to predict PHI and possible therapies**

**PHI risk factors**

According to the relation of TIC to PHI, some coagulopathy parameters can be used as risk factors or predictors. Several coagulopathy parameters have been studied and proved to be independent risk factors of PHI, including INR, aPTT, PT, platelet count, pathologic fibrinogen and D-dimer. Juratli and co-workers have reported that TBI patients with a low platelet count are six
times more likely to conflict with PHI, and pathologic fibrinogen levels can be an independent risk factor resulting in a three-fold higher risk for early PHI. Tian and co-workers\textsuperscript{24} specially studied D-dimer and found plasma D-dimer level is higher in patients who demonstrated PHI compared with those who did not. A recent study also found that a smoking history and a low triglyceride (TG) level <150 mg/dL can significantly increase the risk of PHI. It is important to recognize these risk factors for PHI, as they can help predict patients who have higher tendency to develop PHI.

**PHI prognostic models**

Some prognostic models have been established to predict the occurrence of PHI after TBI. A score system has been developed by using the following features in a descending order of importance: high D-dimer level, prolonged PT, low platelet count, a midline shift, a high glucose level, older age, slightly low PLT count, and intra-axial bleeding/brain contusion.\textsuperscript{1} This model has been tested in both development and validation cohort. However, a prognostic model should never replace clinical assessment of an individual patient. It should be used in conjunction with professional knowledge and care in certain clinical decision. A recent study suggested that higher plasma copeptin level independently can predict TIC and PHI.\textsuperscript{8} Other possible predictors such as CT scan characteristics are also included and need further studies.

**Possible therapies**

To date, no specific guideline of therapy for PHI has been established. Since TIC is associated with PHI, therapeutic strategies focused on hemorrhage control and anti-coagulopathy should be considered. Here, we discuss some possibly effective therapy options.

Recombinant factor VIIa (rFVIIa). Many studies have been done on rFVIIa and the results are controversial. Some previous studies showed using rFVIIa is a safe and cost-effective way to correct coagulopathy and reduce the occurrence of PHI rapidly.\textsuperscript{11,24} While some other studies found no significant trend for rFVIIa dose response (80–120 μg/kg) to limit PHI.\textsuperscript{4} However, a recent study found that the use of low-dose rFVIIa (20 μg/kg) is effective for correcting coagulopathy in patients with TBI without increasing thromboembolic events and is more effective for preventing the occurrence of PHI.\textsuperscript{7}

Omega-3 Fatty Acids. Hasadri and co-workers\textsuperscript{27} represented a nutritional intervention that may be of therapeutic benefit in TBI. Omega-3 Fatty Acids can repair cellular damage and have anti-inflammatory effects, which play important roles in the development of PHI. Therefore, Omega-3 Fatty Acids may be a possible therapy for PHI and we advocate further study on it.

Other anticoagulants such as antifibrinolytic treatment, fresh frozen plasma (FFP) and platelets remain to be studied. The relatively high risk of bleeding associated with the use of these components may be a limiting factor.\textsuperscript{4,6,24}

**Conclusion**

The main mechanism in relation of TIC to PHI may be hypo-coagulability. Clinical therapeutic interference can be developed and established. However, studies on the risk factors, predictors and possible therapies of TIC and PHI remains to be a controversial topic. Therefore, we advocate more studies on the mechanisms of TIC and PHI, especially the relation between them. We believe that such studies have a promising future for the research of PHI.

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