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SPECIAL ISSUE INSIGHT

Manipulating temperature: devices for targeted temperature management (TTM) in brain injury

Fabio S. Taccone[1,3*], Katia Donadello[2] and Stephan A. Mayer[3]

Body temperature regulation, which is tightly controlled by several mechanisms in healthy individuals, is often altered after an acute brain injury (ABI) because of either non-infectious (i.e. tissue damage, systemic or cerebral inflammation, vascular injury, hemorrhagic lesions, deep venous thrombosis) and/or infectious causes [1]. As such, ABI patients often experience fever (variously defined as a body temperature exceeding 37.5 to 38.5 °C), regardless of the type of brain disease and site of temperature measurement. In both experimental and human studies, fever has been associated with exacerbated ischemic injury, cerebral edema, intracranial hypertension and with temporary neuro-worsening; moreover, ABI patients experiencing fever had also an increased risk of mortality and of poor neurological outcome [2]. Preventing and/or treating fever is therefore currently implemented and considered standard of care in the clinical management of ABI patients. Moreover, lowering body temperature below normal ranges (i.e. hypothermia) can reduce intracranial pressure and provide some neuro-protective effects, although its benefits in clinical studies remains highly controversial [3]. The term "targeted temperature management" (TTM) encompasses these different approaches; however, the optimal method to provide optimal TTM is unknown.

Methods to provide TTM

Different devices have been developed to implement TTM in clinical practice that have progressively replaced less modern approaches, such as intravenous cold fluids, cold blankets, ice packs and pads. These systems, i.e. surface cooling devices and intravascular methods (Fig. 1), although being more expensive and usable only in controlled settings (i.e. intensive care uni (ICU), operative room, cath lab) than others, can more precisely control body temperature, have shorter and more predictable time to target temperature and, using a feedback control to adjust to patient's temperature, reduce healthcare workload [4]. A summary or existing TTM approaches is shown in Supplemental Table 1. Surface cooling devices are based on the principle of thermal conductivity (i.e. cold liquid or air circulating through cooling pads in contact with the patient's body). Intravascular methods are more invasive, as they require central venous catheter placement, in which a cold solution circulates within a closed circuit. Intravascular methods can generally reach target temperature faster than surface cooling devices, although there is a potentially high risk of adverse events (i.e. infections, bleeding at the site of catheterization and deep venous thrombosis) [4]. Whether surface cooling devices and intravascular methods can improve patients' outcome in ABI patients when compared to other TTM strategies is widely debated. However, the use of these devices can provide "high quality TTM", i.e. faster time to target, less temperature variability during maintenance, controlled rewarming and an appropriate control of fever.

TTM devices in post-anoxic brain injury

Recent guidelines on post-resuscitation care have recommended actively preventing fever (defined as a temperature > 37.7 °C) for at least 72 h in patients who remain unconscious after cardiac arrest [5]; these guidelines were mainly driven by a recent randomized trial of 1850 out-of-hospital cardiac arrest survivors, which showed similar outcome between those treated with TTM at 33 °C and those treated when body

*Correspondence: fabio.taccone@ulb.be
[1] Department of Intensive Care, Hôpital Universitare de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium
Full author information is available at the end of the article

