Therapeutic Hypothermia in Children and Adults with Severe Traumatic Brain Injury

低温治疗在重型颅脑外伤成人与儿童患者中的应用

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THERAPEUTIC HYPOTHERMIA AND TEMPERATURE MANAGEMENT

低温治疗与温度管理

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Abstract

Great expectations have been raised about neuroprotection of therapeutic hypothermia in patients with traumatic brain injury (TBI) by analogy with its effects after heart arrest, neonatal asphyxia, and drowning in cold water.

The aim of this study is to review our present knowledge of the effect of therapeutic hypothermia on outcome in children and adults with severe TBI.

与其影响心脏骤停，新生儿窒息，溺水相比，低温治疗用于创伤性脑损伤（TBI）患者神经保护这一远大预期已被提出。本研究的目的是回顾现有的低温治疗对重型创伤性脑损伤儿童和成人的影响。

Abstract

- A literature search for relevant articles in English published from year 2000 up to December 2013 found 19 studies. No signs of improvement in outcome from hypothermia were seen in the five pediatric studies. Varied results were reported in 14 studies on adult patients, 2 of which reported a tendency of higher mortality and worse neurological outcome, 4 reported lower mortality, and 9 reported favorable neurological outcome with hypothermia.

（方法）：检索从2000年到2013年12月已发表的19项相关英文文献。

（结果）：五个儿科研究结果显示：低温没有改善治疗效果。14项成人患者不同研究结果中,2例报道倾向于较高的死亡率和较差的神经学结果,4例报道倾向于低死亡率,9例报道显示低温有利于神经系统。

Abstract

- The quality of several trials was low. The best performed randomized studies showed no improvement in outcome by hypothermia—some even indicated worse outcome.TBI patients may suffer from hypothermia-induced pulmonary and coagulation side effects,from side effects of vasopressors when re-establishing the hypothermia-induced lowered blood pressure, and from a rebound increase in intracranial pressure (ICP) during and after rewarming.

一些试验的质量较低。高质量的随机研究结果显示，低温没有改善治疗效果，甚至结果更糕。TBI患者可能遭受低温诱导肺和凝血的不良反应，当重新恢复低温引起的低血压时，复温期间、之后均会造成患者颅内压（ICP）升高。

Abstract

- The difference between body temperature and temperature set by the biological thermostat may cause stress-induced worsening of the circulation and oxygenation in injured areas of the brain. These mechanisms may counteract neuroprotective effects of therapeutic hypothermia.

体温和生物恒温器设置的温度差异可能会导致循环恶化和影响大脑受伤区域的氧合情况，这些机制可能会抵消低温对神经保护的作用。

Abstract

- We conclude that we still lack scientific support as a first-tier therapy for the use of therapeutic hypothermia in TBI patients for both adults and children, but it may still be an option as a second-tier therapy for refractory intracranial hypertension.

（结论）：我们还缺乏低温作为成人和儿童TBI患者一线治疗的科学支持，但它可以作为难治性颅内高压二线治疗的一种选择。

Introduction

- Traumatic brain injury (TBI) is a major cause of death and disability in industrialized countries. In the United States, for example, an estimated 1.6 million people sustain TBI every year, with about 50,000 deaths and 80,000 permanent neurological disabilities.

- TBI在工业化国家是导致死亡和残疾的主要原因。在美国，假如每年遭受脑外伤的160万患者中，大约有5万人死亡，8千人为永久性神经系统障碍。

Introduction

- Several neuroprotective substances showing beneficial effects in animal studies, such as nimodipine, glutamate inhibitors, the competitive N-methyl-D-aspartate receptor antagonists, magnesium sulfate, and scavenging agents, have been analyzed in randomized trials in TBI patients, but none of these potential neuroprotective substances have been shown to be beneficial .

- 一些动物实验研究显示：神经保护物质，如尼莫地平，谷氨酸盐抑制剂，N-甲基-D-天冬氨酸受体拮抗剂，硫酸镁及其清除剂是有益的。 但在TBI患者的随机试验分析得出，这些神经保护物质没有被证明是有益的。

Introduction

- Modern therapy of TBI has improved outcomes over the last 20 years, but mortality and number of patients with severe disability have remained high.

- 在过去的20年，TBI的现代疗法已改善治疗结果，但此类患者的死亡率和重度残疾数仍居高不下。

Introduction

- Increased body temperature after a brain trauma is associated with increased cytokine release and worsening of outcome.Based on this and the neuroprotective effect of active hypothermia after global brain ischemia, such as after cardiac arrest and after neonatal asphyxia , and fromcase reports showing good recovery after drowning in cold water, great expectations have been raised about active cooling as a breakthrough in TBI patients.

- 创伤性脑损伤后体温升高与细胞因子的释放增加和结果恶化有关。基于此，积极的低温治疗对于全脑缺血的神经保护，如病例报告中的心脏骤停，新生儿窒息，溺水等都有良好的作用，对于TBI患者来说也是一项极大的期望和重大的突破.

Introduction

- Hypothermia as a potential therapy after stroke is also under debate . Active cooling of patients with TBI was described first by Fay in 1945 and has become a major area of research during the last two decades. Spontaneous hypothermia, for example, as a consequence of progressive shock and inability to maintain normal temperature is, however, a poor prognostic factor.

- 而作为中风患者潜在的治疗仍在争论中。TBI患者低温治疗是于1945年由费伊首次提出，在过去20年里已成为一个主要的研究领域。自发低温，例如，如渐进性休克和不能保持正常温度，是预后不良的一个因素。

Therapeutic hypothermia in severe TBI

- There are several studies from the 1990s evaluating the effect of therapeutic hypothermia in severe TBI patients. Harris et al. (2002) reviewed seven randomized controlled trials from that period and found no beneficial effects of hypothermia on outcome. Another meta-analysis of eight randomized studies from the 1990s found no reduction in mortality from hypothermia.

