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ORIGINAL RESEARCH

Implementation of Targeted Temperature Management After Out-of-Hospital Cardiac Arrest: Observations From the Los Angeles County Regional System

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BACKGROUND: Despite the benefits of targeted temperature management (TTM) for out-of-hospital cardiac arrest), implementation within the United States remains low. The objective of this study was to evaluate the prevalence and factors associated with TTM use in a large, urban-suburban regional system of care.

METHODS AND RESULTS: This was a retrospective analysis from the Los Angeles County regional cardiac system of care serving a population of >10 million residents. All adult patients aged ≥18 years with non-traumatic out-of-hospital cardiac arrest transported to a cardiac arrest center from April 2011 to August 2017 were included. Patients awake and alert in the emergency department and patients who died in the emergency department before consideration for TTM were excluded. The primary outcome measure was prevalence of TTM use. The secondary analysis were annual trends in TTM use over the study period and factors associated with TTM use. The study population included 8072 patients; 4154 patients (51.5%) received TTM and 3767 patients (46.7%) did not receive TTM. Median age was 67 years, 4780 patients (59.2%) were men, 4645 patients (57.5%) were non-White, and the most common arrest location was personal residence in 4841 patients (60.0%). In the adjusted analysis, younger age, male sex, an initial shockable rhythm, witnessed arrest, and receiving coronary angiography were associated with receiving TTM.

CONCLUSIONS: Within this regional system of care, use of TTM was higher than previously reported in the literature at just over 50%. Use of integrated systems of care may be a novel method to increase TTM use within the United States.

Key Words: cardiac arrest ■ out-of-hospital cardiac arrest ■ targeted temperature management

The annual incidence of out-of-hospital cardiac arrest (OHCA) in the United States is nearly 400 000, with large regional variation in survival to hospital discharge ranging from 3.4% to 22% and survival with good neurologic outcome ranging from 0.8% to 20%.[1] Randomized studies support the use of targeted temperature management (TTM) for patients with return of spontaneous circulation (ROSC) following OHCA from shockable ryhthms.[2,3] Observational studies, a single randomized trial and recent practice guidelines also encourage the use of TTM for non-shockable rhythms.[4–8] Despite its benefits, recent publications suggest that TTM is underutilized in the United States.[9–12]

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CLINICAL PERSPECTIVE

What Is New?

- Targeted temperature management (TTM) is beneficial for out-of-hospital cardiac arrest with return of spontaneous circulation but is underutilized within the United States.
- Prior studies have not evaluated the in-hospital use of TTM within regional cardiac systems of care.

What Are the Clinical Implications?

- TTM use significantly increased from 49.4% in 2011 to 55.7% in 2017.
- Younger age, male sex, an initial shockable rhythm, witnessed arrest, and receiving coronary angiography were associated with receiving TTM.
- Use of integrated cardiac systems of care may be a novel method to increase TTM use within the United States.

Nonstandard Abbreviations and Acronyms

OHCA	out-of-hospital cardiac arrest
ROSC	return of spontaneous circulation
TTM	targeted temperature management

Regionalization of care with dedicated cardiac care centers for OHCA has been independently associated with increased overall survival and favorable neurologic outcomes.[13,14] Characterization of TTM in regional systems of care has not been adequately described. The objective of the current study was to evaluate the prevalence and factors associated with TTM use in a large, urban-suburgan regional system of care, as well as describe trends in TTM use over time.