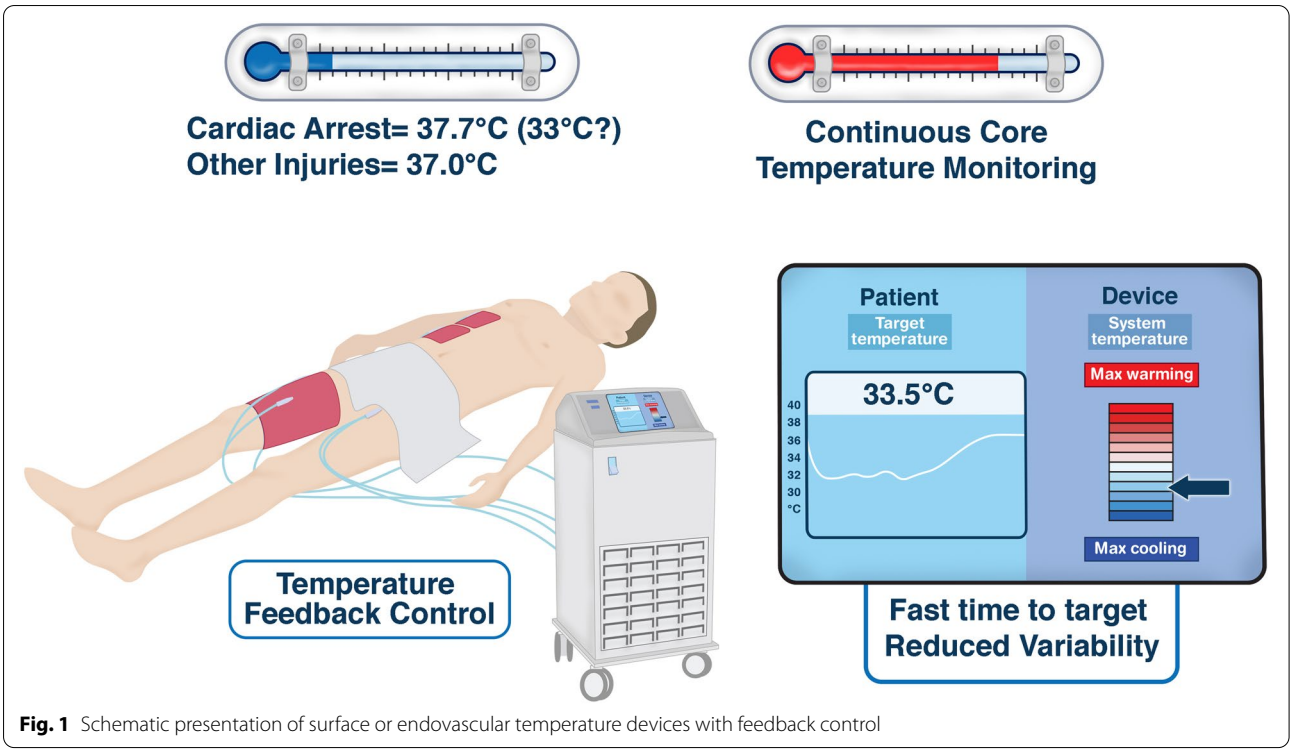

Fig. 1 Schematic presentation of surface or endovascular temperature devices with feedback control

temperature exceeded 37.7 °C [6]. In this study, surface cooling devices and intravascular methods were used in both groups to achieve target temperatures; as such, nearly 50% of patients in the 37.7 °C group required such devices. Although randomized trials found no differences in survival and neurological outcome between intravascular methods and surface cooling devices, systematic reviews and meta-analyses of non-randomized data have yielded interesting results: (a) invasive and temperature feedback TTM methods were associated with a lower probability of unfavorable outcome, but not mortality, although these effects were mainly driven by non-randomized trials; (b) intravascular methods were associated with improved neurological outcomes when compared to all types of surface devices; (c) the benefits of intravascular methods were mainly observed in comparison with surface devices without temperature feedback [7, 8]. These data suggest that either surface or intravascular cooling devices should be considered as the ideal cooling technique in cardiac arrest survivors undergoing TTM, in particular those using temperature feedback systems. Importantly, in cardiac arrest survivors initially requiring veno-arterial extracorporeal membrane oxygenation (VA ECMO) therapy, the heat exchanger of the ECMO device is efficient without additional devices to accurately provide TTM at 33 or 36 °C [9].

TTM devices in other types of brain injury

Fever has been associated with adverse outcomes in all forms of ABI. In non-anoxic brain injured patients, the optimal management of fever remains poorly defined. Different guidelines recommend targeting normothermia (i.e. core temperature around 37 °C) in patients with stroke and traumatic brain injury [10, 11], despite the lack of randomized trials to support this strategy. In an population of ABI patients with cerebrovascular disease, the use of intravascular methods significantly reduced the burden of fever when compared a conventional approach (i.e. anti-inflammatory drugs and surface cooling devices) without an increased risk of adverse events and with no significant difference in mortality and neurologic long-term outcome [12]. One non-randomized trial found that the use of surface TTM devices with temperature feedback aiming at normothermia was associated with improved long-term neurological outcome in patients with subarachnoid hemorrhage, when comparted to antipyretics [13]; however, this approach resulted also in longer ICU stay, prolonged sedation and higher rate of tracheostomy. Another study reported that the use of intravascular methods to obtain normothermia in ABI patients was associated with a significant reduction of fever burden and no higher risk of infections, when compared to conventional therapies [14]. Other studies found that water-circulating surface TTM

devices or endovascular catheters were more effective in avoiding fever and maintaining normothermia than other systems (i.e. non-temperature feedback cooling blankets or antipyretics), although the incidence of shivering was higher [15]. In this setting, another important advantage of surface cooling devices and intravascular methods is the possibility of reducing temperature variability during TTM in these patients. In one study, high level of temperature variability in traumatic brain injury patients during the first 48 h was associated with poor long-term neurological outcome [16]. The ongoing INTREPID trial (ClinicalTrials.gov Identifier: NCT02996266) is currently testing the clinical impact of proactive fever control using a surface cooling system in patients with severe acute ischemic or hemorrhagic.

In patients undergoing TTM after an acute brain injury, the implementation of surface cooling devices and intravascular methods with feedback control results in a more adequate maintenance of core temperature within desired targets and a precise assessment of the "dose" of TTM (i.e. the exposure of the patient to a specific level of temperature over time). In unconscious patients after cardiac arrest, these devices appear to be associated with an improved neurological outcome; however, these findings are mainly driven by non-randomized trials and their role in avoiding fever needs to be further evaluated. In patients with a non-anoxic brain injury, surface cooling devices and intravascular methods are more effective in maintaining normothermia and reduce temperature variability; due to the relative paucity of high quality data as compared to the cardiac arrest field, their effects on clinically relevant patients' outcome remain to be demonstrated.

Supplementary Information
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Author details
[1] Department of Intensive Care, Hôpital Universitare de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium. [2] Department of Anesthesia and Intensive Care B, Department of Surgery, Dentistry, Gynaecology and Paediatrics, University of Verona, AOUI-University Hospital Integrated Trust of Verona, Policlinico G.B. Rossi, P.le L. Scuro, Verone, Italy. [3] Westchester Medical Center Health System, New York Medical College, Valhalla, NY, USA.

Declarations

Conflicts of interest
FST has received lecture fees from ZOLL and BD. KD has received lecture fees from BD. SM has received consulting fees from BrainCool.

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