Editorial

Does untreated post-cardiac-arrest fever counteract the benefit of therapeutic hypothermia?

The debate on the influence of body temperature on mortality and neurologic outcome of arrested patients has taken on great significance since the recommendation in 2005 to lower core body temperature to 32–34 °C as soon as possible after return of spontaneous circulation (ROSC). Therapeutic hypothermia (TH) should become common practice in emergency medical services and departments, though recent reviews point out that the level of evidence is still low and experts call for high-level clinical trials.

In animal models it has been shown that hypothermia attenuates all cascades leading to neurological cell death after ischaemic events. These include depression of electrical activity, reduction of metabolism and inhibition of the release of amino acids such as glutamate, which promotes Ca<sup>2+</sup> influx into neurons and contributes to induction of apoptosis and cell death. During reperfusion, hypothermia attenuates oxidative stress and lipid peroxidation, which are also responsible for the induction of apoptosis.

From the physiological perspective there is good reason to assume that if lower temperatures protect, higher temperatures may harm the human organism. However, results are ambiguous regarding the effect of fever on outcome of arrested patients. The question, already posed by Cronberg and Nielsen in this journal, remains fundamental: does post-cardiac-arrest fever only reflect the severity of ischaemia and therefore act as a harmful prognostic indicator or does it have the potential to deteriorate existing organ dysfunction and thus require treatment?

Only few investigations have focused on post-ischaemic effects of fever. Animal experiments have demonstrated that the induction of high core body temperatures (e.g. by heat exposure or administration of pyretics) is detrimental after an ischaemic insult. For instance in dogs, even a minimal rise in temperature of 1–2 °C resulted in substantial alterations in post-ischaemic neurologic function and cerebral histopathology. In a rat model of forebrain ischaemia, hyperthermia delayed by 24 h more than doubled the number of ischaemic neurons, triggered chronic neurodegeneration in the penumbra zone and caused immunohistochemical neurodegeneration similar to that seen in Alzheimer’s disease. But the effect of treatment of post-ischaemic fever has only been reported in one study using a rodent model. In this experiment the group with spontaneous fever after transient ischaemia was treated with antipyretics or external cooling and compared to the untreated group. Suppression of fever markedly diminished neuronal damage in the neocortex and hippocampus. Thus, from experimental studies it seems there is increasing reason to support that fever after an ischaemic event may not be only a surrogate marker for severe ischaemia but may also deteriorate pre-existent ischaemic damage and should therefore be treated.

In this issue, Bro-Jeppesen et al. present a prospective observational study with the objective to assess the prognostic implication of post-hypothermia fever (PHF) in comatose (GCS < 8) survivors after out-of-hospital cardiac arrest with sustained ROSC. Hypothermia was induced out-of-hospital as soon as possible by cold infusions and in-hospital by surface cooling and maintained for 24 h at 33 °C core temperature. The population was stratified post hoc according to the median peak temperature into two groups, with PHF (≥ 38.5 °C) and without PHF. The authors found a higher 30-day mortality in patients with PHF compared to patients without (36% vs. 22%; plog-rank = 0.02) and higher frequency of unfavourable neurological outcome (Cerebral Performance Category 3–5) at hospital discharge (39% vs. 25%; p = 0.02). Likewise, at one-year follow up mortality (38% vs. 26%; p = 0.03) and unfavourable neurological outcome (43% vs. 27%; p = 0.007) were higher in patients with PHF compared to patients without PHF. The maximum temperature and duration of PHF were independent predictors of 30-day mortality in multivariable models.

The PHF incidence in this cohort (50.4%; 136/270) is higher than that reported by Winters et al. (29.8%; 42/141), but this may be explained by the observation period (36 vs. 24 h, respectively). In both studies PHF was defined as temperature >38.5 °C. Leary et al. reported a PHF rate of 41% (69/176) within 24 h after rewarming and Gebhardt et al. reported 42% (141/336) within 48 h after cardiac arrest (which also corresponds to ~24 h after rewarming), and both defined PHF as temperature >38 °C. The incidence of post-cardiac-arrest fever without TH is similar and ranges from 20 to 78%, suggesting that episodes of temperature >38 °C are likely to occur in all patients after cardiac arrest irrespective of whether TH was administered. The data of Bro-Jeppesen et al. suggest that while the effect on neurological outcome is detectable in all patients with temperature ≥38.5 °C, the effect on mortality becomes important only with temperatures ≥39 °C and a minimum duration of PHF of 7 h. In a smaller sample (n = 167) Leary et al. did not find any effect of fever on survival and neurological outcome, but a maximum temperature >38.7 °C was similarly associated with worse neurologic outcome.

Bro-Jeppesen et al. are to be applauded for this well performed study because it is the largest prospective observational study on the prognostic implications of PHF since the introduction of TH in post-resuscitation care. Nevertheless, the existing level of evidence on the benefit of PHF treatment remains poor; and the literature reveals that standardization of temperature-related
parameters is lacking, e.g. temperature thresholds for fever, level and duration of TH, differentiation between core and peripheral temperature measurement and respective recommendations for measurement location, and duration of post-hypothermia observation. This is the reason for the high variability in existing studies and prevents conclusive statements on temperature management. We suggest that an add-on of the Utstein-style template for body temperature management could be useful to improve evidence in body temperature-related research questions and to enhance the Formula for Survival in Resuscitation in the future.

References

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