



## Hypothermia-rewarming: A Double-edged sword?

Yi Hou<sup>a,b,c,1</sup>, Yuanyuan Qiao<sup>d,1</sup>, Ming Xiong<sup>d,\*</sup>, Dajin Zhang<sup>d</sup>, Wei Rao<sup>a,b,c,\*</sup>, Chenghe Shi<sup>d,\*</sup>



<sup>a</sup> CAS Key Laboratory of Cryogenics, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, China

<sup>b</sup> Beijing Key Laboratory of Cryo-Biomedical Engineering, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, China

<sup>c</sup> School of Future Technology, University of Chinese Academy of Sciences, Beijing 100049, China

<sup>d</sup> Research Center of Naval Battle Wound Treatment, The Six Medical Center of PLA General Hospital, Beijing 100037, China

### ARTICLE INFO

#### Keywords:

Hypothermia

Rewarming injury

Thermoregulation

### ABSTRACT

Hypothermia is a condition in which the body's core temperature drops below 35.0 °C. Hypothermia is the opposite of hyperthermia, which the metabolism and body functions are abnormal. Severe hypothermia is a life-threatening problem that may cause atrial and ventricular dysrhythmias, coagulopathy, cardiac, and central nervous system depression. What is worse, it is fatal when untreated or treated improperly. Accidental deaths due to hypothermia resulting from immersion in cold water, especially involving naval fighters and maritime victims have occurred continually in the past years. Currently, the treatment of hypothermia has become a research focus. Rewarming is the only approach that should be considered for hypothermia treatment. However, the treatment is of low efficiency, and few active rewarming cases have been reported. It is well known that timely reperfusion is the best way to save the lives of patients with ischemia. Similarly, reoxygenation is effective for hypoxia. However, several studies have identified that improper reperfusion of ischemic tissues and reoxygenation of hypoxic tissues give rise to further injury. Analogically, this study attempts to propose the hypothesis that hypothermia-rewarming injury may also exist. When suffered from hypothermia, both the blood circulation and the oxygen supply in the body will be affected in a deficient state, an injury may also appear in the improper rewarming process. In a word, hypothermia-rewarming may be a double-edged sword.

### Introduction

Hypothermia is a typical low-frequency but high-impact diagnosis in a widely varied population who suffers from environmental exposure, anesthesia, illness, medications, or trauma [1–4]. Body temperature is usually maintained near a constant level of 36.5–37.5 °C through biologic homeostasis or thermoregulation. If persons are exposed to a cold environment, and their internal metabolic heat production cannot replenish the heat dissipation, the body's core temperature falls. This can occur due to excessive cold or health problems that decrease a person's ability to generate heat. Characteristic symptoms depend on the temperature levels of hypothermia. In mild hypothermia, symptoms manifest as shivering and mental confusion. The treatment of mild hypothermia involves heated drinks, warm clothing, and staying active [5]. Minimizing movements along with heating blankets and warmed intravenous fluids are recommended in moderate hypothermia treatment. In severe hypothermia, risk of cardiac arrest

increases [6]. Extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass is beneficial for severe hypothermia treatment. For patients without vital signs, cardiopulmonary resuscitation (CPR) is indicated along with the above measurements. When a patient has a cardiac arrest, rewarming is the primary treatment until a person's body temperature is greater than 32 °C. Mortality rate of severe hypothermia patients is more than 50%, therefore, effective treatment modality is still the focus of research [7–9].

The goal of hypothermia therapy is to return the core temperature to a normal level that restores the regular physiologic function of all body processes. Currently, rewarming is the primary treatment. Therefore, we think the high modality of severe or profound hypothermia treatment is closely related to the rewarming process. As we know, recovering blood supply and oxygen supply to the heart and brain tissue are the best ways to save the lives of patients with cerebrocerebral ischemia and hypoxia, but restoring blood perfusion or oxygen supply will bring new damage to the heart and brain tissue, namely,

\* Corresponding authors at: CAS Key Laboratory of Cryogenics, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, China (W. Rao) and Research Center of Naval Battle Wound Treatment, The Six Medical Center of PLA General Hospital, Beijing 100037, China (M. Xiong and C. Shi).

