Protocol for the use of therapeutic hypothermia in the ICU department.
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K.H. Polderman, senior consultant in intensive care medicine, VU university medical center.

1. Introduction

Therapeutic hypothermia can be defined as the controlled reduction of body temperature with the aim of preventing (additional) damage to tissue and cells. Usually this concerns limitation of damage to brain cells; however, hypothermia is also used for the protection of the spinal cord and in patients with acute myocardial infarction, to reduce the size of the infarction. The goal of the treatment in all cases is to counteract injurious processes that occur on a cellular level after a period of ischemia or following trauma.

These injurious occur over a a period of a few minutes to several days following ischemia or trauma. The processes can be re-initiated by new ischemic insult or a period of increased intracranial pressure, even when they have already been suppressed or brought to a standstill (see below). An overview of these mechanisms can be found in Table 1

Table 1. Possible mechanisms underlying protective effects of hypothermia

Mechanism	**Explanation**	**Time frame after injury**
Prevention of apoptosis	Ischemia can induce apoptosis (i.e., programmed cell death. Hypothermia can prevent this.	Hours-many days or even weeks
Reduction in production of free radicals	Production of free radicals such as super oxide, peroxynitrite, hydrogen peroxide and hydroxyl radicals is a hallmark of ischemia. Moderate hypothermia is able to block this event.	Hours-days
Mitigation of reperfusion injury		Hours-days
Reduced permeability of the blood-brain barrier and the vascular wall; reduced edema formation	Blood-brain barrier disruptions induced by trauma or ischemia are moderated by hypothermia. The same effect occurs with vascular permeability and capillary leakage.	Hours-days
Reduced permeability of cellular membranes	Decreased leakage of cellular membranes with associated improvements in cell function and cellular homeostasis, including decrease of intracellular acidosis	Hours-days
Improved ion homeostasis	Ischemia induces accumulation of excitatory neurotransmitters such as glutamate and prolonged excessive influx of Ca^{2+} into the cell. This induces a state of permanent excitability “exitotoxic cascade” that can be moderated by hypothermia.	First minutes-72 hours
Reduction of metabolism	Reduced oxygen and glucose requirements	Hours-days
Reduction of pro-inflammatory reactions and depression of the immune response and inflammation.	Sustained destructive inflammatory reactions and secretion of pro-inflammatory cytokines following ischemia can be blocked or mitigated by hypothermia	1^{st} hour-5 days
Reduction in cerebral thermo-pooling.	There are areas in the brain with 2-3^{o}C higher temperatures than the surrounding areas and measured core temperature. These differences increase dramatically in injured brains. Hyperthermia can increase damage to injured brain cells; this is mitigated by hypothermia.	Minutes-many days

It is important to emphasize that **therapeutic hypothermia can, in principle, be applied to all forms of potential post-hypoxic neurological injury.**
In addition, on theoretical grounds it is plausible that the most favourable effects can be achieved in patients with relatively mild damage.

The amount of evidence supporting the various clinical applications varies considerably. This protocol discusses only those indications for which induced hypothermia is currently frequently used within the VUmc (VU university medical center). However, the same practical guidelines can be used if a decision is made to use hypothermia for other indications.

Therapeutic hypothermia after circulatory arrest and CPR
A number of studies have convincingly demonstrated that short-term use of induced hypothermia improves the neurological prognosis for certain categories of patients after cardiopulmonary resuscitation (CPR). Therefore, some patients admitted to the ICU with decreased consciousness following CPR will be cooled to 32-33^{o}C for a 24-hour period provided there are no vital contra-indications. Cooling should be initiated as quickly as possible, but even if some time (hours) has already been lost some effects can still be expected, and thus cooling should not be withheld unless more than 12 hours have passed.

The decision to use hypothermia is made by the ICU consultant on call for the ICU ward where the patient has been admitted.
After cooling patients must be re-warmed slowly. The usual method is passive re-warming. The reason for this is that rapid warming can worsen the prognosis. This means that most patients will reach temperatures of > 36 degrees only 12 -24 hours after active cooling has been stopped. In some situations treatment with hypothermia will be continued for longer periods of time.