METHODS

Los Angeles County Emergency Medical Services Registry

This is a retrospective study of data from the Los Angeles County Emergency Medical Services (EMS) registry. The study was approved with waiver of informed consent by the Institutional Review Board at the University of Southern California. The data that support the findings of this study are available from the corresponding author upon reasonable request. Prior reports have described the regional system of care in Los Angeles County, which currently includes 36 designated cardiac arrest receiving centers.[13–15] Los Angeles County has a population of >10.2 million with EMS provided by 30 municipal fire departments and 1 law enforcement agency with ≈3900 licensed paramedics. The Los Angeles County EMS Agency provides oversight of providers operating within the county, establishes protocols and procedures, and designates specialty care centers. Since 2011, countywide protocols mandate transport of all OHCA patients of presumed cardiac etiology with ROSC in the field to a cardiac arrest center with an institutionally approved TTM protocol and the ability to provide 24/7 emergent coronary angiography and percutaneous coronary intervention (PCI). At the onset of the system of care in 2011, participating hospitals were encouraged to institute TTM with a target temperature of 32°C to 34°C within 6 hours of ROSC and to maintain it for a minimum of 20 hours. In September 2016, this policy was revised to encourage temperature control between 32°C to 36°C for at least 24 hours. The final decision to initiate or withhold TTM was guided by individual institutional policy and at the discretion of the treating physician at the local hospital. TTM was not initiated in the field and the specific method for TTM (endovascular cooling, cooling blankets, etc) was not mandated.

Los Angeles County EMS policy encourages resuscitation on scene to achieve ROSC before transport. For patients meeting criteria, termination of resuscitation in the field is supported by official policy since 2007. Termination of resuscitation is based on medical futility determined by paramedics in consultation with online medical direction and agreement of immediate family on scene. Since April 2011, all cardiac arrest centers have reported demographics, in-hospital mortality, and neurologic outcome to a registry maintained by the Los Angeles County EMS Agency.

Study Population

This database was queried from April 2011 through August 2017, representing all available data at the time of analysis. Patients aged ≥18 years resuscitated from OHCA that were transported to a designated cardiac arrest center were included. Patients with traumatic cardiac arrest and those aged <18 years were excluded. Additionally, patients who would not benefit from TTM were excluded from the analysis to mitigate the selection bias toward or against TTM given the observational design of the study. We therefore excluded patients awake and alert in the emergency department (ED) and patients who died in the ED before consideration for TTM. Patients with termination of resuscitation in the field were not transported by protocol and, therefore, were not eligible for inclusion in the data registry nor this current study.

Individual centers are responsible for data collection. Staff members charged with data entry abstract the data points from the medical record, including the prehospital care records. Greater than 90% of staff responsible for data extraction and entry are registered nurses in the departments of emergency medicine, cardiology, and quality improvement. Completeness and accuracy of the entered data are continually reviewed by the Los Angeles County EMS Agency with verification performed during annual site visits. Biannual system-wide meetings are held for data review.

Covariates and Definitions

Study variables included age, sex, race/ethnicity, location of arrest, initial rhythm, witness to arrest, bystander cardiopulmonary resuscitation, ST-segment–elevation myocardial infarction on the prehospital or first ECG in the ED, coronary angiography, PCI and the location where TTM was initiated (ED, cardiac catheterization laboratory, intensive care unit). Initial rhythm refers to the first rhythm documented by prehospital personnel and includes ventricular fibrillation, ventricular tachycardia, shocks advised by an automated external defibrillator (presumed ventricular tachycardia or ventricular fibrillation), asystole, and pulseless electrical activity. Shockable rhythms were classified as ventricular fibrillation, ventricular tachycardia, and shocks advised by an automated external defibrillator. Non-shockable rhythms were classified as asystole and pulseless electrical activity. The reasons that TTM was not initiated were categorized according to the data in the registry including an existing do not resuscitate order, other rationale not otherwise specified, persistent hypotension, active bleeding, terminal illness, core temperature <35°C, preexisting coma, and other relative contraindications. These rationale were documented by the treating hospital and more than 1 reason could be documented on 1 patient.

Outcomes

The primary outcome was the prevalence of TTM use in patients with OHCA and ROSC treated at cardiac arrest receiving centers within this regional system of care. The secondary analyses were to describe trends in TTM use over time and explore factors associated with TTM use. We also evaluated the association of TTM with survival to hospital discharge and survival with good neurologic outcome, defined as cerebral performance category (CPC) 1 or 2.

