Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest

Evaluation of a Regional System to Increase Access to Cooling

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Background—Therapeutic hypothermia (TH) improves survival and confers neuroprotection in out-of-hospital cardiac arrest (OHCA), but TH is underutilized, and regional systems of care for OHCA that include TH are needed.

Methods and Results—The Cool It protocol has established TH as the standard of care for OHCA across a regional network of hospitals transferring patients to a central TH-capable hospital. Between February 2006 and August 2009, 140 OHCA patients who remained unresponsive after return of spontaneous circulation were cooled and rewarmed with the use of an automated, noninvasive cooling device. Three quarters of the patients ($n=107$) were transferred to the TH-capable hospital from referring network hospitals. Positive neurological outcome was defined as Cerebral Performance Category 1 or 2 at discharge. Patients with non–ventricular fibrillation arrest or cardiogenic shock were included, and patients with concurrent ST-segment elevation myocardial infarction ($n=68$) received cardiac intervention and cooling simultaneously. Overall survival to hospital discharge was 56%, and 92% of survivors were discharged with a positive neurological outcome. Survival was similar in transferred and nontransferred patients. Non–ventricular fibrillation arrest and presence of cardiogenic shock were associated strongly with mortality, but survivors with these event characteristics had high rates of positive neurological recovery (100% and 89%, respectively). A 20% increase in the risk of death (95% confidence interval, 4% to 39%) was observed for every hour of delay to initiation of cooling.

Conclusions—A comprehensive TH protocol can be integrated into a regional ST-segment elevation myocardial infarction network and achieves broad dispersion of this essential therapy for OHCA. **(*Circulation*. 2011;124:206-214.)**

Key Words: cardiac arrest ■ regional system ■ therapeutic hypothermia

Approximately 300 000 out-of-hospital cardiac arrests (OHCA) occur annually in the United States,[1] and these events are typically catastrophic. Survival rates are notoriously dismal (6% to 9%),[2,3] and adverse neurological sequelae are common and disabling among survivors, with a minority experiencing a return to pre-event functional status.[4,5] Therapeutic hypothermia (TH) has emerged as an innovative, cardiocerebral resuscitation therapy that both improves survival and mitigates unfavorable neurological outcomes in cardiac arrest survivors.

Clinical Perspective on p 214

Two seminal trials[6,7] and subsequent endorsements by the International Liaison Committee on Resuscitation[8] and the American Heart Association[9] have led to a recent flourish of translational research related to postresuscitation TH. Retrospective studies, single-center implementation reports, and large multinational registries of OHCA patients treated with TH[10–15] have since documented the feasibility, effectiveness, and safety of TH outside the context of randomized trials, but use of TH in resuscitated cardiac arrest patients remains uncommon in the United States.[16,17] The consistent and marked reduction in mortality achieved through the use of TH warrants a commitment to broader dispersion of the therapy.

In 2006, the Minneapolis Heart Institute (MHI) implemented Cool It, a progressive initiative aimed at improving survival and neurological recovery after OHCA by securing TH as the standard of care for resuscitated cardiac arrest patients throughout Minnesota. Cool It is a multidisciplinary system of care that affords regional and timely access to TH

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through (1) the rapid and coordinated transfer of patients to a central TH-capable facility in Minneapolis via an integrated network and (2) the use of a standardized protocol that incorporates TH care elements across the course of care, from initial prehospital response to post-TH support. This report highlights key aspects of Cool It and presents data from 140 resuscitated OHCA patients treated with TH during the initial 4 years of the program.

Methods

Setting and Program Development

Abbott Northwestern Hospital (ANW) is a tertiary hospital located in Minneapolis that offers state-of-the-art cardiovascular services and maintains long-standing relationships with a network of hospitals in Minnesota and parts of Wisconsin that routinely transfer patients to MHI-ANW for emergency cardiac care. In 2003, MHI-ANW implemented the Level 1 program,[18,19] a regional system that provides for the rapid transfer of patients with ST-segment elevation myocardial infarction (STEMI) for primary percutaneous coronary intervention (PCI) at ANW from across a network of 33 hospitals within a 210-mile radius of ANW. MHI provides training, education, protocols, and tool kits to participating hospitals, emergency medical services (EMS) agencies, and emergency transport providers. Building on the Level 1 experience, MHI has introduced protocols for other cardiac emergencies, including acute aortic dissection.[20] An interdisciplinary team at MHI-ANW developed a standardized protocol for cardiac arrest that includes timely initiation of TH and implemented the program as a further adjunct to the Level 1 system in 2006. Comprehensive education and protocol training were conducted at each participating hospital and at the helicopter and ground bases of 45 independent EMS providers.

