Rapid Surface Cooling by ThermoSuit System Dramatically Reduces Scar Size, Prevents Post-Infarction Adverse Left Ventricular Remodeling, and Improves Cardiac Function in Rats

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Background—The long-term effects of transient hypothermia by the non-invasive ThermoSuit apparatus on myocardial infarct (MI) scar size, left ventricular (LV) remodeling, and LV function were assessed in rat MI model.

Methods and Results—Rats were randomized to normothermic or hypothermic groups (n=14 in each group) and subjected to 30 minutes coronary artery occlusion and 6 weeks of reperfusion. For hypothermia therapy, rats were placed into the ThermoSuit apparatus at 2 minutes after the onset of coronary artery occlusion, were taken out of the apparatus when the core body temperature reached 32°C (in ≈8 minutes), and were then allowed to rewarm. After 6 weeks of recovery, rats treated with hypothermia demonstrated markedly reduced scar size (expressed as % of left ventricular area: hypothermia, 6.5±1.1%; normothermia, 19.4±1.7%; $P=1.3\times10^{-6}$); and thicker anterior LV wall (hypothermia, 1.57±0.09 mm; normothermia, 1.07±0.05 mm; $P=3.4\times10^{-5}$); decreased postmortem left ventricular volume (hypothermia, 0.45±0.04 mL; normothermia, 0.6±0.03 mL; $P=0.028$); and better LV fractional shortening by echocardiography (hypothermia, 37.2±2.8%; normothermia, 18.9±2.3%; $P=0.0002$) and LV ejection fraction by LV contrast ventriculography (hypothermia, 66.8±2.3%; normothermia, 56.0±2.0%; $P=0.0014$).

Conclusions—Rapid, transient non-invasive surface cooling with the ThermoSuit apparatus in the acute phase of MI decreased scar size by 66.5%, attenuated adverse post-infarct left ventricular dilation and remodeling, and improved cardiac function in the chronic phase of experimental MI. (***J Am Heart Assoc.*** 2015;4:e002265 doi: 10.1161/JAHA.115.002265)

Key Words: hypothermia • left ventricular remodeling • myocardial infarction

The ThermoSuit® System was developed by Life Recovery Systems (Kinnelon, NJ). This system is a noninvasive surface cooling device designed to induce rapid therapeutic hypothermia by continuously circulating ice water across the skin surface of a body at a rapid rate, which has been described previously in detail.[1] In a multi-center clinical trial, Howes et al[2] reported that conductive-immersion surface cooling using the ThermoSuit® System is a rapid, effective

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method for inducing therapeutic hypothermia in post–cardiac arrest patients. The median rate of cooling using the ThermoSuit® System was 3.0°C/h, which was faster than the reported cooling rate of other cooling methods. For example, Hoedemaekers et al[3] compared the cooling rate of 5 different cooling methods in intensive care unit patients, and reported that the rate of temperature decline was 1.33°C/h with water-circulating blankets, 1.04°C/h with gel-pads, 1.46°C/h with intravascular cooling, 0.31°C/h with conventional cooling, and 0.18°C/h with air-circulating blankets.

Our research group[1] previously reported that in the setting of acute myocardial infarction, the ThermoSuit device induced rapid hypothermia and limited infarct size and no reflow in both the rabbit and rat myocardial ischemia/reperfusion models. Both rabbits and rats were subjected to 30 minutes of left coronary artery occlusion followed by 3 hours of reperfusion. Hypothermia was initiated at 5 minutes after the onset of coronary artery occlusion to a target temperature of ≈32°C in rabbits, and at 2 minutes after the onset of coronary artery occlusion to a target temperature of ≈30°C in rats. Target temperature was reached in ≈20 minutes.

Compared with the normothermic group, hypothermia therapy reduced infarct size by 82% and the no-reflow zone by 89% in rabbits. Hypothermia caused a 73% reduction in infarct size and a 99% reduction in the no-reflow area in rats. However, in this pilot study, only 3 hours of reperfusion was allowed and animals did not reach baseline temperature at the end of the protocol. Therefore, the benefits that were observed in the early phase of myocardial infarction may not represent the long-term effects during the chronic phase of myocardial infarction. Therefore, in the present study, we evaluated the impact of rapid and transient therapeutic hypothermia administered during the acute phase of infarction on the long-term myocardial damage, post-infarction left ventricular remodeling, as well as cardiac function in rats.

