Neuroscience & Medicine, 2022, 13, 145-160
https://www.scirp.org/journal/nm
ISSN Online: 2158-2947
ISSN Print: 2158-2912

A Cardiac Surgical Perspective on Hypothermia for Protection of Neural Tissues

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How to cite this paper: Elefteriades, J.A., Simmons, J. and Ziganshin, B.A. (2022) A Cardiac Surgical Perspective on Hypothermia for Protection of Neural Tissues. *Neuroscience & Medicine*, **13**, 145-160.
https://doi.org/10.4236/nm.2022.134014

Received: September 29, 2022
Accepted: December 23, 2022
Published: December 26, 2022

Abstract

Background: In clinical and basic science medicine, we often isolate ourselves in silos, unaware of developments in other related disciplines. Our team has had substantial experience, both in the operating room and in the laboratory, with protecting the brain and the spinal cord via hypothermia. Herein, we briefly share this experience with our colleagues in Neurology, eager for comments and advice from the neurologic perspective. Methods: 1) *Clinical brain protection via deep hypothermic circulatory arrest* (*DHCA*) *for surgery of the aortic arch*. For aortic arch replacement (performed for aortic arch aneurysm or aortic dissection), the aortic arch must be opened and native perfusion stopped. We have decades of experience in many hundreds of patients with this technique. This experience is reviewed. 2) *Experimental protection of the spinal cord via cooling*. We review our laboratory experience with a novel, recirculating cooling catheter for the vulnerable spinal cord. 3) *Experimental protection of the brain via an intraventricular cooling catheter*. We review our laboratory experience cooling the brain with a balloon-tipped catheter residing the lateral ventricles. Results: 1) Deep hypothermic circulatory arrest for aortic arch surgery provides superb brain protection for periods up to 45 minutes or longer. Clinical neurologic function, and quantitative neurologic tests, show excellent brain preservation. 2) The novel spinal cooling catheter provides excellent cooling of the spinal cord in a large animal model, without apparent injury of any type. 3) The intraventricular brain cooling catheter provides excellent cooling of the brain, documented by both direct temperature probe and high-tech brain imaging. Conclusions: We wish herein (in this article) to share this experience across our disciplines (Cardiac Surgery and Neurology). We welcome advice from the Neurology community on these surgically-directed methods for cooling and protection of neurological tissue in both the brain and the spinal cord.

Keywords

Hypothermia, Deep Hypothermic Circulatory Arrest, DHCA, Spinal Cooling, Paraplegia, Aortic Surgery, Neuologic Testing

1. Background

It can be instructive to examine healthcare topics from alternate points of view. We all work in silos within our specialties, and we often are not exposed to important information arising in other disciplines. In this paper, we review, from the standpoint of cardiothoracic surgery, our clinical and experimental work in protection of brain and spinal cord via hypothermia. We hope that sharing this work with specialists in Neurology will lead to cross-fertilization of ideas between disciplines and engender suggestions to improve and enhance our efforts within the cardiothoracic surgical field.

2. Methods

With this in mind, we share in this report a cardiac surgical perspective on hypothermia for protection of neural tissues. We present and summarize published work emanating from both the laboratory and the clinic that involves hypothermic protection of brain and spinal cord. These studies were performed and reported individually over more than a decade. Herein, we synthesize these findings into an integrated report on preservation of neural tissues, both brain and spinal cord. We discuss the fascinating real-world application of Deep Hypothermic Circulatory Arrest (DHCA) for operations on the aortic arch. This technique represents suspended animation in the truest sense. We then move on to discuss two promising new topical hypothermic technologies for the spinal cord and for the brain. Specifically, we explore our experimental application of topical spinal cord cooling for protection against neurologic injury during descending thoracic aortic surgery. Finally, we present our experimental work with direct brain cooling, via a special catheter inserted directly into the brain substance, for potential mitigation of a variety of cerebral injuries.

3. Results

3.1. Part A. Deep Hypothermic Circulatory Arrest for Brain Protection in Aortic Surgery

In order to operate on the aortic arch, the segment of aorta that gives rise to the innominate, left carotid, and left subclavian arteries, it is necessary to stop the heart-lung machine and suspend perfusion to the brain and body.

At Yale University we have accumulated experience (JAE) in over a thousand patients with aortic arch replacement surgery with all circulation stopped—a technique called Deep Hypothermic Circulatory Arrest (DHCA). This represents real-life suspended animation. Perfusion is stopped after about 35 minutes of active cooling (on cardiopulmonary bypass), when the brain temperature has fallen to 18˚C. Multiple network television programs have been produced in our operating room highlighting this technique, which fascinates the general public [1] [2] [3]. During the interval of DHCA, the body and the brain receive no circulation whatsoever (See **Figure 1** and **Figure 2**). There is no blood flowing and no exchange of oxygen with the brain or other tissues.

