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Cooling Heads and Hearts Versus Cooling Our Heels

Lance B. Becker, MD

Evidence suggests that full implementation of therapeutic hypothermia after cardiac arrest could save thousands of lives each year. Critical unanswered questions persist, beginning with a lack of evidence in regard to how early cooling should be initiated, which cooling strategy is most effective at cooling the brain, and, ultimately, what method of cooling is most optimal for survival. Two reports in this issue of *Circulation*, from Castren et al¹ and Bernard et al,² begin to provide some of these needed data. Given the immense logistic difficulty of performing randomized field studies, the teams of investigators involved in both studies are to be congratulated for conducting this important research. The presented results begin to explore the important question of how quickly and by what methods cooling should be started in the field. Although they provide some answers, they also provoke new questions. For clinicians using therapeutic hypothermia with cardiac arrest patients, it is important to clearly understand the pros and cons of earlier cooling initiated in the field with the newer techniques explored in these 2 reports. It is also important to understand the differences between the findings in these studies, along with the practical implications and limitations of each technique, before conclusions are drawn about the manner in which these studies may influence practice.

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Bernard and colleagues² report on the use of cooling with intravascular ice-cold Ringer's solution delivered during ambulance transport of the subset of cardiac arrest patients presenting with ventricular fibrillation only and after return of spontaneous circulation (ROSC). Castren and colleagues¹ report on a novel intranasal intra-arrest cooling strategy used for cooling all cardiac arrest patients, irrespective of rhythm, before ROSC. Intra-arrest cooling is novel because it attempts to cool during the cardiac arrest in the midst of cardiopulmonary resuscitation (CPR). Intra-arrest cooling versus cooling after ROSC is an important question. Currently most patients are cooled only on arrival at the emergency department (ED) or hospital and often hours later in the intensive care unit. Only rarely are patients cooled in an ambulance, let alone in the chaos of their homes or on the pavement.

The study of Bernard et al presents data on earlier cooling in the ambulance after ROSC within a small subset of cardiac arrest patients, and the authors detected no differences in survival outcomes. Patients who received earlier paramedic cooling were on average 0.8°C cooler on arrival than patients cooled in the ED by traditional cooling methods. Their data raise the question of whether ice-cold 4°C intravenous Ringer's solution is the ideal coolant. Iced saline has volume-loading effects on the right heart and in actual practice is a relatively slow cooling method. Often iced saline is not ice-cold at 4°C when it enters the patient; it may warm as it goes through the tubing or the cooler/refrigerators used for storage may fail to maintain the proper temperature.³ Taskinen et al³ report that storage/refrigeration devices intended to keep saline at 4°C often fall short of this temperature. Even more challenging are observations that significant cooling power is lost because ice-cold saline warms as it travels through a length of intravenous tubing. This cooling loss may be significant. There is also the concern that volume loading may be harmful during CPR. Swine studies show that ice-cold saline delivered during cardiac arrest reduces coronary perfusion pressure (CPP).^{4,5} Yannopoulos et al⁴ found that iced saline reduced CPP during CPR from 24 mm Hg to only 4 mm Hg, an alarmingly low value that makes survival unlikely. In a swine model of cardiac arrest, Yu et al⁵ directly compared the volume-loading effects of intravenous saline versus nasopharyngeal cooling that has no volume load on the venous side. After 5 minutes of CPR, the CPP was significantly better with nasopharyngeal cooling than with the intravenous ice-cold saline infusions (CPP of 23 versus 11 mm Hg; $P=0.02$).

Another potential challenge with intravenous saline in the ambulance is that although the patient receives some cooling during transport, it is not clear that these efforts at cooling are continued once the patient arrives at the ED or hospital. Of particular note is the data from the present study of Bernard et al, which demonstrate that most patients seemed to "warm up" significantly after being cooled with intravenous saline in the ambulance. As seen in Figure 2 of their article, patients with cooling by paramedics presented to the ED with a temperature of 34.4°C after in-ambulance cooling but appeared to have warmed up to 34.7°C at the end of the first hour. By contrast, the subjects in the control group presented to the ED with a temperature of 35.2°C but were on average cooled to 34.7°C, so that both groups had identical temperatures after the first hour. Obviously, the patients who received intravenous saline in the ambulance did not receive another intravenous cold saline bolus or some other method for continued cooling in the ED. The extremely low intensity of in-hospital cooling in both groups is further demonstrated by the 6 to 8 hours required to cool both groups of patients to a target temperature of 34°C, noteworthy because the patients were already at 34.4°C on ED arrival. The fact that it required

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6 hours for the hospital cooling teams to lower the temperature by only 0.4°C is a stark reality check on the difficulty of cooling protocol implementation in the real world, even in the more controlled setting of EDs and hospitals.