Methods

All of the procedures outlined in this study were approved by the Institutional Animal Care and Use Committee of the Heart Institute at Good Samaritan Hospital, which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. This investigation was performed in accordance with the guidelines for the care and use of laboratory animals (NIH publication No. 85-23, National Academy Press, Washington DC, revised 2011).

Surgical Preparation of Myocardial Infarction

Female Sprague-Dawley rats (≈400 g) were weighed and anesthetized with intraperitoneal injection of a mixture of ketamine (75 mg/kg) and xylazine (5 mg/kg). The trachea of the anesthetized rats was intubated and ventilated under positive pressure with room air, using tidal volume of 1 mL per 100 g body weight at a rate of 60 cycles per minute. A thermocouple probe was inserted into the esophagus behind the heart to monitor the core body temperature. Under aseptic conditions the heart was exposed via a left thoracotomy through the 4th intercostal space after the chest wall was infiltrated with 0.1 mg/kg bupivacaine for local analgesia. After the pericardium was incised, the left coronary artery was encircled with a 4-0 silk suture. The ends of the suture were pulled through a small plastic snare, and clamped in order to induce coronary artery occlusion for 30 minutes. Appearance of cyanosis and akinesis of the left ventricular (LV) anterior free wall confirmed successful left coronary artery occlusion. Reperfusion was visually confirmed after the clamp was removed and ligature loosened and removed. The chest incision was then closed in layers. The rats were allowed to recover under postoperative care. Subcutaneous analgesic injection of Buprenex (0.001 mg/100 g body weight, twice per day) was administered for 2 days. All rats were housed for 6 weeks in a climate-controlled environment in which a 12-hour light–dark cycle was maintained, and were given water and standard rat chow ad libitum.

Experimental Groups and Surface Cooling

Rats were randomized to the normothermic group or hypothermic group. Esophageal temperature of the rats in the normothermic group was maintained at 37°C throughout the surgical procedure. In the hypothermic group, the baseline esophageal temperature was maintained at 37°C. At 2 minutes after coronary artery occlusion, the rats were placed into the ThermoSuit® device, and whole body surface cooling was initiated by circulating ice water in accordance with the product's instructions for use (Life Recovery Systems, Kinnelon, NJ), which was previously described in detail.[1] The rats were removed from the cooling device when the esophageal temperature reached 32°C. The esophageal temperature continued to drop to 27.5°C, then slowly warm up. Finally, the rats were re-warmed using heating pads, back towards normal body temperature.

Echocardiography

At 6 weeks after surgery, rats were anesthetized as described above. Rats were placed in a supine position and an echocardiography probe was placed in gentle contact with the chest. Transthoracic echocardiographic parameters were measured in each rat using a 15-MHz transducer and Sonos 5500 ultrasound system (Philips Medical System, Andover, MA). Parasternal short axis views of the LV cavity were collected at the level of the papillary muscle. M-mode echocardiography was performed. Based on M-mode images, left ventricular fractional shortening (LVFS, %), which was expressed as [(LV end-diastolic diameter−LV end-systolic diameter)/LV end-diastolic diameter] ×100%, was analyzed in 3 consecutive beats and averaged.

LV Contrast Ventriculography

After the completion of echocardiography, a catheter was inserted into left jugular vein and 1 mL nonionic contrast medium was injected into the circulation. LV contrast ventriculography was performed with a XiScan 1000 C-arm x-ray system (XiTec, Inc; 3-inch field of view). Video images of both anterior-posterior and lateral projections were acquired on half-inch super-VHS videotape at 30 frames per second under constant fluoroscopy. The end systolic and end diastolic LV volume was measured and calculated in a blinded manner. LV stroke volume and LV ejection fraction (LVEF, %), expressed as [(end diastolic LV volume−end systolic LV volume)/end diastolic LV volumes]×100%, was calculated over both anterior-posterior and lateral projections, and averaged over 3 consecutive cycles.