- 上世纪90年代的多个研究评估了低温治疗在重型脑外伤患者的效果。Harris等人回顾那个时期的7项随机对照研究发现，低温对此类患者预后是有益的。另一项meta分析调查了上世纪90年代的8个随机研究表明，低温治疗对减少死亡率没有影响。

Therapeutic hypothermia in severe TBI

- McIntyre et al. (2003) summarized the results of 12 studies from the 1990s, of which only 2 of the studies were graded high-quality studies. They concluded that the scientific support for therapeutic hypothermia so far is weak. In summary, the studies performed during the 1990s give no clear support for therapeutic hypothermia in TBI patients.

- McIntyre等人总结了12项研究结果，其中仅2项为梯度高质量的研究。他们指出,迄今为止，低温治疗的科学依据仍不足。总之，20世纪90年代进行的研究没有给出低温在TBI患者中明确支持。

Therapeutic hypothermia in severe TBI

- We will also present possible side effects of active hypothermia based on the specific pathophysiology of these patients. The studies analyzed included patients who suffered a severe TBI (Glasgow Coma Scale [GCS] scorep8) and a control group that was not exposed to active cooling.

- 同样，我们也会提出低温对这些病人可能产生的不良病理生理反应。这些研究对比分析了包括遭受重型脑外伤（GCS≤8）患者，而对照组未采用低温治疗。

Therapeutic hypothermia in severe TBI

- Hypothermia may still be beneficial by better planning of the studies and by optimizing the protocols as aimed at in later studies. The purpose of this review was therefore to present and evaluate the current literature on therapeutic hypothermia in TBI patients from the year 2000 up to December 2013.

- 在以后的研究中，通过更好地研究规划和更佳的方法，低温治疗可能是有益的。因此，这篇综述的目的是介绍和评估从2000年至2013年12月文献中涉及低温治疗在TBI患者中的作用。

Pathophysiology in TBI

- The pathophysiology of brain injury after head trauma is complex and can be characterized by the initial primary injury and the subsequent secondary injury that develops over the days after the trauma. The primary injury occurs at the moment of impact and can be focal and/or more diffuse.

- 创伤性颅脑损伤的病理生理较复杂，可以以原发性损伤为特征，在创伤后的几天发展为继发性损伤，原发性损伤发生在冲击的那一刻，可以是局灶性和/或多个弥散性的.

Pathophysiology in TBI

- The focal damage is seen as contusions, contusional bleedings, lacerations, intracranial hemorrhages, and local ischemia, and is an immediate effect of the trauma. The diffuse brain damage involves components such as neurons, neuronal processes, transmitter mechanisms, glial cells, blood vessels It can also include diffuse axonal injury, which is a predictor of poor recovery . Children suffer more severe edema after TBI than adults.

- 局灶性损害被视作有挫伤、挫伤出血，裂伤，颅内出血，和局部缺血，是创伤直接作用所致。而弥漫性脑损伤包括多个成分，如神经元，神经元过程，发送器的机制，神经胶质细胞，血管和弥漫性脑肿胀，也可包括预后不良的弥漫性轴突损伤。儿童脑外伤后比成人遭受更严重的水肿。

Pathophysiology in TBI

- The center of the primary brain injury is often severely hypoxic and more or less insensitive to therapeutic interventions, and most cells of these areas will die irrespective of therapy ,while injured cells of the surrounding areas have greater potential to survive.

- 原发性脑损伤的中心区域往往是严重缺氧、或多或少的对治疗性干预不敏感，即便治疗，这些区域的大多数细胞仍会死亡，而受伤周边区域的细胞则有更大的存活机率。

Pathophysiology in TBI

- Secondary brain injury is initiated at the moment of injury with progression over the ensuing minutes, hours, and days a phenomenon termed hemorrhagic progression of a contusion .The development of secondary brain damage is a major factor determining the patient’ s clinical outcome.

- 继发性脑损伤是在受伤后数分钟，数小时，数日形成的，这种现象称为进展性出血挫伤。继发性脑损伤的转归是决定患者临床效果的一项主要因素.

Pathophysiology in TBI

- A main target is therefore to reduce the development of secondary brain damage, by improving the survival of injured but not dead cells. The pathophysiological mechanisms behind the secondary damage are not fully understood. Acceleration, deceleration, and rotational forces of the brain may induce damage of axons and other brain cells.

因此，提高损伤细胞的生存率成为减少继发性脑损伤情况恶化的主要目标，继发性损伤潜在的病理生理机制尚不完全清楚。加速，减速，和大脑的旋转力可诱发轴突和其他脑细胞的损伤。

Pathophysiology in TBI

- Overall effects of biomolecular and physiological changes in the injured brain, including neuroinflammatory processes with release of cytokines,excitotoxic substances, cerebral edema, increased ICP, and compromised cerebral blood flow with cerebral ischemia and apoptosis, may be involved.

- 在脑损伤生物分子和生理变化的整体影响下，包括细胞因子释放的神经炎症过程，兴奋毒性物质，脑水肿，ICP升高和脑缺血后的脑血流量灌注不足与及细胞凋亡，都可能参与其中。

Pathophysiology in TBI

- A specific goal with the use of neuroprotective substances has been to reduce the development of secondary injuries by reducing the direct toxic cell damage, and the cytotoxic brain edema. The pathophysiology, however, seems to be more complex, as neuroprotective substances tested so far in patients have failed to improve outcome.

