# Safety and Efficiency of Intravascular Temperature Management for Therapeutic Hypothermia

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## Introduction

Therapeutic moderate hypothermia currently is recommended for treatment of patients with out-of-hospital cardiac arrest (OHCA) and for newborns with neonatal hypoxic/ischemic encephalopathy.(2, 23) For patients with OHCA, hypothermia has been shown to result in a 68% greater likelihood of a favorable neurologic outcome early after the event, and a 44% greater likelihood of being alive with a favorable neurologic outcome at 6 months after the arrest, as compared with patients who are not cooled.(1, 7, 26) These studies led the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association (AHA) to recommend that patients with an initial rhythm of ventricular fibrillation following OHCA should be cooled for 12 to 24 hours.(12, 42) For neonates with clinical evidence of hypoxic/ischemic encephalopathy at birth, cooling to 33 -35 C for 48-72 hours, and begun within 6 hours after birth, is recommended based on the results of three separate randomized, controlled trials reported in 2005 by Gluckman et al., Shankaran et al., and Eicher et al..(16, 21, 47)

Therapeutic moderate hypothermia also has been used for the acute care of patients with severe traumatic brain injury in at least nine major clinical trials during the past 15 years.(9, 10, 19, 28, 34, 44, 48, 49, 57) Careful analysis of most of the clinical trials where ICP data is provided suggests that hypothermia is associated with a significant decrease in the incidence of intracranial hypertension.(8, 10, 19, 28, 34, 39, 41, 49, 53-55) And a new metaanalysis completed by the evidence-based guidelines group at the University of Oregon Health Sciences Center, and published in the Third Edition (2007) of the Guidelines for the Management of Severe Traumatic Brain Injury, found that hypothermia was associated with a 46% greater likelihood of a good outcome (GOS of 4-5).(3) Inspired by these findings, a new multicenter prospective randomized clinical trial of therapeutic moderate hypothermia for pediatric traumatic brain injury has been initiated by David Adelson at the University of Pittsburgh. *(R01 NS052478-01A2 (Adelson); Pediatric Traumatic Brain Injury Consortium: Hypothermia)*

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But the potential clinical benefits of therapeutic moderate hypothermia for these and other diseases may not be fully realized because of delays in reaching the target temperature.(33) Such delays are inherent with the use of surface cooling techniques, and in most of the adult studies cited above the target temperature was not reached for 6-12 hours after initiation of cooling. Given the unavoidable delays in the discovery, resuscitation, and transport of patients with cardiac arrest (CA), stroke or traumatic brain injury (TBI), it is very likely that significant secondary injury already has occurred by the time hypothermia is initiated. The sooner the patient is cooled to target temperature, the more likely they are to benefit from the therapy. In addition, surface cooling techniques are relatively inefficient, and in their study of cooling using ice packs for patients with OHCA, Holzer reported that they were able to reach target temperature in only 30% of their patients.(1) Study groups for the use of hypothermia in cardiac arrest, neonatal hypoxia/ischemia, and traumatic brain injury all have suggested that reaching the target temperature sooner may allow for hypothermia to be even more beneficial than has already been demonstrated.(2, 3, 23)

## Intravascular Cooling Technology

Intravascular temperature management (IVTM) systems have been approved for the rapid cooling of patients treated with therapeutic hypothermia. An early version of IVTM involved cooling catheters inserted into the superior vena cava via the subclavian vein, and a large clinical trial found that this system was 64% more effective than surface cooling techniques for limiting fever in the neuro-intensive care unit.(13) In a subsequent study of patients who were successfully resuscitated after cardiac arrest, Holzer, et al, compared outcomes in 97 patients treated with IVTM for 24 hours to the outcomes in 941 patients who had been treated with "standard" postresuscitation therapy.(27) The likelihood of survival with a favorable neurologic outcome at 30 days after the arrest was 2.15 fold greater in the group receiving IVTM than the standard postresuscitation group.

There now are at least 12 clinical reports of the use of IVTM for the induction and maintenance of therapeutic hypothermia to treat OHCA, acute myocardial infarction (AMI), or ischemic stroke.(Table 1) Among the 8 studies where data is reported, the mean rate of cooling with IVTM is 1.7 C/h.(4, 14, 18, 20, 22, 30, 43,58) Most reports of surface cooling describe a maximum attainable cooling rate of less than 1 C/h. In addition to a more rapid rate of cooling, these studies also show that IVTM allows for tight control of the temperature once the target temperature is reached. In one recent study, IVTM with the Icy catheter (Alsius Corporation) was found to be significantly better than 4 other commonly used temperature management methods for maintaining the target temperature.(58) And in all but one of the studies, the target temperature could always be reached, but surface cooling methods often were not sufficient to reach the target temperature.(12,17,18,58)

