

Induction of Mild Systemic Hypothermia With Endovascular Cooling During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

Simon R. Dixon, MBChB, FRACP,* Robert J. Whitbourn, MBBS, FRACP,†
Michael W. Dae, MD, FACC,‡ Eberhard Grube, MD,§ Warren Sherman, MD, FACC,||
Gary L. Schaer, MD, FACC,¶ J. Stephen Jenkins, MD, FACC,# Donald S. Baim, MD, FACC,**
Raymond J. Gibbons, MD, FACC,†† Richard E. Kuntz, MD, FACC,** Jeffrey J. Popma, MD, FACC,**
Thanh T. Nguyen, DO,* William W. O'Neill, MD, FACC*

Royal Oak, Michigan; Melbourne, Australia; San Francisco, California; Siegburg, Germany; New York, New York; Chicago, Illinois; New Orleans, Louisiana; Boston, Massachusetts; and Rochester, Minnesota

| | |
|--------------------|---|
| OBJECTIVES | The purpose of this study was to evaluate the safety and feasibility of endovascular cooling during primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI). |
| BACKGROUND | In experimental models of AMI, mild systemic hypothermia has been shown to reduce metabolic demand and limit infarct size. |
| METHODS | In a multi-center study, 42 patients with AMI (<6 h from symptom onset) were randomized to primary PCI with or without endovascular cooling (target core temperature 33°C). Cooling was maintained for 3 h after reperfusion. Skin warming, oral buspirone, and intravenous meperidine were used to reduce the shivering threshold. The primary end point was major adverse cardiac events at 30 days. Infarct size at 30 days was measured using ^{99m} Tc-sestamibi SPECT imaging. |
| RESULTS | Endovascular cooling was performed successfully in 20 patients (95%). All achieved a core temperature below 34°C (mean target temperature 33.2 ± 0.9°C). The mean temperature at reperfusion was 34.7 ± 0.9°C. Cooling was well tolerated, with no hemodynamic instability or increase in arrhythmia. Nine patients experienced mild episodic shivering. Major adverse cardiac events occurred in 0% vs. 10% (p = NS) of treated versus control patients. The median infarct size was non-significantly smaller in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80). |
| CONCLUSIONS | Endovascular cooling can be performed safely as an adjunct to primary PCI for AMI. Further clinical trials are required to determine whether induction of mild systemic hypothermia with endovascular cooling will limit infarct size in patients undergoing reperfusion therapy. (J Am Coll Cardiol 2002;40:1928-34) © 2002 by the American College of Cardiology Foundation |

Early and sustained reperfusion remains the only proven method of salvaging jeopardized myocardium following acute coronary artery occlusion (1-3). Yet, in spite of contemporary therapies, many patients develop complications, such as congestive heart failure and death, attributable to extensive myocardial damage. Because infarct size is one of the most important predictors of early and late survival after acute myocardial infarction (AMI), there is a clear

need for novel approaches to improve myocyte protection during reperfusion therapy (4-6).

Experimental data suggest that myocardial temperature is an important determinant of the extent of tissue necrosis during AMI (7,8). Several studies have demonstrated that lowering myocardial temperature even a few degrees reduces metabolic demand and may cause a profound reduction in infarct size, even when hypothermia is initiated after coronary occlusion (7-14). The purpose of this study was to evaluate the safety and feasibility of inducing mild systemic hypothermia in patients with AMI undergoing primary percutaneous coronary intervention (PCI), employing a novel endovascular heat-exchange system.

METHODS

Study population and design. From February to July 2001, 42 patients with acute anterior or inferior myocardial infarction were randomized to primary PCI with or without endovascular cooling. Patients were enrolled at seven centers

From *William Beaumont Hospital, Royal Oak, Michigan; †St. Vincent's Hospital, Melbourne, Australia; ‡University of California San Francisco, San Francisco, California; §Heart Center Siegburg, Siegburg, Germany; ||Beth Israel Medical Center, New York, New York; ¶Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; #Alton-Oschner Medical Center, New Orleans, Louisiana; **Brigham and Women's Hospital, Boston, Massachusetts; and the ††Mayo Clinic, Rochester, Minnesota. This study was supported in part by a grant from Radiant Medical, Inc., Redwood City, California. Presented in part at the 74th Annual Scientific Session of the American Heart Association, Anaheim, California, November 2001.