Patients

Consecutive OHCA patients in whom spontaneous circulation was restored were referred for the Cool It protocol via the Level 1 network. Patients were eligible if they remained unresponsive after return of spontaneous circulation (ROSC) and if time from collapse to ROSC was <60 minutes. Patients were eligible regardless of initial cardiac rhythm, hemodynamic instability, or presence of STEMI. No age restrictions were imposed, but ANW primarily admits adult patients. Patients were excluded if they were comatose before arrest, had active bleeding, or had a do-not-resuscitate directive. In all cases, the arrest was presumed to be of cardiac origin before cooling. Institutional review board approval was obtained for the treatment protocol, data collection, and follow-up.

The Cool It Protocol

Overview

The Cool It protocol enables rapid, coordinated, and consistent delivery of TH and promotes optimal supportive care of TH patients throughout transport, cooling, and rewarming. An emergency department (ED) physician in the network activates the protocol with a telephone call to ANW and designates the patient as Cool It (cardiac arrest only) or Cool It/Level 1 (cardiac arrest with evidence of STEMI). A digital page is delivered immediately to members of the TH care team at ANW who then prepare for patient arrival. EMS personnel and referring hospital ED staff execute standing orders for initial management and expedited transfer. Once at ANW, standardized cooling is implemented either in the intensive care unit (Cool It) or catheterization laboratory (Cool It/Level 1). For patients presenting directly to ANW, cooling is initiated in either the ED (Cool It) or catheterization laboratory (Cool It/Level 1).

Prehospital Cooling

Initial field response mirrors American Heart Association guidelines for resuscitation of patients with nontraumatic cardiac arrest[21] but additionally includes a directive for noninvasive surface cooling. First responders, paramedics, and network hospital ED personnel are instructed to place ice packs on the groin, head, neck, and chest during initial management and transfers. This immediate field cooling was not part of the original protocol in February 2006 but was instituted in response to an evolving theory that cooling should be applied as soon as possible after ischemic insult to maximize neuroprotection. Many patients now arrive at ANW with core temperature reduction significantly under way. The protocol does not include use of iced saline.

Cooling and Rewarming

A cardiologist and an intensivist partner in coordinating care during the induction, maintenance, and rewarming phases of TH. Core temperature is reduced to 33°C typically within 2 to 4 hours, with the use of a device that draws chilled water through hydrogel pads placed directly on the torso and lower extremities (Arctic Sun, Medivance Inc, Louisville, CO). Core temperature is monitored via an esophageal temperature probe, and the target temperature is maintained for 24 hours. Neuromuscular blockade controls shivering. Supplemental oxygen is adjusted to the lowest concentration capable of maintaining an arterial oxygen saturation of >92%. Mean arterial pressure is maintained at >60 mm Hg. Inotropic agents are administered or an intra-aortic balloon pump is deployed as necessary, targeting a cardiac index >2.5. Antiarrhythmic medications are continued, and intravenous heparin is given to achieve anticoagulation in patients with STEMI. After 24 hours, rewarming commences at a rate of 0.5°C per hour until a core temperature of 37°C is reached, typically within 8 hours. The device is designed to counteract accelerated rewarming to prevent rebound hyperthermia.

Simultaneous Therapeutic Hypothermia and Angiography/Percutaneous Coronary Intervention

Patients meeting established ECG criteria for STEMI are transferred directly to the catheterization laboratory, where angiography/PCI and TH occur simultaneously. The protocol development team worked to ensure that the 2 therapies could be synchronized without compromising door-to-balloon time and found success in a carefully choreographed work flow, a systematic approach to the configuration of equipment, and the selection of a cooling system compatible with vascular intervention. The gel pads are radiolucent and have been designed so that vascular access is preserved during cooling.

Neurocognitive Assessment and Follow-Up

The protocol includes neurological monitoring and recovery. Neurological assessments are conducted on discharge from the intensive care unit and the hospital, including assignment of the Cerebral Performance Category (CPC) score,[22] which grades the level of neurofunctional status after cardiac arrest as follows: CPC 1=good; CPC 2=moderate disability; CPC 3=severe disability; CPC 4=comatose or vegetative state; and CPC 5=death. A protocol subcommittee identified additional tests to assess cognitive compromise and outlined processes to support the remediation of identified deficits. Monitoring and early rehabilitation continue throughout the hospital stay and after discharge. A follow-up assessment is conducted 1 month after discharge to ascertain recovery and safe return to independence.