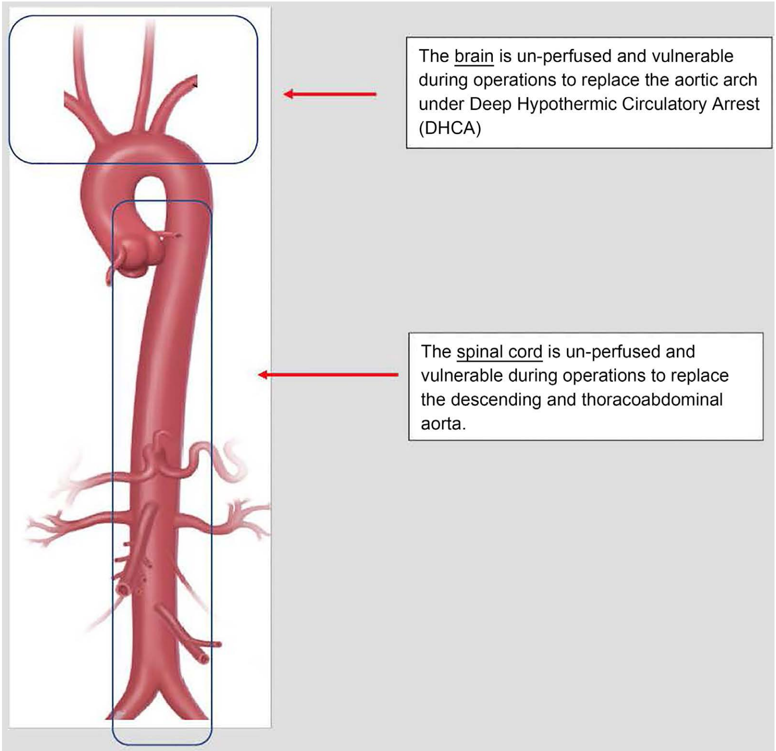

Figure 1. Vulnerabilities during aortic arch or descending and thoracoabdominal aortic replacement. See text.

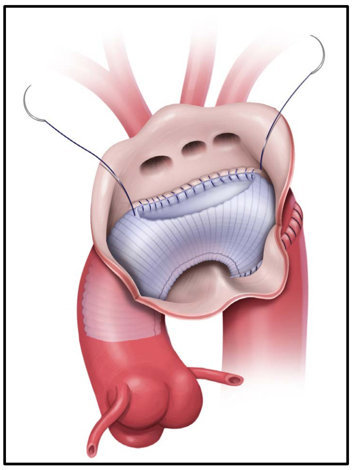

Figure 2. Aortic arch replacement under DHCA (deep hypothermic circulatory arrest). The patient has been cooled to 18˚C. The heart-lung machine has been stopped. There is no perfusion of the brain for the 30 - 45 minutes it takes to perform the aortic arch replacement. Note the uncluttered operative field, with no lines or tubes getting in the way (Reproduced with permission from *Practical Tips in Aortic Surgery*. Elefteriades JA and Ziganshin BA. Springer. 2022).

For surgeons uncomfortable with DHCA, there are means available to provide some blood flow to the brain while body perfusion is stopped. Specifically, small catheters can be placed in one, two, or even three of the branches of the aortic arch (innominate artery, left carotid artery, and left subclavian artery), through which some direct perfusion can be supplied. This technique has issues of its own, mainly related to direct trauma to the cannulated vessels and incomplete brain perfusion resulting from the vagaries of the circle of Willis. Also, it has been shown that virtually 100% of patients experience some particulate embolism to the brain tissues when this direct perfusion method is applied [4]. Alternatively, some surgeons perfuse the superior vena cava (SVC), hoping that the "backwards" flow of blood into the veins reaches the brain tissue to deliver oxygen. Whether this technique actually delivers oxygen to the brain has been seriously questioned, as most flow seems to divert via venous collaterals to the body, not the brain.

The surgeon author (JAE) has not used these substitute arch vessel perfusion techniques, preferring the simplicity and effectiveness of DHCA (See again **Figure 2**). Thus, this Yale experience provides vital information on the tolerance of the brain to lack of perfusion and on the effectiveness of cooling in protecting brain tissue. This experience proves that, in deep hypothermic ranges, the brain is extremely tolerant of lack of perfusion.

DHCA is said to have begun in Siberia with the bold, brash, revered cardiac surgeon Meshalkin, who cooled small infants in the abundant outdoor snow of his home environment. He then carried the children into the operating room, where he quickly repaired congenital heart lesions like atrial and ventricular septal defects. The babies were then warmed, and their hearts resumed function, and they recovered.

Today, of course, the cooling for our DHCA cases is done with the heat exchanger intrinsic to the heart-lung machine. The patients are cooled to 18˚C - 20˚C, and all circulation is stopped. We open the aortic arch widely and are thus able to operate in a beautiful, bloodless, still surgical field (See again **Figure 2**). We have 45 to 60 minutes of safety in which to perform the complex, delicate replacement of the aortic arch and its branches. Then, the heart-lung machine is restarted, and the patient is rewarmed gradually (never exceeding a gradient of 10˚C between the warm perfusate and the cold body tissues).

Decades ago, Bigelow [5] performed the vital experiments that underlie modern DHCA (See **Figure 3**). He showed that the oxygen requirements of brain tissue fall exponentially as temperature drops—about 50% per 6˚C. So, at 18˚C, the oxygen requirements are only 12.5% of normal. Subsequently, Griepp [6] first applied hypothermia to permit aortic arch surgery under no-flow DHCA. After that landmark report, use of DHCA for aortic arch surgery proliferated. **Figure 4** shows the range and profile of time intervals under DHCA from one of our reports.

In our extensive Yale experience, we have found aortic arch surgery under DHCA to be extraordinarily safe—with a mortality for these complex operations,

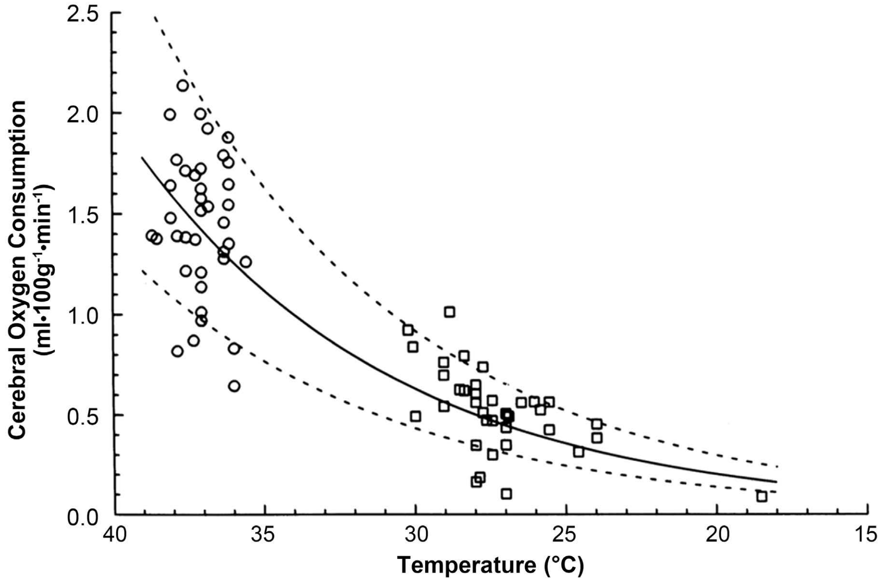

Figure 3. Fall in oxygen consumption with hypothermia. Reproduced with permission from Reference [5].