Manuscript received April 2, 2002; revised manuscript received June 12, 2002, accepted July 18, 2002.

Abbreviations and Acronyms

- AMI = acute myocardial infarction
- MACE = major adverse cardiac events
- PCI = percutaneous coronary intervention
- TIMI = Thrombolysis In Myocardial Infarction

in the U.S., Australia, and Germany. All patients presented within 6 h from symptom onset and had chest pain >30 min duration with ST-segment elevation ≥ 1 mm in two contiguous leads. Patients with inferior AMI were required to have ≥ 1 mm reciprocal ST-segment depression in two precordial leads. Exclusion criteria were cardiogenic shock, rescue angioplasty, previous AMI <1 month, Raynaud's disease, hypersensitivity to buspirone or meperidine, treatment with a monoamine oxidase inhibitor in the previous 14 days, bleeding diathesis or coagulopathy, severe hepatic or renal impairment, pregnancy, patient height <1.5 m, or the presence of an inferior vena cava filter. The institutional review board at each center approved the protocol, and all patients provided written informed consent. Clinical follow-up was obtained at one month.

Endovascular cooling. Endovascular cooling was initiated either in the emergency room or in the cardiac catheterization laboratory before primary PCI using the SetPoint

Endovascular Temperature Management System (Radiant Medical Inc., Redwood City, California). This consists of a proprietary triple-lobed, helically wound, heat-exchange balloon catheter that is placed in the inferior vena cava via the femoral vein, and a microprocessor-driven controller that precisely alters core temperature. The catheter with the unexpanded balloon has a 9.2F diameter and is inserted through a 10F femoral introducer sheath until the distal tip of the catheter is positioned at the level of the diaphragm. The catheter is connected via insulated lines to a peripheral cassette consisting of a pump that circulates the saline and a thin walled heat-exchange bag that lies on a thermal transfer plate. This cools or warms the saline circulating through the cassette and catheter without administration of fluids to the patient (Fig. 1).

The target core body temperature was 33°C (monitored with a naso-esophageal probe). Cooling was maintained for 3 h after reperfusion; re-warming was then performed over a 1 to 2 h period to 36.5°C. Shivering was suppressed using skin warming with a forced air blanket (Bair Hugger, Augustine Medical, Eden Prairie, Minnesota), oral buspirone (30 to 60 mg), and intravenous meperidine (75 to 100 mg loading dose over 15 min, followed by an intravenous meperidine infusion at 25 to 35 mg/h) (15).

Coronary intervention. Cardiac catheterization was performed using conventional techniques and equipment. All