Program Evaluation

Data Collection

A comprehensive prospective database is used to monitor progress and guide process improvement. Data are collected by specially trained clinical research assistants using 3 sources: the electronic health record at ANW, EMS run sheets, and correspondence with referring hospitals. Data are recorded on standardized case report forms following the Utstein style[23] and are reviewed by the senior project cardiologist (M.R.M.). The Cool It committee regularly conducts case-specific reviews.

Outcomes and Measures

Two primary outcomes were examined: (1) survival to hospital discharge and (2) positive neurological result on survival, defined as

CPC 1 or 2 at hospital discharge. Transfer patients were defined as those who initially presented at a referring hospital and then were transported to ANW. Transport distance (miles between referring hospital and ANW) and transport time (interval between departure from the referring hospital and arrival at ANW) were computed. Information regarding time of arrest, time of ROSC, bystander response, and prehospital cooling were available from EMS run sheets. For unwitnessed arrests, the time of collapse was estimated with the time of the 911 call. Initial rhythm was classified as ventricular fibrillation (VF)/ventricular tachycardia (VT) or asystole/pulseless electric activity (PEA). Established clinical and hemodynamic criteria were used to define cardiogenic shock.[24] Time to first cooling was defined as time between ROSC and application of prehospital cooling (eg, ice packs) or the time between ROSC and the application of the cooling device at ANW in cases in which no prehospital cooling was attempted. Two door-to-balloon time intervals were examined for patients receiving PCI: (1) arrival at ANW to balloon and (2) first door to balloon, which represents the total time from initial presentation (ie, at the referring hospital for transfer patients) to balloon. Program year, defined as year 1 (February 2006 to January 2007), year 2 (February 2007 to January 2008), year 3 (February 2008 to January 2009), and year 4 (February 2009 to August 2009), is used to describe longitudinal change in process measures.

Statistical Analysis

Means and frequencies were generated for patient and event characteristics. Medians and interquartile ranges were used to describe time-to-treatment intervals in subgroups defined by discharge status (alive versus dead), transfer status (ANW versus transfer patient), and presence of STEMI (yes versus no), and a Wilcoxon rank sum test was used to compare subgroup medians (see the online-only Data Supplement). Logistic regression models were used to compute the crude odds ratio (95% confidence intervals) of survival to hospital discharge according to patient and event characteristics and within tertiles of time-to-treatment intervals. Cox regression was used to analyze the relative hazard of death as a function of time from ROSC to cooling. Positive neurological outcome was described with the use of frequencies and proportions.

Results

Between February 2006 and August 2009, 140 consecutive OHCA patients met inclusion criteria and were treated with TH. Patients were predominantly male and aged <75 years (Table 1). Approximately three quarters of the patients presented at a non-TH hospital and were transferred to ANW, with an average transport distance of 56 ground miles. In 43% of cases, some type of initial cooling was applied before arrival at ANW. The case series includes 32 patients who had asystole/PEA (24%) and 61 patients who were in cardiogenic shock (44%). Approximately half of the patients had STEMI in conjunction with cardiac arrest.

Median time from arrest to ROSC was 22 minutes, and median time between ROSC and application of the cooling device was 117 minutes (Table 2). A shorter interval between collapse and ROSC was strongly associated with survival. Time to first cooling was comparable for transfer and nontransfer patients, suggesting consistent initial management efforts. However, as a result of transport time, transfer patients experienced significantly longer times to standardized hydrogel pad cooling at ANW. Presence of STEMI was not associated with increased time to cooling. Among 43 patients with STEMI who underwent PCI, median time intervals between arrival at ANW and balloon in transferred (n=35) and ANW (n=8) patients were 26 and 63 minutes, respectively, and are similar to the median times reported for Level 1 patients before implementation of the TH protocol.[19]

Table 1. Patient and Event Characteristics

Variable	Frequency or Mean±SD (Range)	%
Age, mean±SD (range), y	62±13 (15–85)	. . .
Age >75 y	30/140	21
Male	108/140	77
Transfer patient*	107/140	76
Transport distance, mean±SD (range), miles†	56±35 (2–173)	. . .
Transport time, mean±SD (range), min†	28±21 (6–184)	. . .
Medical history		
Diabetes mellitus	27/140	19
Coronary artery disease	50/140	36
Prehospital care		
Arrest witnessed	115/140	82
Bystander CPR	86/130	66
Bystander use of AED	42/138	30
Prehospital cooling‡	60/140	43
Arrest characteristics		
VF/VT	102/134	76
Asystole/PEA	32/134	24
STEMI	68/140	49
Cardiogenic shock	61/140	44
Cardiac intervention		
Angiography	101/140	72
PCI	56/140	40

CPR indicates cardiopulmonary resuscitation; AED, automatic external defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electric activity; STEMI, ST-segment elevation myocardial infarction; and PCI, percutaneous coronary intervention.