Statistical Analysis

We conducted all analyses using SAS, version 9.4, (SAS institute Cary, NC). Patient characteristics were determined for the entire cohort and stratified by treatment with TTM. Descriptive statistics were summarized using medians and interquartile ranges or frequencies and proportions. Groups were compared with the Hodges-Lehmann or Chi square test as appropriate. An exploratory analysis of predictors of TTM use was performed. All potential predictors available in the dataset (age, sex, race, shockable rhythm, witnessed arrest, bystander cardiopulmonary resuscitation, and receiving coronary angiography and PCI) were included and a backwards selection logistic regression was conducted using a generalized estimating equation and a backward elimination technique, which also accounted for clustering by hospital. A test for collinearity of variables was done in the multivariate models. There was no indication of collinearity for any of the variables, based on the observation that the variance inflation factor was <10 for all variables. Predictors were retained at an alpha of 0.05. The annual trend in TTM use was evaluated using the Cochran-Armitage Trend Test. Unadjusted survival to hospital discharge and unadjusted survival to hospital discharge with good neurologic outcome (CPC 1 or 2), were determined for the entire cohort and for those receiving and not receiving TTM. Logistic regression analysis for survival to hospital discharge with good neurologic outcome (CPC 1 or 2) with versus without TTM was performed, adjusting for age, sex, race, initial shockable rhythm, witnessed arrest, bystander cardiopulmonary resuscitation, and receiving coronary angiography and PCI.

RESULTS

From April 2011 to August 2017 there were 12 238 patients with OHCA and ROSC in the registry, of whom 8072 were eligible for TTM and make up the study cohort (Figure 1). TTM was initiated in 4154 patients (51.5%) and was not initiated in 3767 patients (46.7%). For the entire cohort, median age was 67 years (interquartile range, 56 to 79 years), 4780 patients (59.2%) were men, 3427 patients (42.5%) were White, and 1997 patients (24.7%) were Hispanic (Table 1). The most common location of OHCA was a personal residence in 4841 patients (60.0%) and a skilled nursing facility in 1216 patients (15.1%). The initial rhythm was ventricular tachycardia/ventricular fibrillation in 2184 patients (27.1%) and a non-shockable rhythm in 5303 patients (65.7%). Bystander was the witness to arrest in 5404 patients (67.0%). Bystander cardiopulmonary resuscitation occurred in 3306 patients (41.0%). ST-segment–elevation myocardial infarction was present in 1137 patients (14.1%) and coronary angiography and PCI were performed in 1480 patients (18.3%) and 779 patients (9.7%), respectively. For patients who received TTM, it was initiated in the ED in 2627 patients (63.2%) and in the intensive care unit in 1264 patients (30.4%).

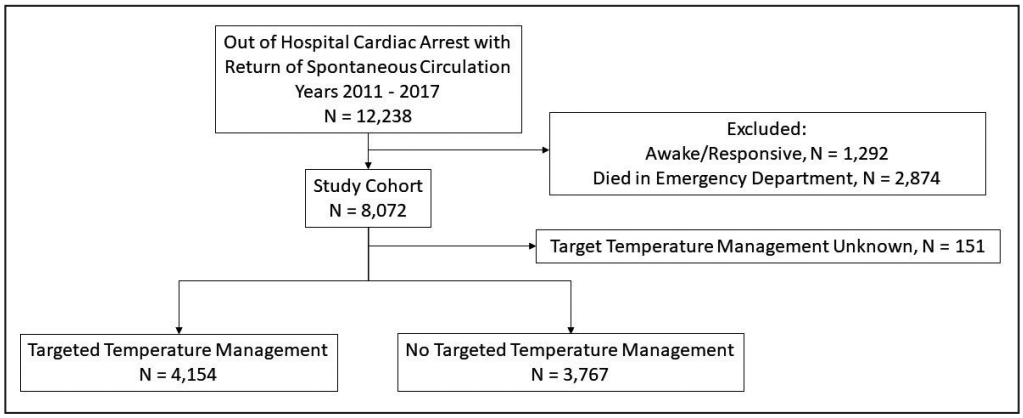

Figure 1. Study flow diagram.

In univariate analysis, patients receiving TTM were more likely to be younger, men, non-White, with location of arrest in a personal residence, had an initial shockable rhythm, had bystander witnessed arrest, and were more likely to present with ST-segment–elevation myocardial infarction, and undergo coronary angiography and PCI (Table 1). Patients not receiving TTM were more likely to have the arrest occur in a skilled nursing facility. There was a significant increase in the use of TTM from 2011 to 2017, from 49.4% to 55.7%, *P* value for trend was 0.005. (Table S1).

