Emergency preservation and resuscitation (EPR), also referred to as suspended animation or therapeutic hypothermia, is demonstrating great promise in saving patients from exsanguination-related cardiac arrest.

Deaths from multiple organ failure, wound sepsis and other related problems have been of great interest to the military. The leading cause of death in the Vietnam conflict was rapid exsanguination in the first 5 to 20 minutes after injury. Cardiopulmonary resuscitation (CPR), and restoration of hemodynamics failed to help exsanguination-related cardiac arrest patients. Many of these combat casualty victims were reached by a medic within minutes, and one-third of them would have had trivial lesions if they had been in a trauma bay. Exsanguination-related cardiac arrest is re-emerging as a problem in the Iraq War. While blast injuries present a new form of mortality and morbidity, exsanguination-related cardiac arrest retains its spot as a leading cause of death in that war.

Exsanguination-related cardiac arrest also is an important problem in civilian trauma, where successful resuscitation with good outcome remains dismal — in the 5% range, said Patrick M. Kochanek, MD, FCCM, from the Safar Center for Resuscitation Research and the University of Pittsburgh.

**History of Emergency Preservation and Resuscitation**

Dr. Kochanek provided a brief history of EPR. In 1984, Peter Safar, MD, FCCM, with advice from Col. Ronald Bellamy, the foremost authority on combat casualties during the Vietnam conflict, developed a revolutionary new concept targeting battlefield death from rapid exsanguination. This approach involved transient “preservation” of the victim to allow evacuation, transport and emergency “damage-control” surgery, followed by a delayed resuscitation using cardiopulmonary bypass. This concept, first described in the literature by Samuel Fisherman, MD, FCCM, from the University of Pittsburgh (Fisherman et al. J Trauma. 1990;30:636), was called deep hypothermia for preservation and resuscitation. In further studies, the process was called suspended animation for delayed resuscitation and eventually emergency preservation for resuscitation.

The Safar Center spearheaded clinical trials in EPR. The first report of this work used a rapid aortic flush after exsanguination cardiac arrest in a dog model and demonstrated that up to 30 minutes of preservation could be achieved with intact outcome after cardiac arrest. In these pioneering studies, emergency preservation was achieved by rapid cooling to about 7°C, and resuscitation was achieved using cardiopulmonary bypass with slow re-warming (Behringer et al. Anesthesiology. 2000;93:1491). Subsequent studies from the Safar Center demonstrated that emergency preservation could be achieved with intact outcome after cardiac arrest lasting as long as 2 hours and possibly longer (Behringer et al. Crit Care Med. 2003;31:1523). In 2005, the first consensus meeting was held at the Safar Center for clinical investigators interested in the application of EPR to the victims of otherwise lethal exsanguination cardiac arrest. The Safar Center is anticipating funding of the first clinical trial of EPR in fall 2007.

Dr. Kochanek described the new approach to rapid exsanguination cardiac arrest. “The thought is to ‘pickle’ the victim to allow transport and damage-control surgery, and then resuscitate the patient with cardiopulmonary bypass. Essentially, this stops the clock to buy time. Ultimately, cardiopulmonary bypass provides a perfect resuscitation, followed by intensive care,” he said.

“Inducing hibernation is a very efficient way to try to do this,” explained Dr. Kochanek. “But the problem is that our scenario is quite different from controlled hibernation. During hibernation, there is no cardiac arrest or ischemia before the insult. Hibernation certainly lowers metabolic demands and oxygen consumption and induces hypothermia.”

**Testing Different Scenarios**

When a canine model of exsanguination cardiac arrest was first studied, researchers thought rapid brain and heart perfusion would protect both organs. They simulated combat injury with rapid exsanguination cardiac arrest over 5 minutes. They then waited 2 minutes to simulate the clinical or battlefield scenario, because one would not consider trying to induce this unless he or she knew the person was in full arrest. Subsequently, a cold flush was used to induce EPR, which lasted anywhere from 20 to 120 minutes.