Practical guideline resulting from these considerations: ***all patients admitted to the intensive care unit following circulatory arrest who do not obey commands, and in whom therefore there is a risk for post-anoxic injury, must be treated with induced hypothermia unless severe counter-indications are present in this patient. If a decision is made that a patient will not be treated with hypothermia, this decision and the underlying reasons must be noted in the patient chart. An expected favourable neurological recovery is not a valid reason to withhold treatment with hypothermia. Similarly, patients with an expected unfavourable prognosis including unwitnessed arrests should still be treated with hypothermia unless the prognosis is so unfavourable that the patient is not admitted to the ICU.***

Cooling should commence as quickly as possible (at best in the ambulance or immediately upon admission to the emergency room. The physicians from the ICU will assist in this treatment wherever it is initiated. Negotiations with the Department of Cardiology for a common protocol are ongoing. All patients in whom the circulatory arrest occurred ≤8 hours ago should definitely be treated with hypothermia under the conditions listed above.

Therapeutic Hypothermia after severe head injury.
In patients with severe head injury, hypothermia can be used as a method to reduce intra-cranial pressure. Whether neurological outcome is improved and mortality reduced

by hypothermia is currently still controversial, but the overall evidence suggests that this is the case if the treatment is applied carefully (with attention to side effects) and, most importantly, for a sufficiently long period of time (usually several days).

In these patients the use of hypothermia (both the depth and duration) will be guided by intracranial pressure (ICP) measurements. Hypothermia will be used when ICP rises in spite of adequate sedation and analgesia, administration of mannitol and/or hypertonic saline, and in spite of possible surgical interventions. These patients will be cooled to 32^{o}C, but if ICP normalises (i.e., decreases to $\leq$20mmHg) before this target temperature has been reached the temperature should not be reduced further. Re-warming will also be guided by intracranial pressure. If ICP rises during (passive) re-warming cooling will be re-initiated until ICP decreases to <20 mmHg.

The decision to use hypothermia is taken by the ICU consultant on call, together with the consultant neurosurgeon.

Practical guideline resulting from these considerations: ***induced hypothermia will be used in all patients with severe traumatic brain injury with refractory intra-cranial hypertension (ICP >20mmHg lasting ≥5 minutes in spite of appropriate sedation and analgesia, treatment with mannitol and/or hypertonic saline, and neurosurgical intervention when appropriate). Hypothermia will be induced to a level where the patients' ICP decreases below 20mmHg. This temperature is maintained for at least 24 hours; subsequently the patient can be slowly re-warmed up (maximum re-warming rate: 1,0 degrees per 12 hours). If the ICP rises to >20mmHg, cooling is re-initiated until ICP decreases below 20 mmHg.***

In patients who have undergone a decompressive craniotomy, brain swelling will only lead to a very limited increase in ICP. This implies that especially in these patients even small increases in ICP (for example, to 22mmHg) should be treated promptly and aggressively.

Patients with neurological injuries and fever
Experimental studies and clinical investigations have shown that the occurrence of fever (irrespective of the cause, both infectious and "central"/neurological) can have a severe negative impact on neurological outcome. The effects of treatment with paracetamol or similar agents are very limited, particularly if the cause of fever is non-infectious; in these patients it is usually very difficult to lower body temperature using drugs alone. This group of patients can also be treated with therapeutic hypothermia, with the understanding that these patients are usually cooled to a normal temperature (36^{o}C or 37^{o}C). The decision to use hypothermia is made by the senior ICU consultant on duty.

Therapeutic hypothermia in patients with subarachnoid haemorrhage
In the VU medical center hypothermia is also used to reduce intracranial pressure in patients with subarachnoid haemorrhage. In addition, there is some evidence that (prolonged) use of hypothermia reduces the risk of vascular spasms, and can mitigate or control the severity of vascular spasms that have already developed. The use of induced hypothermia for this purpose is still experimental, and it has not been proven that hypothermia also improves the prognosis of these patients. However, it is a highly effective method to reduce ICP. The decision to use hypothermia is made by the senior ICU consultant on duty.

