

# PRINCE: Prehospital intranasal cooling after cardiac arrest feasible, may improve survival

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**AHA**

**Orlando, FL** - Use of a new device that allows therapeutic hypothermia to be instituted in the field has been shown to be feasible and safe for patients in cardiac arrest.

With the use of a portable system that cools the brain via nasal prongs, similar to those used to deliver oxygen, target brain temperature was reached three hours in advance of those patients in whom cooling was begun in the hospital. Although the study was not powered to assess clinical outcomes, researchers did see some indication of improved survival and neurologically intact survival in patients in whom hypothermia was instituted prior to hospital arrival, particularly in the subgroup of patients where CPR was begun within 10 minutes of the arrest.



Dr Maaret Castrén

Results of the **Pre-Resuscitation Intranasal Cooling Effectiveness** (PRINCE) trial, funded by BeneChill (San Diego CA), which makes the RhinoChill system, were presented here at the **American Heart Association 2009 Scientific Sessions**.

"We can conclude that the PRINCE trial, the first randomized intra-arrest cooling study, showed that intranasal cooling using RhinoChill is feasible and safe during arrest," **Dr Maaret Castrén** (Karolinksa Institute, Stockholm, Sweden) concluded.

"Even if the study was not powered for outcome, we can cautiously say that survival and neurologically intact survival to discharge was significantly higher when CPR was initiated within 10 minutes," she said.

## Transnasal access

It's now well established that therapeutic hypothermia provides a survival benefit for patients in cardiac arrest. In 2002, two randomized trials were published in the same issue of the *New England Journal of Medicine*, both showing improved outcomes with hypothermia in patients resuscitated after cardiac arrest [1,2].

In those trials, cooling was begun in-hospital between 30 minutes and two hours after the collapse, Castrén noted. The PRINCE trial was an attempt to begin therapeutic hypothermia outside the hospital during CPR, using a transnasal system that introduces a mixture of volatile coolant and oxygen into the nasal passages directly under the large vessels of the brain.



The evaporation of the gas cools the nasal cavity quickly to about 2°C, and from there, the cold is transmitted to the brain. Eventually the rest of the body also cools, but it's the brain that is the target, said **Dr Denise Barbut** (BeneChill). "The brain cannot get too cold," she said. "The colder it is, the better off it is, as long as it doesn't actually freeze. The body can't go below a certain temperature before complications arise, so cooling the brain fast and early is critically important."

The device is portable, housed in a backpack weighing about 25 lbs, and has intranasal catheters that deliver the coolant directly into the nasal cavity. No electricity is required. "It's very simple and easy to use," said coauthor **Dr Per Nordberg** (Karolinska Institute). "You apply it within a minute, and it takes 30 to 60 seconds to start cooling."

The current study was a safety and feasibility trial of use of the system by first responders during CPR. In the trial, 200 patients who experienced a witnessed cardiac arrest with CPR begun within 20 minutes were randomized to prehospital transnasal cooling or standard advanced cardiac life support (ACLS) care. Cooling was begun as soon as was considered feasible without interfering with ACLS protocols, they noted. Patients in both groups received therapeutic hypothermia once they arrived at the hospital. All arrests were included, regardless of the initial rhythm.



Dr Per Nordberg

Of 200 randomized patients, 18 were eventually excluded from the analysis, often because they were later found to have "do-not-resuscitate" orders or other exclusion criteria, Castrén noted, leaving 83 in the intranasal-cooling group and 99 in the standard-care group.

The target tympanic temperature of 34°C, used as an approximation of brain temperature, was reached three hours earlier in the group receiving prehospital cooling, and the target core body temperature was reached two hours earlier.

Adverse events were minor, she said, with nasal discoloration being the most common.

**PRINCE: Adverse events with intranasal cooling vs no intranasal cooling**

Device-related events	Intranasal cooling (n=83), n (%)	No intranasal cooling (n=99), n (%)
<b>Nasal discoloration</b>	13 (15.6)	0 (0)
<b>Epistaxis</b>	3 (3.6)	0 (0)
<b>Perioral bleed</b>	1 (1.2)	0 (0)
<b>Periorbital emphysema</b>	1 (1.2)	0 (0)
<b>Serious adverse events unrelated to device in admitted patients (sepsis, AMI, rearrest)</b>	6/30 (20)	14/42 (33.3)

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Although the study was not powered to look at efficacy, 31.1% of the standard-care patients admitted to the hospital survived vs 46.7% of those receiving intranasal cooling (p=0.15), not a statistically significant difference.

When they looked at survival to discharge in the 75% of patients who received CPR within 10 minutes of collapse, they saw a significant increase, from 29.4% in the standard group to 59.1% in the intranasal-cooling group ( $p=0.028$ ).

Of those with ventricular fibrillation, survival to discharge was not significantly different, at 47.6% in the standard-care group vs 62.5% in the cooled group.

Finally, neurologically intact survival was 21.4% with standard care vs 36.7% in those treated with intranasal cooling ( $p=0.15$ ). Again, significant benefit from cooling was seen in the subgroup that received CPR within 10 minutes of arrest, with neurologically intact survival rising from 17.6% with standard care to 45.5% with intranasal cooling ( $p=0.025$ ).

Among the limitations of the study are that no data were collected on CPR quality, Castrén pointed out, nor was there a standardized postresuscitation protocol. Now that the device has been shown to be safe and feasible, future studies will introduce the cooling device earlier in the resuscitation protocol, she added.

The device is already approved in Europe, but has not yet been commercialized because the evidence to support its use was not available prior to this study, Barbut noted. The system should be available in Europe by the first quarter of 2010, and the company plans in the future to approach the **Food and Drug Administration** about possible approval in the US.

### Promising data



Dr Michael R. Sayre

Asked for comment on these findings, **Dr Michael R Sayre** (Ohio State University Medical Center, Columbus) called the findings promising but cautioned that the results will require replication before they can be generalized.

"Cardiac arrest is extremely common," he said during an interview. "Approximately 200 000 Americans have a cardiac arrest every year outside the hospital, and today, less than 20 000 of those survive, so if these results are confirmed in other settings, this could be really important."

The study included patients with all rhythms at baseline, he noted, which is important, because when introducing a technology such as this, it is critical to ensure it is safe in all kinds of patients. Sayre said he looks forward to further data on the efficacy of the device.

*The study was funded by BeneChill. Barbut is president and CEO of BeneChill.*