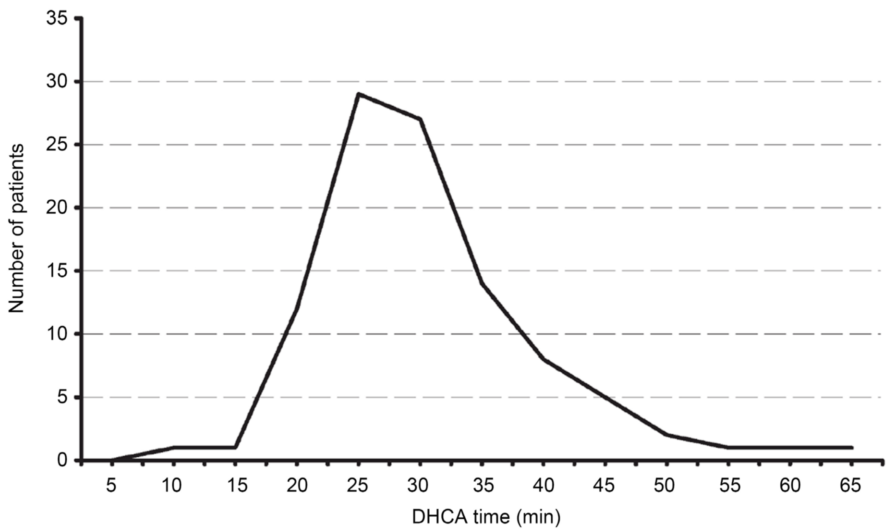

Figure 4. Profile of time duration of circulatory arrest in our DHCA (deep hypothermic circulatory arrest) cases. Reproduced with permission from Reference [7].

when done electively, of only 1.4%, and a stroke rate of only 1.4%. Essentially, in this modern era, these complex aortic arch operations can be performed with a similar level of safety as a routine coronary artery bypass (CABG) operation.

Now, we have evaluated, in multiple ways, the efficacy of brain protection during these aortic arch operations performed under straight DHCA.

1) *Clinical observation*. Firstly, patients have done very well clinically, with no obvious neurologic deficits on awakening from anesthesia or in long-term clinical follow-up, as reported by our team in multiple publications [7] [8] [9] [10] [11].

2) *Quantitative neurocognitive evaluation*. We went farther than gross neurologic observation, evaluating neurologic function quantitatively. We adminis-

tered a battery of neuropsychometric tests, both pre- and post-operatively, focusing especially on the areas of memory and processing speed, which were considered most potentially in jeopardy. In addition, we applied the Clock Drawing Test (CDT), which is considered very sensitive for detecting deficits in global cognitive function, executive functions, and integration of advanced cortical functions. We compared results of DHCA patients with those in patients undergoing simpler open-heart procedures that did not require DHCA. Simply put, there were no significant differences in post-operative vs. pre-operative scores in any cognitive domain tested between the DHCA and non-DHCA groups (See Figure 5).

3) *High cognitive need group*. We went a step further. We considered whether subtle deficits might be missed by our patients in reporting excellent function in common, everyday life. Accordingly, we examined specifically a group of our DHCA patients whose professions imposed exceptionally high cognitive needs (scientists, administrators, authors, artists, musicians, physicians, deans, etc.). A 21-part questionnaire (adapted from A.F. Jorn's Short From IQCODE) was distributed to both the patient and an "informant" (usually a spouse). There were no differences in scores between our DHCA patients and a control group undergoing simpler open-heart procedures without DHCA (See Figure 6).

4) Lastly, we even looked at long-term survival following procedures done under DHC, thinking that even small deficits in cognitive function might be reflected in decreased survival. In fact, long-term survival in patients undergoing aortic arch replacement under DHCA, remarkably, was not even different from that of the *general population* (See Figure 7).

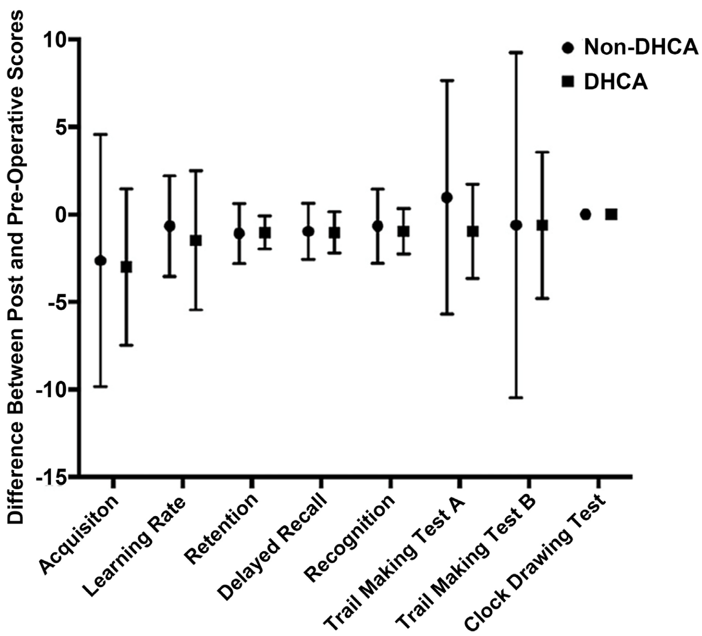

Figure 5. Differences between pre-operative and post-operative scores. Mean and standard deviation of the difference between post-operative and pre-operative scores for the non-DHCA and DHCA groups. Reprinted with permission from Reference [9].