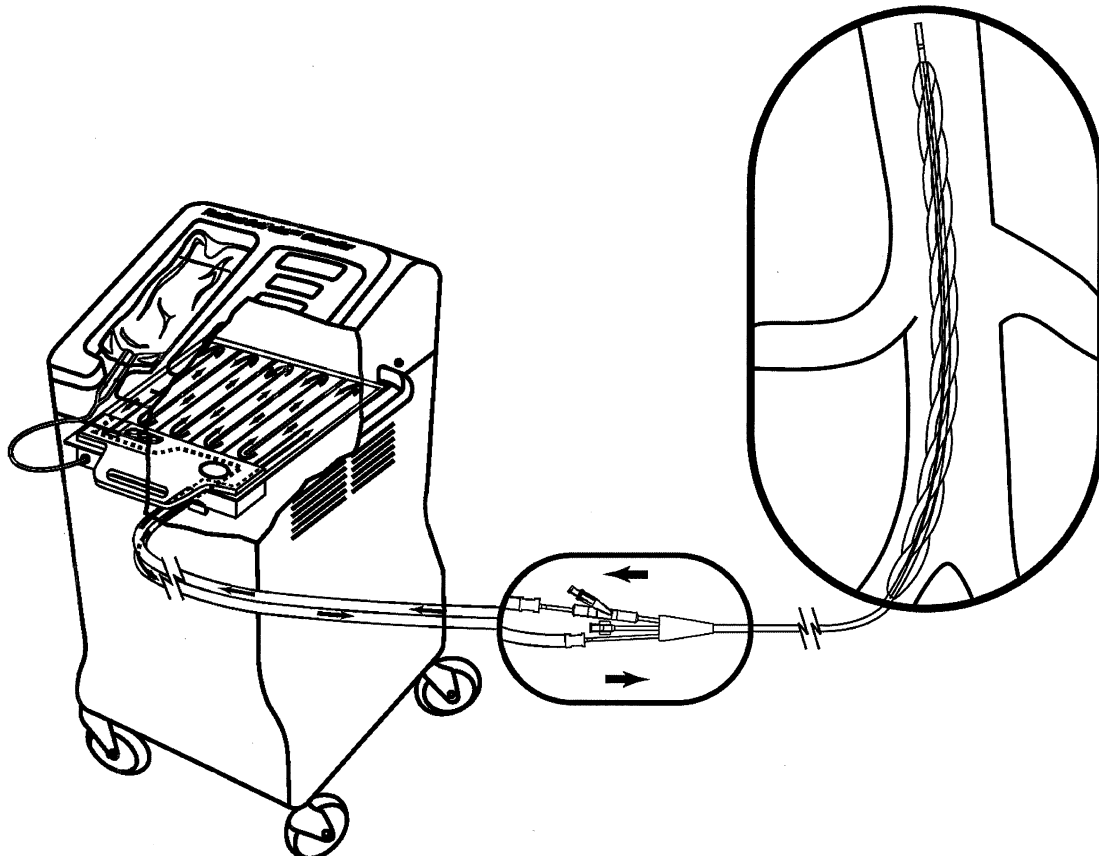


Figure 1. Diagram of the endovascular cooling system.

Table 1. Clinical and Angiographic Data

| | Cooling (n = 21) | Control (n = 21) |
|---|---------------------|---------------------|
| Age (mean ± SD; range) | 52 ± 9 (39-73) | 58 ± 14 (32-83) |
| Women | 2 (10%) | 5 (24%)† |
| Hypertension | 5 (24%) | 12 (57%)* |
| Diabetes | 4 (19%) | 6 (29%) |
| Hyperlipidemia | 9 (43%) | 5 (24%) |
| Current smoker | 14 (67%) | 11 (52%) |
| Previous MI | 3 (14%) | 1 (5%)† |
| Previous PCI | 1 (5%) | 0 (0)† |
| Previous CABG | 1 (5%) | 0 (0)† |
| Infarct location | | |
| Anterior | 9 (40%) | 10 (48%) |
| Inferior | 12 (60%) | 11 (52%) |
| Symptom-onset to hospital arrival (min) | 118 ± 84 | 100 ± 62 |
| Door-to-balloon (min) | 87 ± 30 | 104 ± 44 |
| PCI performed | 20 (95%) | 21 (100%) |
| Peak creatine kinase | 1905 ± 1820 | 2030 ± 1726 |
| Infarct related artery | | |
| Left anterior descending artery | 7 (34%) | 10 (48%) |
| Right coronary artery | 11 (52%) | 10 (48%) |
| Circumflex artery | 3 (14%) | 1 (5%) |
| Initial TIMI flow grade‡ | | |
| 0/1 | 16 (76%) | 14 (67%) |
| 2 | 0 (0) | 3 (14%) |
| 3 | 5 (24%) | 4 (19%) |
| Stent | 15 (71%) | 16 (76%) |
| AngioJet thrombectomy | 3 (14%) | 4 (19%)† |
| Glycoprotein IIb/IIIa inhibitor | 15 (71%) | 18 (86%) |
| TIMI flow grade post PCI‡ | | |
| 0/1 | 1 (5%) | 0 (0) |
| 2 | 1 (5%) | 2 (10%) |
| 3 | 19 (90%) | 19 (90%) |

*p = 0.03. All other comparisons non-significant. †Fisher two-sided exact test used. ‡Core lab assessed.

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

patients received aspirin 325 mg before catheterization, and heparin was administered during the procedure to maintain the activated clotting time >250 s. Coronary stenting, adjunctive thrombectomy, and use of glycoprotein receptor inhibitors were permitted at the operator's discretion.

