Cooling Strategies Targeting Trauma

Moderator: John Povlishock, PhD¹

Participants: Shoji Yokobori, MD, PhD,² Yasuhiro Kuroda, MD, PhD,³ and Kees Polderman, MD, PhD⁴

Therapeutic hypothermia and temperature management are currently being used in many institutions throughout the world to treat the devastating consequences of traumatic brain injury (TBI). In the 1990s and early 2000s, several single-institutional studies provided encouraging evidence for early cooling in improving outcome in patients with severe TBI. However, subsequent multicenter trials failed to show efficacy, with more recent studies emphasizing the importance of subpopulations of TBI patients being included in future hypothermia trials. This particular session brought together experts in the field of neurotrauma to discuss the status of managing hypothermia and fever control in the TBI population. Dr. John Povlishock, professor and chair, Department of Anatomy and Neurobiology at Virginia Commonwealth University, presented exciting preclinical data emphasizing the benefits of hypothermia in combination with various drugs in treating diffuse axonal injury and some of the vascular perturbations associated with TBI. This led to important discussions regarding what agents would be best to combine with hypothermia in future clinical studies. Dr. Shoji Yokobori, a visiting professor in the Department of Neurological Surgery at the University of Miami Miller School of Medicine, provided results concerning preclinical studies where hypothermia was tested in a decompression model of subdural hematoma. These studies emphasized the benefits of cooling the brain before decompression surgery and emphasized a potential subgroup of TBI patients that could benefit from early cooling. Dr. Yasuhiro Kuroda, professor, Department of Emergency Medicine, Kagawa University School of Medicine, presented new data concerning a clinical trial in TBI assessing the effects of hypothermia compared to strict normothermia in patients with severe TBI. Additional discussions concerned the limitations of showing the benefit of hypothermia in this heterogeneous patient population. Finally, Prof. Kees Polderman, Department of Critical Care Medicine, University of Pittsburgh, presented information regarding the ongoing Eurotherm 32–35 clinical study targeting TBI. This interesting study is using intracranial pressure (ICP) as a guide to direct the depth and duration of hypothermia in terms of patient management. Together, these studies emphasize the complexity of our se-

vere TBI human population but also emphasize the significant progress we have made in this challenging field.

Question: *Hypothermia has been reported not to be effective in several multicenter trials, but yet there are strong suggestions that it may be effective in specific subpopulations of patients. I think we all agree that because of the complexity of the disease, clinical trials that lump patients with TBI together as a homogenous group for the purpose of a trial design are probably making a fundamental mistake. I think that the slide we all show at meetings showing the commonality or differences in injury is instructive. The consensus of a recent NIH report is that, as we move forward in the treatment of TBI, we must have protocols that are pathomorphologically or pathophysiologically based, selecting more homogenous patient populations for entrance into clinical trials. Also, as part of that, we talk about multiple treatment strategies. But also, the issue came up of polypharmacy or poly-approaches including the combination of hypothermia with other drugs on board. Now in that context, I was very curious to hear about a recent Japanese report, because I know that their studies were well done; I heard that the Japanese use a radical scavenger. Is it Edaravone?*

Dr. Yasuhiro Kuroda: Yes. Edaravone is frequently used for decreasing reperfusion injury in acute stroke in Japan. Some physicians also use Edaravone for TBI or coma patients after resuscitation from cardiac arrest.

Dr. John Povlishock: Was that used in your TBI study?

Dr. Yasuhiro Kuroda: No. I hope that some cases using Edaravone are included in the B-HYPO study. Unfortunately, the use of Edaravone was not counted in this B-HYPO study in Japan.

Dr. John Povlishock: It was not. I was often wondering because that is a very potent radical scavenger that is used in Japan. It would be very interesting if you tested a subpopulation of severe TBI patients with that drug.

¹Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, Virginia.

²Department of Neurological Surgery, University of Miami Miller School of Medicine, Miami, Florida.

