Does Cool Reperfusion Limit Myocardial Infarction Injury?

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In this issue of Circulation: Cardiovascular Interventions, a pilot study by Göteborg et al1 deserves notice. It may have major implications for clinicians who deal with myocardial infarction, and it suggests important insights into the poorly understood area of human reperfusion injury.

The investigator team is to be congratulated for successfully surmounting a formidable implementation challenge. Within 30 minutes, they were able to rapidly cool patient body temperatures to an average less than the target temperature of <35°C without allowing the induction of cooling to interfere with or prolong the door-to-balloon time for percutaneous coronary intervention. To put this 30-minute speed of cooling into perspective, a 2010 investigation of human hypothermia from Australia reported a nearly 8-hour time interval to achieve temperatures <34°C in patients with cardiac arrest.2 The Göteborg pilot study goes on to describe a 38% reduction in infarct size and 43% reduction in peak troponin T release for the patients who received cooling before coronary reperfusion versus controls who received standard reperfusion within the same time period. The study raises an important clinical question that we must address: Is cool reperfusion the best reperfusion?

An even more crucial scientific question lies just beneath the surface of these data: Does reperfusion injury exist in humans, and if so, does it have any relevance in terms of long-term function or tissue injury? Reperfusion injury remains controversial since its first description in the 1970s when it was observed that reoxygenation of the ischemic perfused isolated heart resulted in a large release of cardiac injury enzymes along with structural cellular damage seen extensively during reperfusion but only very minimally during the preceding ischemia.3,4 The notion of reperfusion injury suggested that some portion of cell death was caused by the conditions of reperfusion, not simply by the conditions or injury produced by the period of ischemia alone.5,6 The critical experiment to prove the existence of reperfusion injury was to demonstrate that long-term cell death or infarct size could be reduced by a therapy delivered after the ischemia. Much animal data seemed to support the existence of reperfusion injury, but nearly all the human trials of cardioprotection have failed to support the idea that any therapy could significantly alter cell death or infarct size after the ischemia had occurred.7 There are a few important exceptions to this general failure, but thus far in routine cardiovascular practice, there are no widespread therapies to treat or prevent reperfusion injury. The failure of cardioprotection after reperfusion in clinical trials has been interpreted by many as evidence that reperfusion injury is quite negligible or does not exist.7,8 Moreover, our current paradigm for the treatment of acute myocardial infarction is founded on this assumption, and early reperfusion has become the primary goal for the treatment of ischemic cardiac syndromes.9 Could this simple pilot study with 20 patients significantly alter our view of the treatment of ischemia? If these results are confirmed in a larger trial, the answer is yes. This study has the potential to change our fundamental understanding of the mechanisms of cell death following ischemia and how it should be treated.

The Göteborg pilot study comes close to satisfying the experimental conditions required to prove the existence of significant reperfusion injury in humans but does not completely fulfill all criteria. One requirement to prove reperfusion injury is that the therapy must only be delivered during reperfusion, not beforehand. Both cooled patients and controls had the same length of ischemia; however, the cooled patients had a slightly lessened “ischemic burden” because they were being cooled to 35°C during the last 30 minutes of the 174-minute period of ischemia. So it is fair to suggest that the 2 groups do not have completely identical ischemia injuries. In other words, an insult of 170 minutes of normothermia is expected to be slightly worse than 140 minutes of normothermia plus 30 minutes of ischemia at 35°C. This single criterion to prove the existence of reperfusion injury is what this pilot study lacks. Although most would argue that this very mild reduction in the severity of ischemia alone could not have resulted in the reductions observed in infarct size and troponin release, it is important to note that this study does not completely prove reperfusion injury on the basis of this alternative explanation.

But there is another ischemic condition for which the existence of reperfusion injury has already been proven conclusively: cardiac arrest and the use of therapeutic hypothermia after resuscitation from cardiac arrest.10–13 Hypothermia begun after return of spontaneous circulation has been demonstrated to improve long-term outcome and is rapidly becoming the standard of care. It is now recommended by the American Heart Association for selected patients after cardiac arrest and has a solid basis in animal and human survival studies to show its effectiveness.14 Hypothermia after cardiac arrest meets all the criteria needed to prove the existence of reperfusion injury, and thus, the demonstration of a similar

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benefit following focal myocardial ischemia should not be a surprise to us. Moreover, there are other proof-of-concept human studies with reperfusion protection that support this notion of limiting reperfusion injury, although they are far from being fully confirmed. Postconditioning protocols, atrial natriuretic peptide, and cyclosporine A have all been seen to diminish infarct size in small human trials.14–16 These protective agents also await larger trials to test their value as reperfusion injury-directed therapies.