Radionuclide imaging. Final infarct size was measured 30 days after primary PCI using ^{99m}Tc-sestamibi SPECT imaging. Radionuclide images were obtained using single- or multi-head gamma camera systems with images acquired in a 64 × 64 matrix. All images were analyzed for final infarct size by the Mayo Clinic Nuclear Core laboratory, which was blinded to treatment assignment (16). Using a previously reported method, the analysis pre-specified that patients who died before final infarct size determination were assigned values equal to the largest infarct size measured in survivors according to infarct location; those lost to follow-up were assigned values equal to the median infarct size in the group (17).

Study end points and definitions. The primary end point of the study was the presence of major adverse cardiac events (MACE) at 30 days. The secondary end point was infarct size at 30 days, measured using ^{99m}Tc-sestamibi SPECT imaging. Safety was also assessed through hemodynamic

and electrocardiographic monitoring as well as review of any vascular or bleeding complications. MACE was defined as death, non-fatal re-infarction, and ischemia-driven target vessel revascularization. Re-infarction was defined as the recurrence of clinical symptoms or new electrocardiographic changes accompanied by a rise in creatine kinase-MB levels.

Data analysis. Statistical analysis was performed using SAS software (Version 6.18, Cary, North California). Categorical variables were examined using a Pearson chi-squared test in all cases, except as noted when a Fisher two-sided exact test was used. Continuous variables were examined using a Student *t* test. Final infarct size in each group was compared using a Wilcoxon rank test. A p value of <0.05 was considered statistically significant.

RESULTS

Clinical and angiographic data. Twenty-one patients were randomized to primary PCI with endovascular cooling. Clinical and angiographic characteristics are shown in Table 1. Patients in the control group were more likely to have hypertension (57% vs. 24%, p = 0.03). Primary PCI was performed in 41 patients (98%); one patient was

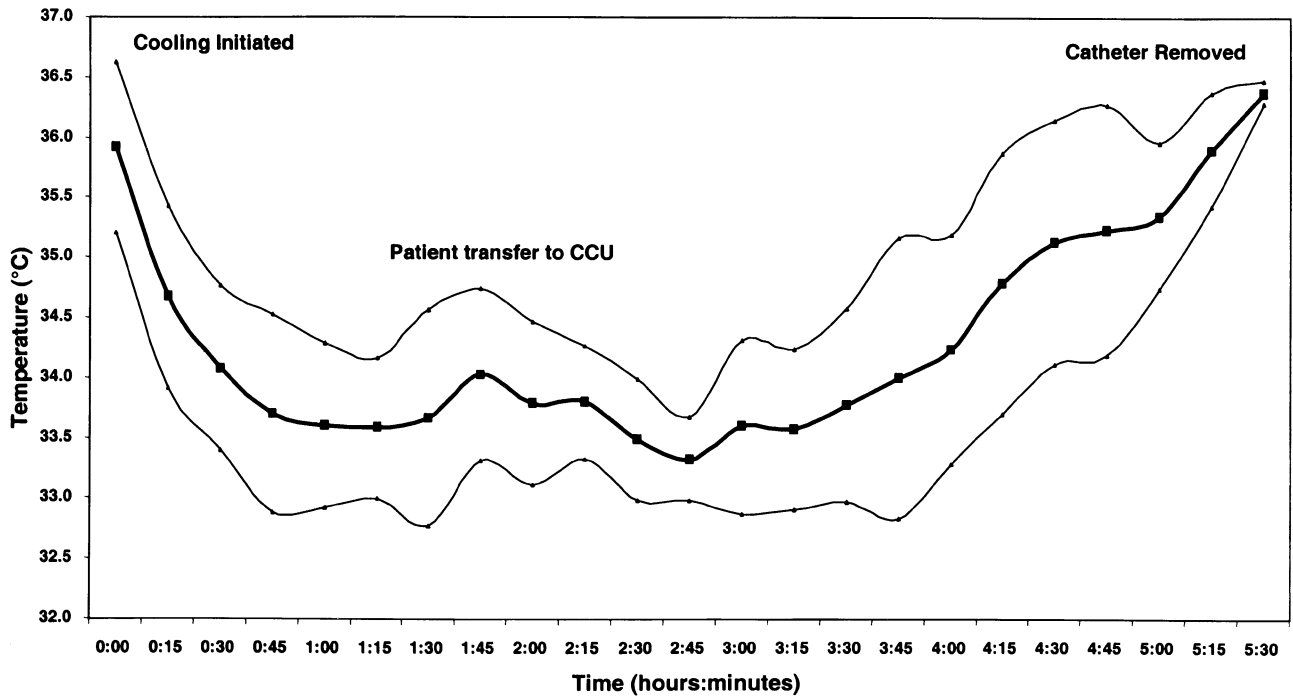


Figure 2. Mean core body temperature in patients treated with endovascular cooling (mean \pm SD shown). CCU = coronary care unit.

