

Potential Complications of Patient Cooling

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The increased use of therapeutic patient cooling has led to a heightened interest in the potential complications of this treatment. The selection of patient cooling methods requires careful attention to the risks associated with each method. This report touches on several key publications related to this topic [LRS Scientific Review, Dec. 2013].

Summary

The incidences of complications of therapeutic hypothermia vary with cooling methods. Weak cooling methods such as intravenous saline infusion and conventional cooling blankets can prolong exposure of patients to temperatures which cause shivering, a factor which increases metabolic demands. Ice packs introduce a risk of frostbite if used for longer than 20 minutes. Adhesive-based cooling pads and invasive cooling catheters are associated with significant risks of injuries. The LRS ThermoSuit System offers a unique combination of rapid patient cooling and a high level of safety.

Hypothermia

It is well known that hypothermia carries significant risks for certain patients. Accidental hypothermia resulting from exposure to extreme climactic conditions can be life-threatening if core temperature drops below 28.0°C (82.4°F)¹. Alternatively, surgical procedures can result in perioperative hypothermia, the potential complications of which include increased incidences of surgical wound infection, intraoperative blood loss, and cardiac arrhythmias, as well as altered drug uptake, shivering, and thermal discomfort².

Despite the potential risks of hypothermia, there has recently been a growing adoption of intentional “therapeutic hypothermia” to treat a number of critical medical conditions. The mechanisms which have been cited for therapeutic benefits both during and following prolonged ischemia include reduced oxygen demand and suppression of inflammatory and apoptotic mechanisms associated with reperfusion injury. Most notably, the latest patient care guidelines from the American Heart Association³, recommend therapeutic hypothermia as a treatment for patients who are comatose after resuscitation from cardiac arrest. The current guidelines, which are based primarily on clinical studies that were published in 2002^{4,5}, recommend cooling these patients to 32-34°C (89.6 - 93.2°F) for a period of 12 to 24 hours to improve the prospects of patient recovery to normal neurological status. As yet, the optimal rate, time of initiation, method, depth, and duration of cooling are not well

understood. New research is adding to the understanding of these variables, including the potential complications the various cooling methods. The following discussion reviews some of the data associated with the potential complications of patient cooling.

Shivering

Shivering is one of the body’s natural defenses against hypothermia. This physiologic response reduces the ability of the body to be cooled. Severe shivering nearly triples oxygen consumption in patients treated with therapeutic hypothermia, and the metabolic reduction of therapeutic hypothermia as compared to normothermia is only seen in patients who have no to mild shivering⁶. If patient cooling is provided and core body temperature falls below 35.5°C (95.9°F), the shivering response is typically activated, and this usually continues until a core temperature of 33.5°C (92.3°F) is reached⁷. When conventional cooling methods such as cooling blankets and pads are used, the patient will remain in the shivering zone for several hours, as cooling to target usually requires 3 to 4 hours or more⁸. In contrast, the ThermoSuit cooling method cools in approximately 37 minutes⁹ and the patient spends only a few minutes in the shivering zone. This difference is highlighted below.

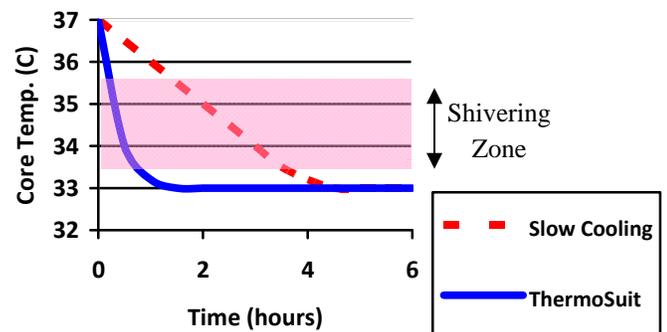


Figure 1: Impact of cooling rate on time spent in shivering zone. Note that slow cooling (as provided by cooling blankets and Medivance Arctic Sun) place the patient in this zone for hours, while the rapid ThermoSuit cooling approach reduces temperature below the shivering zone in minutes.

Many clinicians employ muscle relaxants to suppress shivering, but these carry their own potential complications^{10,11,12}. If the goal of cooling is to induce therapeutic hypothermia in a critically ill patient, a rapid cooling induction is desirable to minimize the amount of time spent in the shivering zone⁷. Prior research in the use of cold water immersion (as is used with the LRS ThermoSuit cooling device) has demonstrated that shivering is further suppressed if this cooling method is used with a water temperature of 2°C¹³.