The reasons TTM was not initiated are listed in Table 2. The most common reasons were an existing do not resuscitate order in 716 patients (19.0%), other rationale not otherwise specified in 629 patients (16.7%), and persistent hypotension in 481 patients (12.8%). A significant number of patients had no reason documented (645 patients, 17.1%). In the exploratory analysis of factors associated with TTM use, an initial shockable rhythm, witnessed arrest, and receiving coronary angiography were associated with receiving TTM (Figure 2). In contrast, female sex and increasing age were associated with not receiving TTM.

Survival to hospital discharge was 34.1% for the entire cohort. Survival to hospital discharge was 41.3% and 25.9% for those receiving and not receiving TTM, respectively. Among survivors, survival to hospital discharge with CPC 1 or 2 was 47.7% overall, and 54.2% and 38.6% for those receiving and not receiving TTM, respectively. TTM was associated with improved odds of survival to hospital discharge with CPC 1 or 2; adjusted odds ratio, 1.71; 95% CI, 1.40 to 2.09 (Table S2).

DISCUSSION

In the current study, we report a contemporary analysis of a large regional system of care for OHCA that includes 36 hospitals serving a population of >10 million individuals. The study population was ethnically diverse with a high proportion of Hispanics and a high prevalence of women. We found the prevalence of TTM use to be ≈51% and observed a significant increase in TTM use over the study period. Further, we identified several patient and arrest characteristics that were associated with the use of TTM. Of note, we applied broad inclusion criteria, excluding only those who arrived awake and alert and those who died in the ED before the initiation of TTM. We chose these criteria in an attempt to make relevant observations about the true clinical use of TTM in this regional system of care.

Although TTM after OHCA has been associated with improved survival and neurologic outcomes, it remains underutilized in the United States.[9,11,16,17] An initial publication by Patel et al using the National Inpatient Sample found that <1% of patients received TTM.[9] In a more recent analysis from the same data set, Dresden et al found that the prevalence of TTM use increased to 2.5% in 2010 with significant variation among hospitals and geographic locations.[11] Despite the challenges of characterizing TTM use with an administrative database, these markedly low rates suggest infrequent use nationally.

Studies using CARES (Cardiac Arrest Registry to Enhance Survival) reported higher use of TTM. Coute et al reported on 8115 patients included in CARES from the state of Michigan from 2014 to 2015 and found variable use of TTM by hospitals, ranging from 29% to 68%.[16] In a larger analysis from CARES including >45 000 patients treated at 649 hospitals throughout the United States from 2013 to 2016, overall TTM use was 46%.[17] These rates of TTM use are similar to our results from the Los Angeles regional cardiac care system. However, EMS systems and hospitals self-select to contribute to CARES, and may achieve greater outcomes than their non-participating peers and so are not representative of the true national prevalence of TTM use. A more recent study by Khera et al reported

Table 1. Characteristics for All Patients and for Those Receiving and Not Receiving Targeted Temperature Management