Hemodynamic Evaluation

Following the LV contrast ventriculography, a 2F high-fidelity, catheter-tipped micromanometer (model SPR-869, Millar, Inc) was inserted into the right carotid artery and advanced into the ascending aorta to record arterial blood pressure and heart rate. Then the catheter was further advanced into the LV cavity to record LV systolic pressure, LV end diastolic pressure, +dP/dt (LV positive change in pressure over time) and −dP/dt (LV negative change in pressure over time).

Post-Mortem LV Volume Measurements

Rat hearts were arrested in diastole by intravenous injection of 1 mL of potassium chloride (149 mg/mL) while the rats were under deep anesthesia. The hearts were excised and hung on a syringe filled with 13 cm high 10% formalin to keep the pressure constant for 1 hour. The pressure of 13 cm high column (equal to 9.6 mm Hg) was applied based on the end diastolic LV pressure of infarcted hearts in rats. After immersing the pressure-fixed hearts in 10% formalin for 24 hours, the post-mortem LV volumes were measured by filling the cavity with water and weighing. The LV volume was measured 3 times and averaged for each heart.

Histological Examination

Each formalin-fixed heart was sliced into 4 transverse sections and was embedded in paraffin. The paraffin-embedded tissue was sectioned in 5 μm thickness and stained with hematoxylin and eosin, as well as with Picrosirius red staining. The stained sections were digitally photographed and were analyzed using Image J software. The scar size, scar thickness (average of 5 equidistant measurements), and noninfarcted septal thickness (average of 3 equidistant measurements) were measured based on the stained sections.

Statistical Analysis

All reported data are expressed as means±SEM. Values between groups were compared by Student t test. Significant differences were established at the $P<0.05$ level.

Results

Esophageal Temperature During Surgical Procedure

Baseline body temperature was comparable in the hypothermic group (37.1±0.03°C) and the normothermic group (37.0±0.05°C). The detailed changes of body temperature during the surgical procedure in the hypothermic group is
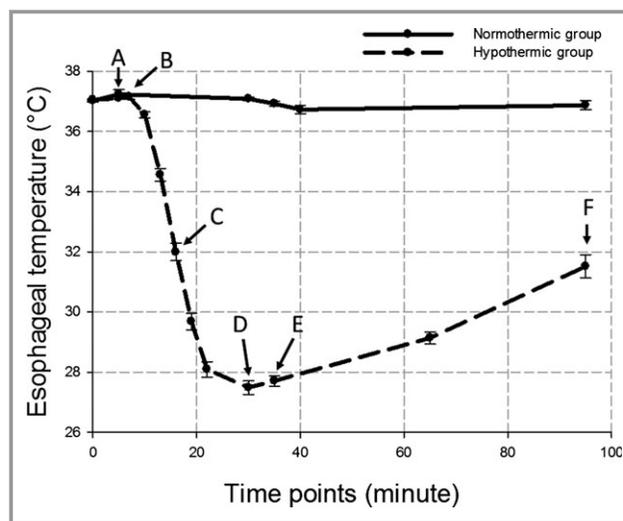

Figure 1. The esophageal temperatures at different time points during the surgical procedure. In the hypothermic group (dotted line), the coronary artery was occluded at time point A (37.1°C) and the rat was placed into circulating ice water 2 minutes later (point B). The body temperature rapidly dropped to 32°C in 8 minutes (at 10 minutes after start of coronary artery occlusion) and the rat was taken out of the circulating ice water in the ThermoSuit apparatus at point C. The body temperature continued dropped to the lowest 27.5°C (point D) at 5 minutes before reperfusion (point E), despite taking the rat out of the device at point C. The body temperature slowly rewarmed to 31.5°C at 1 hour after the reperfusion (point F). In the normothermic group (solid line), the body temperature remained 37°C during the surgical procedure. Data are expressed as mean±SEM (standard error bars).

shown in Figure 1. In the hypothermic group, body cooling to 32°C occurred by 8 minutes of ThermoSuit therapy, and the esophageal temperature dropped further to 27.5°C and then warmed up. The body temperature remained at ≈37.0°C during the surgical procedure in the normothermic group (Figure 1).