E-mail addresses: [houyi17@mails.ucas.ac.cn](mailto:houyi17@mails.ucas.ac.cn) (Y. Hou), [wldxming@126.com](mailto:wldxming@126.com) (M. Xiong), [dajinzhang@sina.com](mailto:dajinzhang@sina.com) (D. Zhang), [weirao@mail.ipc.ac.cn](mailto:weirao@mail.ipc.ac.cn) (W. Rao), [shichenghe0333@sina.com](mailto:shichenghe0333@sina.com) (C. Shi).

<sup>1</sup> Equal Contribution.

<https://doi.org/10.1016/j.mehy.2019.109387>

Received 30 July 2019; Received in revised form 27 August 2019; Accepted 29 August 2019

0306-9877/ © 2019 Elsevier Ltd. All rights reserved.

ischemia-reperfusion and hypoxia-reoxygenation injury. In 1960, Jennings *et al.* found for the first time in dogs that ischemic reperfusion aggravated myocardial necrosis [10]. In 1985, Braunwald and Kloner proposed the concept of “myocardial ischemia-reperfusion injury” [11]. Reperfusion improves the supply of blood to the myocardium. At the same time, it also aggravates the injury caused by simple myocardial ischemia and causes arrhythmia, enlarged infarct size, and persistent ventricular systolic dysfunction. The mechanism of ischemia-reperfusion injury is complex. Currently, it is believed to involve a variety of biologically active molecules and intracellular signal transduction pathways, such as reperfusion-induced reactive oxygen species (ROS) outbreaks and reduced nitric oxide rate, *etc.* In addition, a large number of studies have shown that after myocardial hypoxia-reoxygenation, there are free radical production and LPO enhancement, the release of CPK, LDH, *etc.* in cells increases, the myocardium is severely damaged [12].

Similarly, rewarming is central to hypothermia treatment. In recent years, there have been many studies on the methods for reheating at low temperatures. However, the rewarming effect is not very satisfactory, and the efficiency of rewarming in moderate to severe hypothermia is not high. And sometimes the rewarming even causes more severe injuries [13,14]. When the body temperature is below normal state, both the blood circulation and the oxygen supply in the body will be affected in a deficient state. The blood oxygen supply gradually recovered when rewarmed, but previous studies had shown that after myocardial hypoxia-reoxygenation, the myocardium severely damaged. Respiration turns from initial tachypnea to bradypnea and alveolar hypoventilation happens. At the same time, anemia-hemoconcentration, dehydration (cold diuresis) thrombocytopenia, lowered cardiac output and disseminated intravascular coagulation also happen [15]. Therefore, the hypothesis of hypothermia-rewarming damage is proposed in this paper. When the body is rewarmed from low temperature to normal state, improper thermoregulation may also cause new damage to the body tissue.

## Hypothesis

We propose that there exists hypothermia-rewarming injury resembling hypoxia-reoxygenation and ischemia-reperfusion injury. When suffered from hypothermia, the enzymatic activity slows down, the capacity to generate heat decreases, the functions of different body organs progressively weaken, hypoxemia and hemoconcentration happen [16–21]. Then, rewarming to normal core temperature is critical and essential to the patients. However, unclear and incomplete understanding of the ideal rewarming curve results in a high modality of severe hypothermia treatment. Therefore, the hypothesis we intend to establish is that an unreasonable rewarming method can lead to hypothermia-rewarming injury.

## Evaluating the hypothesis

Rewarming is essential when suffered from hypothermia, increasing research results have been explored on rewarming area. Several pieces of research have indicated that rapid rewarming worsens the outcomes, which include the decrease in survival rate and tissue injury. Moreover, they show that the inflammatory response and intracellular calcium concentration may be altered in patients when rapid rewarming begins [17,22–27]. In addition, therapeutic hypothermia has been reported to increase mortality and tissue injury in several models [28–34]. And inflammatory reaction levels could be changed in different therapeutic hypothermia situations [35]. Therefore, some studies investigated the administration of anti-inflammatory drugs or anti-oxidant agents in hypothermia and rewarming model. And they found that gradual rewarming and administration of anti-inflammatory drug dexamethasone improved survival and reduced acute lung injury suffering therapeutic hypothermia in a rat model [22]. In a hemorrhagic shock model,

rewarming was found to lower blood pressure and increase heart rate and the synthesis of ROS [26]. In patients with a traumatic brain injury has been found induced derangement of cerebrovascular activity [16]. In cardiac arrest patients, the inflammatory cytokines and complement and adhesion molecules changed [17]. Although part of rapid rewarming cases has shown worse results, the optimal rewarming protocol that is the core of rewarming efficiency has not been shown yet. Recently, gradual rewarming over a 6–8 h period is recommended for out of hospital cardiac arrest therapeutic hypothermia treatment, though there is little evidence to support this mode of rewarming [22]. Therefore, further relevant researches about rewarming rate are of great value and significance to improve the therapeutic hypothermia and targeted temperature management.