The study of Bernard et al highlights that in-ambulance intravenous saline cannot be the end of hypothermia but is merely the beginning of a 24-hour therapy that must be vigilantly maintained. We are left with the question of whether disruption of the normal cooling care for these patients may have been an unintended consequence of cooling by paramedics. In the final analysis, it is not surprising that survival rates are similar in the 2 groups because although the cooling by paramedics during transport was superior for the in-ambulance group, the effectiveness of cooling in the ED for the first hour was far superior in the control group, with no temperature differences observed between the groups beyond the first hour. When drawing conclusions from these data, it is important to separate the cooling strategy from the specific implementation, protocols, and cooling devices employed. From this study, we can see some drawbacks to cooling that are specific to the use of intravenous saline, including the following: volume loading, decreased CPP, lack of cooling power, need for refrigeration in the ambulance, and requirement of an intravenous device. The study highlights the challenges of clinical cooling studies but is not able to answer the important question about the need for earlier cooling. It also suggests that ice-cold saline may not be an ideal human coolant for in-ambulance cooling and even less so for intra-arrest cooling, in which CPP is more of an issue than in the post-ROSC setting.

Castren and colleagues report their findings on a strategy that uses "intra-arrest" cooling, defined as the initiation of cooling during a cardiac arrest in the midst of CPR. The authors use a novel nasopharyngeal cooling method, which allows for rapid initiation of cooling during the intra-arrest period. The nasal device produces cooling by rapid gas-driven evaporation of a volatile coolant. This is a phase-change cooling system that provides significant cooling power to the nasopharynx, immediately beneath the forebrain and brain stem and adjacent to the major vascular structures of the brain during the cardiac arrest. Although the study was not powered to show a survival benefit, Castren et al demonstrate the feasibility and safety of this approach and show that the intra-arrest cooling group achieved the target temperature much more rapidly. In a subgroup analysis of patients with ventricular fibrillation, the absolute improvement in survival rate was 15% for transnasally cooled patients. Although the numbers are too small to reach significance, they provide some tantalizing cooling rates and survival trends that suggest that improved outcomes from intra-arrest nasal cooling may be found in a larger clinical trial.

Importantly, the study of Castren et al is the first clinical intra-arrest cooling trial, and the results support its feasibility and safety for future clinical trials. Intra-arrest cooling is an intriguing strategy for cooling that was first developed from cellular and animal models and was demonstrated in laboratory models to provide significantly superior protection over our current practice of delayed cooling after ROSC. Shao et al⁶ studied the cardioprotective effects of intranscemic

cooling in isolated contracting cardiomyocytes just before reperfusion (intra-arrest cooling for cells) compared with cooling just after reperfusion. They reported that "cool reperfusion" was superior even at the expense of a time delay in reperfusion of ischemic cells. Abella et al^{7,8} also demonstrated the neuroprotective superiority of intra-arrest cooling in a murine model of cardiac arrest wherein mice cooled intra-arrest 90 seconds before ROSC demonstrated 60% survival at 72 hours, whereas mice cooled a mere 20 minutes after ROSC had only 10% survival. In addition, Yannopoulos et al⁴ demonstrated a similar superiority for "intra-CPR" cooling in swine over cooling just after ROSC. The study of Castren et al is an important step forward in the exploration of intra-arrest cooling in a human clinical trial.

It is also noteworthy that Castren et al use a novel device in their study, one that is relatively noninvasive and easy to administer. A strength of this approach appears to be its relative noninvasiveness and ease of administration. It is likely that insertion of the transnasal catheter is much faster and easier than insertion of an intravenous catheter, and vastly easier than insertion of an intravenous catheter during cardiac arrest. It may prove an ideal device for the emergency medical services setting. The data reveal a significant reduction in the time to target temperature. The nasopharyngeal intra-arrest cooling was associated with attaining a tympanic membrane temperature in patients of $\leq 34^{\circ}\text{C}$ in 102 minutes versus 291 minutes ($P=0.03$) for standard cooling. Although the outcome data from this small trial do not reach significance, there is a trend toward finding benefit in the subgroups of patients with ventricular fibrillation and especially in those who received CPR <10 minutes after the 911 call, irrespective of rhythm. Recall that the Hypothermia After Cardiac Arrest (HACA) trial in 2002, which started much of the momentum for the use of hypothermia, reported data for only the small subset of admitted patients with ventricular fibrillation. If we examine the identical ventricular fibrillation cohort from the data of Castren et al, survival was 62.5% for patients who received intra-arrest transnasal cooling versus 47.6% for those cooled in the hospital ($P=0.37$). Although these results are not statistically significant because of the low numbers of patients with ventricular fibrillation, if the improvement by nearly 15% in absolute survival over our traditional hospital cooling rates could be reproduced in a larger clinical trial, it could lead to a major advance in cardiac arrest care. Equally interesting is the nearly 27% absolute improvement (56.5% versus 29.4%; $P=0.04$) for all patients with transnasal cooling who received CPR in ≤ 10 minutes regardless of rhythm. These data become even more significant when good neurological outcome is taken into consideration, consistent with the notion that transnasal cooling may be particularly protective of the brain. A reduction in days in the intensive care unit was also seen for nasopharyngeally cooled patients. Therefore, the primary message from this study is that the data are encouraging and that a larger trial powered for survival should be undertaken.

