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Managing Hypothermia in Cardiac Arrest and Rewarming

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Many institutions are currently utilizing therapeutic hypothermia to target cardiac arrest as well as different types of brain injuries. Confounding issues including accidental hypothermia as well as the need to carefully rewarm patients with some types of physiological monitoring strategies are an area of active investigation and discussion. This particular session brought together experts in the field from cardiology, surgery, and trauma to discuss current strategies for managing hypothermia and temperature maintenance in various patients with different types of disorders. Dr. Eric Zoog, medical director of the Emergency Department, Mississippi Baptist Medical Center, provided an interesting summation of how he and his colleagues developed a successful hypothermia program in a community hospital. Several important points were made in terms of the processes, including convincing various services to help with this important program. Dr. Robert Silbergleit, Department of Emergency Medicine, University of Michigan Health System, discussed his experience in various clinical trials, including the use of hypothermia in cardiac arrest as well as patients undergoing aneurysm surgery. His experience emphasized the importance of introducing careful strategies to monitor brain function during cooling and rewarming phases. Dr. Josh Levine, Department of Neurology, University of Pennsylvania, discussed the use of hypothermia in various brain injury conditions. Most importantly, he and his colleagues have been investigating the importance of developing surrogate biomarkers that could aid in the assessment of the status of the brain. Most importantly, these biomarkers could be used to individualize treatments based on active processes. This session had a very interesting question-and-answer exchange, again emphasizing the interest in using therapeutic hypothermia and temperature management strategies during various emergency situations.

Question: ***I think we want to do everything we can to monitor the brain to see how it is doing. If we can develop therapies that target individual subjects, that's great. Do you think we'll be able to achieve that goal in the near future? Most of the time, we are talking about trying to do clinical studies that have a pretty rigid regimen predetermining what we can do and what we cannot do. Then there is the expense of using invasive or noninvasive techniques to monitor the brain condition, or is this something that you see happening globally in the near future?***

Dr. Josh Levine: By nature, I am a realist, but here I'm optimistic. I think that we have already seen this beginning to occur in other fields of medicine. I'll give you an example that many of you in the room may be familiar with, which is goal-directed therapy for sepsis. This was an emergency room–run study showing that outcomes for sepsis could be improved by following an algorithm. What I think was landmark about that study was not that better outcomes were achieved, it was the algorithm used. It incorporated things like central venous oxygen saturation, which is much more relevant to physiology than just keeping blood pressure above a certain arbitrary limit. They titrated the blood pressure and other therapies, for example, blood transfusions, to achieve a certain mixed venous oxygen saturation. So that is an example of when a clinical trial was done with an algorithm. But the algorithm was a step more sophisticated in my opinion than the algorithms that we typically use, because they incorporated individualized physiology. I think that algorithms and individualizing care are not mutually exclusive. They can be done together. You just have to design the right algorithms. To me, that was a landmark article for that reason and would be the equivalent of titrating therapy for the brain using a jugular venous oxygen saturation. We can do that. This technology is cheap, it's been around forever. It doesn't require that much expertise to learn how to use it, so I am optimistic. I think a lot of the technology I showed is far-fetched and will not make its way into the mainstream. But others might, and I think that's all we need. We need to be more sophisticated about how we design our algorithms.

Dr. Robert Silbergleit: I think the big problem is figuring out what to do with the information collected. What are the effective treatment algorithms used to respond to the monitoring? That's the real challenge. That's the threat to your optimism. *Early* goal-directed therapy for sepsis followed a dozen trials of *late* goal-directed therapy for sepsis that didn't work. Trials using pulmonary artery catheterization to guide ICU therapy showed harm from the way the information was used after 20 years of practice of pulmonary artery catheters. Given the complexity of brain injury, and the potential insight offered by a number of devices discussed, it makes sense to try

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to figure out how to make it all work. It makes perfect sense, you're right. I think the future *is* goal directed therapy. But in terms of whether it is in our near future or not, I'm not so sure. It's a daunting challenge.

Dr. Josh Levine: I completely agree with everything you have just said, and I think that in many ways in clinical medicine, by necessity, we put the cart before the horse, and we study things before we have a full understanding of the physiology. I agree that this is a long-term goal. We need to understand much better the physiology and which physiologic parameters are really important, which ones aren't. That is still something that is debated. We need to understand the technology better, what are the risks, what are the benefits. A lot of these algorithms employ bundles of therapy, and it is hard to understand. If you include one thing in your bundle that is harmful and the rest are beneficial, you might not see any effect. It takes a long time to sort that out. I think that what I'm advocating is that we start to think more this way, that just broadly applying average values is not going to serve all of our patients well. It looks nice for a clinical study, but it is not necessarily the best way to treat patients. You're right, I think that there are centers like ours who are beginning to do this but we're studying it and trying to understand the physiology. I'm optimistic that it will happen, but I also recognize that it's a long way off, and it's exceptionally complex.