*Patient initially presented at another hospital and transferred to Abbott Northwestern Hospital.

†Defined only for transfer patients.

‡Any type of cooling initiated before patient arrived at Abbott Northwestern Hospital.

Overall, 56% of patients survived to hospital discharge, and 51% had a positive neurological outcome (92% of survivors; Table 3). Advanced age, asystole/PEA, and cardiogenic shock were all associated with increased mortality, but among survivors, only advanced age was associated with adverse neurological sequelae. There was no difference in survival between transferred and nontransferred patients.

The elapsed time between arrest and ROSC was strongly associated with survival, with only 36% of patients who were down for >30 minutes surviving to hospital discharge (Table 4). When the elapsed time between ROSC and the application of the cooling device at ANW was >2.5 hours, patients were 63% less likely to survive to discharge than when that time remained <1.5 hours. When modeled continuously, the relative hazard estimate for a 1-hour increase in time from ROSC to first cooling was 1.20 (95% confidence interval, 1.04 to 1.39), indicating that for every 1 hour in delay to initiation of cooling, the risk of death increased by 20%. The

Table 2. Median Time-to-Treatment Intervals (Minutes) by Hospital Discharge Status, Transfer Status, and Presence of STEMI

Time Segment	All Patients (n=140)	Discharge Status			Transfer Status			STEMI		
		Alive (n=78)	Dead (n=62)	*P*	ANW (n=33)	Transfer (n=107)	*P*	Yes (n=68)	No (n=72)	*P*
Collapse to ROSC	22 (12, 35)	15 (8, 26)	27 (20, 40)	$<$0.001	21 (10, 32)	22 (12, 35)	0.48	20 (11, 34)	23 (12, 35)	0.67
ROSC to first cooling*	60 (30, 138)	63 (29, 135)	85 (38, 188)	0.14	64 (40, 110)	67 (30, 161)	0.45	59 (28, 147)	78 (34, 142)	0.42
ROSC to application of cooling device at ANW	117 (80, 174)	107 (76, 151)	136 (90, 203)	0.02	80 (50, 121)	132 (89, 183)	$<$0.001	101 (78, 173)	132 (89, 178)	0.18
ANW arrival to application of cooling device	33 (14, 84)	28 (13,72)	47 (17, 111)	0.03	41 (30, 72)	29 (12, 90)	0.09	28 (12, 93)	35 (22, 80)	0.20
ROSC to target temperature achieved	287 (206, 377)	284 (205, 370)	290 (201, 400)	0.69	243 (173, 314)	296 (221, 400)	0.03	263 (178, 362)	315 (215, 383)	0.13
ANW-to-balloon time†	36 (21, 44)	34 (20, 44)	36 (21, 46)	0.86	64 (42, 87)	27 (20, 41)	0.001	36 (21, 44)	NA	NA
First door-to-balloon time†	105 (86, 130)	104 (86, 121)	109 (80, 154)	0.40	64 (42, 87)	110 (89, 138)	0.008	105 (86, 130)	NA	NA

Time values are expressed as median (25th percentile, 75th percentile). STEMI indicates ST-segment elevation myocardial infarction; ANW, Abbott Northwestern Hospital; and ROSC, return of spontaneous circulation.

*Time to first cooling of any type (ie, prehospital or cooling device at ANW).

†Among STEMI patients with percutaneous coronary intervention (n=43) (alive=28, dead=15; ANW=8, transfer=35).

total time from ROSC to target hypothermic temperature, however, was not significantly associated with survival. Among patients in the highest tertiles of time to cooling intervals who survived, normal or near-normal neurological function was preserved in 95% to 100%. Patients who underwent angiography were significantly more likely to have a positive neurological outcome than patients who did not.

Substantive gains in operational efficiency were achieved (Figure). Over the initial 4 years of the program, the median time between ROSC and attainment of target core temperature was reduced by nearly 90 minutes (345 versus 258 minutes), and the median time from ROSC to first cooling was shortened by 2 hours (161 versus 35 minutes), reflecting increased efforts to initiate early surface cooling. Through ongoing education and outreach, the proportion of cases receiving some cooling before arrival at ANW has risen consistently and dramatically, from 6% to 69% (year 1=6%, year 2=38%, year 3=61%, year 4=69%). Care providers at the TH hospital also have dramatically reduced the time that elapses between patient arrival in the ED and application of the cooling device, from a median of 96 minutes to a current median of 20 minutes.