Most investigators in the field of reperfusion biology suggest that reperfusion injury takes place very rapidly, within mere minutes of reperfusion.5 If this is the case, then when therapeutic hypothermia is attempted, it is important that target temperature be achieved some few minutes before reperfusion and may explain why many clinical trials may have failed. The cellular mechanisms cited involve a rapid release of free radicals from mitochondria due to the reintroduction of oxygen in the setting of an electron-rich or reduced electron transport system.4,6,17,18 In animal studies, free radical generation has been described as peaking within 10 seconds of reintroduction of oxygen,19 and in isolated cardiomyocyte studies, peak free radical generation is seen within 3 to 5 minutes.20,21 In addition, calcium dysregulation, proteolytic enzyme activation, and mitochondrial permeability transition occur rapidly during this early period of reperfusion.5,6 After these early events are initiated, multiple destructive biochemical pathways can be observed to become activated in tissues, including those that lead to cell death, dysfunction of organelles, and the amplification of the inflammatory system. Under the reperfusion injury concept, the patients in the Göteborg study who received cooled reperfusion benefited from attenuated free radical generation and destructive metabolism that would have occurred in the first minutes, and the noncooled patients suffered an additional injury due to reperfusion with normal-temperature blood.

The idea that conditions for which we practice widely to achieve standard reperfusion lead to additional myocardial injury is concerning. It is important to recognize that the reduction in infarct size seen after 3 days as demonstrated in this study is quite significant and demonstrates very similar results to prior studies conducted using cool reperfusion in swine with coronary occlusion.22 We are left with a question: If reperfusion injury exists and is significant, then are we not yet treating any of our ischemic conditions optimally? In fact, we are inadvertently extending additional harm while we attempt to treat ischemic conditions. We currently have no routine treatment that we routinely deliver targeted to reperfusion injury except for hypothermia following cardiac arrest. It is important to note that reperfusion injury strategies do not suggest that it is good to delay the reperfusion of ischemic cardiac tissue. Rather, the proposed solution to reperfusion injury is “controlled reperfusion,” such as the cool reperfusion in this study, wherein the conditions of reperfusion are controlled to avoid setting off additional injury and are altered from the normal condition of the blood before the ischemia.23,24 By cooling the blood on reintroduction to the ischemic tissues, injury appears to have been reduced.

Part of why this concept is important has to do with the implications for other protective agents that may be helpful during reperfusion. Cooling appears to be the first widely accepted form of successful controlled reperfusion, but it will not be the last. There are additional new approaches to controlled reperfusion after cardiac arrest that show promise, including hypothermia along with other metabolic modifications that alter conditions within the blood from normal. It is likely that these mechanisms will translate into acute myocardial reperfusion protection. They are potential mechanistic targets for reperfusion injury, and in the future, we may be able to provide the protection of hypothermia without having to cool the patient.

The data presented in Göteborg et al are more sobering when we understand that reperfusion injury and reperfusion therapies promise important breakthroughs beyond acute myocardial infarction syndromes. Consider that there are >400,000 in-hospital and out-of-hospital cardiac arrests per year wherein the entire body is ischemic and the likelihood of death rises steeply after just a few minutes.25 Reperfusion injury mechanisms are triggered by restoration of circulation, but involve changes throughout the entire body with highly complex amplification of multiple metabolic cascades. As we better understand reperfusion injury, we need to discover its contribution to these deaths. Consider neurological emergencies, including 795,000 new or recurrent ischemic strokes each year in the United States,25 that share a similar ischemia and reperfusion physiology and treatment conundrum. Consider trauma, the leading cause of death in the United States for persons aged 1 to 44 years,26 that often is associated with ischemia followed by attempted resuscitation with blood or oxygen. If future studies demonstrate that reperfusion injury exists, then the likelihood exists that it also contributes to all of these conditions. If true, reperfusion injury arguably is the most significant preventable injury for which our current standards of care offer almost no attempted treatment.

Hypothermia and studies using cooling have brought us a new understanding of ischemia and reperfusion. It is vital to understand that hypothermia is only the very beginning of this new science in the area of protection after ischemia. If hypothermia is proven to improve reperfusion therapies for acute myocardial infarction, we will see more agents for cellular protection following ischemia for a variety of disorders. We look forward to additional studies that provide insight into this important science. For the time being, clinicians should be aware that we have enticing preliminary data for cool reperfusion that require confirmation from a larger study. The possibility looms large before us that our standard therapies promote a significant reperfusion injury that we could prevent. We all should be wondering whether the reperfusion that we ourselves would want is cool reperfusion.

Disclosures

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neChill Inc, 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 slurry as a human coolant, devices to create slurry, 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.

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