Cardiac Function Assessed by Echocardiography and LV Ventriculography

At 6 weeks after coronary artery occlusion/reperfusion, echocardiography demonstrated that left ventricular fractional shortening (LVFS) was significantly higher in the hypothermic group (37.2±2.8%) than in normothermic group (18.9±2.3%, $P=0.0002$; Figure 2). LV ventriculography showed significantly lower LV diastolic (0.46±0.02 mL) and systolic volume (0.15±0.01 mL) in the hypothermic group compared to the normothermic group (diastolic volume 0.52±0.02 mL, $P=0.039$; systolic volume 0.23±0.01 mL, $P=0.0006$). The stroke volume was comparable in the hypothermic group (0.31±0.01 mL) and the normothermic group (0.29±0.02 mL, $P=0.41$). LVEF was significantly greater in the hypothermic group (66.8±2.3%) compared to the normothermic group (56.0±2.0%, $P=0.0014$; Figure 2 and Table 1).
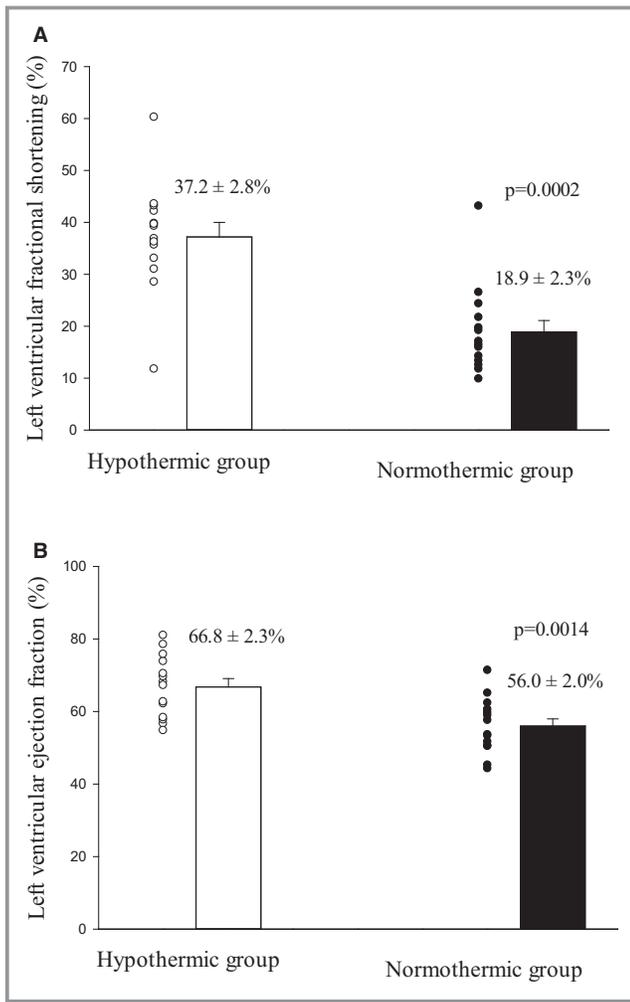
Figure 2. Cardiac function was assessed by echocardiographic analysis (A) and LV ventriculography (B) at 6 weeks after coronary artery occlusion/reperfusion. A, LVFS; (B) LVEF. Hypothermic therapy significantly improved left ventricular function at 6 weeks after treatment compared to normothermic group. Data are expressed as mean±SEM (standard error bars). LVEF indicates left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

Hemodynamics

There were no significant differences in heart rate, systolic and diastolic blood pressure between the 2 groups at 6 weeks after surgery. The LV positive/negative dP/dt, end systolic LV pressure, end diastolic LV pressure were comparable between the 2 groups (Table 1).

Post-Mortem LV Volumes

There was a significantly lower post-mortem LV volume in the hypothermic group (0.45±0.04 mL) compared with the normothermic group (0.60±0.03 mL, P=0.028), and it remained significantly lower when the LV volume was