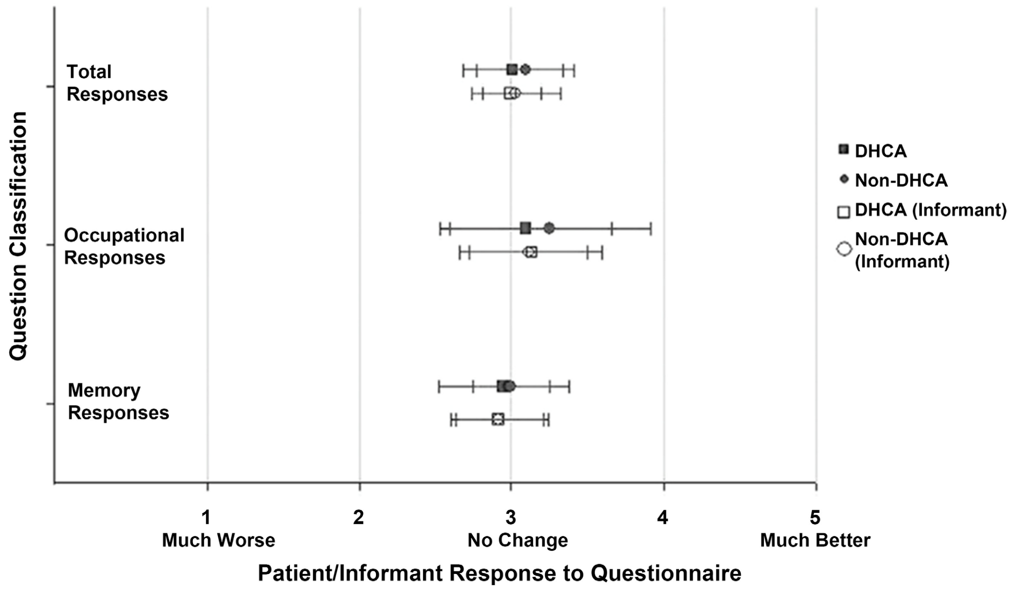

Figure 6. Questionnaire results. "High cognitive" group study. Note near identity of response grades for DHCA (deep hypothermic arrest) and non-DHCA groups both according to patient and according to informant. Reprinted with permission from Reference [8].

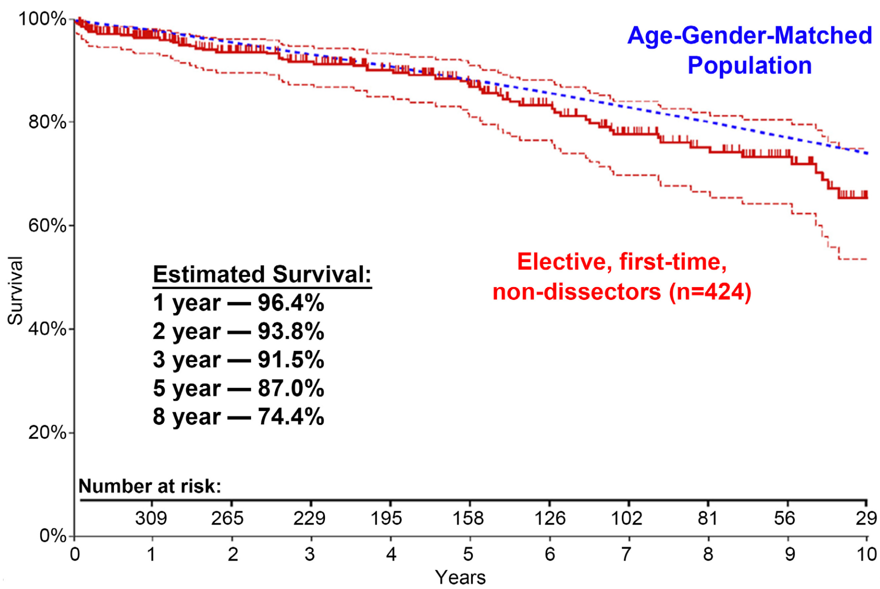

Figure 7. Near normal long-term survival is achieved after aortic arch operations performed under DHCA (deep hypothermic circulatory arrest)—even approximating the longevity of non-aneurysm afflicted individuals. Reproduced with permission from Reference [11].

We feel that the sum total of this body of evidence regarding the technique of DHCA speaks eloquently toward the exceptional power of hypothermia to preserve neural tissue—in this case, the brain.

A picture can indeed be worth a thousand words. The woman seen in Photo 1 is 78 years old. She underwent total aortic arch replacement the day before this photo. It is 7 am the following morning. Probably more telling than all the charts

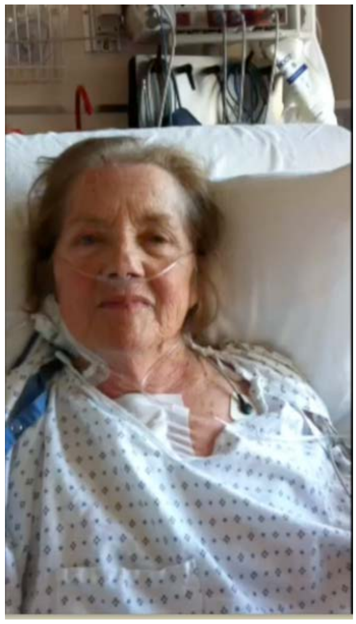

Photo 1. This 78 yo woman underwent total aortic arch replacement the day before, under Deep Hypothermic Circulatory Arrest (DHCA). It is 7 am on POD #1. She is seen here spelling the author's complex name (Elefteriades), forwards, *and then backwards as well.* We view this as strong confirmation of the effectiveness of brain protection under DHCA.

and figures found above in this manuscript, this woman spells the author's complex name (Elefteriades)—forward and *backward*, no less. This likely constitutes better confirmation of the tremendous ability of hypothermia to preserve neural tissue than any of the formal quantitative assessments presented above.