managed conservatively and later underwent repeat coronary artery bypass graft surgery. Stenting was performed in 31 patients (74%); seven (17%) required adjunctive thrombectomy. Most patients received a glycoprotein receptor inhibitor. A high rate of final Thrombolysis In Myocardial Infarction (TIMI) grade flow-3 flow was achieved in both groups.

Endovascular cooling. Baseline core temperature was similar in each group (cooling $36.0 \pm 0.7^\circ\text{C}$ vs. control $35.7 \pm 1.2^\circ\text{C}$, $p = 0.58$). Endovascular cooling was performed successfully in 20 patients (95%); all achieved a core temperature below 34°C (mean temperature during cooling $33.2 \pm 0.9^\circ\text{C}$) (Fig. 2). One patient was not cooled, because of technical problems. The mean core temperature at first balloon inflation was $34.7 \pm 0.9^\circ\text{C}$, and the mean duration of cooling was 241 ± 29 min. Re-warming was performed over 65 ± 26 min (mean target $36.6 \pm 0.3^\circ\text{C}$). Nine patients experienced mild episodic shivering during cooling. Four of these were managed successfully with additional meperidine and surface warming; five patients required a small increase in target core temperature to between 33.5°C and 34.2°C . The mean doses of meperidine and buspirone

administered were 177 ± 71 mg and 51 ± 17 mg, respectively.

Clinical events. Endovascular cooling was well tolerated. No hemodynamic instability was observed during cooling (Table 2). Three patients in the cooling group and six in the control group had a ventricular arrhythmia requiring DC cardioversion; all patients in the cooling group were defibrillated without difficulty. At 30 days, MACE was observed in 0% versus 10%, respectively, of treated and control patients ($p = \text{NS}$) (Table 3).

Infarct size. Thirty-six patients (86%) had final infarct size analyzed at 30 days (excluded patients had technical problems with the image [2], technical problems where cooling was not provided per protocol [2], no primary PCI performed [1], or unstable angina [1]). The median infarct size in the cooling and control groups was 2% (90th percentile 19.0%) and 8% (90th percentile 44%) of the left ventricle, respectively (Wilcoxon rank, $p = 0.80$) (Fig. 3). Patients with an occluded infarct artery at initial angiography (TIMI grade flow 0 or 1 flow) had a larger median infarct size than those with a patent infarct artery (8.5% vs. 0% of the left ventricle, $p = 0.047$).

Table 2. Hemodynamic Parameters and Respiratory Rate in Cooling and Control Groups

| | Baseline | | 1 h | | 2 h | | 3 h | |
|-----|------------------|------------------------|------------------|------------------|------------------|------------------|------------------|--------------------|
| | Cooling | Control | Cooling | Control | Cooling | Control | Cooling | Control |
| SBP | 133.5 ± 25.9 | 121.5 ± 26.4 | 129.6 ± 26.5 | 124.6 ± 27.4 | 124.9 ± 17.8 | 119.3 ± 20.2 | 129.8 ± 24.3 | $122.7 \pm 26.5^*$ |
| DBP | 78.8 ± 16.0 | 70.1 ± 17.2 | 74.4 ± 21.7 | 73.6 ± 20.6 | 76.3 ± 15.7 | 68.3 ± 15.9 | 81.7 ± 18.0 | $70.6 \pm 18.0^*$ |
| HR | 71.4 ± 14.2 | 70.1 ± 17.2 | 75.9 ± 12.7 | 80.3 ± 16.5 | 71.2 ± 21.6 | 75.7 ± 14.7 | 70.5 ± 20.1 | $73.3 \pm 20.0^*$ |
| RR | 17.2 ± 2.5 | $20.4 \pm 4.5^\dagger$ | 16.1 ± 3.2 | 15.6 ± 3.1 | 15.8 ± 3.4 | 17.1 ± 4.4 | 16.4 ± 2.7 | $16.4 \pm 4.6^*$ |

* $p = \text{NS}$ for trend (repeated measures analysis of variance). $^\dagger p = 0.03$ for cooling vs. control. All other comparisons for cooling vs. control nonsignificant. DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min); RR = respiratory rate (breaths/min); SBP = systolic blood pressure (mm Hg).