Discussion

A recent policy statement from the American Heart Association[25] highlights the need for formal evaluation of regional systems of care for OHCA, and this report describes one such initiative. Cardiac arrest patients across Minnesota are now benefiting from TH, and mortality among the first 140 TH-treated patients did not differ significantly by whether the patient presented at a network hospital or directly to the central TH-capable hospital in Minneapolis. We have demonstrated that simple cooling with ice bags initiated soon after arrest can be associated with incrementally improved outcomes, even if transfer to a specialized TH center is required, and that TH is an achievable standard of care that can be applied in urban and rural settings equally where regional systems of care have been developed.

Process Improvement

Our experience demonstrates that regional STEMI systems can be further developed to increase access to TH, but continuous quality improvement activities have been paramount to success. Through work flow refinement, the TH care team at ANW has improved their ability to rapidly connect patients with concurrent cooling and cardiac intervention, taking 77 minutes off of the median time from arrival to cooling since the inception of the program. In addition, when interim Cool It analyses and supporting evidence from published animal models[26,27] suggested a possible association between rapid time to cooling and positive outcomes, the program education team revisited all network hospitals and EMS providers and delivered new education about how to initiate early cooling with the use of ice packs and exposure. Median time between ROSC and first cooling is now 35 minutes versus 161 minutes during the first year of the protocol. In 465 cooled OHCA patients across 19 European sites between 2003 and 2005, the median time from ROSC to initiation of cooling was 131 minutes.[15] These improvements underscore the importance of maintaining a project database and the significance of continuous program monitoring.

Age and Time to Return of Spontaneous Circulation

Advanced age and extended time between collapse and ROSC were both associated with a less favorable outcome in our cohort. Cardiac arrest patients aged >75 years, a demographic excluded from the Hypothermia After Cardiac Arrest clinical trial,[6] comprise 21% of Cool It patients to date. Advanced age was not significantly associated with higher mortality, but elderly survivors were the least likely to experience a full or near-full neurological recovery among all of the subgroups we examined, perhaps because of diminished pre-event neurological status. Cardiac arrest victims with delays to ROSC >30 minutes are known to have a very poor prognosis,[2,14,28,29] and we observed a precipitous decrease in survival after time to ROSC exceeded even 15 minutes. Still, 36% of arrest victims with ROSC >30 minutes survived to discharge, and 100% of those survivors had a CPC score of 1 or 2. A CPC score of 1 or 2 was achieved in

Table 3. Survival and Neurological Outcome by Patient and Arrest Characteristics

					Positive Neurological Outcome*			
	Survival to Hospital Discharge				All Patients		Survivors Only	
Variable	Frequency	%	OR†	95% CI	Frequency	%	Frequency	%
All patients	78/140	56			72/140	51	72/78	92
Age								
≤75 y	65/110	59	Reference category	. . .	63/110	57	63/65	97
>75 y	13/30	43	0.52	(0.23–1.20)	9/30	30	9/13	69
Transfer status								
ANW	17/33	52	Reference category	. . .	14/33	42	14/17	82
Transfer	61/107	57	1.25	(0.57–2.52)	58/107	54	58/61	95
Arrest witnessed								
No	11/25	44	Reference category	. . .	11/25	44	11/11	100
Yes	67/115	58	1.78	(0.74–4.25)	61/115	53	61/67	91
Bystander CPR								
No	21/44	48	Reference category	. . .	21/44	48	21/21	100
Yes	52/86	60	1.68	(0.81–3.49)	49/86	57	49/52	94
Bystander use of AED								
No	49/96	51	Reference category	. . .	46/96	48	46/49	94
Yes	28/42	67	1.92	(0.90–4.09)	25/42	60	25/28	89
Prehospital cooling‡								
No	42/80	53	Reference category	. . .	39/80	49	39/42	93
Yes	36/60	60	1.36	(0.69–2.67)	33/60	55	33/36	92
Initial rhythm								
Asystole/PEA	7/32	22	Reference category	. . .	7/32	22	7/7	100
VF/VT	68/102	67	7.14	(2.81–18.17)	62/102	61	62/68	91
STEMI								
No	34/72	47	Reference category	. . .	31/72	43	31/34	91
Yes	44/68	65	2.05	(1.04–4.04)	41/68	57	41/44	93
Cardiogenic shock								
No	55/79	70	Reference category	. . .	49/79	62	49/55	89
Yes	23/61	38	0.26	(0.13–0.53)	23/61	38	23/23	100

OR indicates odds ratio; CI, confidence interval; CPR, cardiopulmonary resuscitation; AED, automatic external defibrillator; STEMI, ST-segment elevation myocardial infarction; ANW, Abbott Northwestern Hospital; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Defined as Cerebral Performance Category 1 or 2.