3.2. Part B. Spinal Cord Protection in Descending/Thoracoabdominal Aortic Replacement

There is another area in cardiac surgery in which hypothermia is exploited for neural protection: surgery of the descending/thoracoabdominal aorta (See **Figure 1**).

It has been known for many decades that the intercostal arteries (including a special intercostal-based "artery of Ademkiewicz") supply blood flow to the spinal cord. These blood flow sources are crucial to integrity of the spinal cord, as the supply from the anterior spinal artery terminates well before the bottom of the cord. The segments from T10 to L2 are especially important, as that represents the anatomic range from which the spinal artery of Ademkiewicz usually originates.

When we resect long portions of the descending and thoracoabdominal (D/TAA) aorta, of necessity, we detach the corresponding intercostal arteries, which originate from the resected aortic wall itself. For this reason, post-operative paraplegia has been the scourge of DTAA surgery since its inception and even now. Post-operative paraplegia devastates quality of life, incurs extreme care costs, and proves almost invariably lethal in the short to medium term (See **Figure 8**).

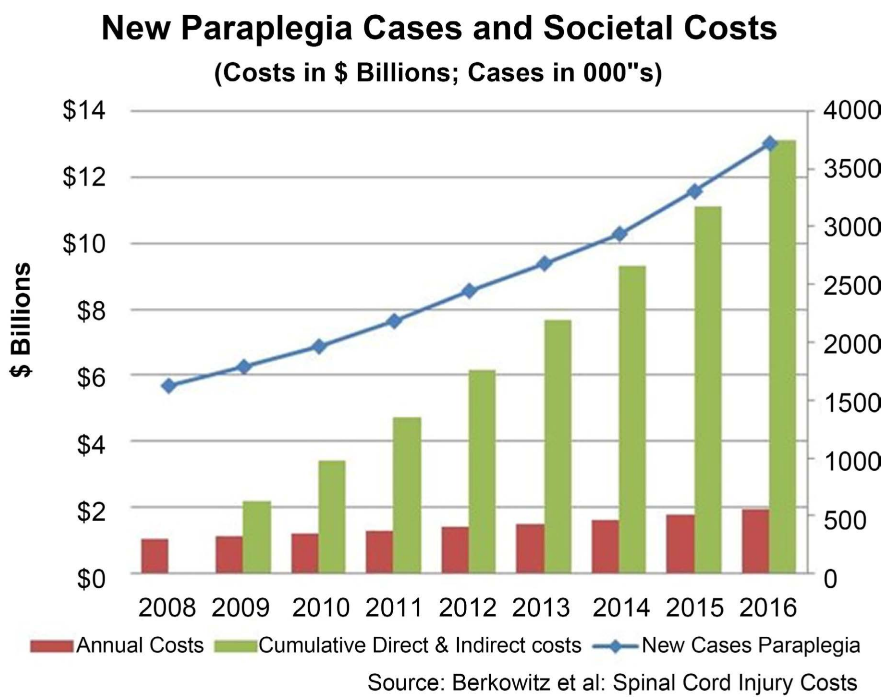

Figure 8. The increasing societal costs of paraplegia.

We use a number of adjuncts to prevent or discourage paraplegia. We often re-implant the intercostal arteries thought to be located in a key zone; this is a delicate and exacting procedure. We use perfusion (via a smaller modification of the heart-lung machine) to provide oxygenated blood to the lower aorta while the resection and grafting are being performed. We drain the spinal fluid to decrease the external pressure on the spinal cord, thus encouraging forward blood flow into the spinal cord. And, we cool the body physically, usually to about 34 degrees. We cannot cool much lower, as the heart needs to continue to beat during these operations, in order to perfuse the remainder of the body. We cool systemically in order to capitalize on the temperature-related reduction in O2 requirements of the spinal cord cells (as shown by Bigelow, above). In fact, one expert, Dr. Kouchoukos, does his operations on DHCA (as we described above for ascending aortic surgery), with very low paraplegia rates; however, use of DHCA for DTAA surgery has never "caught on" with other surgeons, due to other adverse impacts on surgery in the DTAA region (especially, excess bleeding).

For several decades, Cambria has capitalized on the neuroprotective effects of cold temperature in descending aortic operations [12]. His system infuses cold saline directly into the spinal canal via one catheter and recaptures the saline via a second catheter. The cold saline mingles with the spinal fluid. This technique worked well in Cambria's exceptional hands, yielding acceptably modest rates of paraplegia, and establishing the principle of direct spinal cord cooling. However, this method was not widely adopted—likely due to three reasons. First, the technique is somewhat cumbersome in nature, requiring two catheters actually placed into the spinal canal, with an attendant to control inflow and outflow of fluid.

Secondly, the IV fluid actually co-mingles with the cerebrospinal fluid (CSF), raising the specter of potentially devastating infection of the spinal canal. Finally, the influx of fluid into the spinal canal raises the CSF pressure; this is opposite to the requirement to keep the CSF pressure low during descending aortic surgery, to avoid external pressure that can decrease forward spinal cord blood flow.

Zhu [13] has reviewed beautifully various engineering technologies that have been applied previously for cooling of the brain or spinal cord to prevent or limit injury. These include skin surface cooling, instillation of a cold perfusate (chilled saline) directly into the bloodstream (whole body cooling), direct blood cooling (intravascular catheter), localized direct ice-pad cooling of the spinal cord or brain during open spinal cord or brain surgical procedures, and nasopharyngeal cooling (by cold air or by a nasal cooling catheter).

