Another Intriguing Application of Hypothermia

And Some Words of Caution

EVERYTHING I know about pain-related science (and it isn't much) has come from the pages of ANESTHESIOLOGY; I am not an expert in the area. However, I do know a great deal about therapeutic hypothermia, and I was fascinated by the article in this month's issue of the Journal.[1] Tsai *et al.* examined the impact of both localized and whole-body cooling on the electrophysiologic, biochemical, and functional consequences of nerve ligation-induced neuropathic pain in the rat. Both regional and whole-body cooling were effective in attenuating pain-related dysfunction (thermal hyperalgesia and tactile allodynia), spontaneous nerve firing, as well as various changes in the cuneate nucleus (*e.g.*, glial activation, cytokine accumulation). Cooling started either before the injury or at 5 h after injury was more effective than later interventions (although whole-body hypothermia as late as 3 days after injury had a measurable effect). Others have shown that hypothermia can protect against ischemia-induced neuropathic pain, but this is the first study to show a similar effect with a more selective (and controllable, reproducible) nerve constriction model.

"… hypothermia provides another controllable tool for further explorations [of neuropathic pain development]. But whether it has a clinical future is completely unknown."

The authors do a good job of reviewing the known effects of hypothermia on a variety of neuropathologic processes and in trying to tie these to their own work. In some ways, their observations are not surprising. Hypothermia can attenuate the depolarization of neurons, and the authors demonstrate that cooling reduces the repetitive, spontaneous firing of the injured nerve. Preventing the development of neuropathic pain by blocking the initial nociceptive input to the central nervous system is a reasonable mechanism for the impact of regional and whole-body cooling and is consistent with work showing that local anesthetics or nerve blockade can have similar effects. The rather narrow time window for the effect of local cooling is also consistent with this; localized cooling that is applied days after the injury cannot influence input-related central nervous system changes that have already begun. Cooling also has profound effects on the depolarization-induced release of numerous neurotransmitters, perhaps most notably excitatory transmitters believed to be involved in the development of neuropathic pain in the spinal cord or brain. Whole-body cooling should influence these processes when applied at any time, and the authors' demonstration of a treatment effect even 5 days after ligation suggests that preventing or reversing such changes (glutamate-induced glial activation, inflammation) may be efficacious even after the initial activation (before changes are fully established?).

The authors are also to be congratulated for limiting their comments regarding the clinical application of hypothermia, although I'm certain that many readers immediately will begin to speculate. This is where some words of caution and skepticism are required. The ability to prevent or treat an enormous number of central nervous system disorders *in small animals, under controlled conditions* by mild, moderate, or deep hypothermia is well known. Cooling prevents neuronal death (as well as inflammation and many associated neurochemical changes) in the face of ischemia (global or focal, brain or spinal cord), hypoxia, trauma (brain or spinal cord), subarachnoid hemorrhage, encephalitis, and many other situations. In some of these situations, the magnitude of the benefit is almost magical. Unfortunately, despite literally thousands of laboratory experiments and an equal number of articles extolling the benefits of cooling and studying ways to cool people or measuring associated clinical changes (without ever bothering to ask whether it is benefi-

Photo: J. P. Rathmell.

Accepted for publication November 15, 2011. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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◆ This Editorial View accompanies the following article: Tsai Y-J, Huang C-T, Lin S-C, Yeh JH: Effects of regional and whole-body hypothermic treatment before and after median nerve injury on neuropathic pain and glial activation in rat cuneate nucleus. ANESTHESIOLOGY 2012; 116:415–31.

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cial), the track record for the human application of cooling is limited and frankly unimpressive. Perhaps the only unequivocal value of cooling is for controlled circulatory arrest during cardiac surgery, and that requires deep hypothermia. Trials have failed to demonstrate any value of hypothermia in head trauma, neurovascular surgery, myocardial ischemia, and probably stroke (no controlled studies, but uncontrolled studies suggest that there is an unacceptably high complication rate). An ongoing debate continues regarding the magnitude of the benefit associated with the hypothermic treatment of witnessed cardiac arrest because the two (albeit well-done) 2004 studies have not been replicated, and their study populations were very narrowly defined. The value of extending hypothermic treatment to other etiologies of arrest is completely unknown (although hypothermia is being applied for all kinds of ischemic or hypoxic events). Similar uncertainties exist regarding cooling for neonatal asphyxia, although cooling for both witnessed cardiac arrests and neonatal asphyxia is recommended by national and international organizations.

Why is there such an enormous discrepancy between laboratory studies and clinical reality? The answer probably lies in the differences between the controlled conditions of the laboratory and the infinitely more varied (messy) conditions of human disease and treatment. Basically, controlled cooling of a carefully bred, genetically homogenous, healthy young rodent that is started before or after the precise application of a controlled injury may have nothing to do with what we encounter in the real world of human trauma, stroke, or peripheral nerve injuries. Patients and their diseases are not homogenous. The nature and timing of their injuries are not uniform. And the medical establishment is not very good about uniformly or safely applying any kind of treatment 24 h a day across thousands of hospitals (big and small, urban and rural, public and private, rich and poor) by millions of differently trained providers (physicians, nurses, technicians, and administrators).

Thus, although I find the work by Tsai *et al.* to be scientifically fascinating, I remain skeptical regarding its applicability. This work unquestionably can help us to better understand the mechanisms of neuropathic pain development; hypothermia provides another controllable tool for further explorations. But whether it has a clinical future is completely unknown. I confess that the value of acute, regional cooling intrigues me more (because it so much easier to apply in a broad setting than is whole-body hypothermia). But it will be necessary to demonstrate its value under a much broader range of disorders and then to determine whether it is even remotely feasible in a clinical setting.

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Reference

1. Tsai Y-J, Huang C-T, Lin S-C, Yeh JH: Effects of regional and whole-body hypothermic treatment before and after median nerve injury on neuropathic pain and glial activation in rat cuneate nucleus. ANESTHESIOLOGY 2012; 116:415–31

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