Other purposes.
Hypothermia can also be used for other purposes. These will not be discussed at length here. **Application of hypothermia should be strongly considered in all patients with (possible) post-hypoxic injury, regardless of the cause.** Examples of such situations include drowning victims, patients with accidental hypothermia and possible ischemic injury, post-asphyxia, etc.
Patients with accidental hypothermia for whom there is a suspicion of possible neurological injury can be warmed to 32°C and held at this temperature for a duration of at least 24 hours.

2. Practical Guidelines.
Induction of hypothermia (cooling phase)
A number of possible cooling methods are listed in Table 2. In the VUmc multiple methods are used simultaneously in order to be able to reduce the body temperature as quickly as possible. This is necessary because the speed of cooling is of key importance to improve efficacy, and using only one of these methods is often not quick enough. Once the target temperature has been reached this temperature is maintained using surface cooling or special catheters.

Cold fluid infusion: this is generally used only in the induction phase of hypothermia, as an accessory cooling method for all patients treated with hypothermia. The infusion fluids are stored in a refrigerator located in the ICU (in both locations). The temperature of the infusion fluids is 4-6°C. Generally, saline 0.9% is used for cooling, although other types of fluid (Ringers Lactate or Geloplasma) can also be used for this purpose.
On average, 1500 to 2500 ml of fluids will have to be infused to reach the target temperature. This methods allows for direct cooling of the core compartment rather than indirect cooling via the surface/peripheral compartment.

Surface cooling: cooling can be achieved using rubber cooling blankets (Figures 1 and 2), special mattresses attached to the skin with a special adhesion layer (Figure 3) or using “wrapping garments” (figure 4).

The ***rubber cooling blankets*** are placed both above and below the patient during the cooling phase (figure 1), during which the temperature is continuously measured. These measurements are made centrally (via a central venous- or PA catheter) or via a probe placed in the rectum, oesophagus or bladder of the patient. Peripheral measurements of the temperature (axilla, groin, etc) are unreliable in hypothermic patients.

During the induction phase (i.e., the period during which the patients’ temperature is dropping) the temperature of the cooling blankets is set to 4°C. When using the feedback system (automatic mode) the target temperature is set at the lowest possible value (30°C for the new CSZ devices). The reason for this is that otherwise the cooling capacity of the device will not be optimally used. When the target temperature is set significantly below the actual temperature the water in the cooling blankets will be cooled to the lowest possible value (4°C) and will circulate at maximum speed so that heat transfer from the patient’s skin to the blanket is maximized.

When the temperature reaches a value within 1-1½ degree of the target temperature (for example, 33.0°C when the target temperature is 32°C) the device must be set at to the actual target temperature (Figure 3). In case of a patient temperature of 37°C and a

target temperature of 32^{0}C the target temperature of the cooling device is initially set at 30^{0}C; when the patient temperature reaches 33.5^{0}C this temperature is re-set to 32.0^{0}C.

As a consequence, because the target temperature is set at a low level and the patient is maximally cooled during this stage, it is of key importance to monitor the patient continuously during this stage. This implies that the patient must be continuously watched by a nurse or physician during this time.
NB: the rectal temperature lags behind the "actual" core temperature by about 10 –15 minutes. Therefore, the rectal temperature will continue dropping for 10-15 minutes even after the target temperature is reached. It is therefore important to adjust the target temperature on time, that is when the temperature is within 1-1½ degree of the target temperature. At all times the physician should be mindful of the possibility of dislocation of the temperature probe.