Table 1. Cardiac Function and Hemodynamics

	Hypothermia (n=14)	Normothermia (n=14)	P Value
LVFS, %	37.2±2.8	18.9±2.3	0.0002
LV diastolic volume, mL	0.46±0.02	0.52±0.02	0.039
LV systolic volume, mL	0.15±0.01	0.23±0.01	0.0006
Stroke volume, mL	0.31±0.01	0.29±0.02	0.41
LVEF, %	66.8±2.3	56.0±2.0	0.0014
HR	204±7	207±6	0.69
Systolic BP	120±3	122±4	0.66
Diastolic BP	86±2	89±3	0.54
Mean BP	98±2	100±3	0.54
Pes	109±4	109±5	0.96
Ped	2.5±1.1	1.0±1.4	0.4
+dP/dt	6011±211	5620±284	0.28
−dP/dt	4461±192	4229±208	0.42

Data are expressed as mean±SEM. +dP/dt indicates LV positive change in pressure over time (mm Hg/s); −dP/dt, LV negative change in pressure over time (mm Hg/s); BP, blood pressure (mm Hg); HR: heart rate (beats/min); LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; Ped, end diastolic left ventricular pressure (mm Hg); Pes, end systolic left ventricular pressure (mm Hg).

standardized by LV weight (0.54±0.03 mL/g in hypothermic group versus 0.71±0.03 in normothermic group; P=0.009) (Table 2).

Histological Parameters

Scar size, expressed as percentage of LV area, was significantly smaller in the hypothermic group (6.5±1.1%) compared with the normothermic group (19.4±1.7%, P=1.3×10^{-6}). Infarcted wall thickness was greater in the hypothermic group (1.57±0.09 mm) compared with the normothermic group (1.07±0.05, P=3.4×10^{-5}; Figure 3). The LV septal thickness was comparable between the 2 groups (Table 2).

Table 2. Post-Mortem Left Ventricular (LV) Volume and Histological Parameters

	Hypothermia (n=14)	Normothermia (n=14)	P Value
LV volume, mL	0.45±0.04	0.60±0.03	0.028
LV weight, g	0.83±0.03	0.84±0.02	0.78
LV volume/LV weight, ml/g	0.54±0.03	0.71±0.03	0.009
Scar size (% of total LV)	6.5±1.1	19.4±1.7	1.3×10^{-6}
Infarcted wall thickness, mm	1.57±0.09	1.07±0.05	3.4×10^{-5}
Septum thickness, mm	1.58±0.07	1.64±0.06	0.47

Data are expressed as mean±SEM.
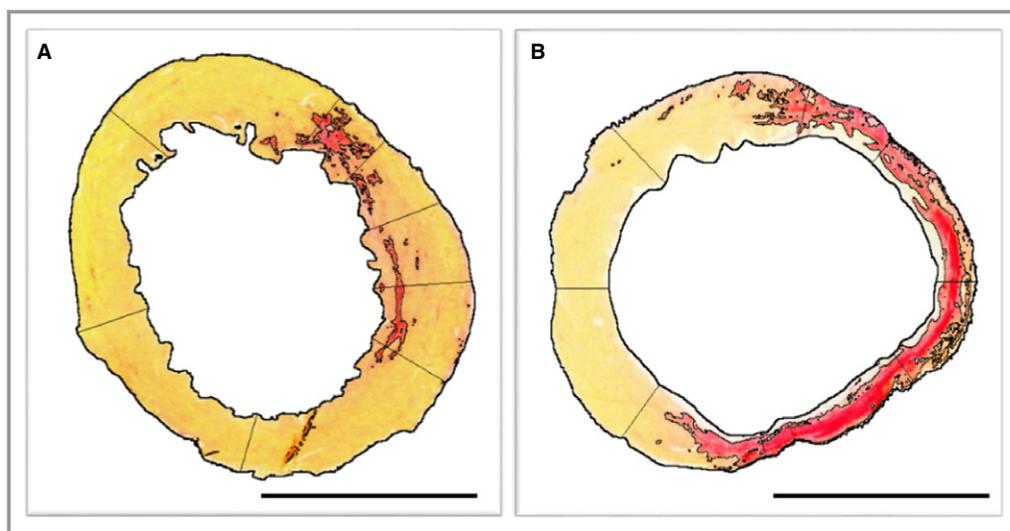
Figure 3. Representative pictures stained with picrosirius red staining demonstrated that muscle cells stain yellow while collagen (scar) stains red. A, Hypothermia-treated heart; (B) Normothermia-treated heart as control. Note that red stained collagen area was significantly smaller in the hypothermia-treated heart compared to the normothermic-treated heart, and the infarcted wall thickness was significantly thicker in the hypothermia-treated heart than in the normothermic-treated heart (Scale bar=5 mm). Scars are outlined for planimetric analysis.