Undercooling

The 2010 American Heart Association guidelines³ recommend cooling of indicated patients to 32 to 34°C for 12 to 24 hours. Not all cooling methods are able to reliably cool patients to this therapeutic range of temperature. In a recent study in which therapeutic hypothermia was initiated in 1,367 patients, target temperature was not achieved within 24 hours in 44.3% of patients¹⁴. This may have reflected the use of ineffective methods of cooling. Cool air has been observed to be unsuccessful in cooling patients to target temperature 20% of the time⁴. Intravenous cold saline infusions generally provide less than 1°C of cooling, and patients often rewarm themselves after being cooled by this method¹⁵. Some intravascular cooling catheters have been reported as being unable to maintain temperature below 34°C in 30% of patients¹⁶. The use of an underpowered cooling method not only fails to provide the therapeutic cooling, but places the patient at risk of an extended period of shivering.

A recently published clinical study¹⁷ compared the use of target temperatures of 33°C (91.4°F) and 36°C (96.9°F) and reported no significant differences in patients treated with the two target temperatures. On the surface, this might suggest that a higher target temperature than current guidelines might be acceptable. However, **the 33°C (91.4°F) target temperature in this study was not reached until 8 to 12 hours after resuscitation.** This is later than the treatment window which is targeted in the guidelines, and the results must be regarded with caution. Prior laboratory research has suggested that the therapeutic benefits of cooling are significantly diminished when the achievement of the 33°C temperature is delayed beyond four hours post-resuscitation^{18,19}.

Delayed Cooling

The importance of time to target temperature has been the subject of considerable study and discussion. Based on a review of data available as of early 2010, the American Heart Association recommended that hospitals initiate hypothermia as soon as feasible when indicated²⁰.

Several clinical studies have supported the premise that earlier achievement of target temperature is beneficial. A trend for a benefit of earlier cooling was reported for the use of nasal cooling²¹, and statistically significant benefits of earlier achievement of target temperature were reported with cooling catheters²² and surface cooling²³ methods. The use of the rapid ThermoSuit cooling method yielded clinical results which showed a trend for improvement in patients in whom target temperatures were achieved earlier⁹.

Some other analyses of clinical data have failed to demonstrate an advantage of earlier cooling to target temperature. One cooling method which has been used in an attempt to accelerate induction of hypothermia is the use of cold intravenous saline. This method potentially extends the period of stressful shivering, as noted above, and introduces additional venous loading which may unfavorably impact perfusion pressures²⁴. The largest randomized trials investigating this method in the pre-hospital setting showed a trend for worsened outcomes^{15,25}. Retrospective analyses of patient populations in which intravenous cold saline infusion was used in a high percentage of subjects have failed to demonstrate a benefit of earlier cooling^{26,27}.

The advantages of faster achievement of target temperature are most apparent when adjustments are made for patient comorbidities as part of the data analysis; patients who have suffered more severe cerebral injury tend to lose the ability to conserve their own body heat and are more easily cooled²⁸. Previous studies which have not made such adjustments have sometimes failed to demonstrate a benefit of faster achievement of target temperature^{29,30}.

Numerous laboratory studies have demonstrated benefits of fast, early cooling^{31,32,33,34,35,36,37,38}. Temperature dependent adverse biochemical reactions are inhibited by hypothermia. Early intervention clearly minimizes the time that these reactions have to accumulate adverse byproducts. While additional clinical studies investigating the relationship between cooling speed and outcomes would be helpful, studies conducted thus far support the hypothesis that the use of faster cooling methods is beneficial to patients. Likewise, these studies have shown no significant evidence that the use of faster cooling methods is harmful.

The choice of cooling method can have a significant impact on the time delay to achievement of target temperature, as highlighted in [Figure 2](#) below.

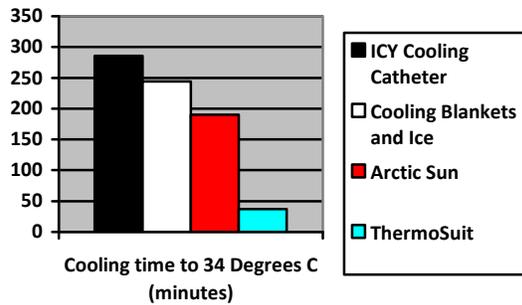


Figure 2. Patient cooling times to 34°C reported for induction of therapeutic hypothermia (from Refs. 8,9,41)