Characteristic	All Patients (n=8072)	Targeted Temperature Management (n=4154)	No Targeted Temperature Management (n=3767)	*P* Value
Age, median (IQR), y	67 (56–79)	64 (53–75)	72 (59–83)	<0.0001
Sex				
Men	4780	2637 (63.5)	2053 (54.5%)	Ref
Women	3283	1513 (36.4)	1711 (45.4)	<0.0001
Unknown	9			
Race/Ethnicity				
White	3427	1771 (52.7%)	1572 (45.9%)	Ref
Hispanic	1997	1034 (51.8%)	935 (46.8%)	0.97
Black	1151	671 (58.3%)	464 (40.3%)	0.0002
Asian	956	423 (44.2%)	521 (54.5%)	<0.0001
Unknown	541			
Location of arrest				
Personal residence	4841	2584 (53.4%)	2217 (45.8%)	Ref
Skilled nursing facility	1216	345 (28.4%)	863 (71.0%)	<0.0001
Public site	739	525 (71.0%)	208 (28.1%)	<0.0001
Physician office	230	112 (48.7%)	115 (50.0%)	0.05
Industrial site	37	25 (67.6%)	12 (32.4%)	0.08
Unknown	1009			
Initial rhythm				
Shockable				
Ventricular tachycardia/ fibrillation	2184	1546 (70.8%)	618 (28.3%)	Ref
Non-shockable				
Asystole	2967	1368 (46.1%)	1579 (53.2%)	<0.0001
Pulse electrical activity	2336	1071 (45.8%)	1248 (53.4%)	<0.0001
Unknown	585			
Witness to arrest				
Bystander	5405	2964 (54.8%)	2403 (44.4%)	<0.0001
Unwitnessed	1597	741 (46.4%)	836 (52.3%)	Ref
Emergency medical services	840	383 (45.6%)	453 (53.9%)	0.8
Unknown	230			
Bystander CPR	3306	1761 (53.3%)	1526 (46.2%)	0.13
ST-segment–elevation myocardial infarction	1137	705 (62.0%)	391 (34.4%)	<0.0001
Coronary angiography	1480	1082 (73.1%)	350 (23.6%)	<0.0001
Percutaneous coronary intervention	779	572 (73.4%)	178 (22.8%)	<0.0001
Location TTM initiated				
Emergency department	…	2627 (63.2%)	…	NA
Cardiac catheterization laboratory	…	145 (3.5%)	…	NA
Intensive care unit	…	1264 (30.4%)	…	NA
Unknown		118 (2.8%)		NA

CPR indicates cardiopulmonary resuscitation; IQR, interquartile range; NA, not applicable; and ref, reference group; and TTM, targeted temperature management.

on ≈8000 patients from 186 hospitals participating in the Resuscitation Outcomes Consortium Cardiac Arrest Epistry from 2012 to 2015 and found the median prevalence of TTM use was only 27%.[12] These data may provide a better estimate of TTM use throughout the United States. Notably, there was significant hospital variation and, unlike in our system, use of TTM significantly decreased over the study period. The

Table 2. Reasons Targeted Temperature Management Not Initiated (n=3767)*

Existing do not resuscitate order	716 (19.0%)
Other rationale	629 (16.7%)
Persistent hypotension	481 (12.8%)
Active bleeding	372 (9.9%)
Non-shockable initial rhythm	332 (8.8%)
Chronic renal disease	322 (8.5%)
Septic shock	304 (8.1%)
Terminal Illness	209 (5.5%)
Core temperature <35°C	161 (4.3%)
Preexisting coma	121 (3.2%)
ROSC care terminated	77 (2.0%)
Resuscitation duration >60 min	75 (2.0%)
Coma because of drug overdose	61 (1.6%)
Uncontrolled ventricular dysrhythmia	57 (1.5%)
Major head trauma	47 (1.2%)
Severe bradycardia	46 (1.2%)
Major surgery within 14 d	16 (0.4%)
Greater than 6 h from return of spontaneous circulation	11 (0.3%)
Pregnancy	7 (0.2%)
No reason documented	645 (17.1%)

ROSC indicates return of spontaneous circulation.
*More than 1 reason could be documented on a single patient.

relatively high prevalence of TTM use found in the current study and the increase in TTM use over the study period may be related to several factors. The regional system of cardiac care in Los Angeles County is well established and has been in place for over 10 years. Coordinated efforts by EMS leadership provide systemwide policies, which are continually reviewed and updated, and provide evidence-based guidelines on appropriate use. Bi-annual meetings are held to review data and share best practices for post-resuscitation care and include particular emphasis on TTM.