The Arctic Sun system consists of five ***rubber adhesive strips*** that are attached to the patient's skin (Figure 3). After attaching the cooling hoses to the connecting joints of the rubber strips the device is switched on, and the target temperature is set. When using the Arctic Sun the ***actual target temperature*** should be entered (not a lower value as is the case when using the re-usable rubber blankets). NB: to avoid errors the target temperature of the Arctic Sun cannot be set lower than 32^{o}C.
Here also, the temperature is measured either centrally or using a probe placed in the rectum, oesophagus or bladder of the patient. Similar caveats as outlined above apply.

The other methods (cooling catheters, wrapping blankets and special cooling beds) are not yet being used at this time. It is expected that trials with these methods will start in the first months of 2005 in the context of tests and clinical trials. The protocol will be updated at that time.

Finally, during the cooling phase all skin surfaces of the patient that are not covered by cooling blankets or strips should be exposed to the open air, and moistened as thoroughly as possible with water or alcohol to promote heat loss.

Using these methods, core temperature can usually be lowered to below 34 degrees within 40-90 minutes. The risk of side effects is greatest in this phase; therefore this phase requires very close monitoring and management.

In particular, the fluid balance (beware of hypothermia-induced diuresis) and the risk of electrolyte disorders (especially hypomagnesaemia) must be carefully monitored, and disorders pre-empted or corrected, during this phase. Upon the decision to initiate hypothermia treatment all patients should receive 3 grams of magnesium sulphate intravenously. Serum magnesium levels should be maintained at levels >1.0 mmol/l; even when serum levels of magnesium are normal intracellular deficiencies can occur, so that supplementation may be required in the presence of normal serum values.

Induction of hypothermia is a major intervention, which may have significant potential side effects. The physiological effects of hypothermia and the potential side effects are listed in tables 1 – 3.

Maintaining hypothermia (hypothermic phase)
Once the target temperature has been reached it can be maintained by using a single cooling blanket. The target temperature is set to the actual target temperature, for

example 32 or 33 degrees. In this phase the patient is usually much less “unstable” (in the sense of fluid requirements/hypovolemia, risk of electrolyte disorders, etc.). Extra attention by the nursing staff should now be paid to the avoidance of bed sores. Due to vasoconstriction in the skin, immobilization and immune suppression patients treated with hypothermia have an increased risk for developing bedsores. There is also an increased risk for airway infections. Potential physiological and patho-physiological changes are shown in tables 3 – 5. Nursing care considerations are listed in table 6.

It is also important to stress that the patient should not be “over-treated” because physiological changes are incorrectly interpreted. An example is the metabolic acidosis that can occur as a normal consequence of hypothermia.

Practical recommendations
Rubber cooling blankets (Cincinatti Sub Zero company): After the decision has been made that a patient will be treated with therapeutic hypothermia, the patient is placed on a cooling blanket, after which another blanket is placed on top of the patient. The patient is moistened to promote heat loss. No blankets or sheets should be placed to cover the patient. The target temperature is set at 4 degrees.

Cold fluid infusion is initiated; the infusion bags can be found in the refrigerator located in the case-bay in the ICU. In principle, 2000 ml are infused over a period of one hour. After infusion of each 500-ml phial the patients’ CVP is measured. If the CVP has risen the attending physician must should be consulted. (NB: hypothermia itself leads to an increase in CVP). When the patients’ core temperature has dropped below 33.5 degrees the target temperature is adjusted to 32 degrees.

Lab measurements: see Table 4. In particular, glucose and electrolytes should be checked frequently.
Sedation: only for shivering or agitation. In principle, propofol and fentanyl will be used for sedation. To counteract shivering a bolus of fentanyl should be given as initial treatment (0.5 cc = 0.05 mg, repeat 1 x as required). Alternative for propofol: midazolam. Also refer to sedation protocol. The target sedation (Ramsey) score is 5-6.