Discussion

This study demonstrated that transient non-invasive surface cooling with the ThermoSuit apparatus during the early phase of an acute myocardial infarction significantly reduced scar size, prevented long-term adverse postinfarction LV remodeling, and improved long-term cardiac function in a chronic myocardial infarction model in the rat. These findings are consistent with our previous results obtained in the setting of acute rat myocardial infarction model,[1] suggesting that hypothermia therapy can effectively salvage jeopardized myocardium as an adjunct to reperfusion therapy. This study shows that only a brief window of hypothermia in the acute phase of myocardial infarction is necessary to result in long-term benefits of cardiac structure and function.

Therapeutic hypothermia has been a promising treatment for myocardial infarction. Hamamoto et al[4] subjected male sheep to 1 hour of ischemia followed by 3 hours of reperfusion, and maintained the body temperature at either 39.5°C, 38.5°C, 37.5°C, 36.5°C, or 35.5°C for the entire period of ischemia and reperfusion. The animal's temperature was managed by cooling/warming pads, ice bags, and a halogen warming light. Comparison of the acute myocardial infarct size at different temperatures demonstrated that myocardial response to ischemia/reperfusion insult is exquisitely sensitive to the temperature. For every 1°C reduction in temperature the infarct size was reduced by over 10%. In a chronic protocol, Hamamoto et al subjected sheep to 1 hour of ischemia followed by reperfusion, and maintained the body

temperature at either 39.5°C or 37.5°C for the entire period of ischemia and 3 hours of reperfusion, then allowed the temperature to passively normalize. At 8 weeks after infarction, echocardiography showed that subtle degrees of hypothermia can significantly improve long-term LV remodeling after infarct reperfusion. The limitations of this study are that the hypothermia was initiated prior to ischemia, and most importantly, the infarct size was not quantified directly in the chronic study. Our research group[1] also observed that rapid surface cooling limited infarct size and no reflow in rabbits and rats that were subjected to 30 minutes of left coronary artery occlusion followed by 3 hours of reperfusion. In the present study, we demonstrated that rapid surface cooling initiated after coronary artery occlusion and during the early phase of ischemia significantly reduced infarct size and LV diastolic volume in the rat myocardial infarction model, and provided direct experimental evidence to support the long-term cardioprotective effects of rapid surface cooling as an adjunctive therapy to coronary artery reperfusion. However, Figure 1 showed that the body temperature continued to drop to 27.5°C even after the surface cooling was stopped at 32°C. Further studies are needed to investigate whether the cardioprotective effects would be lost if the degree of temperature had been mild. Hypothermia has been classified as mild (32°C to 35°C), moderate (28°C to 32°C), severe (20°C to 28°C), or profound (<20°C) according to the core body temperature. Mild hypothermia is tolerated well by both animals and humans, which are awake and shivering. Patients will be drowsy and not shivering at moderate hypothermia. As

an adjunctive therapy of reperfusion, a 4°C to 10°C reduction in normal body temperature have been utilized in most laboratory and clinical studies.[5]

The time point of initiation of cooling during myocardial ischemia and subsequent reperfusion is most critical to myocardial salvage. Hale et al[6] subjected anesthetized rabbits to 30 minutes of coronary artery occlusion followed by 3 hours of reperfusion. Topical myocardial cooling with a bag of ice-cold saline was started at 10 or 25 minutes after coronary occlusion. Early cooling started at 10 minutes resulted in a significant reduction in infarct size; however, cooling just before reperfusion failed to modify infarct size. The results suggested that it is important for the reduction in temperature to be produced as early as possible following coronary artery occlusion to protect the ischemic myocardium. Kanemoto et al[5] subjected rabbits to 30 minutes of occlusion of the proximal segment of a large branch of the circumflex coronary artery followed by 3 hours of reperfusion, and initiated surface cooling with a water blanket at the time of coronary occlusion, 15 and 25 minutes after coronary occlusion, and at the time of reperfusion. In the normothermic group, animals were maintained at 39.5°C. All