As summarized beautifully by Zhu [13], this large variety of imaginative hypothermic techniques (both systemic and topical) have been applied in an attempt to limit damage to neural tissue in the brain or spinal cord from trauma, stroke, or other insults. Results have been mixed, with some evidence of benefit in specific situations with specific technologies applied. We feel that our technologies (described below) deserve exploration for multiple reasons. Specifically, our localized, closed-catheter systems 1) do not mingle fluids with the CSF, 2) provide direct cooling of brain and spinal cord tissues via the CSF, and 3) avoid systemic cooling, with its myriad of adverse consequences.

Our team at Yale University, via the Yale spin-off CoolSpine, has investigated a novel method to capitalize on the benefits of hypothermia for the spinal cord without other toxicities—namely, by cooling the spinal fluid directly via a specialized "spinal cooling catheter". We have done extensive experiments with this catheter in sheep, whose body size and spinal anatomy replicate the human reasonably well. This work has been supported by Phase I, Phase II, and Phase II Supplemental support from the National Science Foundation (NSF).

Figure 9 demonstrates the location of the catheter itself within the spinal canal. **Figure 10** shows the catheter itself. This has three lumens. Two lumens permit inflow and outflow of refrigerant (cold saline). The third (central) lumen permits drainage of spinal fluid through the very same catheter, thus accruing the benefits of a very low intrathecal pressure (improved spinal cord blood flow). A console cools the saline and circulates the fluid.

Figure 11 shows a close-up cross-section of the catheter, demonstrating the inflow and outflow lumens and the central cerebrospinal fluid drainage lumen.

We have done extensive *in vivo* experimentation with this catheter.

This spinal cord cooling catheter and system are currently at an advanced pre-clinical stage.

We are hopeful that this system may well lessen the incidence and severity of spinal cord injury from surgery of the D/TAA.

There are additional potential uses for the cooling catheter outside DTAA surgery, including traumatic spinal cord injury and peri-procedural protection of the spinal cord in surgery of the bony spine or the spinal cord itself.

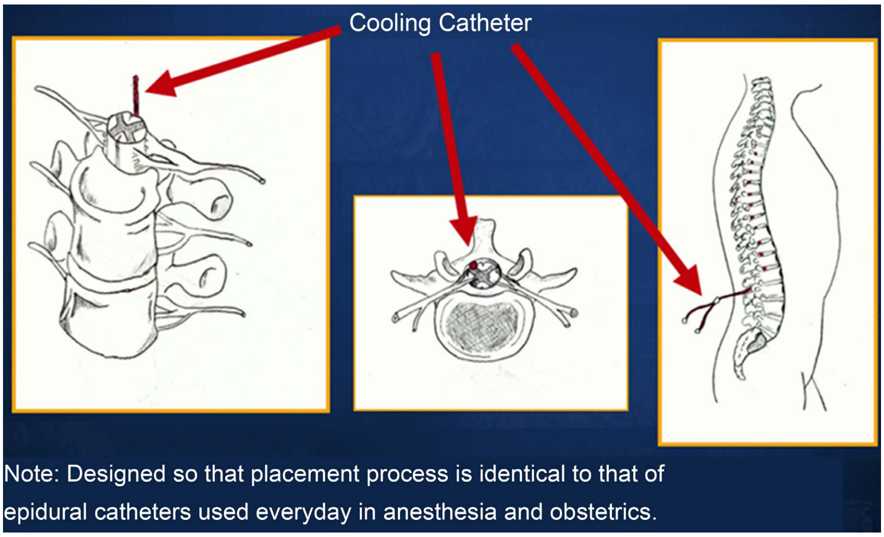

Figure 9. The position of the catheter in the spinal canal is shown.

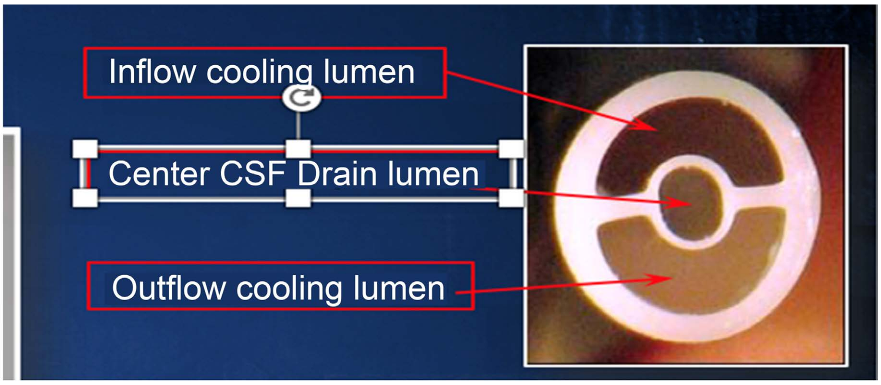

Figure 10. A cross-section of the catheter. Note the three lumens.

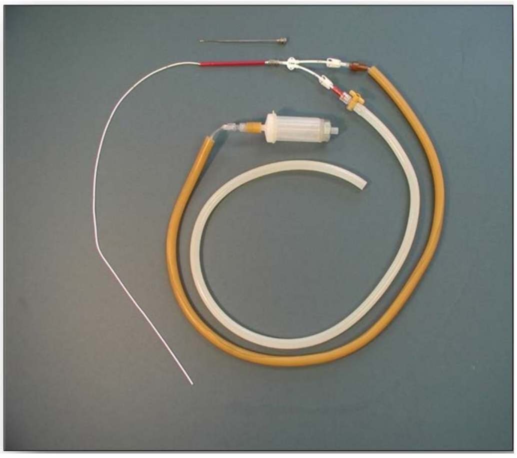

Figure 11. The catheter and the connecting tubing.