The aorta was flushed with a variety of solutions and temperatures in the initial experiments, from a room temperature flush to one using iced saline of 0°C, said Dr. Kochanek. The team tested the effects of typanic temperatures and then resuscitated with cardiopulmonary bypass between 15 minutes and 3 hours. The animals were treated with full intensive care unit (ICU) support over 72 to 96 hours, receiving sedation, analgesia, and Swan-Ganz catheters. The outcome was evaluated with an overall performance category, neurologic deficit score, and brain histopathology. In looking for a breakthrough, the investigators focused on the goal of achieving an overall performance category (OPC) of 1, or normal.

In the first study, the researchers began with a 5-minute cardiac arrest from exsanguination and then waited 2 minutes (Behringer et al. Crit Care Med. 2003;31:1523). They flushed with 500 mL/kg of either room temperature or iced saline, which lowered brain temperature to 33° or 34°C. They then waited 20 minutes with the animal in a state of emergency preservation. “Remarkably, we could achieve a vast majority of OPC 1s with just this simple approach, only reducing brain temperature to 33° or 34°,” Dr. Kochanek commented. Increasing the flush volume a little allowed even longer arrests with good outcomes.

**Larger Arrest Times**

Looking at this in a battlefield application, reparative surgery and transport would require less than the researchers had investigated previously. “To target 60 minutes, we tested different temperatures,” explained Dr. Kochanek (Behringer et al. Crit Care Med. 2003;31:1523). Researchers tried 20°, 15°, and 10°C. They performed a substantial flush, as much as 300 mL/kg, to get down to about 10°C for a 60-minute experiment. If they targeted 15° or 10°C, they had excellent outcome.

“Next we pushed the envelope to 90 or 120 minutes,” Dr. Kochanek said (Behringer et al. Crit Care Med. 2003;31:1523). “We needed to be able to account for transport and repair in time.” For the 2-hour experiment, researchers went with 20 L of flush, targeting about 0°C. With the longer preservation times, some animals developed acute renal and distal spinal cord ischemia. Although brain function remained intact, the experiment did not achieve the team’s goal. Some of the animals were okay, but there was more of a spread once the animals reached 120 minutes.

“It is still impressive that one can go 2 hours with just a saline flush,” said Dr. Kochanek. In the later, long-duration experiments of 2 and 3 hours, they used an extremely large-bore femoral cannula to infuse 20 L at a rate of 1.6 L/min.

The military then asked the researchers to investigate how long flush administration can be delayed after cardiac arrest begins. They tried a 30-minute cardiac arrest with 100 mL/kg of iced saline at 4°C and delayed the flush for 2, 5, 8 or 10 minutes. They found the break point was between 5 and 8 minutes (Fisherman. Crit Care Med. 2004;32 [Suppl 2] S16).

“At this point, we found that the efficacy of the flush for emergency preservation was a result of flush temperature, flush volume, balloon position, and the time between arrest and flush,” explained Dr. Kochanek. These are all factors that determine the onset, depth and distribution of hypothermia.

**Pharmacologic Intervention**

The research tested 14 different pharmacologic strategies, from ultra-contemporary anti-apoptosis strategies to some of the classics. Only one drug, tempol – a brain-penetrating antioxidant – improved outcome in the paradigm after being screened in the 20-minute model. It showed some benefit, but did not produce a complete breakthrough (Behringer et al. J Cardiothorac Vascul Anesth. 2002;16:201).

“We concluded that, at least with what we know now - and we didn’t know a lot about penetration of drugs across the blood-
brain barrier - the drug paled in comparison to hypothermia," said Dr. Kochanek.

**Trauma and EPR**
The military also asked researchers to add trauma to the model. Could they still perform successful EPR in the face of trauma-induced coagulopathy and cytokine release? The investigators added trauma to a 30-minute arrest (Nozari et al. J Trauma. 2004;57:1266). The animals underwent a laparotomy spleen injury, emergency thoracotomy exanguination, cardiac arrest, 2 hours of EPR, and then surgical repair, simulating a splenectomy done during the emergency preservation period in the operating room. This resulted in coagulopathy and multiple organ failure. Dr. Kochanek noted that these studies were done by re-infusing the dog's blood. "We thought that doing these long-term outcome studies without blood products such as FFP was severely limiting," he said. To attack the coagulopathy in the acute phase, investigators conducted three single-volume plasma exchanges and were able to achieve 2 hours of emergency preservation. Indeed, some of the animals were able to achieve intact outcome with OPC 1.