- 使用神经保护物质的特定目标是通过降低细胞毒性和脑水肿的直接损伤从而减少继发性损伤的危害。神经保护物质在目前试验中对患者均未能改善预后效果，因此其病理生理机制显得更为复杂。

Pathophysiology in TBI

- One can speculate that primary hypoxia, especially in and around contusions, may be an important additional triggering mechanism behind the pathophysiological alterations after a TBI. If so, one goal in the treatment of these patients should be to counteract the effects of hypoxia of the brain, e.g., by hypothermia.

- 可以推测的是，挫伤中心及其周围区域主要的缺氧，可能是脑损伤后重要的触发病理生理机制的改变。如果是这样，应该对这些患者实施低温治疗来改善大脑缺氧的目标。

Pathophysiology in TBI

- TBI is supposed to increase the permeability of the tight cerebral capillaries (open the intact blood–brain barrier).

  Failure of the blood–brain barrier means that the normally impermeable capillaries become passively permeable to small solutes, which may cause leakage of fluid into brain tissue, a mechanism responsible for the so-called vasogenic brain edema.

TBI可能引起脑部毛细血管通透性增高（打开完整的血脑屏障），血脑屏障受损意味着对于小分子溶质而言，正常的防渗毛细血管变为被动且易于渗透，导致体液渗透到脑组织，这就是所谓的血管源性脑水肿机制。

Pathophysiology in TBI

- Brain edema can also be an effect of swelling of brain cells, because of cell membrane damage from hypoxia, and cytotoxic and excitatory substances (Liang et al., 2007). Brain edema and intracranial hematomas will increase ICP and reduce cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure and ICP.

- 脑水肿也可能是由于细胞膜受到缺氧，细胞毒性和兴奋性物质的损伤导致脑细胞肿胀所致。脑水肿和颅内血肿会导致ICP增高和脑灌注压（CPP）降低，定义为平均动脉压和ICP之间的差。

Pathophysiology in TBI

A high ICP correlates to worse outcome in patients with TBI and is an important cause of death after severe TBI. Low CPP values, especially combined with hypovolemia, may cause brain ischemia in areas with compromised circulation.

脑损伤患者预后不良及重型颅脑损伤死亡均与ICP升高有关。低脑灌注压，特别是结合低血容量，可能会导致循环不足区域脑缺血.

Therapeutic Hypothermia in TBI

As mentioned in the Introduction, hypothermia has neuroprotective effects related to global hypoxia. This initiated the view that the neuroprotective effect of active hypothermia in combination with its ICP-reducing effect might be an important therapeutic option also in TBI patients.

正如引言中所述，低温治疗对全脑缺氧有神经保护作用。这被认为，积极的低温治疗降低了ICP并保护神经系统，成为治疗TBI患者重要的选择。

Therapeutic Hypothermia in TBI

Brain metabolism is reduced by about 5–7% per ^{0}C reduction in core temperature .The ICP reduction by active hypothermia can be explained by cerebral vasoconstriction caused by reduced metabolic rate resulting in reduced intracranial blood volume.

核心体温每降低1^{0}C脑代谢减少5-7%，积极的低温治疗降低ICP的机制可以解释为：脑代谢率降低引起脑血管收缩从而导致颅内血容量减少。

Therapeutic Hypothermia in TBI

Reduction in brain metabolic rate may be one mechanism for neuroprotection by hypothermia, that is, by causing a more favorable balance between cerebral oxygen and glucose supply and demand.The same decrease in metabolic rate from barbiturate treatment was, however, not associated with improved outcome.

脑代谢率降低的机制可能是由于低温对神经保护的作用，即更好地平衡脑氧和葡萄糖之间的供需。巴比妥治疗时脑代谢率同样降低，但不会改善治疗结果。

Therapeutic Hypothermia in TBI

The effect of hypothermia is more complex than just a reduction in metabolic rate. Many posttraumatic adverse events at the cellular and molecular level are highly temperature sensitive.Protective factors by therapeutic hypothermia may also be attenuation of proinflammatory cytokines, decrease in free radicals,decrease in toxic metabolites and excitatory substances, prevention of reperfusion injury, prevention of apoptosis, preservation of high-energy phosphates, reduced mitochondrial dysfunction, and a reduction in oxidative stress.

低温治疗不仅仅是一个代谢率降低的过程，许多创伤后不良反应表现为细胞和分子对温度十分敏感。低温治疗神经保护因素可能是衰减促炎细胞因子，减少自由基，减少有毒代谢产物和兴奋性物质， 预防再灌注损伤，防止细胞凋亡， 保存高能磷酸盐，降低线粒体功能障碍，减少氧化应激。

Therapeutic Hypothermia in TBI

Posttraumatic hypothermia treatment has also been shown to attenuate the burden of axonal damage in rodent models of TBI.

在TBI啮齿动物模型试验中表明：低温减轻了轴索损伤负担。

Cooling Technique and Protocol

Cooling of the whole body (systemic cooling) has been used in most larger clinical TBI outcome studies so far. Local cooling of the brain has been discussed to reduce systemic complications such as pulmonary complications and coagulation disturbances .Selective brain cooling can be obtained by a cooling cap or by intranasal cooling with circulating cold water via a tubing/balloon system inserted into the nose.

全身降温的方法在大多数大型临床脑外伤研究中使用至今，脑部局部降温用以减少全身并发症，如肺部并发症和凝血障碍的作用已被讨论，选择性脑部降温可通过冰帽或有循环冷水系统的探头插入鼻内方式获得。

Cooling Technique and Protocol

Local cooling, especially with an intranasal cooling technique has difficulty in reaching target temperatures within reasonable times Liu et al. and Qiu et al. both succeeded in reducing the brain temperature to 33–35^{0}C using a cooling cap in combination with an ice neck strap, and they reported positive results on outcome, and a lower risk of pneumonia compared with systemic hypothermia.

