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Novel method for inducing rapid, controllable therapeutic hypothermia in rats using a perivascular implanted closed-loop cooling circuit

Jessica A. Lamb*, Padmesh S. Rajput, Patrick D. Lyden

Department of Neurology, Cedars-Sinai Medical Center, 127 S. San Vicente Blvd, Los Angeles, CA 90048, United States

HIGHLIGHTS

- We developed a rapid, simple, inexpensive model for inducing hypothermia in rats.
- This system allowed us to quickly (0.3C°/min) lower the rat's body temperature.
- We were able to tightly regulate temperature to within ±0.09C° for 4 h.
- This new model simulates human endovascular cooling techniques.

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ABSTRACT

Background: Hypothermia is the most potent protective therapy available for cerebral ischemia. In experimental models, cooling the brain even a single degree Celsius alters outcome after global and focal ischemia. Difficulties translating therapeutic hypothermia to patients with stroke or after cardiac arrest include: uncertainty as to the optimal treatment duration; best target-depth temperature; and longest time delay after which therapeutic hypothermia won't benefit. Recent results from human clinical trials suggest that cooling with surface methods provides insufficient cooling speed or control over target temperature.
Comparison with existing methods: Available animal models incorporate surface cooling methods that are slow, and do not allow for precise control of the target temperature.
New method: To address this need, we developed a rapid, simple, inexpensive model for inducing hypothermia using a perivascular implanted closed-loop cooling circuit. The method allows precise control of the target temperature.
Results: Using this method, target temperature for therapeutic hypothermia was reached within 13 ± 1.07 min (Mean ± SE). Once at target, the temperature was maintained within 0.09 °C for 4 h.
Conclusions: This method will allow future experiments to determine under what conditions therapeutic hypothermia is effective, determine the optimal relationship among delay, duration, and depth, and provide the research community with a new model for conducting further research into mechanistic questions underlying the efficacy of therapeutic hypothermia.

1. Introduction

Therapeutic hypothermia is the most potent neuroprotective therapy ever studied in experimental cerebral ischemia (Subramaniam et al., 2015; Wu and Grotta, 2013). Cooling the brain as little as one degree Celsius significantly alters brain responses to ischemia (Busto et al., 1987). Therapeutic hypothermia exerts multiple effects at multiple stages of the ischemic cascade. Today, in all experimental cerebral ischemia studies, brain temperature must be rigidly controlled to avoid confounding effects (Ginsberg et al., 1992; Morikawa et al., 1992). Translating this potent protective effect to clinical applications has proven problematic. Multiple studies documented powerful protection with therapeutic hypothermia after accidental neonatal hypoxic–ischemic injury (Shankaran et al., 2005, 2014, 2008). Early studies of global cerebral ischemia after cardiac arrest also confirmed powerful protection

* Corresponding author.
E-mail address: Jessica.lamb@cshs.org (J.A. Lamb).

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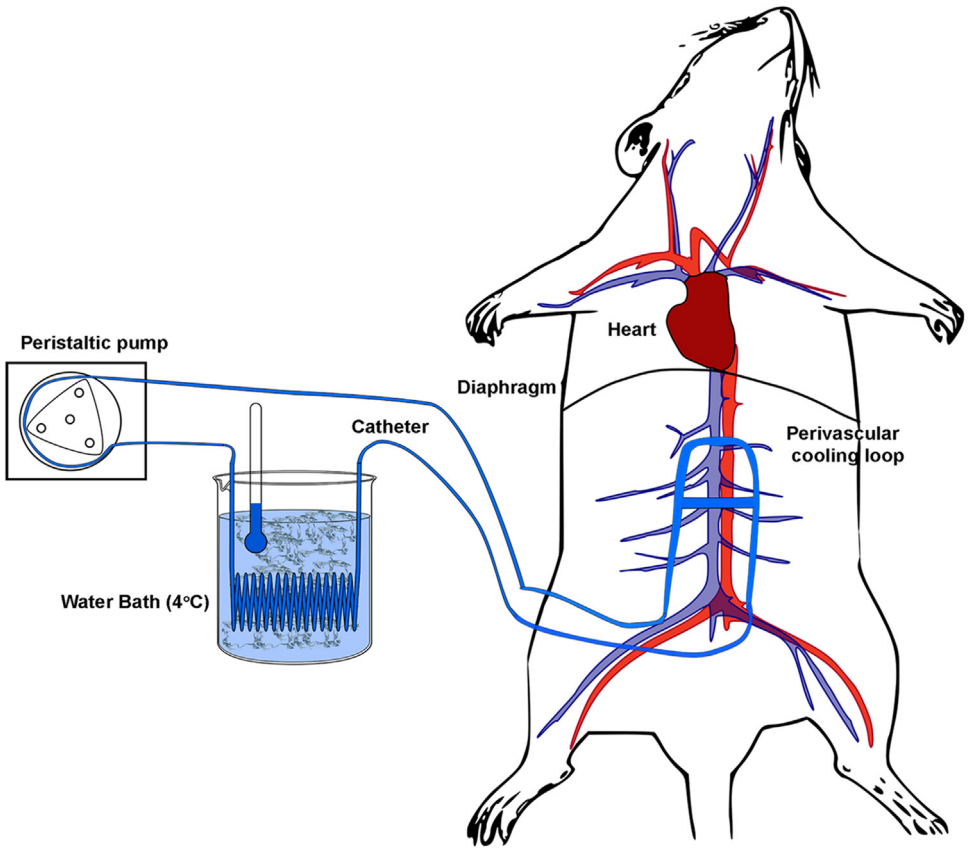