To evaluate the hypothermia-rewarming injury hypothesis, the cell cytotoxicity of IEC-6 after hypothermia-rewarming manipulation was tested. Firstly, cells were induced with hypothermia under 4 °C, 4 h and inoculate density of  $5 \times 10^5$  cells/mL, which is the optimal condition based on the previous experimental results [36].

Then, the cells were rewarmed at 37 °C and 42 °C respectively to see the different rewarming rate effects. The setting of 37 °C and 42 °C as the rewarming condition is based on the previous animal experiment on hypothermia treatment [37,38]. In most studies, the survival rate of animals rewarming at 42 °C is lower than that at 37 °C. However, some studies show that the animals with severe hypothermia may have a delayed afterdrop effect after rewarming at 37 °C, and in other cases, aggravation and a sudden decrease in the survival rate may happen [37,39]. To clarify different rewarming rates on hypothermia treatment, both 37 °C and 42 °C were set in the cell and animal experiments as the ambient temperature. In addition, it is worth noting that the setting rewarming temperature of 42 °C is the temperature of the heating surface, the real temperature of cell culture medium and the tail of the mouse is actually lower than 42 °C.

As shown in Fig. 1, the cell rewarming survival rates after the temperature mentioned above conditions were tested, when the IEC-6 cells were rewarmed at 37 °C, cell damage gradually increased and the injury reached the maximum after rewarming for 2 h. Subsequently, the cell viability began to recover slowly; the viability was close to but not yet reached the initial level until 4 h after rewarming. However, when the IEC-6 cells were rewarmed in 42 °C, cell damage gradually increased during all observation time, the cell viability did not show any improvement. The results demonstrate that improper rewarming temperature can indeed cause irreversible cell injury.

