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Fever Control in Critically Ill Patients

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Regional temperature differences exist between various parts of the body under physiological conditions in healthy individuals. Traditionally, a temperature gradient between the “core comparment” and the “peripheral compartment” has been recognised. The core compartment basically comprises the organs and rump of the body, while the periphery consists of the arms and legs. Temperature differences between core and periphery may range from 2 0C to 10 0C, depending on the temperature of the environment and other circumstances.

It is less well known that small temperature gradients can also exist within the core compartment. Under normal circumstances (absent the presence of a local infection), the organ/area with the highest temperature within the core compartment is the brain.

In healthy individuals, brain temperature is only marginally higher than the measured core temperature; this difference typically ranges from 0.1-0.30C. In addition, there are small temperature gradients between different areas of the brain. These regional differences are related to activity (higher temperatures in more active brain tissue), blood flow (lower temperatures in areas with high flow due to increased capacity to dissipate and remove heat), and (to a lesser degree) to the distance from the skull (the latter being particularly important in newborns and very young children).

The differences in temperature between the brain and measured core temperature can increase significantly under pathological conditions, such as exist following various types of brain injury. Numerous studies have demonstrated that brain temperature in patients with traumatic brain injury, stroke, subarachnoid haemorrhage, encephalitis and other types of neurological injury exceeds measured core temperature by between 0.20C and 40C compared to the “gold standard”, i.e. the blood temperature measured by pulmonary artery catheter, or compared to core temperatures measured at the oesophagus, bladder or rectum. Again, there are temperature differences between different areas of the brain; however, in contrast to the physiological situation these differences can be substantial, up to 20C, with the highest temperatures found in injured areas of the brain. Many authors have described this phenomenon, and it is a frequent occurrence although the extent may vary considerably.

The mechanism underlying this phenomenon is the generation of excess heat by the ongoing pathophysiological processes in injured areas of the brain. It is well recognised that a period of ischaemia or trauma can trigger a cascade of numerous destructive mechanisms. Some of these produce heat, in particular the activation of neuroinflammatory processes, the increase in blood brain barrier permeability, and a phenomenon known as “exitotoxicity”, a self-destructive “hyperactivity” of injured cells caused by a combination of cell membrane leakage, mitochon drial dysfunction, and excessive influx of calcium (Ca2+) into the cell, leading to intracellular calcium overload with excessive enzyme activation, continuous depolarisation and a permanent state of hyperexcitability. In addition, local or general oedema formation will complicate the removal of heat through lymph drainage and venous return, further adding to overheating of injured areas in a phenomenon known as “cerebral thermo pooling”.

The differences between measured core and brain temperature can increase even further when a patient develops systemic fever, a problem that is frequently observed in patients with various types of neurological injury and which is associated with adverse outcome.

The clinical significance of these phenomena is that increasing evidence exists showing that high temperatures can be harmful, especially to injured (brain) cells. Numerous animal studies have demonstrated that (external) induction of hyperthermia significantly increases the risk and extent of neurological injury. Hyperthermia increases the risk that ischaemic areas will become necrotic or apoptotic; it can be detrimental even when it is of short duration, even when it is mild, and even when it occurs long after the initial injury. These effects become more pronounced if hyperthermia coincides with an episode of ischaemia, suggesting that ischaemic brain cells become even more susceptible to the harmful effects of fever.

Numerous clinical studies have confirmed that fever is indeed an independent predictor of adverse neurological outcome and increased mortality

in various neurologic emergencies, including ischaemic stroke, sub arachnoid haemorrhage, intracranial haemorrhage, traumatic brain injury and post-anoxic injury. Azzimondi and co-workers performed a prospective observational study in stroke patients and observed that developing fever was associated with a 3.4-fold increase in the risk for adverse outcome, with a 95% CI of 1.2 to 9.5.v Castillo and associates reported that fever occurring within 24 hours after the onset of ischaemic stroke was independently related to larger infarct volumes (OR 3.23, 95% CI 1.63 to 6.43) and higher neurological deficits (OR 3.06, 95% CI 1.70 to 5.53) at 3 months. Kammersgaard et al. reported that each 10C increase of admission body temperature independently predicted a 30% relative increase in long term mortality risk, with a 95% CI of 4% to 57%. Zeiner et al. observed that fever was associated with a 2.3-fold increase in the risk of adverse outcome in patients following cardiac arrest, with a p-value of 0.008.

Although these observations do not conclusively establish that the relationship between fever and increased neurological outcome is causal, i.e., that fever itself increases neurological injury rather than just being a marker, the temporal relationship, the fact that it persists after multivariate analysis, coupled with the results from animal experiments and the physiological data outlined above provide a strong and convincing framework for the existence of this relationship. This view is strengthened by observations from other animal studies showing that induction of mild hypothermia can prevent fever-related neurological injury, and can improve tissue tolerance for ischaemia.

All this suggests that lowering fever burden and lowering body temperature in febrile patients with neurological injuries could significantly improve outcome. Unfortunately, the use of anti-pyretic drugs is not very effective in this category of patients; various studies have shown that core temperatures decrease by (only) 0.1-0.70C when adult patients with neurological injuries are treated with acetaminophen, aspirin or other anti-pyretic drugs. Therefore, mechanical cooling (with surface cooling devices or intravascular catheters) will usually be required to effectively control fever in these patients.

If this strategy could indeed prevent or reduce (additional) neurological injuries these interventions would obviously be tremendously cost-effective. Translating the observations and insights outlined above into feasible, practical and cost-effective protocols presents a worthy challenge to physicians caring for critically ill ICU patients.

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