To our knowledge, only one prior study specifically evaluated use of in-hospital TTM within a regional system of care in the United States.[18] Mooney et al reported on 104 patients treated at the Minnesota Heart Institute with a newly established TTM protocol in 2011. Given that this protocol was newly established, all 104 patients described in the study received TTM. Our current analysis complements this initial description by the Minnesota Heart Institute. The ability to integrate a TTM protocol into an existing system of care for patients with OHCA has implications for more widespread use throughout the United States. The ability to mandate TTM use in these established systems of care would be expected to increase TTM use and also reduce hospital variation. As noted, prior studies suggest large variations in TTM use throughout hospitals within the United States.[12,16]

There are several limitations to the present analysis. We included all patients with OHCA and ROSC and excluded only patients who were either awake and alert in the ED and those that died in the ED. We chose this approach to be inclusive of all patients being considered for TTM, since the registry data, including rationale for withholding TTM, was abstracted from the chart subsequent to that decision. Differences in the inclusion and exclusion criteria of the current study compared with prior studies may explain some of the variation in TTM use. The current study includes patients treated within a single regional care system that has been operational for >10 years. The applicability of these results to other regional care systems with different treatment protocols remains unclear. Although all patients were evaluated for TTM, the specific approach to cooling was not standardized and included various devices and approaches. This variability may have influenced the ability to proceed with TTM. Given the retrospective nature of data collection, the current analysis was limited to the variables present within the

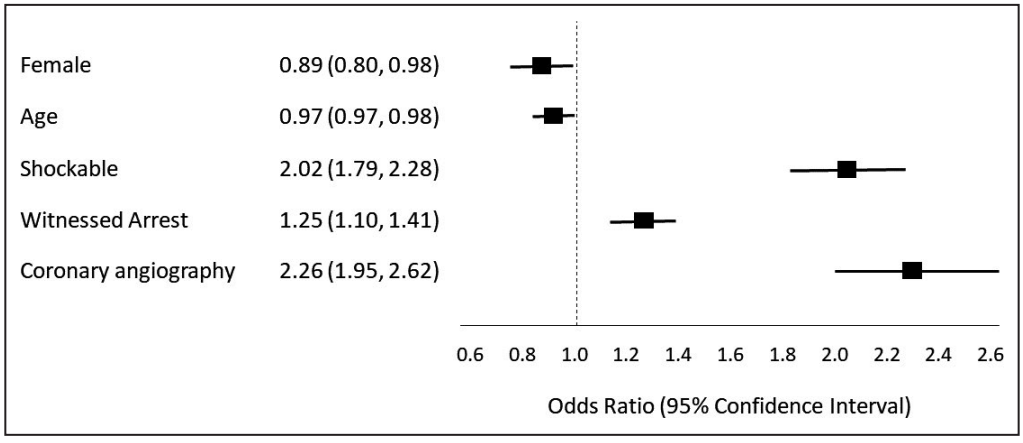

Figure 2. Characteristics associated with use of targeted temperature management.

data registry. Although missing data were minimal for the majority of variables within the data registry, ≈15% of the cohort did not have data extracted for race. Further, causality cannot be determined and, therefore, evaluation of factors associated with TTM use and the association of TTM with clinical and neurologic outcome remain exploratory.

CONCLUSIONS

Within a large regional system of care in Los Angeles County, use of TTM was substantially higher than previously reported in the literature at just over 50%. Use of integrated systems of care may be a novel method to increase TTM use within the United States.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. **Targeted temperature management use by year.**

Year	TTM use N (%*)	Total N
2011	308 (49.4)	626
2012	454 (46.8)	985
2013	603 (53.6)	1141
2014	580 (54.2)	1109
2015	670 (51.8)	1319
2016	743 (52.8)	1435
2017	796 (55.7)	1457

TTM – targeted temperature management

*Percentage of known patients; excludes 151 patients with unknown TTM status.

Table S2. Logistic regression analysis for survival to hospital discharge with cerebral performance category 1 or 2, n = 6875.

Characteristic	Adjusted Odds Ratio (95% CI)
Targeted temperature management	1.71 (1.40-2.09)
Female sex	0.84 (0.72-0.99)
White race (reference: non-white)	1.23 (1.05-1.43)
Age (years)	0.97 (0.97-0.98)
Initial shockable rhythm	4.54 (3.68-5.61)
Witness arrest	1.70 (1.39-2.09)
Bystander cardiopulmonary resuscitation	1.08 (0.98-1.20)
Coronary angiography	1.52 (1.20-1.92)
Percutaneous coronary intervention	0.97 (0.81-1.15)

CI – confidence interval