局部降温，尤其是鼻内降温技术，在适宜的时间难以达到目标温度。Liu 和Qiu使用冰帽和冰颈圈使温度达到33-35^{0}C，他们报道低温的积极作用:与全身低温治疗相比局部降温具有更小的引起肺炎的风险。

Cooling Technique and Protocol

Additional technical developments are necessary before selective cooling of the brain can be used as a reliable technique.

在选择性脑部降温作为一种可靠的技术之前，进一步的技术发展是必要的。

Cooling Technique and Protocol

Systemic cooling can be obtained by surface cooling, most often with a cooling blanketor cooling with endovascular catheters . These techniques have the capacity to cool the whole body to thedesired temperature within reasonable times. Hypothermia is classified as light or mild (>34^{0}C), moderate (32–34^{0}C), or severe (<32^{0}C). The clinical studies reviewed in this study have used light to moderate hypothermia with a goal temperature of 33–35^{0}C.

全身降温可通过体表降温来获得，最常用的是冰毯或冷却血管内导管，这些技术可以在适宜的时间使全身达到目标温度。低温被分为浅低温（>34℃），中度低温（32-34℃），深低温（<32℃）。在综述中的临床研究使用的是轻到中度低温与33-35℃目标温度。

Cooling Technique and Protocol

The degree of hypothermia is normally determined by the core temperature measured rectally, in the esophagus, or in the urinary bladder. Outcome in TBI when using active hypothermia may be related to how long after the accident the cooling began, the goal temperature, time to reach the goal temperature, and time period of cooling and rewarming.

低温的程度通常是由通过测量直肠、食道、膀胱的核心温度来决定的。TBI患者低温治疗的结果可能与事故发生后何时开始低温治疗、目标温度值、目标温度值达到的时间以及降温与复温的时间有关。

Cooling Technique and Protocol

For example, the negative effects of rewarming—that is, the rebound increase in ICP during the rewarming and postcooling phase—may overshadow the neuroprotective effects of cooling. Alternative protocols with a shorter time delay before the start of cooling after the accident, a more long-term cooling period, or an extended rewarming phase and better control of ICP and CPP might strengthen the beneficial effects of hypothermia.

例如：复温的不良发应是在低温治疗后期和复温阶段发生ICP升高，这可能会掩盖低温对神经保护的作用。如果在事故发生后早开始较长时间的低温治疗或延长复温阶段，更好地控制ICP和CPP会强化低温效果。

Evaluation of Outcome

Most studies used the five-category-assessment Glasgow Outcome Scale (GOS) to evaluate outcome: 1, death; 2, vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery. A GOS score of 4–5 is considered as a favorable/good neurological outcome, while a GOS score of 1–3 is unfavorable/poor outcome.

大多数研究使用格拉斯哥转归量表/预后评分（GOS）评估结果：1 死亡；2 植物人；3 重度残疾；4 中度残疾；5 恢复良好。GOS为4-5分被认为是有利的/良好的神经预后，而GOS为1-3分则表明不利/预后较差。

Evaluation of Outcome

The Pediatric Cerebral Performance Category (PCPC) scale was used in 3 of the 5 pediatric trials. PCPC is a sixpoint scale: 1, normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, persistent vegetative state; 6, death.

小儿脑性能分类（PCPC）量表被大多数儿科试验所使用。PCPC量表包括6类：1 正常的表现；2 轻度残疾；3 中度残疾；4 严重残疾；5 持续植物人状态；6 死亡

Cooling Duration and Rewarming

Most studies used a cooling period in the 24–48-hour range, while some studies have used a cooling period longer than 48 hours. One reason for using more long-term coolin is that cerebral swelling and edema often are greatest 3–5 days after injury . If hypothermia is discontinued at an earlier stage, the injury mechanisms may continue to progress with a greater risk of rebound increase in ICP.

大多数研究使用的低温时间为24-48h，而一些研究则超过48h。使用较长的低温时间原因其一是脑水肿往往在受伤后3-5d最明显。如果在治疗早期中断低温治疗，损伤机制将增大并伴有ICP反弹的风险。

Cooling Duration and Rewarming

A study by Jiang et al. (2006),who compared the effects of long-term cooling with shortterm cooling in adults, indicated that longer duration was beneficial.Cooling generally results in a decrease in ICP, both in adults and in children. Only one study has shown an increase in ICP by cooling.

Jiang等人研究显示：成人长期低温比短期低温效果更好。在成人和儿童中，低温通常会降低ICP，仅有一项研究除外。

Cooling Duration and Rewarming

As mentioned above, the recently started Eurotherm3235 Trial is based on the hypothesis that the ICP-reducing effect of hypothermia is favorable.A rebound increase in ICP during the rewarming period has been more common in studies using short-term cooling. A more slow and well-controlled rewarming and better control of ICP, blood pressure, and CPP may reduce the adverse rebound effect of the rewarming phase.

如上面所提到，近期所进行的Eurotherm3235实验正是基于低温治疗有利于降低ICP值这一假定。一些研究显示：短期低温治疗在复温阶段ICP反跳现象很常见。缓慢且较好地控制复温、ICP、血压及CPP可减少复温阶段的不良反应。

Adverse Effects of Hypothermia

Even though cooling is neuroprotective and improves outcome after a general brain hypoxia as described in the Introduction, the situation may be different after TBI, which may affect the therapeutic effect of hypothermia.

尽管低温治疗如前言所描述一样对全脑缺氧后有神经保护作用，但对于脑外伤患者而言可能会影响其治疗效果。

Adverse Effects of Hypothermia

While cerebral circulation is relatively normal or may even be above normal after resuscitation after general hypoxia, the traumatized brain often suffers from compromised circulation and hypoxia in and around the most injured areas of the brain. The traumatized brain also suffers from specific traumainduced inflammatory processes.