Fig. 1. Complete perivascular cooling catheter circuit. The schematic outlines the basic set up for the perivascular approach to cooling the whole body. The perivascular catheter filled with cold saline is inserted in the abdomen and placed on top of the inferior vena. Within the closed-loop catheter, the saline circulates through the ice water bath before entering the body. Cooling rate is controlled by varying the flow rate using the peristaltic pump and a probe inserted into the temporalis muscle monitors the animal temperature. The cooling circuit tubing exits dorsally from between the scapulae.

after therapeutic hypothermia (Bernard et al., 2002; Felberg et al., 2001). National and international guidelines recommend therapeutic hypothermia for selected survivors of cardiac arrest, with profound benefits seen anecdotally (Nolan et al., 2003). More recently however, a study comparing target temperature 33–36 °C failed to demonstrate significant effects in cardiac arrest patients (Nielsen et al., 2013). This recent trial differed from early trials with respect to cooling duration and time to reach target-depth, in that target was not reached until much later than in prior trials.

Clinical trials of therapeutic hypothermia for acute ischemic stroke are underway, but were designed in the face of considerable uncertainty (Kollmar et al., 2012; Lyden et al., 2014). While animal models of global and focal cerebral ischemia have certainly indicated therapeutic hypothermia has a high likelihood of benefiting patients, the optimal design of such therapy is unknown. Available data supports the use of early (delay from stroke onset less than 6 h) therapeutic hypothermia for a duration of 24 h, but the optimal target-depth temperature is not known. Data supports colder target-depth, such as 30 °C or 33 °C while some data supports milder target-depth temperatures of 35 °C or 36 °C (Han et al., 2015; Leshnower et al., 2015). Given the enormous numbers of patients suffering acute cardiac arrest or stroke, and given the great potential benefit of therapeutic hypothermia, there is a compelling and urgent need to optimize the key parameters of therapeutic hypothermia: target temperature depth, duration, and maximal delay after which treatment is futile.

Progress in experimental therapeutic hypothermia has been hampered by the absence of simple, rapid, inexpensive models. The best animal model, exemplified by a series of studies from Corbett and Colbourne, applies surface cooling using implanted telemetered thermistors, radio-controlled water misters and cage-mounted servo-controlled fans (Colbourne et al., 1996). The data and science are quite elegant, but the set-up does not allow extensive modeling for translational research and implementation. Important findings from the Corbett/Colbourne lab so far are that (1) deeper hypothermia to 33 °C is probably better than 35 °C and (2) if the onset to therapeutic hypothermia is delayed, the duration must be longer to obtain the same effect. Other labs have confirmed this interesting relationship between delay and needed duration (Clark et al., 2009; Colbourne et al., 2000; Corbett et al., 2000).

Here we have developed a novel method to induce hypothermia rapidly with a perivascular approach to simulate the intravascular approach currently used in humans (Esposito et al., 2014; Lyden et al., 2012). This approach utilizes a closed-loop cooling circuit that consists of the implanted perivascular cooling catheter, a peristaltic pump, and ice-bath (Fig. 1). The advantage of the perivascular approach for cooling animals is that the technique is powerful and cools the animal to target temperature much more quickly than surface cooling. Perivascular cooling allows more precise control of core body temperature than surface cooling and eliminates the stress response elicited by surface cooling. A simpler cooling approach potentially could open the research field to more labs that do not have the time or money to invest in the complex telemetry and cage system required for servo-controlled surface cooling with computer controlled fans and misters. A perivascular cooling model would allow more rapid translational studies of the optimal depth, delay and duration for therapeutic hypothermia because the model simulates both the rapid cooling and the anesthetic treatment typical of human endovascular cooling techniques. More rapid and