Dr. Robert Silbergleit: ***What about genotype?***

Dr. Josh Levine: What about it? You mean incorporating genetic data and individualizing care accordingly?

Dr. Robert Silbergleit: When individualizing care, it is not just having these measurements, it is the fact that genotype may have an effect.

Dr. Josh Levine: Absolutely, in brain injury that's an area of active research. This is a huge growth area in brain injury research; we have very little concept of which alleles confer benefit, which alleles confer harm. There is a little bit of data in traumatic brain injury about ApoE, but it is very crude. You're right, that's got to be incorporated someday into all of this. But I think the physiology is the final key. No matter what your genotype is, your physiology is what matters most in the ICU. If you can at least measure the physiology, you can begin to individualize therapy even without knowing the genotype. But I do think genotype is important, as well.

Question: ***This is a great talk, and I agree with you. I think that you need to individualize, but you do need some standardization. We can't cool people all at different lengths of time, at 12 hours, 24 hours, or at different temperatures—32, 33, 34°C. So for a unit to be functional, you have to have some kind of a base in which you have some standard practices. Then when you round on individual patients, I think that you have to be able to individualize. I think that what's at risk here, that the biggest unknown is the brain. I think we can figure out the heart pretty quickly, if you go to the cath lab and do all kinds of tests, have a pretty good feeling of what is going on with the heart. But I'm always puzzled as what's going on with the brain. So we have patients at times with hyperthermia becoming very profoundly bradycardic. We wonder is it time to put a pacer in? Is it time to use dopamine? Is it time to do something? A lot of times, we just back off. But in backing off, are we doing harm to the brain? So do we need some kind of way to monitor this? Not everybody has a neuroICU-like approach. What would be your favorite way, with people going away from a lot of Swans and hemodynamic monitoring, is there a noninvasive way that is relatively applicable and practical today for us to use with our patients in our units?***

Dr. Josh Levine: I think all of your points are excellent. I could tell you what my favorite is, but I don't have a lot of confidence because I don't think that these have been studied well enough to actually make a recommendation. We use *jugular bulb oximetry*, we use continuous EEG, we use all of the things I showed you. But the easy ones, relatively easy, are jugular bulb oximetry and EEG. I totally agree that you need standardization for an ICU to run properly. But we have no problem titrating pressors to achieve a certain goal. I would posit that perhaps in the future, we'll be titrating our hypothermia to achieve a certain goal, but it will be a meaningful physiologic goal. Why should everybody be cooled for the same duration for the same depth and then rewarmed at the same rate? They probably shouldn't. We just don't know enough about how to do it, and I think you can still standardize care by having algorithms that incorporate a titration schedule—the way we do with pressors or an insulin infusion or anything else that we titrate routinely in the ICU without really even thinking about it.

Question: ***Is there any kind of relationship between the elements you can measure systemically—such as cardiac output and cerebral blood flow? So for some patients, you can say, I don't need to worry about someone who has a great cardiac output. Are there correlates from what we measure systemically; mixed venous O_2's that we can apply to the brain, as well, so we don't need to worry about this patient?***

Dr. Josh Levine: Great question. That's the key, and the answer is no. There is such individual variability in the status of what the blood vessels in the brain are doing from patient to patient, even within the same patient, that you can't just take the systemic pressures that you are seeing and have any confidence that you know what cerebral blood flow is. Even if you know that cerebral blood flow is okay, are the cells able to utilize the energy that is delivered? There are all sorts of different degrees of cellular energy failure, mitochondrial dysfunction, etc. So we just can't do it, and that's why I think we need to evolve. If our goal is going to be to save brain tissue and improve neurologic outcomes, we've got to, at some point, evolve a way of treating patients that takes into account the cerebral physiology. The only correlation I know is if your blood pressure is zero, I can guarantee you the brain is not doing well. Beyond that, it is very difficult to predict how the brain is doing from systemic physiology.