³Department of Emergency Medicine, Kagawa University School of Medicine, Kagawa, Japan.

⁴Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

Dr. Yasuhiro Kuroda: I think Edaravone is especially effective in a situation with reperfusion, for example, by a concomitant use of tissue plasminogen activator in acute stroke. You mean the combination?

Dr. John Povlishock: The combination, yes. Particularly during the rewarming phase, that might prove efficacy.

Question: *I'm still a little unclear on the hypothesis of the Eurotherm3235 Trial. Is the hypothesis that the hypothermia-treated patients will have better controlled ICPs compared to the control group? Or that equally controlled ICPs will have better outcomes if the method of controlling the ICP was hypothermia?*

Dr. Kees Polderman: In the Eurotherm trial, hypothermia is used to control ICP, but the ICP monitoring is also used as the determinant to guide the duration of cooling. Hypothermia is used to control ICP in the hope that this will improve outcome, and the ICP tells us how long hypothermia is needed, and to which degree. The duration of cooling is as long as is required to control ICP. So in some patients, it may be 1 day and in other patients, it may be 10 days.

Question: *But the control group gets its ICP controlled as well, just not by hypothermia?*

Dr. Kees Polderman: Yes, in the control group, the centers try to control ICP by other means. It would be unethical not to do so.

Question: *At the end of the day, do you expect there to be a difference?*

Dr. Kees Polderman: Yes. The hypothesis is that the hypothermia treatment will be superior because the goal is not only to control ICP but also to improve outcome, and the ICP is used to guide the duration. So as long as your ICP is high or rises when you rewarm the patient, it is assumed that the destructive processes are still ongoing, and therefore the patient still requires temperature management. Hence, the hypothesis is that the intervention group will have better outcomes. Also, the study will show how effective hypothermia is in controlling ICP. The planned number of patients to be enrolled in the trial is 1,800. So differences may be small, but hopefully with this size of study population they will be picked up. But one can't have a control group where you say you can't control ICP.

Question: *John, I just wanted to follow on about your comment on synergistic multiple therapies. We both participated in NIH panels where people are advocating for multiple therapies, but nobody has done an effective trial like that. Maybe hypothermia would be the best agent to use for such a combinatorial trial. So the question for you, having done so many studies, what would be the best pharmacologic agent to add to hypothermia for particularly diffuse axonal injury. That seems to be the hard question, right? Hypothermia has not managed to achieve the translation from bench to bedside for that.*

Dr. John Povlishock: As you know, the combination approach with the immunophilin ligands has been very successful. The immunophilin ligands that are used for immunosuppression have multiple actions. One of the more interesting side actions is the potential to modify and protect mitochondria in what we call the preservation of mitochondrial permeability transition. We do have a new experimental compound that we would love to use, which is a very selective mitochondrial target. It does not have the other baggage of immunosuppressants in the sense that it does not have other sites of action. Now, many people say that the last thing you want to do is give an immunosuppressive agent to a traumatically brain-injured patient. But the reality is that it would be a one-time dosing strategy. As Dr. Bullock knows, we have also considered and published with cyclosporine A. In fact, there was actually quite a bit of preclinical discovery involved in that. Also, in animal models cyclosporine A was extremely neuroprotective. But I'm still very high on these strategies. I will add parenthetically, we will publish shortly that when we've actually genetically modified the mitochondria by knocking out the cyclophilin D subunit of the mitochondrial pore, the animals were remarkably protected after TBI. Their axonal injury burden was reduced, and many other structural changes were reduced. We are quite interested in pursuing that.

Dr. Kees Polderman: I suggest that maybe Xenon would be an interesting agent to look at in combination with hypothermia, for both ischemic injury and traumatic injury.

Dr. John Povlishock: Perhaps, yes, but again, as Dr. Bullock brings up, this is a thing that confounds us all as you point out, it is such a complex disease. One would say that in some patient populations, you are not going to have the huge secondary insults and you are not going to have the ischemic burden. So it is a very heterogeneous population. I think that we have to be more tailored in the conduct of the trial. And that's a problem.