Conventional cooling blankets have been reported to cool to 34°C (93.2°F) in a median time of 244 minutes, and fail to cool patients to 34°C within 4 hours 50% of the time⁸. Gel-faced cooling pads (Medivance Arctic Sun) have been reported to cool to 34°C in a median time of 190 minutes, and fail to reach this goal within 4 hours 29% of the time⁸; the Arctic Sun gel pads sometimes require 8 hours or more to achieve target temperature³⁹. Cooling catheters are sometimes completely unable to cool patients to target temperature^{16,40}. A recent study of 36 patients treated with the Zoll ICY catheter in combination with cold saline infusion found that a mean cooling time of 286 minutes was needed to reach 34°C⁴¹. An earlier clinical registry reported that the use of cooling catheters delayed the initiation of patient cooling by 75 minutes compared to other cooling methods⁴². By comparison, the ThermoSuit cooling method achieved successful cooling induction to 34°C in a median time of 37 minutes and achieved target in 81 minutes or less in 100% of patients treated; median cooling time with the ThermoSuit was shortened to 27 minutes when propofol sedation was used⁹.

Overcooling

The existing AHA guidelines recommend that therapeutic hypothermia be provided in a temperature range of 32 to 34°C (89.6 to 93.2°F)³. This is largely based on the clinical studies which were published in 2002 and targeted this range^{4,5}.

The 32°C (89.6°F) lower limit is supported by a retrospective analysis of 32 patients⁴³. In this study, there was a trend (not statistically significant) for patients who were “overcooled” below 32°C to have worsened outcomes. In their discussion, the authors noted (p. S493), that “overcooling may serve as a marker of underlying postarrest neurologic and temperature control instability and be associated with worse outcomes as an epiphenomenon.” The tendency for increased neurological injury to impair

thermoregulatory response and to facilitate patient auto-cooling has been confirmed elsewhere^{28,44,45}.

The complications of hypothermia have been reviewed by numerous authors. “Mild hypothermia” (32-35°C or 89.6-95°F) is generally accepted as carrying few complications^{46,47}. Several studies have suggested that therapeutic cooling to temperatures slightly below 32°C could be safe, and may even have beneficial effects^{48,49,50,51,52}.

The safety of cooling somewhat below the 32°C level is supported by review of therapeutic hypothermia which noted that “A risk of clinically significant arrhythmias occurs only if core temperature decreases below 30°C” (86°F).⁷ Supporting this, recent clinical research has provided evidence that cooling patients to 32°C may be more beneficial than cooling them to only 34°C⁴¹. These authors noted (p. 6) that “With the results obtained, it is now probably justified to also explore the effect of achieving levels <32°C.”

All surface cooling methods have some potential to overcool patients, as has been reported for cooling blankets and the Medivance Arctic Sun device; overcooling by approximately 4°C (7.2°F) has been reported to occur with both of these methods⁸. The ThermoSuit System was studied in a three-hospital clinical investigation⁹ in which temperatures were allowed to drift after initial cooling induction, and temperature maintenance measures (such as cooling blankets or warm air) were generally not applied unless the patient deviated from the range of 32 to 34°C. Some overcooling was observed, but this did not adversely impact outcomes. The sole adverse event ever reported for the ThermoSuit System occurred in 2011, and that was overcooling as a result of a device malfunction. The root cause of the malfunction was traced to a circuit board malfunction, and a company-initiated recall was conducted to install improved circuit boards in 100% of the devices in commercial use. The satisfactory completion of this recall has been verified by the U.S. Food and Drug Administration⁵³. No other adverse events have been reported in the well over 1000 clinical uses of the ThermoSuit System.

Humans subjected to ice water immersion have been reported to continue to drop in temperature by an additional 0.56°C–1.8°C (1.0-3.2°F) after being removed from the water^{13,54}. The ThermoSuit System, which is the only available product which uses ice water immersion to cool patients, anticipates this “afterdrop” and a message on the display instructs the user to purge the water from the suit at 1.5°C (2.7°F) above the target temperature. The water is automatically purged if the temperature drops within 1°C (1.8°F) of the target. To assure an accurate assessment of core body temperature during rapid

cooling, the Instructions for Use of the ThermoSuit System specify the use of esophageal or nasopharyngeal temperature monitoring, as opposed to bladder or rectal temperature monitoring; this further reduces the probability of overcooling. As an additional measure to avoid overcooling, the Instructions for Use for the ThermoSuit recommend that the user immediately remove the patient from the device upon completion of the purge process, and place the patient on a conventional cooling/warming blanket to assure that the patient remains within the targeted range of temperatures. These measures have been successful in achieving clinically effective temperature management with the ThermoSuit System since the initial studies⁵⁵.

