Impact of Presenting Rhythm on Short- and Long-Term Neurologic Outcome in Comatose Survivors of Cardiac Arrest Treated With Therapeutic Hypothermia*

Samuel W. Terman, MD, MS[1]; Benjamin Hume, BS[1]; William J. Meurer, MD, MS[1,2]; Robert Silbergleit, MD[1]

Objectives: To compare short- and long-term neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest treated with mild therapeutic hypothermia presenting with nonshockable versus shockable initial rhythms.

Design: Retrospective cohort study.

Setting: Emergency department and ICU of an academic hospital.

Patients: One hundred twenty-three consecutive post–out-of-hospital cardiac arrest adults (57 nonshockable rhythms, 66 shockable rhythms) treated with therapeutic hypothermia between 2006 and 2012.

Interventions: None.

Measurements and Main Results: Data were collected from electronic health records. Neurologic outcomes were dichotomized by Cerebral Performance Category at discharge and 6- to 12-month follow-up and analyzed via multivariable logistic regressions. Groups were similar, except nonshockable rhythm patients were more likely to have a history of diabetes mellitus ($p = 0.01$), be dialysis dependent ($p = 0.01$), and not have bystander cardiopulmonary resuscitation ($p = 0.05$). At discharge, 3 of 57 patients (5%) with nonshockable rhythm versus 28 of 66 (42%) with shockable rhythm had a favorable outcome (unadjusted odds ratio, 0.08; 95% CI, 0.02–0.3; adjusted odds ratio, 0.1; 95% CI, 0.03–0.4). At follow-up, 4 of 55 patients (7%) versus 29 of 60 (48%) with nonshockable rhythm and shockable rhythm, respectively, had a favorable Cerebral Performance Category (odds ratio, 0.08; 95% CI, 0.03–0.3; adjusted odds ratio, 0.09; 95% CI, 0.09–0.3). Among those surviving hospitalization, favorable neurologic outcome was more likely at long-term follow-up than at hospital discharge for both groups (odds ratio, 2.5; 95% CI, 1.3–4.7; adjusted odds ratio, 2.9; 95% CI, 1.4–6.2). No significant interaction between changes in neurologic status over time and presenting rhythm was seen ($p = 0.93$).

Conclusions: These data indicate an association between initial nonshockable rhythm and significantly worse short- and long-term outcomes in patients treated with mild therapeutic hypothermia. Among survivors, neurologic status significantly improved over time for all patients and shockable rhythm patients and tended to improve over time for the small number of nonshockable rhythm patients who survived beyond hospitalization. No significant interaction between changes in neurologic status over time and presenting rhythm was seen. (*Crit Care Med* 2014; 42:2225–2234)

Key Words: cardiac arrest; coma; hypothermia; long term; neurologic outcome; rhythm

***See also p. 2303.**

[1]Department of Emergency Medicine, University of Michigan Medical School, Ann Arbor, MI.

[2]Department of Neurology, University of Michigan Medical School, Ann Arbor, MI.

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Address requests for reprints to: Robert Silbergleit, MD, UM Neurologic Emergencies Research, 24 Frank Lloyd Wright Drive, Lobby H, Suite 3100, Box 381, Ann Arbor, MI 48105. E-mail: robert.silbergleit@umich.edu

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Over 420,000 out-of-hospital cardiac arrests (OHCAs) occur each year in the United States, with an estimated overall survival to hospital discharge of 10.4% for emergency medical services (EMS)-treated nontraumatic arrests (1). Neurologic morbidity and mortality are considerable in patients resuscitated from cardiac arrest (2). Mild therapeutic hypothermia (MTH) has been shown in randomized clinical trials to benefit patients presenting with shockable rhythms (SRs), that is, ventricular fibrillation and pulseless ventricular tachycardia (VF/VT) (3–5). However, understanding the impact of presenting rhythm on prognosis is becoming increasingly valuable from a clinical practice perspective given that nonshockable rhythms (nSRs) have been comprising a larger proportion of OHCA over the past several decades (6, 7). Furthermore, current guidelines indicate that MTH may be considered for comatose patients resuscitated from initially nSRs (8) based on conflicting observational data despite lack of randomized data in this population (9–14).