Moreover, an *in vivo* hypothermia rewarming experiment was

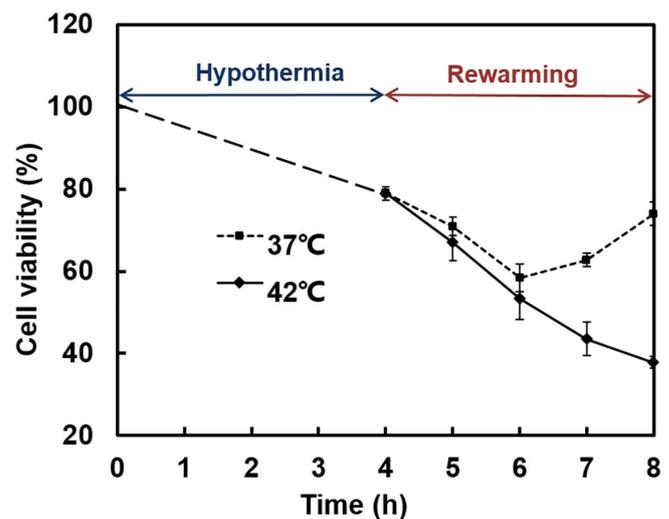
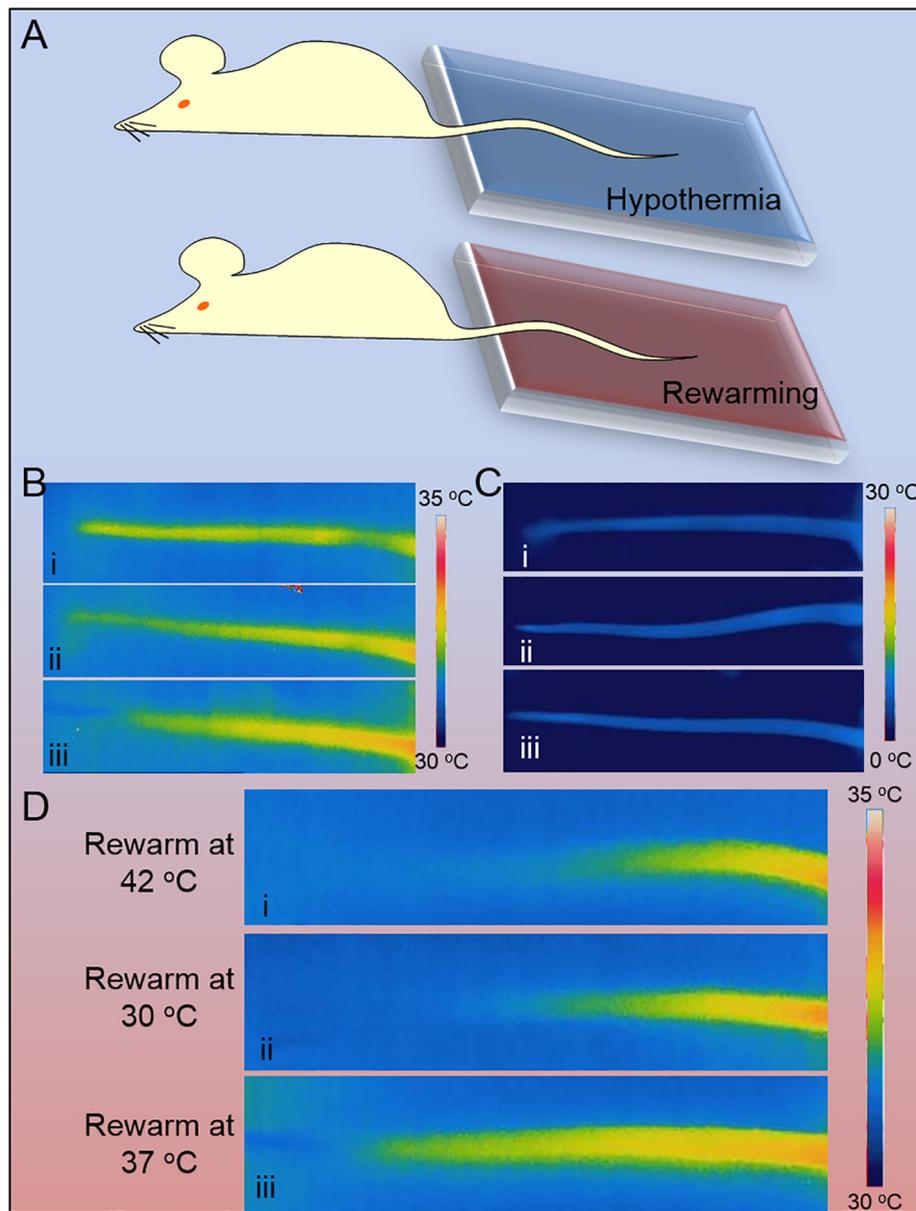


Fig. 1. The cell rewarming survival rates vary under different rewarming temperatures. Cell damage increases when rewarmed at 42 °C while decreases when rewarmed at 37 °C after 4-h rewarming.



**Fig. 2.** A. The hypothermia and rewarming manipulation of mouse tail. B. The initial temperature distribution of mouse tail. C. the temperature distribution of mouse tail after 1 h hypothermia on 4 °C cooling surface; D. The temperature distribution of mouse tail after rewarming at 42 °C, 30 °C and 37 °C for 1 h respectively; i) rewarming at 42 °C, ii) rewarming at 30 °C, iii) rewarming at 37 °C.

conducted to identify whether there exists hypothermia-rewarming injury. Healthy mice were chosen as the animal model. The hypothermia target focused on the tail area that can quickly reflect the temperature changes. Fig. 2A is the illustration of hypothermia and rewarming manipulation. The mouse was anesthetic and the tail was on the cooling surface of 4 °C to serve as animal models of hypothermia. The infrared thermal imager was used to observe the temperature changes during hypothermia and rewarming process. Fig. 2B shows the image of the mouse before the hypothermia treatment. Fig. 2C shows the image of the tail after 1-hour hypothermia, where the temperature is approximate 4 °C. Then, the tail was rewarmed at 30 °C, 37 °C, and 42 °C respectively. Fig. 2D (i-iii) is the rewarming image after 1 h at different rewarming temperatures, the temperature of the tails all began to increase gradually. For the group at 30 °C, the temperature increased gradually, and after another 2 h, the temperature remains unchanged and is lower than the initial temperature without hypothermia. For the group at 37 °C and 42 °C, the temperature of the tail increased faster than that at 30 °C. However, when the tail was rewarmed for 1 h, the

temperature distribution of tail that rewarmed at 37 °C is more close to normal temperature than rewarmed at 30 °C and 42 °C. The results also demonstrate that improper rewarming temperature *in vivo* can indeed lead to injury.