受创脑部的脑循环是相对正常的，甚至可能高于复苏后一般正常的缺氧，但受创中心及周边区域易遭受循环差、缺氧和外伤引起的特异性炎症反应。

Adverse Effects of Hypothermia

Shivering, increased stress, and increased sympathetic discharge and catecholamine release are well-known effects of hypothermia with the physiological aim of resetting body temperature toward the values set in the biological thermostat of the brain.

发抖，肌肉强直，交感神经放电增加，儿茶酚胺释放等是众所周知低温带来的生理反应以实现大脑生物恒温器所设定的温值。

Adverse Effects of Hypothermia

The hypothermia-induced reduction in metabolic rate will therefore be counteracted by a simultaneous stress-induced increase in metabolism. The latter may increase oxygen demand and energy expenditure. It may also compromise brain microcirculation by an increase in release of catecholamines, which may aggravate hypoxia especially in areas in which the perfusion is already significantly reduced.

代谢中低温诱导减少会相应抵消代谢中应激诱发的增加，后者可能会增加需氧量和能量消耗。它也可能通过增加儿茶酚胺的释放影响大脑微循环，特别是加重灌注量已明显减少区域缺氧。

Adverse Effects of Hypothermia

Oddo et al. (2010) showed that coolinginduced shivering can cause a significant reduction in brain oxygenation with an increased risk of brain hypoxia. These authors warned against the use of active hypothermia as prophylactic neuroprotectant in the early phase of TBI.

Oddo等人研究表明：低温引起的寒战可明显减少脑部氧合，增加脑缺氧的危险性。他们反对在脑外伤初期使用低温治疗作为预防性神经保护。

Adverse Effects of Hypothermia

Shivering can be reduced pharmacologically, for example, by neuromuscular blocking agents, but this therapy has well-known side effects, that is, in terms of increased risk of pulmonary emboli, and the increased sympathetic discharge is maintained. Hypothermia is also associated with hypotension, pulmonary infections, thrombocytopenia, hypokalemia, and increased risk of bleedings caused by general coagulation disturbances.

寒战可以减轻药学有效物质，例如，通过神经肌肉阻断剂，但这种疗法具有熟知的副作用，也就是说，会增加肺栓塞的风险和交感神经放电。低温也与低血压，肺部感染，血小板减少，低钾血症，一般凝血障碍引起的出血风险增加有关。

Adverse Effects of Hypothermia

Hypothermia may also trigger a reduction in plasma volume . It may also be clinically relevant that hypothermia reduces and rewarming increases the elimination rate of drugs . Noradrenalin given to compensate for hypothermia-induced hypotension may be beneficial by preserving CPP, but it may also induce pulmonary complicationsand compromised cerebral circulation.

低温还可能引发血容量减少，与临床温度过低和复温时药物消除率增加有关，去甲肾上腺素用于低温所致的低血压，有利于维持CPP，但它也可引起肺部并发症和脑循环不足。

Trials Included and Outcome

We found 19 original articles that met the inclusion criteria,14 of which included all ages or adult patients only, and 5 were pediatric. The characteristics of the trials are given in Table 1. Information about mortality and neurological outcome, complications, and ICP is presented in Table 2.

我们发现，符合纳入标准的19篇原创文章中的14项包括所有年龄段或仅为成人患者，5项为小儿患者，表1为这些试验的项目，表2为患者死亡率及神经系统结果，并发症和ICP值。

Trials Included and Outcome

The studies by Clifton et al. (2001, 2011) can be classified as high-quality studies involving 392 and 97 patients, respectively. There were no significant difference in mortality between the hypothermia group and the normothermia group in these studies.

Clifton等人研究可以被归类为高质量研究，分别为392和97例患者，低温组和常温组患者死亡率之间无显著差异。

Trials Included and Outcome

However, the study from 2001 showed more frequent episodes of hypotension and low CPP with hypothermia therapy, and therewas a longer hospital stayfor patients in the hypothermia group in that study. In the study from2011, noradrenalin was more commonly used to prevent hypotension.

然而，该研究2001年显示：低温组患者出现更为频繁的低血压和低CPP，在该研究的低温组中有一个较长的住院病人。该研究2011年的结果显示：去甲肾上腺素是比较常用的防止低血压药物。

Trials Included and Outcome

In spite of this and that the patients were younger in hypothermia group, outcome was not better in the hypothermia group in that study.This study also showed a tendency of poorer outcome in patients with diffuse brain injury treated with hypothermia compared with the control group, but there was better outcome with hypothermia in the subgroup of patients who underwent surgical removal of intracranial hematomas.

尽管低温组患者更为年轻，但其研究结果并不理想。这项研究与对照组相比显示：低温治疗弥漫性脑损伤患者效果不佳，但对于亚组中颅内血肿清除后患者效果较好。

Trials Included and Outcome

The study by Harris et al. included 12 and 13 patients in the hypothermia and normothermia group, respectively. These authors investigated the effect of local hypothermiawith a cooling cap, but they had difficulty in reaching the target temperature of 33^0C for all patients. They did not find any difference in GOS or in complications between the groups.

Harris等人的研究，低温组和常温组分别有12例和13例患者，他们观察了冰帽局部降温的效果，但很难实现所有患者均达到33^0C的目标值，他们没有发现两组之间GOS或并发症的差异。

Trials Included and Outcome

Four of the studies in adult patients showed lower mortality and more patients with favorable outcome in the hypothermia groups than in the control groups. The study by Liu et al. (2006) had 22 patients in each of the 3 groups: a hypothermia group with selective brain cooling, a hypothermia group with systemic cooling, and a normothermia group.