Question: ***A question for Dr. Silbergleit. I was very interested in your discussion of after-drop and the mechanism looking at compartmentalization of heat in the body as you rewarm. I wonder if you could help me understand something that we've seen when we try to cool patients—that there are a fair number of patients who will go to target very quickly. But there are occasional patients that won't or appear to go in a***

stepwise fashion. One of the theories is that if we administer the cold saline first, before any anti-shivering measures are in place—no skin warming, no Demerol—that there is a peripheral vasoconstriction that essentially isolates the periphery from the central. We are doing endovascular cooling. Do you think there is anything to that? Or could there be another explanation, or does what you taught us about afterdrop not even apply on the way down?

Dr. Robert Silbergleit: I think it probably does apply. There was sort of this flurry of experimentation in the late 1980s and '90s in a number of physiology labs that didn't really seem to have a lot of clinical relevance except for our accidental hypothermia patient population. I think that we start to get a hint now that this work is probably relevant to the therapeutic cooling that we're doing commonly these days. We need to look back and enhance those experiments. The limited data that are available would suggest that the convective mechanism isn't a great explanation for why that is happening. It is probably not safe to assume it, but I don't have a great explanation, for example, as to why it varies from one patient to another patient. Clearly, the notion that the human body is a big vat of water—that you can pour some water in and it will equilibrate out and that will change the temperature—was way wrong. How many compartments communicate with each other is more complex and probably discoverable.

Question: ***I have a question for Dr. Silbergleit, as well. With profound hypothermia that is accidental, when you consider that we are used to monitoring the hypothermia protocol for cardiac arrest, what type of electrolyte monitoring or what type of monitoring are you doing as you are trying to warm these patients up basically as fast as you can? How frequently are you checking your labs and things like that?***

Dr. Robert Silbergleit: So again, this whole field has very little data. The only real data that has been followed in these avalanche victims is potassium, and that really just shows that extremely high potassium levels are irreversible, and there is good data that if you have a potassium level of 12, you cannot be resuscitated.

Question: ***Do we have anything to say about if we want these patients warmed quickly. How quick is too quick? Do we look at these electrolyte shifts? Do we look at them hourly? Do we look at them every two hours? What are our guidelines for warming people quicker? Because I know from the cardiac arrest experience, those that for some reason anecdotally are warmed too quickly end up in cardiac arrest—a lot of them. So I'm wondering, do we just ignore that and expect those shifts? Or because they have been hypothermic for awhile, are the shifts less extreme?***

Dr. Robert Silbergleit: I'm not even entirely sure that the anecdotal experience of not paying attention to electrolytes during therapeutic hypothermia causes death. I think that that needs to be investigated further. I think in the accidental hypothermia population, it probably depends on patient factors like duration of hypothermia and how long they were down and what kind of preservation they had while they were hypothermic. But as a general rule, there is nothing in the published treatment algorithms that suggests that these patients need to be followed closely or in any particular, certain dangerous electrolyte shifts.

Question: ***Dr. Zoog, you mentioned that it took about a year to establish hypothermia in your community hospital. I think that is a pretty good success rate. Even at large university hospitals, we talk about champions and someone with a vision, and you appear to be that person. Early on, who else was supportive of what you were trying to achieve, and again, how did that really happen in making a successful program?***

Dr. Eric Zoog: We were fortunate to have two intensivists that were very interested. We have a situation in which there are two intensivist groups that practice at the hospital, and one group was very interested, the other not so much. You do run into call issues for unreferred patients. The interested group was interested enough to agree to take all the patients even if the other group was on unreferred call. So that was an absolute must, and then the nursing staff were critical as well. ICU and ER nursing for us were the most affected, so our task force included representatives from each of those areas.

Question: ***Where is the Level I trauma center located in Mississippi?***

Dr. Eric Zoog: In Jackson, about a half a mile from us. We don't have a whole lot of experience with hypothermia in the trauma scenario for that reason.

Question: ***Do you have a good working relationship with that hospital for transport and things like that?***

Dr. Eric Zoog: The state trauma network has been around now for 8 or 9 years. The nice thing about that is there are prearranged agreements for transfer. You don't have to go through all the legalities to initiate a transfer of that sort. Our trauma system director is very open to working with nontrauma hospitals in providing care for trauma patients.