3.3. Part C. Brain Cooling Catheter

We have also developed a cooling catheter specific for the brain [14] [15] (See Figure 12). Ischemia and other modes of neuronal injury participate in on-going brain damage in multiple neurologic conditions, including subarachnoid hemorrhage (SAH) and traumatic brain injury (TBI). We anticipate that direct brain hypothermia may attenuate such on-going injury.

The brain cooling catheter is placed through a standard ventriculostomy, as required for routine clinical care in many cases of SAH or TBI (See **Figure 13**). Like the spinal cooling catheter, the brain cooling catheter also has three lumens, two to transmit cold saline in and out, and one for draining CSF as needed to relieve excess pressure.

The brain cooling catheter is designed to function also as a ventricular drain. So, for the same extent of procedure as placing a ventricular drain, one can achieve not only pressure reduction but also dramatic cooling of the brain substance. We think of the brain cooling catheter as equivalent to having a permanent "ice cube" right inside the substance of the brain, spreading its neuroprotective hypothermic benefits.

We have shown that we can effectively cool the brain (See **Figure 14**).

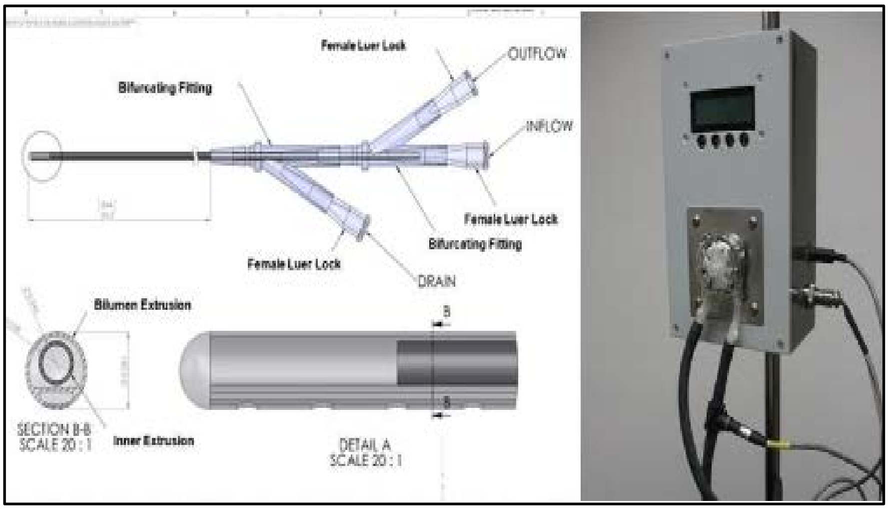

Figure 12. Details of the brain cooling catheter and the circulating pump. Note the soft inflatable balloon at the tip of the catheter, which conforms gently to the confines of the lateral ventricle of the brain. Procedure for placement is identical to that for a standard ventricular drain.

Figure 13. Note the catheter trajectory into the lateral ventricle.

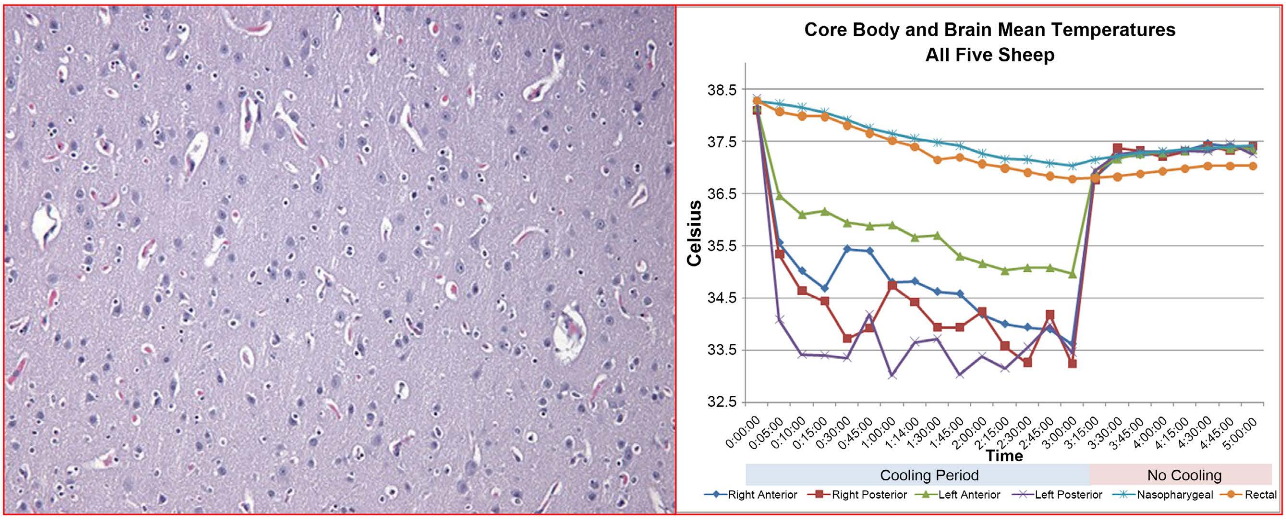

Figure 14. Note substantial brain cooling achieved (right) and normal post-cooling brain histology (left).