**Prolonged Exanguination**
Next, the military wanted to know if EPR was an option for a trauma victim who exsanguinates slowly over several hours, as in the Mogadishu conflict dramatized in the movie Blackhawk Down. "When you think about it, this could really be a bad scenario. Could the cold flush solution used in emergency preservation reach a clamped down liver and gut?" asked Dr. Kochanek.

To test the question, the investigators did a spleen transection and a continuous hemorrhage until cardiac arrest naturally occurred, which was after about 2 hours. The dogs were randomized to receive conventional resuscitation, all-out resuscitation, or 1 hour of EPR followed by cardiopulmonary bypass.

"We set up the model so that the arrest in both groups happened over about 124 to 128 minutes," Dr. Kochanek said. "The animals were in profound shock at the time of arrest. The dogs had pH levels in the 6.8 range and lactate levels of 15. An aggressive conventional resuscitation with CPR, blood, epinephrine was not effective and resulted in multiple organ failure and 100% mortality. The animals lived, but only for a few hours." This mimics what is seen in the resuscitation of human trauma victims presenting in the same difficult circumstances of traumatic arrest preceded by prolonged shock.

Emergency preservation in this strategy initially was disappointing. The animals developed seizures a day or two after they were awakened. "We had never seen seizures before," commented Dr. Kochanek. "When the researchers used Fluoro-Jade B staining for neuropathology, they found the EPR to have some preservation benefit, but were seeing some very subtle and progressive neurologic damage."

To rectify the situation, the researchers added 36 hours of mild hypothermia after the emergency preservation and achieved good outcomes in 3 of 7 animals. The neuropathology in these animals showed preservation of CA-1 hippocampus, the brain region most selectively vulnerable to ischemia (Wu et al. Circulation. 2006;113:1974).

EPR appears to be effective even after prolonged hemorrhagic shock. This raised the question of neurologic complications related to open-heart surgery. "Maybe we shouldn't be in a big hurry to rewarm," suggested Dr. Kochanek. "Maybe we should think about rewarming to 33° or 34°C for a day or two, particularly in situations where there is concern about brain injury during the surgery."

The final study was to test the 2-hour limit (Wu et al. Submitted for consideration). Because some of the Iraq War casualties are facing extremely long transport times, the military needs to know if EPR could be done for a longer period of time. Pilot tests were conducted to study outcomes at 3 hours of emergency preservation. The standard 8°C cooling produced vegetative coma. Next, they tried an ultra-cool flush solution, but saw precipitation in the aorta.

When considering the situation, the researchers noted that it took about 15 minutes to reach target temperature. "During that cooling period, there were considerable metabolic demands, and we were just flushing with saline," Dr. Kochanek commented. "We wondered if we could provide an energy substrate during the flush. So, we added both oxygen and glucose to the flush."

Dr. Kochanek's team decided to test using an oxygenator to deliver oxygen and glucose. Group 1 received oxygen and glucose, group 2 received oxygen without glucose, group 3 received glucose only, and group 4 received neither. They found that even 3 hours could be achieved in some animals. With oxygen plus glucose, OPC 1 was found in 2 of the 3 animals, and even the other animals did fairly well. Oxygen alone also achieved good results.

**Looking Ahead**
Associates of Dr. Kochanek's team are working on novel smart catheter technology because of great interest in taking the technology to the trauma bay. The first trial will be a civilian test of exanguination cardiac arrest in the trauma bay.

Lyn Yaffe, MD, at Aliion Science and Technology is working with a number of corporate partners to develop a smart catheter that could be placed transhoracically in the aorta or left ventricle. They are also considering the development of a bib so that this technology can be done in the field. "That is somewhat futuristic, but it leaves us with the hope that we eventually will be able to say, 'Quick, bring up the emergency preservation team,'" said Dr. Kochanek.

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**Select the best response for the following question:***

3. When performing EPR, what additives to the flush allowed the investigators to maximally augment cold saline so that 3 hours of successful preservation could be achieved?

- a. Tempol
- b. Oxygen
- c. Glucose
- d. Oxygen plus glucose

4. How did researchers improve outcomes in their testing of EPR where cardiac arrest was preceded by 2 hours of hemorrhagic shock?

- a. They added 36 hours of mild hypothermia after EPR.
- b. They injected an antioxidant.
- c. They were unable to improve the outcome.