†Odds of survival computed with univariate logistic regression model.

‡Any type of cooling initiated before patient reached ANW.

69% of surviving patients aged >75 years. These findings illustrate the difficulty of prognostication and demonstrate that despite a tendency toward higher mortality, TH is a reasonable course of care in both the elderly and patients with prolonged time to ROSC.

Non-Ventricular Fibrillation Arrest and Cardiogenic Shock

The landmark clinical trials that gave rise to the current International Liaison Committee on Resuscitation recommendations for TH[6,7] excluded patients with non-VF arrest and cardiogenic shock, and the therapeutic potential of hypothermia in these subgroups remains unclear. Two subsequent TH trials included patients with non-VF initial rhythms,[30,31] but limitations in these studies preclude definitive conclusions. Observational data on the use of TH in patients with asystole/PEA are available[14,15,28,32] and consistently show that the well-described, markedly poorer survival among patients with asystole/PEA compared with those with VF/VT persists even in the presence of TH. However, despite being a robust prognosticator for survival to discharge, initial rhythm did not appear in our data to be associated with quality of neurological recovery among those who survive. Of the 7 Cool It patients with asystole/PEA who survived, all 7 had a positive neurological outcome. Oddo et al[28] likewise reported that although only 2 of 12 asystole/PEA patients treated with TH survived to discharge, both had excellent neurological recovery (CPC=1). Recently published data from the Hypothermia Registry Network[14] similarly describe comparable rates of good neurological recovery (CPC=1 or 2) among survivors of VF (79%) and non-VF arrest (73%). Among Cool It patients with cardiogenic shock, we observed a favorable

Table 4. Survival and Neurological Outcome by Tertiles of Time to Treatment Segments and Cardiac Intervention

					Positive Neurological Outcome*			
	Survival to Hospital Discharge				All Patients		Survivors Only	
Variable	Frequency	%	OR†	95% CI	Frequency	%	Frequency	%
Collapse to ROSC								
0–15 min	42/51	82	Reference category	. . .	38/51	75	38/42	90
16–29 min	20/44	45	0.18	(0.07–0.45)	18/44	41	18/20	90
30–60 min	16/45	36	0.12	(0.05–0.30)	16/45	36	16/16	100
ROSC to first cooling‡								
0–39 min	26/43	60	Reference category	. . .	26/43	60	26/26	100
40–102 min	26/43	60	1.00	(0.42–2.37)	21/43	49	21/26	81
>102 min	19/42	45	0.54	(0.23–1.28)	19/42	45	19/19	100
ROSC to application of cooling device								
0–90 min	33/49	67	Reference category	. . .	29/49	59	29/33	88
91–148 min	25/45	56	0.61	(0.26–1.40)	24/45	53	24/25	96
>148 min	20/46	43	0.37	(0.10–1.33)	19/46	41	19/20	95
ROSC to target temperature reached								
0–234 min	25/46	54	Reference category	. . .	22/46	48	22/25	88
235–346 min	30/48	63	1.40	(0.61–3.19)	27/48	56	27/30	90
>346 min	23/46	50	0.84	(0.37–1.91)	23/46	50	23/23	100
Emergency angiography								
No	15/39	38	Reference category	. . .	12/39	31	12/15	80
Yes, with PCI	32/56	57	2.13	(0.93–4.91)	29/56	52	29/32	89
Yes, without PCI	31/45	69	3.54	(1.44–8.74)	31/45	69	31/31	100

OR indicates odds ratio; CI, confidence interval; ROSC, return of spontaneous circulation; and PCI, percutaneous coronary intervention.

*Defined as Cerebral Performance Category 1 or 2.