Table 3. Clinical Events During In-Hospital Period

| | Cooling (n = 21) | Control (n = 21) |
|-------------------|---------------------|---------------------|
| Death | 0 | 2 (10%) |
| Re-infarction | 0 | 0 |
| Repeat PCI | 0 | 2 (10%)* |
| CABG | 1 (5%)† | 0 |
| MACE | 0 | 2 (10%) |
| Stroke/TIA | 0 | 0 |
| Cardiogenic shock | 0 | 2 (10%) |
| Pulmonary edema | 1 (5%) | 0 |
| VT/VF‡ | 3 (14%) | 6 (29%) |
| Bradycardia§ | 3 (14%) | 4 (19%) |
| Transfusion | 1 (5%) | 0 |
| Hematoma > 6 cm | 1 (5%) | 0 |

*Nontarget vessel; †elective reoperation; ‡requiring defibrillation; §requiring insertion of temporary venous pacemaker. p = NS for all comparisons of cooling vs. control (Fisher two-sided exact test used).

CABG = coronary artery bypass grafting; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; VT/VF = ventricular tachycardia or fibrillation

DISCUSSION

Cooling is used widely during cardio-pulmonary bypass surgery, organ transplantation, and some neurosurgical procedures in order to limit ischemic cellular injury. Although the focus of clinical research on therapeutic hypothermia has been as a neuroprotective strategy, there appears to be an equally sound rationale for the use of cooling to protect ischemic myocardium.

Experimental studies have demonstrated an important relationship between myocardial temperature and the extent of tissue necrosis after coronary occlusion (7,8). Chien et al. (7) found that infarct size changed by about 10% for each 1°C change in myocardial temperature. More recently, Dae et al. (14) investigated the effect of mild hypothermia on

infarct size in human-sized pigs by using endovascular cooling. Infarct size was significantly reduced in the group treated with hypothermia (9% ± 6% vs. 45% ± 8%, p < 0.0001). Moreover, the viability results obtained by triphenyltetrazolium chloride staining were confirmed by sestamibi autoradiography, thus suggesting that cooling exerts a protective effect for both myocytes and the microcirculation.

The beneficial effect of mild hypothermia appears to be independent of hypothermia-induced bradycardia, as the effect persists when heart rate is maintained with pacing (7,10). One possible explanation is that hypothermia reduces metabolic demand in the myocardium at risk. In both dogs and isolated perfused rabbit hearts, hypothermia has been shown to preserve myocardial adenosine triphosphate stores during ischemia (18,19), which may facilitate the maintenance of cell membrane integrity. However, it is likely that the effects of hypothermia are far more complex, and further studies are needed to determine whether myocardial cooling influences other cellular and biochemical processes that may lead to cell death.

Despite the theoretical promise of hypothermia, two important problems have had to be overcome to consider implementing this strategy in AMI. First, currently available cooling techniques are impractical for the induction of hypothermia in patients with AMI. Surface cooling using icepacks or external cooling blankets is too slow and cumbersome to use in AMI and also requires general anesthesia to prevent shivering. Other methods such as extra-corporeal blood cooling circuits, cardiopulmonary bypass, and peritoneal cooling allow for rapid induction of hypothermia but are too invasive to permit widespread application of cooling. For these reasons the introduction of an endovascular cooling technique has been a major advance