#### Discussion and implications for future research

Our proposed hypothesis is that there remains injury in hypothermia-rewarming is firstly proved by cell viability and temperature distribution of animal tail. From above *in vitro* and *in vivo* experiments, when suffered from hypothermia for hours, the hypothermia injury happens. When rewarmed for the same hours or more, the cells viability and tissue temperature cannot come back to the initial levels at improper warming procedure. Hypothermia and associated shivering have been shown related to increased oxygen consumption, increased blood loss and coagulopathies that may worsen the outcome following rewarming treatment [40–43]. Further research should be continued to identify the mechanism underlying the specific injury when rewarming.

## Conclusion

We proposed a hypothesis that improper rewarming procedure could induce hypothermia-rewarming injury. The cell viability under rewarming at 37 °C is significantly higher than that under rewarming at 42 °C. Additionally, the tissue temperature after hypothermia can recover to normal state more quickly under suitable rewarming condition. In summary, a hypothermia-rewarming injury may exist, and selecting ideal rewarming procedure is vital for hypothermia therapy.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China, China (Nos. 51706236 and 51890893), Technology and Strategy of Medical Support for Seawater Immersion Hypothermia, China (project number: BHJ14J009).

## References

- Bierens JJ, Uitslager R, Swenne-van Ingen MM, van Stiphout WA, Knappe JT. Accidental hypothermia: incidence, risk factors and clinical course of patients admitted to hospital. *Eur J Emergency Med Official J Eur Soc Emergency Med* 1995;2:38.
- Vassal T, Benoitonin B, Carrat F, Guidet B, Maury E, Offenstadt G. Severe accidental hypothermia treated in an ICU: prognosis and outcome. *Chest* 2001;120:1998–2003.
- Silfvast T, Pettilä V. Outcome from severe accidental hypothermia in Southern Finland—a 10-year review. *Resuscitation* 2003;59:285–90.
- Lim C, Duflou J. Hypothermia fatalities in a temperate climate: Sydney, Australia. *Pathology* 2008;40:46–51.
- McCullough L, Arora S. Diagnosis and treatment of hypothermia. *Am Fam Physician* 2004;70:2325–32.
- Brown DJA, Brugger H, Boyd J, Paal P. Accidental hypothermia. *N Engl J Med* 2012;367:1930–8.
- Danzl DF, Pozos RS, Auerbach PS, Glazer S, Goetz W, Johnson E, et al. Multicenter hypothermia survey. *Ann Emerg Med* 1987;16:1042–55.
- Farstad M, Andersen KS, Koller ME, Grong K, Segadal L, Husby P. Rewarming from accidental hypothermia by extracorporeal circulation. A retrospective study. *Eur J Cardio-Thoracic Surgery* 2001;20:58–64.
- Kornberger E, Mair P. Important aspects in the treatment of severe accidental hypothermia: the Innsbruck experience. *J Neurosurg Anesthesiol* 1996;8:83–7.
- Jennings RB, Sommers HM, Smyth GA, Flack HA, Linn H. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Arch Pathol* 1960;70:68.
- Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clinical Investigation* 1985;76:1713–9.
- Li C, Jackson RM. Reactive species mechanisms of cellular hypoxia-reoxygenation injury. *Am J Physiol-Cell Physiol* 2002;282:C227–41.
- Zydlowski AW, Hasbargen JA. Hypothermia-induced hypokalemia. *Mil Med* 1998;163:719–21.
- Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 1998;29:2461–6.
- Peek GJ, Davis PR, Ellerton JA. Management of severe accidental hypothermia. Berlin Heidelberg: Springer; 2008.
- Lavinio A, Timofeev I, Nortje J, Outtrim J, Smielewski P, Gupta A, et al. Cerebrovascular reactivity during hypothermia and rewarming. *Br J Anaesth* 2007;99:237–44.
- Bisschops LL, Hoedemaekers CW, Mollnes TE, Jg VDH. Rewarming after hypothermia after cardiac arrest shifts the inflammatory balance. *Crit Care Med* 2012;40:1136–42.
- Jurkovich GJ, Greiser WB, Luteran A, Curreri PW. Hypothermia in trauma victims: an ominous predictor of survival. *J Trauma* 1987;27:1019–24.
- Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. *Injury-Int J Care Injured* 2004;35:7.