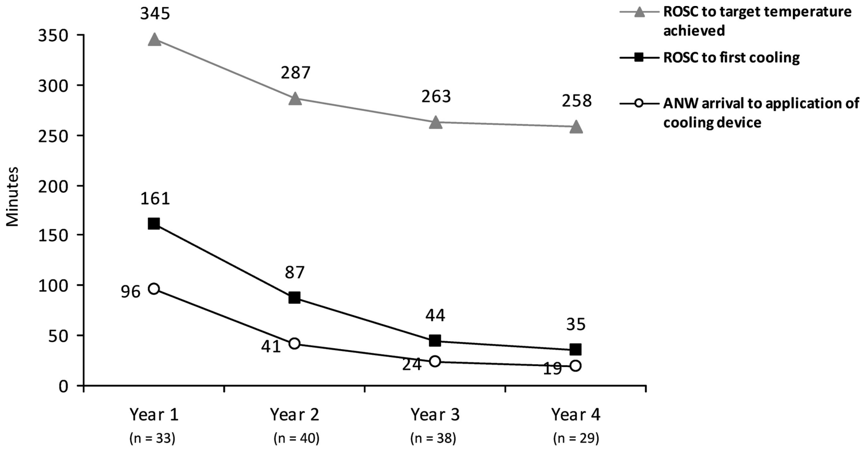
†Odds of survival computed with univariate logistic regression model.

‡Time to first cooling of any type (ie, prehospital or cooling device at Abbott Northwestern Hospital).

neurological recovery in 100% of those who survived the event. These findings suggest that the effect of TH in mitigating damage caused by cerebral ischemia may be independent of the pathogenesis of the ischemia itself and that TH tends to produce a dichotomy of outcomes (ie, either excellent neurological result or death) rather than a continuum of graded outcomes that include severe and permanent neurological impairment (ie, CPC=3 or 4).

Therapeutic Hypothermia in Cardiac Intervention

As others have reported,[11,33–35] we have confirmed that TH and primary PCI can be delivered in combination without



*The median(*25th percentile*, *75th percentile*) values for Years 1 through 4 are: ROSC to target temperature – 345(*269,457*), 287(*205,396*), 263(*148,347*), 258(*166,345*); ROSC to first cooling – 161(*113,254*), 87(*39,139*), 44(*12,84*), 35(*13,71*); ANW arrival to cooling device – 96(*52,153*), 41(*15,81*), 24(*13,56*), 19(*11,29*)

Figure. Median times to treatment by program year. ROSC indicates return of spontaneous circulation; ANW, Abbott Northwestern Hospital.

compromising time to either. Patients with STEMI had significantly better survival than their counterparts without STEMI. Patients who underwent angiography, both with or without PCI, showed a trend toward better survival compared with patients who had no angiography in the postresuscitation period, as recently reported in the Parisian Region Out of Hospital Cardiac Arrest study.[36] Although angiography may be lifesaving, the prevalence of asystole/PEA in our patients with and without STEMI was 15% and 33%, respectively ($P=0.03$), which may partially explain the improved survival in the STEMI group.

Early Initiation of Therapeutic Hypothermia

The benefits of TH are enhanced in animal models when cooling begins during cardiac arrest or soon thereafter,[26,27,37] but confirmatory data in humans are evolving. In 1 study, prompt achievement of core temperature via endovascular cooling was associated with improved neurological outcomes in OHCA patients.[38] In contrast, the International Cardiac Arrest Registry reported that the timing of the initiation of TH was unrelated to outcomes in the presence of other key predictors such as longer time to ROSC.[14] We observed an association between time to cooling and mortality, with a 1-hour delay in time to cooling increasing the risk of death by 20%. This is an important finding because many have assumed that delays of up to 4 hours are acceptable because the Hypothermia After Cardiac Arrest trial[6] included patients who received cooling up to 4 hours after arrest. Still, multivariate analyses are needed to clarify whether this is an independent effect because time to cooling may be a surrogate marker for time to other crucial life-sustaining activities. In survivors, we did not detect a significant association between time to cooling and extent of neurological recovery, but we strongly caution against interpreting this finding as evidence that delays to cooling are inconsequential in terms of neurorecovery. On the contrary, the premise that rapid initiation of cooling maximizes neuroprotection is founded on known physiological processes and has been demonstrated in animal models. In addition, the very narrow range of time-to-cooling values and the high rate of excellent neurological recovery in our survivors likely limited our ability to detect such an association. Only 8% (n=6) of our survivors had a CPC score of 3 or 4, in contrast to outcomes from the Hypothermia After Cardiac Arrest trial,[6] in which 23% of survivors had a CPC score of 3 or 4. Perhaps a time-dependent threshold for the neuroprotection conferred by TH exists, and generally we were successful in inducing hypothermia within a time frame under that threshold. In the later years of the program, half of these patients received cooling within 45 minutes of ROSC.

