Localized therapeutic hypothermia in the brain for the treatment of ischemic stroke

STROKE is, according to the World Health Organization (10), the third most common cause of death in the developed countries, exceeded only by coronary heart disease and cancer. Annually, 15 million people worldwide suffer a stroke. Of these 15 million people, 5.5 million die and 5 million are left permanently disabled, placing a burden on family and community. The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure and reduced levels of smoking. The absolute number of strokes, however, continues to increase because of the aging of the population. Stroke is the major cause of long-term disability and therefore also related to high costs. In the United Kingdom, e.g., the direct and indirect cost caused by stroke was >4% of the National Health Service spending. Therefore, there is a strong demand for therapies aiming to reduce the disability resulting from the ischemic event.

Nowadays, there are several therapeutic approaches to combat acute ischemic stroke. In the first place, one aims to restore the cerebral blood circulation. Most important therapies for the restoration of the blood circulation are systemic, intravenous thrombolysis, using recombinant tissue plasminogen activator (7), or local, intra-arterial thrombolysis (2). More recently, new techniques and devices for mechanical removal of the thrombus (thrombectomy) (3) are being developed. These therapies can only be applied within a certain time window, i.e., until 3 or 6 h after onset of the stroke.

Additional therapies are applied to limit the damage caused by so-called secondary brain injury and also to limit the effects of reperfusion injury caused by free radicals (reduced oxygen species). Therapies aiming to reduce the effects of secondary brain injury are manifold. The most important among these are active maintenance of euglycemia; maintenance of optimal blood pressure using inotropic drugs; osmotherapy to reduce intracranial pressure; free radical scavengers, like ubiquinone; and, last but not least, systemic or locally induced hypothermia.

In this issue of Journal of Applied Physiology, you find an interesting contribution of A. A. Konstas et al. (5) entitled “Selective cooling using intracarotid cold saline infusion in a human brain model: theoretical and practical implications,” which describes a detailed mathematical model to compute spatially dependent brain temperature responses in case of inducing local hypothermia in the brain by means of an intracarotid cold saline infusion. Systematic research on the clinical use of actively induced hypothermia goes back to the late 1940s/early 1950s of the last century. On the basis of the hypothermia research of Bigelow et al. in 1950 (1), the first successful open heart surgery could be performed by Lewis and Taufic in 1952 (6). That hypothermia can extremely reduce the body’s demand for oxygen and glucose was, for instance, clearly demonstrated in a study of 15 patients (9) suffering from accidental deep hypothermia with circulatory arrest of $15 \pm 19$ min. These young and otherwise healthy patients survived accidental deep hypothermia with no or minimal cerebral impairment. The exact mechanisms by which hypothermia protects the brain are not yet completely understood. Clear is that 1) it decreases cellular metabolism by retarding high-energy phosphate depletion and facilitating postischemic glucose use; 2) suppresses the breakdown of the blood-brain barrier; 3) reduces free radical formation; and 4) reduces the cytotoxic cascade by reducing elevations of intracellular calcium, inhibiting release of excitotoxic amino acids and reducing intracellular acidosis (4).

Nowadays, there are several techniques to induce hypothermia in the human body. The simplest way is surface cooling, by cooling the skin. These vary from very simple techniques like rubbing patients with alcohol-water solutions and lowering ambient temperature combined with electric fans to more sophisticated techniques like fluid-circulating cooling blankets and specially developed cooling helmets. A drawback of surface cooling is that it takes several hours to reduce the brain temperature, due to the relatively slow heat conduction process. Much more sophisticated, so-called intravascular cooling techniques, were developed in the last few years. In these approaches, a central venous catheter is used as a heat-exchange element that cools the blood that passes it. The cooling fluid (cold saline) remains in the catheter. With this type of cooling, therapeutic hypothermia can be reached within 1 h and can be maintained for 24 h.

In contrast to the systemic hypothermia techniques mentioned above, Konstas et al. (5) propose in this issue a hypothermia technique in which the brain is selectively cooled, by a cold saline solution, which is released in the carotid artery, one of the main feeding arteries of the human brain. Due to the nearly perfect heat-exchange properties of the brain vasculature (8), the authors report that their model predicts brain-cooling rates that are up to 42 times faster than whole body surface cooling and up to 20 times faster than endovascular cooling. Hypothermia is reached within 10 min, and it can be sustained for a maximum of 3 h. Since the hypothermia is induced only locally, it lacks the adverse effects of systemic hypothermia, which are hypovolemia, arrhythmia, hyper/hypotension, pulmonary complications, and electrolyte abnormalities (4), preventing the technique being used in patients with cardiac disease.

Apart from this, the model derived by the authors is interesting for several other reasons. Whereas previously published temperature models assume either constant cerebral blood flow (CBF) and perfusate temperature, or continuously changing CBF with constant perfusate, the currently presented model solves the Pennes bioheat equations, which can handle continuously changing CBF and continuously changing perfusate temperature in the computation of the brain temperature. Apart from this, the model also allows the computation of temperature effects on the ischemic penumbra and ischemic core.

From a clinical applicability point of view, the proposed method is also highly interesting because it can easily be combined with techniques that aim at restoring the blood circulation, like arterial thrombolysis and thrombectomy. Due to the fact that brain hypothermia is reached very quickly, the therapeutic window, i.e., the time period in which the stroke...
can be treated, is extended, leaving more time for thrombus removal, and improves the patient outcome.

The proposed technique could also be combined with drugs added to the continuously flowing saline solution. For instance, mannitol could be added as an osmotherapeutic to reduce intracranial pressure. Glucose could be added to prevent hypoglycemia, and free radical scavengers could be added to prevent reperfusion damage as soon as the thrombus has been removed.

In conclusion, the approach of Konstas et al. (5) for rapid induction of localized hypothermia by intracarotid cold saline infusion is a very promising one, because it is a relatively simple clinically applicable technique, which, on one hand, enlarges the therapeutic window and, on the other hand, minimizes the infarct size, improving the patients’ chance to survive the stroke with minimal permanent disability.

REFERENCES


J. Slotboom
Institute of Diagnostic and Interventional Neuroradiology
University of Bern, Inselspital
Bern, Switzerland
e-mail: johannes.slotboom@insel.ch

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