Paralyzing cooled patients is usually not necessary. Short-term paralysis can be considered in some cases, for example in severe shivering that does not respond administration of fentanyl bolus. NB: if cooling is accomplished rapidly shivering will also abate quickly; at temperatures < 35 degrees shivering usually diminishes significantly, and shivering will cease when temperatures drop below 33.5 and 34 degrees.
Patients treated with induced hypothermia are mechanically ventilated. Therefore, shivering is not dangerous unless the patient has severe oxygenation problems. Major interventions to control shivering are therefore usually unnecessary. However, shivering *can* make reaching the target temperature more difficult.

An overview of physiological changes and potential effects on laboratory parameters are shown in tables 2 – 4. Table 5 lists the most important considerations for the attending nursing and medical staff.

Table 2. Physiological effects of hypothermia
These effects will occur, in varying degrees, in most patients treated with hypothermia. The temperature limits at which these effects may occur are estimations, and can be influenced by age and co-morbidity (especially cardiovascular disease).

System	Temp	Effect
Physiological attempts to raise body temperature.	30-35°C	In conscious patients: heat production by shivering, peripheral vasoconstriction, increased muscle activity, increased oxygen demands, increased metabolic rate.
	≤30°C	'Hibernation': shivering ceases, lethargy ensues, reduction in metabolic rate.
Metabolism	30-35°C	↓ Oxygen use
		↓ CO_2 production
		↓ Metabolism
		↑ Fat metabolism: ⇒ ↑ Glycerol, free fatty acids, ketonic acids, lactate; metabolic acidosis
	≤35°C	↓ Insulin sensitivity, ↓ insulin secretion
Endocrine	≤35.5°C	↑ Adrenalin / noradrenalin levels
	≤33°C	↑ Cortisol levels
Cardiovascular	≤36->35°C	Tachycardia
	≤35°C	Bradycardia
	≤34°C	Mild elevation of blood pressure (average: 10 mmHg)
	≤32°C	Mild arrhythmia's in some patients
	≤33°C	EKG changes: increased PR-interval, widened QRS-complex, increased QT-interval.
	≤28-30°C	↑↑ Risk of tachyarrhythmia's, starting with atrial fibrillation.
	≤35°C	↑ CVP and ↓ CO
	≤35°C	↑ or = mixed venous saturation
Renal	≤35°C	↑ Diuresis, tubular dysfunction, electrolyte loss and electrolyte disorders.
Hematological	≤35°C	↓ Platelet count, reduced platelet aggregation, and various other disturbances in the coagulation cascade.
	≤33°C	↓ White Blood Cell count, reduced leucocyte function
Gastrointestinal	≤35°C	↓Reduced intestinal passage/subileus, mild pancreatitis (occurs very often!), ↑ liver enzymes
Immune suppression	≤35°C	Reduced granulocyte and macrophage function. Suppression of the production of various pro-inflammatory cytokines. ⇒increased risk of infection (pneumonia and wound infections)
Neurological	≤30-31°C	↓ Consciousness, lethargy, coma.
Pharmacokinetic	≤35°C	Changes in clearance of various drugs (data available for muscle paralyzers, propofol, fentanyl, fenytoïn, pentobarbital, verapamil, propanolol and volatile [inhalation] anaesthetics (reduced clearance), but this may apply to many other drugs). No effect on gentamycine clearance in animal study. No effect on neostigmine clearance in healthy volunteers.

Table 3. Commonly occurring changes in lab results due to induced hypothermia. The degree of change is related to the degree of hypothermia. Lower temperature affect lab values to a greater degree.

Incidence	Effect
Almost always	Mild to intermediate elevation of serum amylase level (300-600 u/l) Mild thrombocytopenia (platelet count 100-150 x 10^{12}) Increased serum lactate levels (2.5-5 mmol/l).
Often	Moderate to severe thrombocytopenia (platelet count 30-100 x 10^{12}) Rise in serum glucose levels (due to reductions in insulin sensitivity and diminished insulin secretion) High serum amylase levels (600-1200 u/l) High serum lactate levels (5-7 mmol/l). Decrease in levels of potassium (K), magnesium (Mg), phosphate (P) and calcium (Ca). Mild leucopenia (WBC count 2-3 x 10^9/L)
Occurring regularly	Mild elevation of liver enzymes (particularly SGOT and SGPT) Metabolic acidosis (due to increased lactate levels and increased production of glycerol, ketones and free fatty acids) Mild elevation of clotting times[1]
Intermittently occurring	Manifest metabolic acidosis, lactate level ≥7 mmol/l Severe leucopenia (<2 x 10^9) Elevation of serum amylase levels ≥1200 u/l Severe thrombocytopenia (platelet count ≤30 x 10^{12}) Gross coagulation disorders with significant increase in APTT and PTT