Question: *I have a question for Dr. Kuroda. You mentioned a 50% beneficial outcome in your severe TBI patients where fever was controlled. That's a pretty good outcome, right?*

Dr. Yasuhiro Kuroda: Yes. I think that even for the normothermia group, neurocritical care management, including controlling systemic circulation, respiration, and nutrition, is very important and effective in the B-HYPO study.

Question: *But then you add hypothermia to the equation and you try to show a significant difference and improvement in the hypothermia group. Maybe by having really excellent critical care management procedures, you are limiting manageable secondary injury mechanisms. Now if you had compared it to a group where you let temperature rise, maybe there would have been a difference. Have you kind of thought about that? Specifically, that the 50% figure is a pretty good outcome, or am I wrong on that? And it may be hard to improve between temperature-controlled and hypothermia group. Do you improve outcome in severe TBI patients? Better than 50% outcome? What is your goal?*

Dr. Yasuhiro Kuroda: In the B-HYPO study, the percentage of poor neurologic outcome in the hypothermia group is 55 and it is 47 in the fever control group. There is no significant difference. I think the B-HYPO study suggests that in the hypothermia procedure, more careful neurocritical care management is needed because the complication rate is small, but higher than that in the normothermia group. Therefore, if hypothermia management is difficult to perform, the physician should select for fever control to get 50% good outcome.

Comment and Question: *With severe TBI, you start a therapy after the injury. You cannot erase the primary injury produced by the traumatic forces, so do you think that one can improve outcome in severe TBI patients better than 50%? What is your goal?*

Dr. Kees Polderman: Ultimately, of course, that would be the goal. Realistically, what you are touching on is one of the problems that affect every clinical trial. Usually, the entry of patients in clinical trials improves outcome in *both* groups, because patients in both groups are better watched and better treated. We devote more attention. So that's one of the reasons we can say that usually patients will benefit even if they are in the control group. Hypothermia, I think, has the potential to mitigate TBI, the secondary injury; but not the primary injury, that's done. You can't recover from that. So realistically, I think that you probably can't get above 60% beneficial outcome in patients with severe TBI who have initial Glasgow coma score of below 8, unless we find treatments that really repair primary injured neural cells, which I don't believe we have at this moment. Not even in animals.

Comment: I'm afraid that unless you pick a subpopulation of severe TBI patients who are undergoing a very pronounced secondary injury mechanism that can be targeted by a drug or hypothermia, you may not have a chance to really make a major improvement in terms of outcome in severe TBI patients because of that degree of the primary injury. Just a thought that you might have a ceiling effect in terms of your therapies. People may turn away from hypothermia because it appears that it is not working, and that would be a shame.

Dr. Kees Polderman: That's true, and I think what might also help us in that, because ICP is a crude measurement, are things like measuring local hypoxia with a Licox probe and measuring disbalances in the penumbra of an injured area, which might help us to better guide depth and duration of therapy, as well. ICP is kind of a final common pathway of a lot of bad things happening. If we are able to more specifically measure the "bad things" and target our therapies using those measurements, that's possibly when we would see the best effect.

Dr. Shoji Yokobori: About ICP monitoring. I would ask you, if we were to add one more monitoring, what would you choose? Which is the best for you?

Dr. Kees Polderman: It's a great question. There is no single answer. I think it depends on the type of injury and the patient. Diffuse axonal injury is different from more regional injuries and local hematomas where you would be interested in measuring at that site and the sites around it. Even the ICP

monitoring itself can be controversial. It is a monitoring tool. No patient gets better by getting a bulb put in their brain. It's what we do with those measurements that, hopefully, can improve outcome. If we do something bad based on that measurement, then you can actually harm the patient. I think hyperventilation is bad, for example. If we use hyperventilation to control ICP, if we use long-term deep hyperventilation, then it is better not to measure ICP because you are doing something harmful based on that measurement. But if you are doing something beneficial, then ICP measurement can improve outcome.