Question: ***The monitoring that we discussed, I really think that is the future. The surrogate biomarker story is also going to allow us to not only assess patients individually on how well the brain is doing, but with the right biomarkers, we may be able to assess the pathophysiology of what is going on in the brain and how we can utilize novel therapies to target those events in a time-dependent fashion. What do you think about that, Dr. Bullock?***

Comment: Yes, I absolutely agree that biomarkers are probably going to be the way of the future. However, the problem is, some of the biomarkers, for example S100, we know are contaminated by peripheral events. So long bone fractures and soft tissue injuries can contaminate those reactions. I think we are still searching for the best biomarker, but there are some talks this afternoon that may address this. Then how do you detect them in a kind of continuous ongoing way? One comment that I was going to make is that the medical device community has done us a big disservice over the years. When you think of what a pilot does when he is flying an F15, you get a million sensors bringing information in; the information

gets processed down so that it is understandable by one person second to second. Whereas, with us in the medical device area, we have a million different languages that the different computers speak. GE machines don't talk to space lab machines and so trying to integrate all these different forms of sensors that Dr. Levine showed very elegantly is difficult. We have to figure out a better way to follow the streams of data—maybe these dashboards that you see, where five different parameters are going red at one time, which means you have to do something. Perhaps systems science has progressed so much that it can be brought to bear in our fields better. I wonder whether the critical care medicine society and other professional groups have to be the leaders.

Comment: That is a good point. I just wanted to say that now we have special units that are monitoring ICUs because the data is so complex. St. Lukes in Milwaukee and several other hospitals have central ICU monitoring stations where doctors and nurses are basically monitoring the data to look for errors of omission by someone not aware that certain data changes are very important. So it is getting very complex. We do need that cockpit.

Question: ***I was also interested—in terms of our previous discussion—in how long we are cooling in cardiac arrest patients. Am I correct in saying that most people are cooling for about 24 hours? Yesterday we saw some interesting biomarker data showing that elevated levels would go on for 72 plus hours. I think that's an area that we really should be thinking about. Maybe some cardiac arrest patients are going to do well with a 24-hour cooling period, but others are going to have to go longer, so we need to consider durations. I guess my question to the panel is, when we talk about duration in terms of cardiac arrest, do we need to prolong the hypothermia to protect the heart, or are we prolonging the hypothermia to protect the brain, or both?***

Dr. Josh Levine: I think, simplistically, both. Because of the bent in our ICU, which is a neurologic bent, we'll often extend the duration of hypothermia based on what we are seeing physiologically in the brain. So, for example, if we have a continuous EEG, which we do on all these patients, and they start to have seizures during rewarming, we'll recool them. We'll keep trying until the seizures go away. If we see that the intracranial pressure rises dramatically during rewarming, we'll either slow it down, or we'll back off and recool them. So I think there's really no way at this point to monitor how it is going to impact survival. We are beginning to have ways to monitor how it is impacting brain physiology, but we are far from knowing what the right thing to do is. The job of a physician is to use the best available evidence and, where there is no evidence, to use clinical judgment based on understanding of physiology. And so that's all we can do at this point. In our ICU, we often modify the hypothermia protocol for brain physiology reasons. I'm not aware of how we would modify it for survival reasons at this point.

Dr. Robert Silbergleit: So there is a difference between saying that titrating therapy is the wave of the future and saying that that is what we need to do now for every therapy. There are a couple of reasons why you might want to titrate duration rather than just study the effects of different durations for everybody. Certainly, there is a danger to every additional day that you are in the ICU, right? I mean, being in the ICU is a hazardous thing to be. So there are good reasons to limit one's ICU exposure. But whether that is enough to necessarily require that duration be titrated, does that create a narrow therapeutic index? Or is the therapeutic index still large? If the therapeutic index is large, there is less of a need for titration. I suspect that a few extra days of therapeutic hypothermia is not so hazardous and may be beneficial. I'm not sure that this is the first place that we have to look toward goal-directed therapy, but we do need a trial to compare durations of cooling in less severe and more severe injuries.

Question: ***People already use radioisotope-labeled pharmaceuticals for cardiac mass perfusion imaging and brain perfusion imaging. So I don't know whether there is application of nuclear medicine like single-photon emission computed tomography (SPECT), computerized axial tomography (CAT) scans in ICU patients, to monitor their cardiac function and brain function simultaneously.***

Dr. Eric Zoog: I think the difficult part is actually getting those studies done. We have a huge resistance to actually moving these patients. I don't know if those studies are portable enough. I would have to convince our facility that it is a good idea. The intravascular management system that we use does not have a battery on it. So I have to disconnect the patient from it to get the testing done if it's not able to be done in the unit. Just a potential confounding factor we would have to figure a way around.

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