However, an important and disconcerting question remains: Why have all of the major randomized cooling studies to date been performed outside of the United States? The HACA trial and now the study of Castren et al were

performed in Europe, and the 2 studies of Bernard et al were performed in Australia.^{1,2,9,10} Furthermore, these studies are all meager in terms of budget compared with the public health impact of cardiac arrest in our society. The void in US clinical studies on cooling should disquiet us all. The problem deserves serious attention because it represents a failure of our medical research community to prioritize and advance research on a fairly low-cost, technologically simple technique that could save thousands of lives in a short time. There can no longer be any doubt that many Americans who have died would be alive today if the research in this country had advanced more quickly. No single factor can explain this delay; the challenges are multifactorial and complex. Contributing factors include the constraints imposed by regulatory agencies, difficulties of obtaining informed consent, restrictions due to the Health Insurance Portability and Accountability Act of 1996, difficulties of funding, and difficulties of obtaining regulatory approval for commercialization. In addition, there are larger systemic challenges such as market forces in which maximal profit drives product development, the primitive generation of cooling devices that are far from optimal, and insurance companies that balk at reimbursement for cooling. It is time that we acknowledge and openly discuss the fact that the cumulative effect of these realities has been to create an unforgiving barrier to clinical trials of therapeutic hypothermia in the United States. The medical research community in the United States has “cooled its heels” when it comes to clinical hypothermia trials. There are no barriers to cooling studies that cannot be surmounted with proper attention. We have a great opportunity to advance our knowledge and save lives from an all-too-common disorder that is treatable yet nearly 95% lethal in most communities. Should we push forward with the research on optimizing the cooling of heads and hearts, or should we continue to cool our heels while disproportionate numbers of patients die prematurely?

In conclusion, we are fortunate to have new data adding to our knowledge of hypothermia therapies. We see that intravenous saline given in the ambulance after ROSC seems to have little long-term effect. We further note that hospital cooling, which we primarily consider to be straightforward, can be very challenging and less than optimal. By contrast, we see that patients attain target temperatures more rapidly with intra-arrest intranasal cooling, and there are trends that make us optimistic about seeing a survival benefit in future studies. Finally and most importantly, we must acknowledge that the US research community has barely contributed to the clinical trials in hypothermia. This is a time of great opportunity to learn more about methods of optimizing the cooling of heart and brains. I hope that we will push ahead to learn even more in the months to come.

Disclosures

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scientific direction of the center, as well as for the financial support of the center. Ensuring adequate financial support for the Center for Resuscitation Science at the University of Pennsylvania involves the active pursuit of federal funding, industrial funding, foundation funding, and philanthropic funding for the projects of the center. Dr Becker has received research support to the University of Pennsylvania from the National Institutes of Health, Phillips Medical Systems, Laerdal Medical, Cardiac Science, BeneChill Inc (which was the sponsor of one of the articles discussed in the editorial), Zoll Medical Corp, Abbott Point of Care, and the Medtronic Foundation. He has previously served as a consultant to Philips Medical Systems and Gaymar Industries and currently is a paid consultant to the National Institutes of Health for the Data Safety Monitoring Board and Protocol Review Committee of the Resuscitation Outcomes Consortium. In addition, he has issued and pending patents assigned to the University of Pennsylvania and the University of Chicago involving the use of medical slurries as a human coolant, devices to create slurries, and reperfusion cocktails. He has received speaking honoraria from multiple universities and is a volunteer for the American Heart Association, which sells training materials worldwide on resuscitation techniques that include recommendations on the use of therapeutic hypothermia. In addition, Dr Becker performed several of the early experiments in animals using intra-arrest cooling discussed in the editorial.

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