- Luna GK, Maier RV, Pavlin EG. Incidence and effect of hypothermia in seriously injured patients. *J Crit Care* 1987;3:1014.
- Valeri CR, Feingold H, Cassidy G, Ragno G, Khuri S, Altschule MD. Hypothermia-induced reversible platelet dysfunction. *Ann Surg* 1987;205:175.
- Kim K, Jo YH, Rhee JE, Kim TY, Lee JH, Lee JH, et al. Effect of speed of rewarming and administration of anti-inflammatory or anti-oxidant agents on acute lung injury in an intestinal ischemia model treated with therapeutic hypothermia. *Resuscitation* 2010;81:100–5.
- Deakin CD, Morrison LJ, Morley PT, Callaway CW, Kerber RE, Kronick SL, et al. International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2010;81(2010):298–324.
- Alam HB, Rhee P, Honma K, Chen H, Ayuste EC, Lin T, et al. Does the rate of rewarming from profound hypothermic arrest influence the outcome in a swine model of lethal hemorrhage? *J Trauma Acute Care Surgery* 2006;60:134–46.
- Gordan ML, Kellermann K, Blobner M, Nollert G, Kochs EF, Jungwirth B. Fast rewarming after deep hypothermic circulatory arrest in rats impairs histologic outcome and increases NFκB expression in the brain. *Perfusion* 2010;25:349–54.
- Vaagenes P, Gundersen Y, Opstad PK. Rapid rewarming after mild hypothermia accentuates the inflammatory response after acute volume controlled haemorrhage in spontaneously breathing rats. *Resuscitation* 2003;58:103–12.
- Warren DE, Bickler PE, Clark JP, Gregersen M, Brosnan H, Mckleroy W, et al. Hypothermia and rewarming injury in hippocampal neurons involve intracellular Ca<sup>2+</sup> and glutamate excitotoxicity. *Neuroscience* 2012;207:316–25.
- Thompson HJ, Kirkness CJ, Cain KC, Mitchell PH. Hypothermia and rapid rewarming of traumatic brain injury patients is associated with worse outcome. *J Neurotrauma* 2005;1202.
- Clifton GL, Miller ER, Choi SC, Levin HS, Mccauley S, Jr SK, et al. Hypothermia on admission in patients with severe brain injury. *J Neurotrauma* 2002;19:293–301.
- Suehiro E, Povlishock JT. Exacerbation of traumatically induced axonal injury by rapid posthypothermic rewarming and attenuation of axonal change by cyclosporin A. *J Neurosurg* 2001;94:493–8.
- Maxwell WL, Watson A, Queen R, Conway B, Russell D, Neilson M, et al. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. *J Neurotrauma* 2005;22:873.
- Mcintyre LA, Fergusson DA, Hébert PC, Moher D, Hutchison JS. Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA, J Am Med Assoc* 2003;289:2992–9.
- Zhi D, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surg Neurol* 2003;59:381.
- Polderman KH, Joe RTT, Peerdeman SM, Vandertop WP, Girbes AR. Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury. *Intensive Care Med* 2002;28:1563–73.
- Polderman KH. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. *Intensive Care Med* 2004;30:556–75.
- Ming X, Dajin Z, Yuanqun Q, Chenghe S. Experimental study on orthogonal design to optimize the damage condition of IEC-6 cells induced by hypothermia stress. *Transl Med J* 2018.
- Huan Jianbo CL, Zhihai Han, Wei Dai, Danfeng Yuan, Jihong Zhou, Chenghe Shi. Experimental study on water bath rewarming in rats with hypothermia by seawater immersion. *Acad J Second Military Med University* 2017;39:101–7.
- Yuan Rui SW, Zhicheng Zhang. The comparative study of Heparin versus Citrate Anticoagulation for continuous renal replacement therapy rewarming in hypothermia dogs with seawater immersion. *China Modern Med* 2017;24.
- Dobson JA, Marini CP. Resuscitation of severe hypothermia by extracorporeal rewarming in a child. *Trauma* 1996;40:483–5.
- Moore K. Hypothermia in trauma. *J Trauma Nursing Official J Soc Trauma Nurses* 2008;15:62.
- Seekamp A, Van GM, Hildebrandt F, Wahlers T, Tscherne H. Adenosine-triphosphate in trauma-related and elective hypothermia. *J Trauma Acute Care Surgery* 1999;47:673–83.
- Schmied H, Reiter A, Kurz A, Sessler DI, Kozek S. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet* 1996;347:289–92.
- Mdash AH, NEJM, Accidental Hypothermia — NEJM, New England Journal of Medicine.