Skin Injuries

Critically ill patients are often susceptible to skin injuries as a result of prolonged exposure to adverse conditions. Pressure concentrations, prolonged exposure to moisture, excessively high or low temperatures, and shear stresses are all capable of precipitating skin injuries. They can prolong hospitalization and if severe can be disfiguring or even life-threatening. Treatment costs of skin injuries can be significant, and in some instances may not be covered by insurance.

Direct cutaneous application of ice in crushed or cubed form, or incorporated into specially designed pads or blankets, is a seemingly straightforward means to achieve cooling induction. However, some have reported frostbite resulting from the use of ice^{56,57}. Published guidelines on the application of ice for soft tissue injuries⁵⁸ provide the following recommendations:

- (1) The most effective duration of application is 20–30 minutes, with a ***maximum safe period of 30 minutes***.
- (2) A damp towel should be placed between the cooling agent and the skin.
- (3) Care should be taken with the application of ice (or cooling agent) on areas with little subcutaneous fat or muscle, and in the region of superficial nerves, with a maximum cooling period of 10 minutes.

The FDA MAUDE database shows that conventional cooling blankets^{59,60} and the Medivance Arctic Sun gel pads⁶¹ have also caused skin injuries. A study of the Medivance Arctic Sun reported that 6% of patients treated with the device experienced skin injuries which were likely to have been caused by the device³⁹. Reports of skin injuries caused by the Arctic Sun gel pads have been published by others, with injuries including skin peeling off upon pad removal⁶², full-

thickness skin necrosis with underlying myonecrosis⁶³, and bullous lesions suspected to have resulted from burn injuries⁶⁴.

The LRS ThermoSuit incorporates a low-shear non-irritating porous lining and underlying pneumatic cushion that create conditions which minimize the potential for skin injury. The circulating water which contacts the patients is above the freezing point, which eliminates the risk of frostbite. With an exposure time of approximately 37 minutes, there is little chance that the device can cause any skin injuries. Correspondingly, no skin injuries have been reported to have been caused by the ThermoSuit in the over 1000 clinical uses of the device thus far.

Complications of Cooling Catheters

These devices are currently marketed by Zoll and Philips. They cool the blood directly in the vena cava or other blood vessel, and carry the same types of complications as other central catheters (such as thrombosis, bleeding, infection). However, the incidences of some of these complications may be higher with these devices than with conventional central catheters, and there are potential complications that are specific to these devices.

A registry of 462 patients treated with therapeutic hypothermia reported clinical results following the use of cooling catheters and other cooling methods. This publication reported that the cooling catheters were associated with a higher incidence of arrhythmias than any other cooling methods (7.2% vs. 0.9%, $p=.01$)⁴². A more recent clinical study reported a 21% incidence (10 of 47 patients) of deep venous thrombosis or pulmonary embolism, and 6 of these 10 (60%) were found to have caval thrombus⁶⁵. Previous reports document instances of thrombophlebitis⁶⁶ and inferior vena cava thrombus⁶⁷ caused by cooling catheters. The FDA MAUDE database of device-related adverse events reports similar complications and others, including system leakage with release of fluid into the intravascular system, catheter separation and loss of catheter components within the body, and fatal retroperitoneal bleeding⁶⁸.

Conclusions

As therapeutic hypothermia grows in its use, there is an increasing need to understand its potential complications. Published data support the value of maximizing cooling speed and minimizing delay of cooling treatment. Some new clinical evidence suggests that slightly deeper cooling than current guidelines is not harmful and may be beneficial. The proper selection of patient cooling method is critical to assure the best combination of treatment safety and

effectiveness. The LRS ThermoSuit System provides an unmatched combination of cooling speed and safety that should make it a highly desirable method for clinical cooling induction. This rapid cooling induction method can be followed with a variety of available temperature maintenance and rewarming methods to achieve optimal targeted temperature management therapy.

FDA-Cleared Indications for the LRS ThermoSuit System:

a. Temperature reduction in patients where clinically indicated, e.g. in hyperthermic patients.

b. Monitoring of patient temperature.

Patient Population

The ThermoSuit System (Size M) is indicated for patients

• Greater than 58" (147 cm) and less than 75" (190 cm) in height

• And less than 26" (66 cm) in width

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