[1]Usually visible only if lab assessment is performed at the patient's actual body temperature, and not (as is the routine procedure) at 37°C.

Table 4. Potential side effects of hypothermia. These are effects that often frequently during cooling, and that are potentially injurious. Often these effects can be avoided or mitigated by appropriate treatments.

Frequency/ size of risk	Effect
High risk	Coagulopathy: increased clotting times, increased bleeding time, increased APTT/CT, thrombocytopenia, thrombocytopathia
	Other coagulation disorders
	Electrolyte disorders* (loss of K, Mg, P, Ca)
	Hypovolemia (through increased diuresis/hypothermia induced diuresis)
	Rise in serum amylase
	Changes in medication effects & metabolism
	Insulin resistance
Low risk	Clinically significant bleeding, serious coagulation disorders (risk may be higher in trauma patients and/or patients that already have bleeding problems from other causes. Hypothermia-induced coagulation disorders can exacerbate bleeding in some situations).
	Airway infections
	Wound infections, impaired wound healing
	Myocardial ischemia
Seldom	Manifest (clinically significant) pancreatitis
	Intra-cerebral bleeding

* Dependent on the category of patients; higher risk in patients with traumatic brain injury and subarachnoid haemorrhage, lower risk in patients with cardiac arrest/CPR.
** Risk significantly higher in patients with traumatic brain injury compared to post cardiac arrest/CPR.

Table 5. Considerations during application of induced hypothermia.

	Highest risks	Actions
Prior to/at commencement of cooling	Begin treatment with SDD & ceftriaxone; insert central line; extensive lab analysis (see below). Lab: At beginning of treatment: Hb/Ht, WBC, platelet count, lactate, SGOT, SGPT, γGT, AF, Bilirubin, Amylase, Na, K, Mg, P. Repeat after 6 hours. Assessment of electrolyte and glucose levels at 1-hourly intervals during induction phase.	
Cooling phase (duration: 30 minutes- a few hours)	Hypovolemia	Careful monitoring; at a minimum replace all fluid losses occurring through diuresis. Avoid hypovolaemia (especially in patients with TBI)
	Electrolyte disturbances	Give 3 grams of magnesium at onset of cooling. Check serum electrolyte levels at hourly intervals. target levels: K ≥4.0, Mg ≥1.0 and P ≥0.9 mmol/l
	Shivering	Opiates or pethidine; if necessary combine with propofol; give paralysers in exceptional cases. NB: shivering is not in itself dangerous for the patient, but may delay cooling and increase oxygen use. If the latter does not lead to hypoxia, this may be (briefly) accepted.
	Arrhythmia's	Check temperature, if <31^{o}C consider actively warming the patient. Check electrolytes and supplement as needed. Give 2 grams of magnesium (even at normal serum levels). If arrhythmia's persist initiate anti-arrhythmic treatment. (1st choice Amiodarone, beware of widening of QT interval and/or severe bradycardia resulting from the combination of amiodarone and hypothermia)
	↓ Oxygen use ↓ CO_2 production	Adjust ventilator settings guided by blood gasses. NB: blood gas analysis is temperature dependent: perform analysis using actual patient core temperature.
Hypothermic phase (duration: 12 hours – many days)	↓Insulin sensitivity ↓Insulin secretion	Insulin pump (high doses may be required!). Check glucose levels at least at hourly intervals.
	Tachycardia (initially) then Bradycardia	Usually no interventions required. For very severe bradycardia (heart rate <40) treatment with isoprenalin may be considered. Atropine is not effective in this situation
	Mild metabolic acidosis (pH 7.21-7.35)	No interventions required
	Elevation serum amylase (<800 u/l)	No interventions required
	Mild elevation liver enzymes (especially OT and PT)	No interventions required
	↓Platelet count	No interventions required unless there is active bleeding. For very severe thrombocytopenia (<30) consider platelet transfusion.
	↓WBC count	General measures & SDD, no specific interventions required.
	Reduced metabolism	Decrease amount of feed (at 32^{o}C required amount is 50-65% of amount required at 37^{o}C; i.e. usually 1000-1250 ml of nutrison standard per 24 hours; adjust to body weight,)
	Electrolyte disorders	See above
	Hyperglycaemia	See above
	Increased risk of airway infections	General care measures; SDD & ceftriaxone.
	Increased risk of bed sores	Frequent change of position, consider use of special beds or mattresses.
	Mildly increased risk of bleeding	No specific measures required
	Altered clearance of various drugs.	Consider dose adjustment (especially of fentalyl, propofol and benzodiazepines)
	Tachycardia Bradycardia	See above