4项成人低温治疗的研究中显示：与对照组相比，低温组患者具有较低的死亡率和预后效果更佳。Liu等人的研究将患者分为3组，每组均有22例患者，分别为选择性头部降温组、全身降温组、常温组.

Trials Included and Outcome

The two hypothermia groups did not differ regarding outcome, but had better outcome than the control group. The randomized trial by Zhi et al. (2003) involved two groups with 198 patients per group and showed that hypothermia was beneficial for neurological outcome and mortality. In the trial by Polderman et al. (2002), the hypothermia group included 64 TBI patients with ICP higher than 20mmHg in spite of standard treatment including barbiturate treatment.

两个低温组间结果无差异，但均比对照组效果更好。Zhi等人的随机试验有2组，分别有198例患者，结果显示：低温有利于神经保护和降低死亡率。Polderman等人试验中低温组为64例ICP≥20mmhg的TBI患者，给予包括巴比妥等标准治疗.

Trials Included and Outcome

Hypothermia was continued until ICP remained at 20mmHg or less for 24 hours. The control group consisted of 72 patients given a standard treatment including barbiturate treatment. This means that the two groups were not fully comparable. The study suffered from the highest mortality reported: 63% and 72% in the hypothermia group and the control group, respectively.

持续低温治疗直到24h内ICP值≤20mmhg,对照组为给予包括巴比妥类药物标准治疗的72例患者，这意味着两组不具有完全可比性。研究中低温组与对照组最高死亡率分别为63％和72％ 。

Trials Included and Outcome

The beneficial effects of hypothermia on mortality and outcome in that study were limited to the subgroup of patients with GCS of 5 or 6 at admission. Inamasu et al. (2006) evaluated the effect of hypothermia for patients with severe TBI (GCSp6) with acute subdural hematoma. They evaluated 18 patients with acute surgery and found improved survival and favorable outcome compared with a historic control group of 15 patients.

这项研究表明：低温具有较低的死亡率和效果更佳仅限于亚组入院时GCS为5或6分的患者,Inamasu等人评估了低温对重型颅脑损伤合并急性硬膜下血肿患者的影响，他们发现：与对照组15例患者相比，18例急性术后患者生存得到改善且预后效果更佳。

Trials Included and Outcome

The trials by Qui et al. (2006), Lee et al. (2010), and Zhao et al. (2011) showed improved favorable neurological outcome with hypothermia, but no effect on mortality. The study by Zhao et al. (2011) had 40 patients in the hypothermia group and 41 patients in the normothermia group.

Qiu，Lee，Zhao等人的研究均显示，低温治疗有利于改善神经系统，但对死亡率无影响。Zhao等人的研究中低温组为40例患者，常温组为41例患者。

Trials Included and Outcome

Three months after treatment, more patients had favorable outcome in the hypothermia group ($p < 0.04$). The study by Qui et al. (2006) had 45 patients in each group. At 6 months after TBI, there was no difference in mortality between the groups, but there were more patients with favorable outcome in the hypothermia group.

3个月治疗后，低温组更多患者效果更佳（p<0.04）。Qiu等人研究，两组均有45例患者。脑外伤6个月后，两组之间死亡率无差异，但低温组也有更多的患者效果更佳。

Trials Included and Outcome

The study by Lee et al. (2010) was randomized, and involved three groups with patients with a GCS score of between 4 and 8. In group 1 (n = 16), the treatment was guided by ICP/CPP. In group 2 (n = 15), the treatment was also ICP/CPP guided, but included moderate hypothermia (33–35^{0}C) as well. Group 3 (n = 14) was guided by measurement of brain issue oxygen and included the same moderate hypothermia.

Lee等人的随机研究，3组GCS值为4-8分的患者。第1组（16例），是根据ICP / CPP治疗。第2组（15例），包括ICP / CPP和中度低温（33-35℃）治疗。第3组（14例）是由大脑组织氧的测量和相同的中度低温进行治疗。

Trials Included and Outcome

- Mortality was low in all groups, and did not differ between thegroups. In another study by Qiu et al. (2007), the effect of hypothermia was analyzed in patients after craniotomy, with a hypothermic group and a normothermic group with 40 patients in each. In this randomized study, mortality was lower and favorable neurological outcome was better in the hypothermia group.

3组死亡率均低且无差异。Qiu等人对低温组和常温组均有40例开颅术后患者的随机研究分析显示：低温组患者神经功能恢复更好且死亡率更低。

Trials Included and Outcome

- A recent large retrospectivemulticenter study fromJapan based on data fromthe JapanNeurotrauma Data Bank including 401 patients showed a tendency of higher mortality, but better favorable neurological outcome in surviving patients in the hypothermia group. The study can be criticized, however, as the patients in the hypothermia group were significantly younger, and inclusion criteria, such as age and method of temperature management, differed between the institutions.

- 最近一项来源于日本神经创伤数据库401例患者的大型的多中心回顾性研究显示：低温组幸存患者神经系统恢复更佳，但死亡率仍较高。研究有一定争议，因为低温组患者均显著年轻化，如年龄和温度管理的方法都应纳入标准，来区别研究结果。

Trials Included and Outcome

- Three of the five pediatric studies analyzed reported that patients treated with hypothermia were slightly more prone to die and two showed no clear effect on mortality and neurological outcome by hypothermia . The study by Biswas et al. (2002) included only 21 patients, and the authors stated that no conclusion could be drawn from their study regarding outcome.