**Table 1: Characteristics of endovascular cooling in studies of patients with out-of-hospital cardiac arrest, acute MI, and stroke ***

| Study | Speed of Cooling | Able to Reach Target Temperature | Maintenance of Target Temperature |
|---|---|---|---|
| Feuchtl (17) | Not Reported | All 19 in IVTM 2/20 SC | Not Reported |
| Flemming (18) | 0.83°C/hr: IVTM 0.09°C/hr: SC | All 31 in IVTM 4/49 in SC | Not Reported |
| Al-Senani (4) | 0.8±0.3°C/h | All patients | 32.7±0.5°C |
| Arrich (5) | Not Reported | All patients | Not Reported |
| Pichon (43) | 1.1±0.4°C/h | All patients | 33±0.4°C in 91% |
| Kandzari (30) | 3.3°C/h | All patients | 33.55±0.35°C |
| Dixon (14) | Est: 3±0.85°C/h | All patients | Est: 33.75±0.5°C |
| DeGeorgia(12) | Not Reported | Not reached in 4/18 | Not Reported |
| Georgiadis(20) | 1.4±0.6°C/h | All patients | 32.8±0.6°C |
| Guluma(22) | 1.59°C/h | All patients | 33.8±0.7°C |
| Hoedemaekers (58) | 1.46°C/h: IVTM 0.72°C/h: SC | All 10 in IVTM 3/10 patients with SC | 3.2% time out of range in IVTM (define as 0.2°C below or above target) 44 to 74% time out of range in SC |
| Merchant (59) | 0.32°C/h: SC | Not reported | Target 32-34°C 63% < 32°C 28% < 31°C 13% < 30°C |

*IVTM: intravascular temperature management system; SC: surface cooling methods not included: Sunde(52)- didn't report these categories; Kliegel(32)- hypothermia induced with cold saline boluses*

## Central venous catheter-related complications

As clinicians consider the use of therapeutic hypothermia, they must carefully weight the risks as well as the potential benefits of the therapy. Medical complications associated with surface cooling techniques, such as shivering , thermal burns, limited patient access, difficulty during target temperature maintaince (overshoot), have been well described and shown in most cases not to be clinically significant. Endovascular cooling, however, involves the insertion of a central venous catheter into the femoral, internal jugular or subclavian vein, and the potential for central venous catheter-related complications. To be sure, this drawback is relative since most patients who would be considered candidates for therapeutic hypothermia require central venous access due to their medical condition. A recent retrospective study describing the use of femoral IVTM for 3-8 days in 10 severely brain-injured patients found subclinical (duplex ultrasound) evidence of catheter related thrombus in the 5 patients who had their catheters in place the longest.(50) None of these patients had a documented pulmonary embolism or any other clinically significant adverse consequence of the thrombus, however. (Of note, the manufacturer's recommendation is that the femoral cooling devices be left in place for no longer than 4 days-see Alsius IFU)

Some have suggested that subclinical thrombosis of the central venous system occurs in 20-30% of patients with indwelling catheters.(46) This is likely related to injury to the vessel endothelium from the catheter tip, thrombogenicity of the catheter itself, and length of time the catheter is left in the vein.(11) In addition, some venous insertion sites appear to be more prone to thombosis than others.

**Table 2: Reported Complications among Patients with Endovascular Cooling**

| Study | Disease | # of Subjects | Complications possibly related to catheters | Clinical or US Evidence of DVT |
|---|---|---|---|---|
| Feuchtl(17) | CA | 19 | Severe bradycardia req. pacemaker | NR |
| Sunde(52) | CA | 29 | Not Reported | NR |
| Flemming(18) | CA | 31 | Not Reported | NR |
| Al-Senani(4) | CA | 13 | Sepsis: possibly 2 cases; | No |
| Arrich(5) | CA | 347: EC 114: SC | Not Reported | No |
| Pichon(43) | CA | 40 | Traumatic false aneurysm: 1 Infectious complications - 18 (no severe sepsis or shock): nosocomial bacteremia=5; pneumonia=5; bronchitis=6; UTI=2 | No |
| Kandzari(30) | AMI | 18 | Not Reported | NR |
| Dixon(14) | AMI | 20 | Not Reported | NR |
| DeGeorgia(12) | Ischemic Strok | 18 | Retroperitoneal hemorr – 1 Positive blood culture – 1 UTI – 1 Pneumonia - 2 | 3/18 (US) |
| Georgiadis(20) | Ischemic Stroke | 6 | Hiccups and pneumonia – all | No |
| Guluma(22) | Ischemic Stroke | 10 | No hematomas; No clinically evident vascular injury | No |