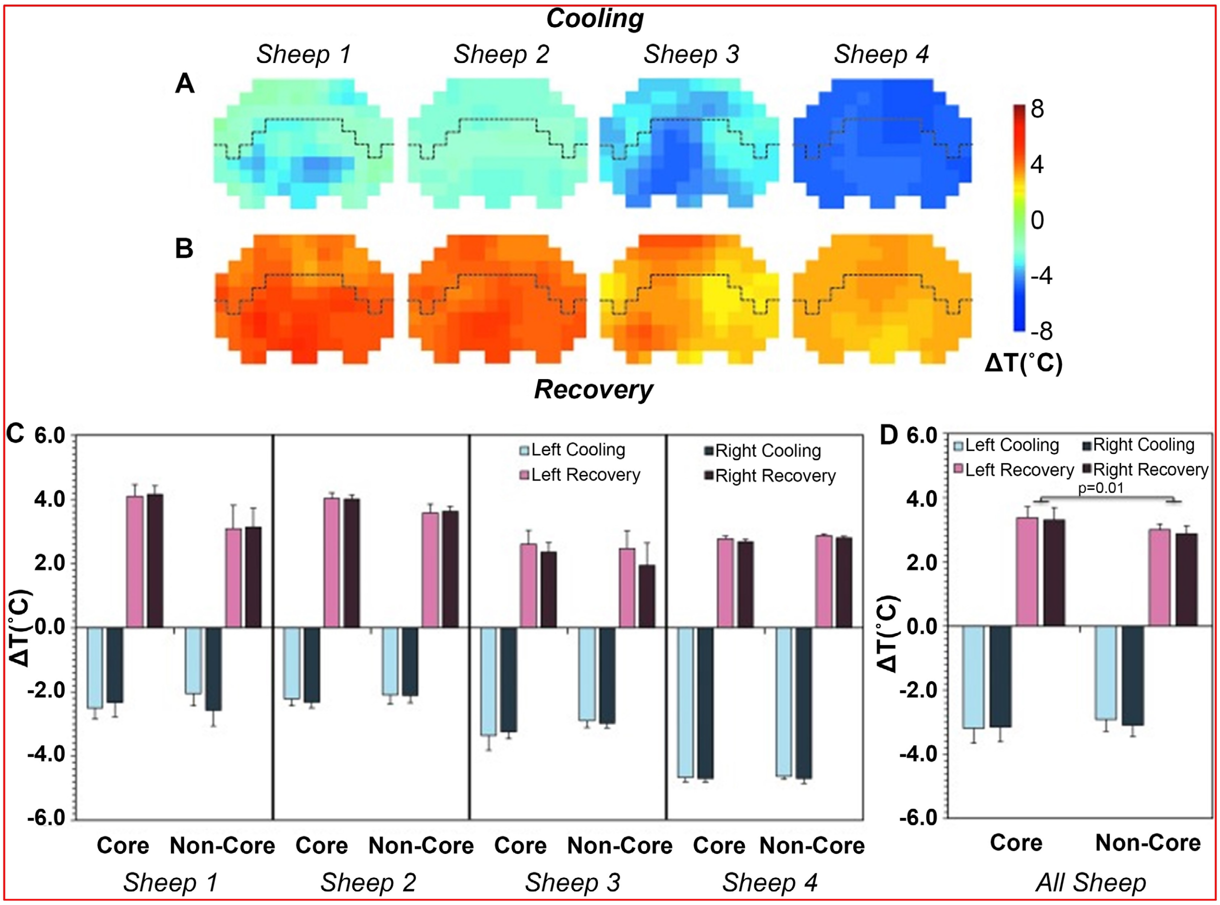

Figure 15. Temperature changes during cooling and recovery in all four sheep. Spatial distributions of the absolute temperature change in an axial slice during the first cooling event using the right catheter (A) and during the first recovery (B). Quantification of the absolute change in temperature during cooling and recovery are shown for both the left and right hemispheres for core and non-core regions of the brain in individual animals (C). Average absolute temperature changes are reported for all animals (D) with significant differences ($p = 0.01$) between core and non-core regions of the brain during recovery. Temperature changes are all reported as average ± standard deviation. The dashed line in (A) and (B) represents the demarcation between the core (bottom) and non-core (top) (B) regions. Reproduced with permission from Reference [14].

In the Figures, one can see the configuration of the catheter, the standard trajectory to the lateral ventricle, and the substantial cooling that is achieved. We have shown that there is no histologic evidence of injury to the spinal cord tissues consequent upon cooling (See again **Figure 14**). We have documented (via high-tech imaging) production of a nicely spreading cooling wave throughout the brain substance, portending well for later human application (See **Figure 15**).

4. Conclusions

Hypothermia holds substantial realized and potential benefits for protection of neural tissues. These have been explored above.

Deep hypothermic circulatory arrest (*DHCA*) *for brain protection in aortic arch surgery*. From human experience with deep hypothermic circulatory arrest for aortic arch surgery, we see that human beings, remarkably, can have all circulation stopped for nearly an hour and still emerge neurologically intact after completion of complex surgical procedures on the aortic arch. (While DHCA has stood the test of time for decades, in more recent years, selective brain perfusion (via individual, small side-arm catheters from the heart lung machine to the innominate ± left carotid artery) has emerged as another alternative for brain protection during aortic arch operations.)

Spinal cooling. Our Yale/CoolSpine team has made strides toward applying hypothermia to inhibit ischemic injury to the spinal cord during descending and thoracoabdominal aortic surgery.

Direct brain cooling. Also, our team has made strides toward direct cooling of the brain via an intraventricular brain cooling catheter.

We share these experiences and investigations here in hopes that these techniques arising from a cardiothoracic surgical perspective can lead to fruitful interactions with specialists in neurologic disease.

We are hopeful that these modes and devices for topical hypothermia that we have presented will permit much better preservation of diverse neural tissues than has proven possible by *systemic* cooling methods, which are fraught with substantial *systemic* adverse consequences. The experimental devices described herein maintain substantial neural cooling while preserving *systemic normothermia*.

While we are encouraged by the results presented herein for the self-contained, recirculating spinal and brain cooling catheters that are described in this report, the ultimate test will be clinical application in humans in real-world clinical settings. The technology is being further refined with investigative human application in mind.

Funding

Parts of this work were supported by Phase I, Phase II, and Phase II (Supplemental) grants from the National Science Foundation.

Dicslosures

Dr. Elefteriades and Mr. Simmons are Principals of CoolSpine, which has no clinical products.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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