animals in the hypothermic group were cooled to reduce left atrial temperature by 2.0°C to 2.5°C. Cooling significantly reduced the infarct size as a percentage of the risk area. Animals cooled earlier demonstrated the best therapeutic effect of hypothermia; cooling at the time of reperfusion had the smallest effect on infarct size. Our present study demonstrated a long-term cardioprotective effect of surface cooling that started when cooling was initiated during the early phase of ischemia. The long-term effects of cooling started at later time points during myocardial ischemia and subsequent reperfusion remain to be determined. The mechanism of hypothermia-induced cardioprotective effects is likely multifactorial, and might be associated with multiple pathologic pathways (Table 3), including slowing cardiac energy metabolism and preservation of adenosine triphosphate (ATP) and glycogen stores in myocardium,[7,8] preserving extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MEK) activity during ischemia,[9] limiting the microvascular injury associated with myocardial reperfusion injury,[10,11] the induction of heat shock proteins,[12] reduced apoptosis,[13] decreased complement activation, and a reduction in neutrophil degranulation.[14,15]

Table 3. Summary of the Therapeutic Effects of Hypothermia

Studies	Experimental Protocol	Hypothermic Effects
Simkhovich et al[7]	In vivo rabbit hearts with 20 minutes of coronary occlusion. Myocardial topical cooling by a bag of ice water at 15 minutes prior to coronary artery occlusion and maintained for the duration of the subsequent 20 minutes of ischemia	Adenosine triphosphate (ATP) and glycogen stores in the ischemic area were preserved
Ning et al[8]	Isolated perfused rabbit hearts were cooled from 37 to 31°C over 20 minutes. Subsequent ischemia during cardioplegic arrest at 34°C for 120 minute was followed by 15 minutes of reperfusion	Myocardial ATP was preserved during subsequent ischemia and reperfusion
Yang et al[9]	Isolated rabbit hearts with 30 minutes of coronary artery occlusion followed by 2 hour of reperfusion. Heart were cooled to 35°C just before and only during ischemia	The activity of extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MEK) were preserved during ischemia
Hale et al[10]	In vivo rabbit hearts with 30 minutes of coronary artery occlusion and 3 hours reperfusion. Myocardial topical cooling by a bag of ice water started 10 minutes before reperfusion and continuing for 2 hour of reperfusion. Myocardial temperature remained about 32°C during the cooling phase	Hypothermic therapy significantly improved myocardial reflow and reduced macroscopic zones of no-reflow and necrosis
Hamamoto et al[11]	In vivo sheep hearts subjected to 1 hour coronary occlusion and 3 hours of reperfusion. Body surface cooling started prior to coronary occlusion and remained to the end of the procedure	Small temperature changes dramatically preserved microvascular integrity
Qing et al[12]	Pig body temperature were reduced to 28°C from 37°C during standardized cardiopulmonary bypass	Moderate hypothermia involved upward regulation of heat shock protein 72 and inhibition of necrosis
Ning et al[13]	Isolated rabbit hearts were perfused and exposed to ischemic cardioplegic arrest for 2 hours at 34°C or at 30°C before and during ischemia	Hypothermia increased expression for the anti-apoptotic Bcl-2 homologue Bcl-x relative to l but decreased expression for the proapoptotic Bcl-2 homologue bak
Anttila et al[14]	Piglets were cooled to a body temperature of 15°C, 25°C, or 34°C during cardiopulmonary bypass	Higher bypass temperature correlated with significantly more adherent and rolling leukocytes, suggesting hypothermia influenced the inflammatory response
Chello et al[15]	Patients received coronary artery bypass grafting, underwent cardiopulmonary bypass with intermittent warm or cold blood cardioplegia	Cold blood cardioplegia significant decreased plasma concentration of C3a, C5a and C5b-9, and associated with a lower activity of neutrophils