Dr. Shoji Yokobori: We have a limitation of pressure monitoring.

Dr. John Povlishock: Do you want to explain the limitation of pressure monitoring?

Dr. Shoji Yokobori: Yes. I'm sure that it might depend on the different types of injury. But we also have a difference in similarity over pressure autoregulation and vascular autoregulation, right? I think this should be a limitation of a pressure-monitoring device. If we can add one more monitoring device, we might then know how long we can control the hypothermia or when we can start. Also in our experiments, we don't know how long or how fast we can rewarm.

Dr. John Povlishock: It is an interesting point. I'm sorry that we don't have the Chinese representative here because I do know that the Chinese studies conducted by Professor Jiang in Shanghai were done well, including long periods of hypothermia. I think it was up to 5 days, followed by a slow rewarming period. Now many people in the United States, including intensivists, balk at that because they think it puts the patient at profound risk for pneumonia and subsequent infection. But yet, because of adequate nursing in many of the discussions we've heard, the Chinese appear more successful than us. This issue remains to be clarified, but this question of duration and rewarming rates still confound the field.

Dr. Kees Polderman: In the trial that I did 10 years ago in Europe, we also used ICP to guide duration and the average duration was 5 days. But the longest patient was 14 days.

Dr. John Povlishock: Tell us about infection. Was that an issue?

Dr. Kees Polderman: No, it was not. Baseline infection rates in the Netherlands are very low, and these patients got antibiotic prophylaxis in the form of selective decontamination of the digestive tract (SDD), both controls and the intervention group. We had one pneumonia, and that was in the control group. Another group in The Netherlands has recently published similar results using a long duration of cooling. Also, they had, I think, a 10% overall infection rate with no patient suffering complications from it.

Dr. John Povlishock: In The Netherlands, do you have ample and very competent nursing care that may have contributed to that?

Dr. Kees Polderman: Yes.

Dr. John Povlishock: So you had large numbers of staff?

Dr. Kees Polderman: Yes. One nurse per patient (one-on-one ratio) for patients in that study.

Dr. Shoji Yokobori: At the time, how do you decide on the length of cooling?

Dr. Kees Polderman: Based on ICP. So if the patient were cooled early, they were rewarmed based on ICP. So that's part of what Eurotherm is based on, that experience. This was used as a rescue therapy in very severely injured patients. Our rate of good outcome in the hypothermia group was 35%, not 50%. But we were expecting them all to die. So we were happy with the result.

Question: *Dr. Povlishock, your laboratory has reported that if you cool rats after experimental TBI, you can protect against axonal pathology. However, clinical data by Clifton and colleagues have shown in a limited number of patients with severe TBI that hypothermia does not protect against diffuse brain injury. Is this apparent discrepancy because our axonal injury markers are really not giving us the total consequences of axonal damage. We might just record a morphological indicator that shows protection, but there are other consequences in terms of differentiation that may also alter brain function that are not being protected.*

Dr. John Povlishock: That's a very interesting question. In fact, Dr. Bullock asked me the same question earlier in the day, and the reality is that there is no doubt in my mind that we can in animals with hypothermia significantly attenuate diffuse axonal injury. The question, as you know from the Clifton trial, it is suggested that actually hypothermia had no efficacy in the diffusely injured patients. So this brings up the question that even if you reduce the burden of axonal damage, will that benefit the patient in the long run? And that is an interesting question. We are beginning now to understand that diffuse axonal injury is not only an issue of axonal damage but disconnection for the patient; it is a disconnection syndrome. We are beginning to understand that, downstream, there are enduring plastic changes, some of which aren't so good for the patient, and others that are very adaptive. It's quite possible that even though we are treating and reducing axonal damage, we are not creating a permissive environment for the brain to rewire. So that's our next challenge that ramps up the complexity. The other thing in animal models is you have to understand that these models are not severe TBI. We do not want to have huge contusions, hematoma formation, or ischemia that would complicate our data analysis. So the protective drug studies that are very well done and all my wonderful fellows from Yamaguchi University who have worked with me over the years are targeting a milder TBI condition. We are not looking at severe human TBI, and that could also be part of the problem. It may be that perhaps it's very effective in moderate and milder injuries and may not be effective in the more severe end of the spectrum. That is unfortunately the problem with preclinical discovery. We need to translate these studies to higher-order animals.