- 5项儿科研究中有3项研究报告分析显示：低温治疗的患者更容易死亡，另外2项研究表明低温治疗对死亡率没有明显的影响。Biswas等人仅21例患者的研究表明，他们对研究结果没有定论。

Trials Included and Outcome

- Special attention should be paid to the higher mortality rate with hypothermia in the properly designed pediatric study by Hutchison et al. (2008) and the lack of any positive effects in the also well-designed recent pediatric study by Adelson et al. (2013). The latter showed no difference in neurological outcome between the hypothermia and the control group and there was a tendency of higher mortality rate (p = 0.15) in the hypothermia group.The study was terminated early after a futility analysis.

- Hutchison等人的小儿研究中强调要特别重视低温带来的高死亡率，Adelson等人近期的小儿研究表明，低温治疗没有任何积极的效果。后者表明，低温组和对照组间神经系统结果没有差异，且低温组有更高的死亡率（P=0.15），该研究因无意义而提前结束。

Trials Included and Outcome

- In a study by Yan et al. (2010), the patients were divided into three groups according to GCS score (GCS 7–8, 5–6, and 3–4) and improved outcome by hypothermia was shown only in the group with GCS score 7–8. In a study by Gal et al. (2002) with 15 patients per group, there was a tendency of better outcome in the hypothermia group.

Yan等人的研究根据GCS评分 (GCS 7–8，5–6, 3–4)将患者分为3组，研究表明GCS为7-8分的患者效果更佳。Gal等人研究，两组均有15例患者，低温组患者预后更佳。

Trials Included and Outcome

- This can be compared with the pediatric study by Adelson et al. (2005), which showed a tendency of reduced mortalitywith hypothermia treatment. The alternative protocol used by Adelson et al. (2013) in terms of an extended cooling period and slower rewarming did not improve outcome.

- 这可与他们05年的一项研究对比，其研究显示低温治疗可降低患儿死亡率。他们的另一种方法即增加低温治疗时间和减慢复温速度，但也没有改善治疗效果。

Trials Included and Outcome

- In the study by Hutchinson et al. (2008), there was higher incidence of hypotension and low CPP during rewarming in the hypothermia group, and higher risk of unfavorable outcome in a subgroup of patients over 7 years of age, with a mortality rate of 21% in the hypothermia group and 12% in the normothermia group (p = 0.06). In a post hoc analysis, Hutchison et al. (2010) suggested that hypotension and low CPP may explain the unfavorable outcome with hypothermia.

- Hutchinson等人的研究显示：在低温组复温阶段患者有较高的低血压和低CPP发生率，亚组中年龄超过7岁的患者预后不良的风险较高，其低温组死亡率为21%，常温组死亡率为12%（p=0.06），他们事后分析认为，低血压和低CPP可以解释低温引起的预后不良。

Trials Included and Outcome

- A recent review summarized that there is no support today for the use of hypothermia in the treatment of children with TBI . This conclusion on therapeutic hypothermia agrees with that from a Cochrane analysis from 2009 for both adults and children. They found 23 trialswith acceptable entry criteria, but only 8 fulfilled the required level of quality, and in these 8 studies the patients treated with hypothermia were slightly more prone to die.

- 近期的一项回顾性研究总结，当今没有有力的依据来证明低温治疗有利于TBI儿童，这个结论与Cochrane 2009年一项关于成人和儿童的研究结果一致。他们发现被纳入标准的23项试验中仅有8项为高质量研究，在这8项研究中，亚低温治疗患儿更容易死亡。

GCS at Admission

- Some studies in this review found that severity of brain injury (GCS score) at admission influenced the therapeutic effect of hypothermia, while others did not. Subgroup analysis in four studies found that hypothermia had no benefit in patients with GCS 3–4 .It may be that patients with GCS 3–4 are so severely injured that they are unable to benefit from hypothermia.

- 本综述中一些研究发现重型颅脑损伤患者入院时GCS评分影响低温治疗结果，一些研究者却不这样认为。Gal，Polderman，Inmasu，Yan等人的四项研究中亚组分析发现：低温对于GCS为3-4分的患者无意义，这可能是因为这些患者受伤极其严重以致他们不能够受益于低温治疗。

GCS at Admission

- If so, trials including a study population with a low mean GCS are more unlikely to show beneficial effects of hypothermia. However, Liu et al. (2006) and Qiu et al. (2007) both with a high percentage (> 50%) of patients with GCS 3–5 found beneficial effects of hypothermia. Neither Clifton et al. (2011) nor Hutchison et al. (2008) found an interaction between GCS at admission and outcome by hypothermia.

- 如果是这样，那么试验中GCS低分值研究人群对低温治疗无效。然而，Liu和Qiu对超过半数GCS为3-5分的患者的研究发现低温治疗是有效的。Clifton和 Hutchison没有发现入院时GCS评分与低温治疗之间的关系。

Intracranial Lesion and Neurosurgery

- A subgroup analysis from the study by Clifton et al.showed that patients who underwent surgical removal of intracrania l hematomas showed beneficial effects by hypothermia. This hypothesis was supported by other studies included in this review .Neurosurgery and type of brain injury are closely linked as hematomas are surgically removed, whereas patients with diffuse brain injury are exposed to surgery to a less extent.

- Clifton等人亚组分析表明：低温治疗对颅内血肿术后患者是有效的，在本综述中这一假定已被其它研究证实，随着血肿清除术的进行，神经外科手术和脑损伤的类型是紧密相连的，而弥漫性脑损伤患者在术中暴露程度更低。

Intracranial Pressure

- All 14 studies on adults, except the one by Clifton et al. , found lower ICP values in the hypothermia group than in the control group. Clifton et al. showed that episodes of raised ICP were significantly more frequent in the hypothermia group than in the normothermia group. A goaldirected therapy on ICP by hypothermia was used in two adult studies, both indicating positive effects.

- 13项成人研究中显示：与对照组相比，低温组ICP值有所降低。但Clifton等人研究表明，与常温组相比，低温组患者ICP升高更加频繁。Polderman和Zhi在成人的两项研究中显示：低温治疗对于ICP有积极的作用.