**Table 3: Reported DVT among Patients with Alsius Femoral Cooling Catheter**

| Study | Disease | # of Subjects | Possible DVT |
|---|---|---|---|
| Flemming(18) | CA | 31 | No |
| Sunde (52) | CA | 29 | No |
| Arrich (5) | CA | 347 | No |
| Feuchtl (17) | CA | 19 | No |
| Kliegel (60) | CA | 9 | No |
| Holzer (27) | CA | 97 | No |
| Kliegel (32) | CA | 26 | No |
| Al-Senani (4) | CA | 13 | No |
| Sunde (62) | CA | 20 | No |
| Pichon (40) | CA | 40 | No |
| Hoedemaekers C(58) | CA & TBI | 10 | No |
| Grimes (56) | CA | 38 | No |
| Thomas (61) | Stroke | 10 | No |
| Georgiadis (20) | Stroke | 6 | No |
| Keller (40) | SAH | 90 | No |
| Keller (31) | SAH | 6 | No |
| McDonagh (35) | Hypoxia | 1 | No |
| Megarbane (36) | Heat Stroke | 1 | No |
| Simosa HF (50) | TBI | 10 | Yes in 5 patients (Doppler US) |
| Lasater (38) | Accidental hypothermia | 1 | No |

The reported incidence of catheter-related thrombosis depends on the detection method used, with clinical observation being the least sensitive, and direct ultrastructural examination of the catheter the most sensitive.(25) Duplex ultrasonography and phlebography are relatively sensitive techniques for the in vivo detection of clots, though the clinical significance of disease detected with these screening tools is unclear.

The most common insertion sites for central venous catheters are the subclavian, internal jugular, and femoral veins. In a study of 76 trauma patients who required unilateral femoral vein cannulation, and who had bilateral venous duplex sonography weekly for one month after cannulation, iliofemoral deep venous thrombosis was identified in 14% of the patients.(37) A study of 80 consecutive patients admitted to a mixed medical/surgical ICU found that the incidence of catheter related femoral vein thrombosis, as detected with phlebography, was 8.5%.(15) However, fibrin sleeves were observed in 15.7% of the cases. In another study of 124 mixed ICU patients who had femoral vein catheterization and were examined with duplex Doppler ultrasonography, 9.6% developed catheter related thromboses.(29) In that study, the incidence of thrombosis was not found to be related to duration of catheterization. Cumulatively, these studies suggest that the incidence of subclinical thrombosis with femoral central venous catheters is 8.5-26.2% in critical care patients with a wide variety of medical and surgical diseases.

To date there have been 21 peer-reviewed publications of the use of endovascular cooling catheters to treat patients with cardiac arrest, ischemic stroke, and several other diseases.(4-6, 12-14, 17, 18, 20, 22, 24, 30-32, 35, 36, 43, 45, 50-52) In patients who suffered cardiac arrest, acute myocardial infarction, ischemic stroke, 12 trials have been published. Six of those studies reported systematic evaluations for catheter related complications, and the incidence of such complications appears to be very low. (4, 12, 17, 20, 22, 43) (Table 2)

The DVT rate among all patients treated with the Icy catheter (Alsius Corporation) also has been examined. Among 20 publications or presentations, only one of the studies reported duplex ultrasound evidence of thrombus, and then only in patients who had the catheter in place for more than 4 days. (Table 3) When all of the published clinical data is critically examined, the relative risk of Doppler ultrasound detected DVT is 0.6% (5/804).

## Conclusions

IVTM is a new technology that, unlike surface cooling techniques, removes or transfers heat directly from the core thermal compartment. Compared with surface cooling methods, IVTM allows for a more efficient rate of cooling, tighter control at target temperature with the need for fewer nursing interventions, less shivering, and less thermal gradients between the peripheral and core compartment.

The benefits and risks for standard central venous catheters are well established. Lower extremity deep venous thrombosis is a known potential complication of a number of different acute medical and surgical diseases. Most critical care patients who would be candidates for therapeutic hypothermia will require central venous access to measure central venous pressure and deliver medications.

Multiple clinical studies have found that IVTM is associated with a less than 0.2% incidence of clinically significant thromboembolic disease. Among those with femoral catheters, the incidence of Alsius endovascular cooling catheter-related thrombosis is very low. There is some evidence that the risk may be higher in trauma patients who have the catheter in place for more than 4 days. When considering methods to induce therapeutic hypothermia, or prevent fever, IVTM has many advantages compared to conventional cooling methods in terms of cooling effectiveness, and the ability to quickly reach and maintain the target temperature.

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