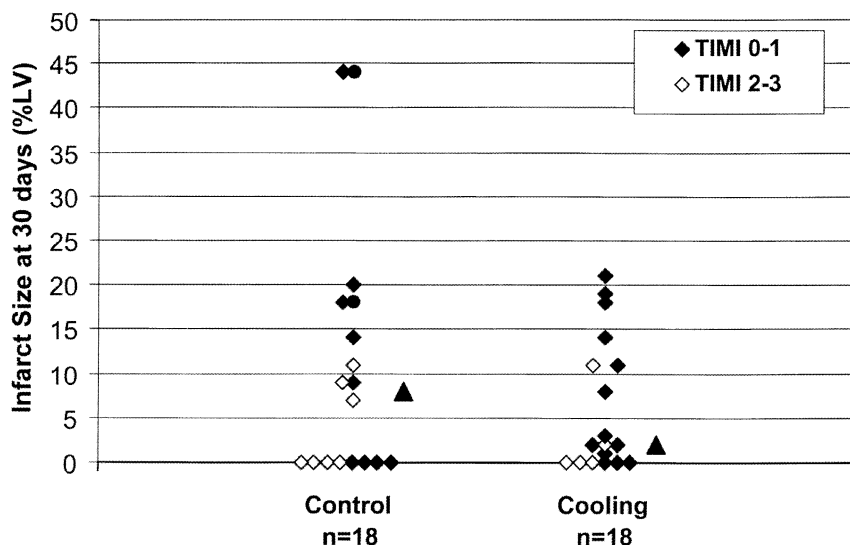


Figure 3. Final infarct size at 30 days in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction with or without endovascular cooling (measured using ^{99m}Tc-sestamibi single photon emission computed tomography imaging). Infarct size is shown according to initial Thrombolysis In Myocardial Infarction (TIMI) flow grade in the infarct vessel (● = assigned infarct size for patients who died; ▲ = median infarct size for group). LV = left ventricle.

in this field. Second, a method was required to counteract the normal thermoregulatory defenses to cooling to allow use of hypothermia in non-ventilated patients. Numerous drugs have been shown to reduce the threshold for shivering, but most are anesthetic agents or major sedatives and require intensive care support with mechanical ventilation. Recently, however the combination of meperidine and buspirone (a 5-HT_{1A} partial agonist) was found to synergistically reduce the shivering threshold in humans without causing respiratory depression (15). This pharmacologic combination was therefore selected for this pilot study.

The primary purpose of this study was to evaluate the feasibility and safety of inducing mild systemic hypothermia in awake patients with AMI using endovascular cooling. The results of this study suggest that: 1) mild systemic hypothermia can be induced in patients with AMI using an endovascular heat-exchange catheter; 2) endovascular cooling is safe and well tolerated during AMI; and 3) shivering can be suppressed successfully in awake patients during endovascular cooling through skin warming and pharmacologic therapy.

Although this is the first study to employ cooling in AMI, the safety of mild hypothermia has been demonstrated in several other high-risk clinical settings, including acute ischemic stroke, traumatic brain injury and cardiac arrest (20-25). Whereas deep hypothermia may cause ventricular arrhythmia, coagulopathy, or immunosuppression, mild or moderate hypothermia has not been associated with these complications. In the present study we found that induction of mild hypothermia during AMI was well tolerated. Although this pilot study was underpowered, there were no unanticipated major adverse events related to cooling. The main adverse reaction in the cooling group was mild episodic shivering, and generally this was well controlled with additional medical therapy or a small increase in core temperature. No hemodynamic instability was seen during cooling, and in contrast with previous studies, no decrease in heart rate was observed.

From a technical standpoint, we found that the heat-exchange catheter could be inserted rapidly in either the emergency room or the catheterization laboratory, and resulted in a rapid reduction in core temperature. All patients treated with cooling achieved a core temperature below 34°C, but in a small number of cases the target temperature of 33°C was not achievable. Whether this is related to sub-optimal heat transfer with this catheter-based system, patient-related factors, or inadequate pharmacologic control of shivering has yet to be established.

Conclusion. Among newer therapeutic approaches in AMI, application of mild hypothermia has generated considerable interest as a potential cardioprotective strategy. This study demonstrated that mild systemic hypothermia can be induced safely in patients with AMI employing a novel heat-exchange catheter. On the basis of these preliminary findings, we believe that further clinical trials are warranted to determine whether adjunctive endovascular

cooling will limit infarct size during reperfusion therapy for AMI.