Dr. Yasuhiro Kuroda: Regarding the B-HYPO studies, Dr. Dietrich mentioned the potential for the control group having

a good outcome yet the hypothermia group showing the worst outcomes. So, we must keep more time in the ICU for monitoring if we do hypothermia therapy. That is one of the outcomes for the B-HYPO studies.

Dr. Kees Polderman: It is one of the things that makes this so difficult to interpret: hypothermia has a lot of complex effects on TBI. The Cambridge group showed several years ago in patients with severe TBI who had been treated with hypothermia that if they developed fever afterward, then they had higher risks of impaired cerebrovascular reactivity than patients with similar severity of TBI who had not been treated with hypothermia. You can, of course, avoid this problem by avoiding fever and continuing with temperature control, but this shows that the brain can become more vulnerable to certain noxious stimulants after hypothermia therapy. So there are a lot of complicated effects that we don't yet fully understand, and we need to be aware of to get the benefit that we could potentially have with hypothermia. It is very challenging.

Question: *I just wanted to make the point that when talking about the mechanistic effects of hypothermia, one topic we haven't discussed at this meeting is the effects of hypothermia on cortical-spreading depolarizations. There has been a transcontinental, European, and North American trial called the Cosbid study that has been running for probably 4 years now, which, I think, is extremely exciting. Maybe for the next hypothermia meeting, somebody should present those data. But basically, the data report that spreading depolarizations are another mechanism for causing brain damage. Interestingly, only two treatments can reduce spreading depolarization in head-injured patients, hypothermia and ketamine, an NMDA antagonist. One other thought relates to the use of hypothermia in status epilepticus. Clinically, this is a question for Dr. Polderman, maybe. Does anybody know whether hypothermia is being used for status epilepticus?*

Dr. Kees Polderman: It's experimental. We use it occasionally for refractory status, and there are a couple of groups that have published case series on this. So it does seem to work for that. There is not a large trial looking at this. I did have it hidden in one of my slides up there that mitigation of spreading depolarizations is one of the mechanisms by which hypothermia could improve outcome. But again, it requires a long-term treatment. So depending on what is going on with the patient, what mechanisms are harming the brain, would in my view affect what treatments we need to give, as well as hypothermia depth and duration. It's even more complicated than just the anatomical differences in injury. It is also that the destructive processes can be different, and they can be different within the same patient over time. In the first 48 hours it might be mainly hyperactivity and it might be neuroinflammation, and then after a week it might be spreading depolarizations. We at this moment don't know that. We probably have to do a much better job at measuring and targeting our therapies. So it's a very complicated disease, and I think we are just beginning to understand how complicated.

Comment: We are now letting some of our animals live for 6 months after TBI, and we are observing evidence for subclinical seizures. Paul Vespa and colleagues are showing

similar electrophysiological changes in head-injured patients. Yes, it appears that a lot of things are apparently going on during the later stages of TBI that need to be measured and targeted. What types of surrogate markers or biomarkers can we use that can tell us when the brain is being stressed at these delayed periods which may ultimately affect clinical outcome. As we do our research, it gets more and more complex.