Although experimental studies demonstrated that myocardial hypothermia as an adjunct to reperfusion therapy after the start of ischemia can effectively salvage jeopardized myocardium after acute coronary artery occlusion, cooling patients rapidly remains a challenge. Many different cooling methods include using intravascular or external methods have been developed in an effort to speed the cooling process and shorten the time to reach the target hypothermia temperature. The cooling methods include placing a bag of iced saline directly on the risk area of the heart during open-chest surgery; endovascular heat-exchange catheters; infusion of cold fluid into the vasculature, into the peritoneum, or into the intrapericardial space; total liquid ventilation; and noninvasive body surface cooling techniques (for review, see ref. 16). Unlike some cooling strategies that require complex or invasive equipment, or delays to reach the target body temperature because of slow cooling rates, the ThermoSuit system is portable, noninvasive, easy to use, effective and rapid in its induction of hypothermia, and is already Food and Drug Administration approved for the treatment of hyperthermia. This surface cooling device requires very little set-up time, and the patient could be cooled starting either at the home of the patient or in the ambulance en route to a catheterization laboratory. Convective-immersion cooling with ThermoSuit reduced temperature to therapeutic levels within ≈20 minutes when compared with several hours of cooling needed by equally noninvasive cooling blankets.[17] Howes et al[2] evaluated the feasibility and speed of convective-immersion cooling using the ThermoSuit device in post-cardiac arrest patients, and demonstrated that the Thermo-Suit system is a rapid and effective method of inducing therapeutic hypothermia in the clinical environment. Skin surface cooling using ice water produces mild cutaneous vasodilatation due to the "Lewis Reaction" or "hunting effect",[18–20] which enhances the rate of heat transfer through the skin and accelerates core cooling. The authors also found that use of propofol as a sedating agent prior to the hypothermic therapy could shorten cooling times further possibly due to its vasodilatory effect, and achieved goal body temperature (<34°C) in 27 minutes. Mokhtarani et al[21] reported that the combination of buspirone and meperidine can be used for patient tolerance to hypothermia and to limit shivering. Although the application of surface cooling with ThermoSuit System in patients is safe, rapid, and effective, its cardioprotective effects as adjunctive reperfusion therapy remains to be determined in clinical studies.

Mixed results have been reported in clinical trials using therapeutic hypothermia (for review associated key clinical trials, see ref. 16). There are some studies that showed benefit clinically when temperatures <35°C were achieved prior to reperfusion of anterior acute ST elevation myocardial infarction. The reasons for the unsuccessful cases may be due to slow cooling rates of some of the cooling methods, suggesting that more effective cooling strategies are needed. In a recent published prospective, multicenter, randomized, controlled pilot trial in patients ST-segment-elevation myocardial infarction within 6 hours of symptom onset, Nichol et al[22] reported that hypothermia was successfully initiated by an automated peritoneal lavage system in 96.3% of patients. The body temperature at first balloon inflation was 34.7°C and remained for 3 hours after percutaneous coronary intervention in the hypothermia groups. However, peritoneal hypothermia prolonged the median door-to-balloon times in the hypothermia groups (62 minutes) compared with the control groups (47 minutes, $P=0.007$), which may have negated any benefit of hypothermia. This invasive technique was associated with an increased rate of adverse events (including stent thrombosis) without reducing infarct size.

In summary, the present study showed that therapeutic hypothermia induced with the ThermoSuit apparatus improved myocardial salvage after reperfusion. Our results demonstrated that rapid, transient non-invasive surface cooling with the ThermoSuit apparatus during the acute phase of myocardial infarction decreased scar size, attenuated adverse post-infarct left ventricular dilation and remodeling, and improved cardiac function in the chronic phase of experimental rat myocardial infarction model. Whether this technique would reduce infarct size in the clinical setting remains to be determined. Note that the time course of cardiomyocyte death in the ischemic risk area are different between human and rat. There is a "wave front" phenomena in the human heart, and the necrosis from endomyocardium to epicardium takes several hours (it can be up to 6 or more hours depending upon the degree of collateral flow), while the necrosis finishes within nearly 30 minutes in the rat heart. So the time frame chosen in the rat would represent early therapy in a human: therapy starting before the patient entered the catheterization laboratory. In humans the Thermosuit could be started in the emergency room or even when the paramedics arrive at the patient's homes. Hence, starting therapeutic hypothermia shortly after occlusion in the rat is a reasonable starting point in a proof of principal study. Future studies should be done also looking at the effects of later application of hypothermia therapy for myocardial infarction.

Sources of Funding

Disclosures

None.

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