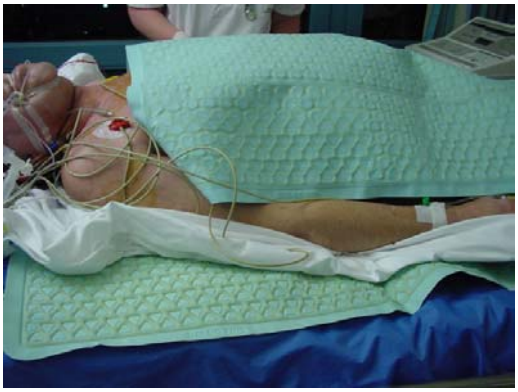
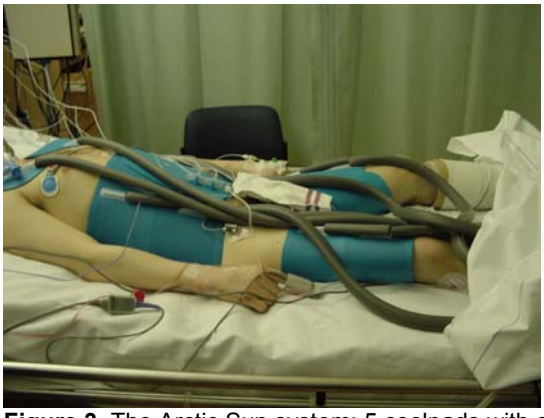


Figure 1. Induction of hypothermia, onset of cooling phase: cooling blankets are placed above and below the patient.

Figure 2. Target temperature (middle) is set at 4°C; temperature of the cooling blanket, left, falls quickly. The core temperature of the patient (right) is still 36.7 degrees.



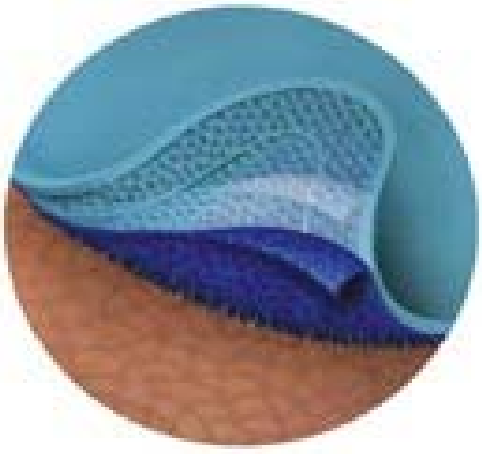


Figure 3. The Arctic Sun system: 5 coolpads with an “adhesive strip” are attached to the patient’s skin.

Figure 4. Wrapping blankets for cooling

Figure 5: Special “cooling beds”, using cooling mattresses and a cooling tent filled with cold air,