Preprotocol Data

To contrast our findings with outcomes from a comparable population of patients not treated with TH, we conducted a retrospective review of 38 cardiac arrest patients treated at ANW in the 2 years before the TH protocol who would have met the inclusion criteria for cooling. The overall survival to hospital discharge in these 38 patients was 58% (22/38). This is comparable to the rate observed in the postprotocol period (56%), but there was a higher proportion of patients with shockable initial rhythms in the preprotocol group (84%) than in the postprotocol group (76%). Among survivors in the preprotocol period, the proportion of those with CPC score of 1 or 2 at discharge was 77% (17/22), substantially worse than the 92% we observed after the implementation of Cool It. Perhaps most importantly, we observed a much higher percentage of survivors with highly undesirable CPC scores of 3 or 4 in the preprotocol period (23%; n=5). These historical data do not represent an ideal comparison but serve to generally characterize outcomes at our facility before Cool It.

Limitations

Some limitations of this work should be acknowledged. First, these data are subject to survivorship bias, reflecting only those patients possessing the demographic, event, and health-care access characteristics that increase the likelihood of survival to medical contact. Second, the relatively small sample size compromises statistical power and the precision of estimates, particularly in subgroup analyses. A substantive number of statistical comparisons were made without adjustment for multiple tests, and therefore the probability of type I error in these results may also be high. As more cases accrue, we anticipate conducting more focused and rigorous multivariate analyses to identify the independent predictors of positive outcomes. Finally, complications from TH are an important consideration, but this information is not currently captured in the Cool It database in reportable fields. Enhanced monitoring of complications should be undertaken so that the risks associated with TH are understood and minimized.

Implications

This work has resulted in several key findings. First, by illustrating the feasibility of integrating a TH protocol into an existing system of care for STEMI, we have provided a generalizable model for increasing regional access to TH. To expand access to TH, providers should capitalize on established emergency cardiac care networks with refined patient transfer mechanisms. Second, given careful planning and appropriate device selection, TH and PCI for STEMI can be achieved concurrently without delay to either. This is crucial given that a significant proportion of OHCA patients who survive to admission will have STEMI requiring timely PCI. Third, our data suggest that each 1-hour delay in the initiation of cooling in OHCA victims may reduce survival by 20%, and therefore it is recommended that TH protocols include a prehospital cooling component. Education and resources should be directed toward EMS and community hospitals to ensure execution of the simple but seemingly effective practice of initiating cooling with ice packs immediately on ROSC. Fourth, we have provided evidence that consideration should be given to broadening the target population for TH. We have opened our Cool It protocol to the elderly, patients with non-VF arrest, and patients in cardiogenic shock, and our work suggests that TH should be extended to these patients because, on survival, they appear to benefit substantially from the neuroprotective effects of TH. Finally, we have demonstrated the value of using a prospective database to monitor progress and guide process improvement efforts.

Conclusion

In this TH-treated cohort, 56% of patients survived to hospital discharge, and among those who survived, 92% experienced a return to normal or near-normal neurological functioning. With the efficacy of TH established, the opportunity to improve outcomes from OHCA lies in the study of how best to deploy the therapy to larger numbers of patients. We have demonstrated that TH protocols that incorporate simple, noninvasive surface cooling before hospital arrival can provide an effective rescue therapy for OHCA and should be readily adopted within the context of existing STEMI networks.

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CLINICAL PERSPECTIVE

This report addresses our experience with a system of care designed to provide therapeutic hypothermia (TH) to survivors of out-of-hospital cardiac arrest. The current rate of usage in the United States falls far below the expectations of the community and guideline recommendations, and we demonstrate that a mature ST-segment elevation myocardial infarction network can be further developed to include a TH protocol. We observed that the application of simple ice packs in the prehospital setting was incrementally lifesaving and allowed for the transfer of patients to a remote regional center. We include in our report the outcome of high-risk patients excluded from initial randomized trials, including transfer patients, those in cardiogenic shock, unwitnessed arrests, and patients needing emergency ST-segment elevation myocardial infarction treatment. Outcomes in these patients were better than expected in terms of both overall survival and the quality of neurological recovery. Furthermore, TH is an achievable standard of care that can be applied in urban and rural settings with equivalent outcomes. In this TH-treated cohort, 56% of patients survived to hospital discharge, and among those who survived, 92% experienced a return to normal or near-normal neurological functioning. With the efficacy of TH established, the opportunity to improve outcomes from out-of-hospital cardiac arrest lies in the study of how best to deploy the therapy to larger numbers of patients. We have demonstrated that TH protocols that incorporate simple, noninvasive surface cooling before hospital arrival can provide an effective rescue therapy for out-of-hospital cardiac arrest and should be readily adopted within the context of existing ST-segment elevation myocardial infarction networks.