Dr. John Povlishock: I don't want to end on a note of discouragement and complexity. I mean, I was in Washington, DC, several years ago, and not to offend any neurologists in the audience, but I was grilled by a panel of neurologists who said, why hasn't there been more progress in TBI? I say, the truth of the matter is, I think the progress has been stellar. I mean it really has been; its modern history is less than 30 years. It is an incredibly small group of investigators, and we have really made major understanding of the disease and treatment approaches. I mean, look at stroke, where there are tens of thousands of investigators dealing with a just a single lesion, one lesion, and yet our advances in stroke and its treatment remain relatively simplistic. So I think we've made a lot of progress in trauma. I think we've seen potential applications for hypothermia. So I don't want to leave this sort of on a fatalistic note. I think we now know that, unfortunately, neurotrauma is complex, and we know the issues. I think we are going to have to move forward with better inclusion criteria in our patient populations and more targeted therapeutic approaches. But again I feel pretty proud of what we've done in a relatively short time frame with a very modest cadre of people.

Key References from Panel Participants

- Andrews PJ, Sinclair HL, Battison CG, Polderman KH, Citerio G, Mascia L, Harris BA, Murray GD, Stocchetti N, Menon DK, Shakur H, De Backer D; Eurotherm3235Trial collaborators. European society of intensive care medicine study of therapeutic hypothermia (32–35 °C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial). *Trials* 2011;12:8.
- de Waard MC, Biermann H, Brinckman SL, Appelman YE, Driessen RH, Polderman KH, Girbes AR, Beishuizen A. Automated peritoneal lavage: an extremely rapid and safe way to induce hypothermia in post-resuscitation patients. *Crit Care* 2013;17:R31. [Epub ahead of print]
- Fujita M, Oda Y, Wei EP, Povlishock JT. The combination of either tempol or FK506 with delayed hypothermia: implications for traumatically induced microvascular and axonal protection. *J Neurotrauma* 2011;28:1209–1218.
- Fujita M, Wei EP, Povlishock JT. Effects of hypothermia on cerebral autoregulatory vascular responses in two rodent models of traumatic brain injury. *J Neurotrauma* 2012;29:1491–1498.
- Kawai N, Kawakita K, Yano T, Abe Y, Kuroda Y, Tamiya T. Use of intracerebral microdialysis in severe traumatic brain injury. *No Shinkei Geka* 2010;38:795–809.
- Lafrenaye AD, McGinn MJ, Povlishock JT. Increased intracranial pressure after diffuse traumatic brain injury exacerbates neuronal somatic membrane poration but not axonal injury: evidence for primary intracranial pressure-induced neuronal perturbation. *J Cereb Blood Flow Metab* 2012;32:1919–1932.
- Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008;371:1955–1969.
- Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med* 2009;37:S186–S202.
- Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 2009;37:1101–1120.
- Povlishock JT, Wei EP. Posthypothermic rewarming considerations following traumatic brain injury. *J Neurotrauma* 2009;26:333–340.
- Smith DH, Hicks R, Povlishock JT. Therapy development for diffuse axonal injury. *J Neurotrauma* 2013;30:307–323.
- Yokobori S, Bullock R, Gajavelli S, Burks S, Mondello S, Mo J, Wang KK, Hayes RL, Bramlett H, Dietrich D. Preoperative-induced mild hypothermia attenuates neuronal damage in a rat subdural hematoma model. *Acta Neurochir Suppl* 2013;118:77–81.
- Yokobori S, Frantzen J, Bullock R, Gajavelli S, Burks S, Bramlett H, Dietrich WD. The use of hypothermia therapy in traumatic ischemic/reperfusional brain injury: review of the literatures. *Ther Hypothermia Temp Manag* 2011;1:185–192.
- Yokobori S, Gajavelli S, Mondello S, Mo-Seaney J, Bramlett HM, Dietrich WD, Bullock MR. Neuroprotective effect of preoperatively induced mild hypothermia as determined by biomarkers and histopathological estimation in a rat subdural hematoma decompression model. *J Neurosurg* 2013;118:370–380.