Intracranial Pressure

- In these studies, the management was tailored individually, with cooling up to ICP had normalized. The negative study by Clifton et al. (2011) and the positive study by Zhi et al. (2003) used equal rewarming rates, but had conflicting results regarding ICP levels and outcome. Note that no beneficial effect on outcome was observed with similar reduction in ICP following reduced metabolic rate by barbiturate treatment.

- 在这些研究中，采用特定方法使ICP趋于正常。Clifton等人负面研究和Zhi等人正面研究均使用相等复温率，但对于ICP值结果却不同。需要注意的是，巴比妥药物治疗后，ICP值没有随代谢率的降低而降低。

Intracranial Pressure

- Four of the pediatric studies reported ICP reported that ICP was lower in the hypothermia group at all time points tested, while Biswas et al. noted just a trend of lower ICP levels in the hypothermia group.Hutchison et al. reported a significantly lower ICP during the cooling period and a significantly higher ICP during rewarming in the hypothermia group. Adelson et al. showed similar results, but ICP differed between the groups only within the first 24 hours.

- 四项儿科研究报告显示：低温组中所有测试时间点ICP均是较低的。而Biswas指出，低温组中ICP降低只是一个趋势。Hutchison等人研究显示，在低温期间ICP显著降低，在复温阶段ICP显著升高。Adelson等人研究显示了类似的结果，但组间ICP差异仅表现在最初24h。

Intracranial Pressure

- It is difficult to draw any general conclusion from the studies analyzed in this review regarding correlation between ICP, rewarming rate, rebound increase in ICP, and outcome. The newly started Eurotherm3235 hypothermia trial specifically evaluating the effect of ICP on outcome will be a welcome contribution to bring light on this issue.

- 很难从本综述分析的研究中得出关于ICP、复温率、ICP反弹及其结果的一般性结论。
- 新开始的Eurotherm3235低温试验特别评估了低温治疗对ICP的影响，这将为这个课题带来一个新的亮点。

Complications

- Ten of the 14 studies in adults had data on complications, which can be referred to hypothermia. The type of complications included coagulopathy, cardiovascular complications, and pneumonia ,Qui et al. and Liu et al.reported an increase in thrombocytopenia in hypothermic patients. In addition, Qui et al. reported an increase in pulmonary infections with hypothermia.

- 14项成人研究中有10项产生了关于低温治疗的并发症，包括凝血功能障碍，心血管并发症，肺炎。Liu等人研究报道显示：低温患者中血小板减少症人群增多。此外，Qiu等人报道：低温导致肺部感染增多。

Complications

- A Cochrane analysis also concluded that hypothermia can be associated with complications, especially pulmonary complications.No difference in complications between hypothermia and normothermia was reported in four of the five pediatric studies .One of the pediatric studiesfound a trend of increased arrhythmias in the hypothermia group.

- 一项Cochrane分析同样认为，低温与并发症的发生有关，特别是肺部并发症。5项儿科研究中的4项研究表明：低温组和常温组并发症无差异，其中一项研究发现：低温组患者心律失常增加。

Limitations

- Like most clinical studies, the hypothermia studies analyzed in this review had limitations and the generalizability of the data is limited. Several authors did not report if the difference in outcome between groups was significant or not, and the numbers of patients were small in several studies.

- 与大多数的临床研究相似，本综述中所分析的研究一般性数据有限，也存在局限性。一些作者没有报道两组之间结果是否有显著差异，多数研究中患者样本量太小。

Limitations

- The management protocols differed with different inclusion criteria, patient characteristics, and cooling and rewarming performance, and the risk of confounders was high. Penetrating trauma, multiple injuries, hypotension, and acute isolated epidural hematomas are examples of inclusion criteria used in some studies but not in others. The follow-up time after the accident varied between the studies.

不同的纳入标准有不同的研究方法，如病人的特点，低温和复温的性能，高混合性因素等。穿透伤，多发伤，低血压，急性硬膜外血肿等均应纳入标准。各研究对事故发生后后续时间报道不同。

Limitations

- Several of the studies reviewed could not be assessed as high quality because of relatively few patients included, unclear randomization, unclear allocation concealment, and/ or insufficient blinding of outcome assessment.

- 一些研究因研究对象太少，不明确的随机化，不清楚分配隐藏，和/或结果评价不充分而无法评为高质量研究。

Summary

- The studies included showed conflicting results regarding mortality and neurological outcome and varied in quality. Several trials showed improved neurological outcome with hypothermia and a trend of lower mortality rates, but the bestperformed studies showed no difference in outcome or even a tendency of worse outcome, especially in the pediatric population.

- 本综述中提到的研究在关于死亡率和神经系统结果方面有冲突且质量各不相同。一些试验结果表明低温可以改善神经系统并倾向于较低的死亡率，但高质量的研究显示结果无差异甚至显示出更糟糕的结果，特别是在儿科人群中。

Summary

- Adverse effects of hypothermia in TBI patients, such as pneumonia, coagulation disturbances, rebound increase in ICP, and stress-induced decrease in oxygenation of hypoxic areas, may counteract its neuroprotective effects. We conclude that we still lack scientific support for the use of therapeutic hypothermia as a first-tier therapy in TBI patients for both adults and children, but it may still be an option as a second-tier therapy for refractory intracranial hypertension.

- TBI患者低温治疗的不良反应，如肺炎，凝血功能障碍，ICP反弹和缺氧区域应激诱导氧合减少，可能会抵消其神经保护作用。我们的结论是：我们仍缺乏低温作为TBI成人和儿童患者一线治疗的科学支持，但它可作为治疗难治性颅内高压二线的选择。

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Thanks for listening!