Acknowledgments

We are grateful to Judith A. Boura MS, for her statistical advice. We also thank all the investigators who contributed to the successful completion of this study.

Reprint requests and correspondence: Dr. Simon R. Dixon, Division of Cardiology, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, Michigan 48073. E-mail: sdixon@smtpgw.beaumont.edu.

REFERENCES

1. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987;317:850-5.
2. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded. *Circulation* 1989;79:441-4.
3. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-22.
4. Cerqueira MD, Maynard C, Ritchie JL, Davis KB, Kennedy JW. Long-term survival in 618 patients from the Western Washington Streptokinase in Myocardial Infarction Trials. *J Am Coll Cardiol* 1992;20:1452-9.
5. Miller TD, Christian TF, Hopfensperger MR, Hodge DO, Gersh BJ, Gibbons RJ. Infarct size after acute myocardial infarction measured by quantitative tomographic ^{99m}Tc-sestamibi imaging predicts subsequent mortality. *Circulation* 1995;92:334-41.
6. Burns RJ, Gibbons RJ, Yi Q, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *J Am Coll Cardiol* 2002;39:30-6.
7. Chien GL, Wolff RA, Davis RF, van Winkle DM. "Normothermic range" temperature affects myocardial infarct size. *Cardiovasc Res* 1994;28:1014-17.
8. Duncker DJ, Klassen CL, Ishibashi Y, Herrlinger SH, Pavek TJ, Bache RJ. Effect of temperature on myocardial infarction in swine. *Am J Physiol* 1996;270:H1189-99.
9. Voorhees WD, Abendschein DR, Tacker WA. Effect of whole-body hypothermia on myocardial blood flow and infarct salvage during coronary artery occlusion in dogs. *Am Heart J* 1984;107:945-9.
10. Hale SL, Kloner RA. Myocardial temperature in acute myocardial infarction: protection with mild regional hypothermia. *Am J Physiol* 1997;273:H220-7.
11. van den Doel MA, Gho BCG, Duval SY, Schoemaker RG, Duncker DJ, Verdouw PD. Hypothermia extends the cardioprotection by ischaemic preconditioning to coronary artery occlusions of longer duration. *Cardiovasc Res* 1998;37:76-81.
12. Miki T, Liu GS, Cohen MV, Downey JM. Mild hypothermia reduces infarct size in the beating rabbit heart: a practical intervention for acute myocardial infarction. *Basic Res Cardiol* 1998;93:372-83.
13. Hale SL, Dave RH, Kloner RA. Regional hypothermia reduces myocardial necrosis even when instituted after the onset of ischemia. *Basic Res Cardiol* 1997;92:351-7.
14. Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *Am J Physiol Heart Circ Physiol* 2002;282:H1584-91.
15. Mokhtarani M, Mahgoub A, Morioka N, et al. Buspirone and meperidine synergistically reduce the shivering threshold. *Anesth Analg* 2001;93:1233-9.

16. Gibbons RJ, Christian TF, Hopfenspirger M, Hodge DO, Bailey KR. Myocardium at risk and infarct size after thrombolytic therapy for acute myocardial infarction: implications for the design of randomized trials of acute intervention. *J Am Coll Cardiol* 1994;24:616–23.
17. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction. *J Am Coll Cardiol* 1999;34:1711–20.
18. Carrier M, Tourigny A, Thoribe N, et al. Effects of cold and warm blood cardioplegia assessed by myocardial pH and release of metabolic markers. *Ann Thorac Surg* 1994;58:764–7.
19. Ning XH, Xu CS, Song YC, et al. Hypothermia preserves function and signaling for mitochondrial biogenesis during subsequent ischemia. *Am J Physiol* 1998;274:H786–93.
20. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 1998;29:2461–6.
21. Krieger DW, De Georgia MA, Abou-Chebl A, et al. Cooling for acute ischemic brain damage (COOL-AID). An open pilot study of induced hypothermia in acute ischemic stroke. *Stroke* 2001;32:1847–54.
22. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997;336:540–6.
23. Felberg RA, Kreiger DW, Chuang R, et al. Hypothermia after cardiac arrest. Feasibility and safety of an external cooling protocol. *Circulation* 2001;104:1799–804.
24. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
25. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.