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Thesis abstract

The effects and mechanisms of the therapeutic hypothermia on intracranial pressure regulation following ischaemic stroke in rats

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Background: Intracranial pressure (ICP) rises to dangerous levels 2 to 5 days after large ischaemic stroke. ICP following small stroke is not routinely monitored, although animal data suggests ICP rises 24 hours following small experimental stroke. Cerebral oedema has been thought to be the primary cause for ICP elevation. This assumption may have risen because ICP has only been monitored in patients with large infarct and oedema volumes. Since small ischaemic infarcts cause less cerebral swelling, ICP elevation may be the result of a different mechanism(s). Recent human imaging data indicates that patients deteriorating soon after minor stroke do so on the basis of cerebral collateral blood flow failure. Until now there has not been a plausible explanation for this "collateral failure". Long-duration hypothermia has been shown to lower ICP in patients. Long durations of cooling increase the risk of infection and rebound ICP during rewarming. Short-duration hypothermia has shown overwhelming efficacy in animal models of stroke but has not been tested in humans. I hypothesise: that ICP increases at 24 hours after small stroke; that this rise is not due to cerebral oedema; that ICP elevation reduces collateral blood flow; and that short-duration moderate or mild hypothermia prevents ICP elevation post-stroke. Methods: An epidural ICP monitoring technique was developed. Experimental ischaemic stroke (middle cerebral artery occlusion) was performed in Long Evans, outbred Wistar and Sprague-Dawley rats and ICP was monitored. Infarct and oedema volumes were calculated using wet-dry weight calculations, histology or in vivo magnetic resonance imaging. Collateral blood flow was visualized using fluorescent microspheres through a closed cranial window and recorded using a high-speed microscope-mounted recording camera. Short-duration moderate (32.5°C) or mild (35°C) hypothermia, or normothermia (37°C) was administered 1 hour post-stroke. Results: Mean ICP was 9.1 ± 5.2 mm Hg at baseline (pooled – all animals). ICP was significantly elevated 24 hours post-stroke in all normothermic animals (40.3 ± 16 mm Hg, pooled normothermic animals, $p < 0.0001$ vs. baseline). Mean infarct volume was 22.6 ± 17.5% of contralateral hemisphere. Oedema volumes were small and were not correlated with ICP post-stroke ($r^2 = 0.09$, $p = 0.15$). There was a strong correlation between ICP elevation and collateral blood flow decrease ($r = -0.62$, $p < 0.0001$). Early intervention of short-duration hypothermia completely prevented ICP rise post-stroke (10.3 ± 6.5

mm Hg, pooled hypothermic animals at 24 hours, $p < 0.0001$ vs. normothermic animals at 24 hours). Conclusions: In this thesis, I have presented data that contradicts the accepted wisdom in several ways and has important implications for patients with stroke. It suggests that ICP could be elevated in patients with small stroke and that a factor other than oedema is the primary cause of this ICP elevation. The data also suggest that ICP elevation following stroke is the likely mechanism of collateral failure leading to neurological deterioration in stroke patients. Finally, I have demonstrated that short-duration hypothermia is an effective ICP preventative treatment following experimental stroke, and suggests that short-duration hypothermia clinical studies in humans is warranted. These findings suggest that a fundamental rethink of ICP regulation post-stroke is necessary and have potentially important and exciting implications for the future treatment of stroke and stroke-in-progression.

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