An important limitation of many available observational data is that they often do not assess neurologic outcome beyond hospital discharge (10, 11, 14). Studies that have followed patients beyond hospital discharge are largely noninformative regarding the impact of presenting rhythm on recovery due to either recording only one time point or not studying patients of both SRs and nSRs (4, 12, 15–19). Consequently, the long-term impact of rhythm including the likelihood that survivors of both rhythms will recover neurologic function from their postdischarge status remains unclear. Since neurologic recovery may not plateau for weeks to months after a cardiac arrest, both hospital discharge evaluation and long-term follow-up are needed to determine the effect of presenting rhythm on ultimate functional outcome. Patients with nSR versus SR arrests may differ in either the rate or magnitude of recovery (or both), and these may be identified by examining change between short- and long-term outcomes. Furthermore, comparing outcomes of nSR arrests with those of SR arrests may inform clinical practice of whether to cool nSR arrests by suggesting whether benefits of MTH are sustained over time.

In this study, we sought to compare short- and long-term neurologic outcomes in patients presenting with nonshockable versus shockable initial rhythms after implementation of MTH. We hypothesize that patients presenting with nSR will have a worse prognosis than those with SR, but that survivors of both rhythms will remain stable or improve over time.

METHODS

Study Design

This was an observational retrospective cohort study (20). Patients were classified by their initial presenting rhythm by EMS or Emergency Department records and followed in time via electronic health records. Being classified as “shockable” means that an automatic external defibrillator was applied which advised a shock, or the emergency department (ED) or EMS flowsheets/runsheets mark the presenting arrest rhythm as either VF or pulseless VT. Being classified as “nonshockable” means that either it was document that an automated external defibrillator did not advise a shock, ED or EMS flowsheets/runsheets specify pulseless electrical activity or asystole as the presenting cardiac rhythm, or else presenting rhythm and defibrillation is not specifically mentioned, but there exists sufficient medical documentation detailing resuscitative efforts such that it would be reasonable to assume that a defibrillation would have been documented if it had been delivered.

Patient Selection

Electronic health records were screened for all patients presenting to the University of Michigan Emergency Department with a presentation or diagnosis coded as OHCA following implementation of MTH program between July 1, 2006, and September 14, 2012. To ensure that we captured all eligible subjects, we also screened patients included on an independent log of therapeutic temperature modulation equipment use. Patients were excluded if they were less than 18 years old at the time of arrest, received temperature management therapy for a diagnosis other than cardiac arrest (i.e., rewarming after environmental hypothermia), initial rhythm could not be ascertained, or if cooling protocol was initiated but aborted before actually receiving cooling. All patients meeting the above criteria with either SR or nSR were included.

Therapeutic Hypothermia

MTH at our institution consisted of endovascular cooling (Innercool-Phillips, San Diego, CA) for 24 hours at a target of 33°C followed by controlled rewarming over 24 hours back to normothermia. Placement of the endovascular temperature control catheter typically occurred in the Emergency Department, but sometimes occurred in the interventional cardiology suite or the ICU depending on clinical situation. Cold IV crystalloid bolus was allowed to initiate cooling if placement of the catheter may be delayed. This hypothermia protocol is applied to all rhythms consistently, and protocol at our institution is to cool patients of both rhythms.

Data Collection and Outcome Assessment

This project was reviewed and determined exempt by the University of Michigan Institutional Review Board (HUM00018775). Data were collected and modeled after Utstein recommendations (21) and reported according to accepted standards in chart review research (22).

All data were abstracted from University of Michigan electronic medical health records by the primary author (S.W.T.). The author was not blinded to the study purpose or patients’ presenting rhythm. Details regarding demographics, past medical history, the event and resuscitation, hypothermia protocol, and discharge vital status were determined. Return of spontaneous circulation (ROSC) defined for purposes of the patient flow diagram is interpreted as more than transient return of spontaneous circulation, that is, pulse on two consecutive pulse checks and no immediate rearrest.

Data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools (23, 24) hosted by the University of Michigan.

Neurologic outcomes were characterized by Cerebral Performance Category (CPC) (25–27). Outcomes were dichotomized as favorable (CPC 1–2, i.e., no symptoms and/or independence) or unfavorable (CPC 3–5, i.e., dependent, comatose, or dead) at hospital discharge and 6–12 months postdischarge. Outcomes were determined by reviewing inpatient and outpatient physician and Physical/Occupational Therapy evaluations. Determination of CPC from chart review has been previously determined to have moderately good correlation with that determined by patient interview (28). CPCs were determined by two independent reviewers (S.W.T., R.S.). Initial interrater agreement was

85% and 73% for nondeceased CPC categories at discharge and follow-up, respectively, and when discordant, resolved by consensus. We used the first note after 6 months that provided sufficient information relevant to neurologic symptoms on which to base our assessment. If no informative note existed in the relevant time interval but medical records indicated a consistent CPC before and after the interval of interest without mention of significant intervening event, such records were incorporated. If no such note existed or the patient was lost to follow-up from the University of Michigan electronic records, they were recorded as having a missing CPC. If 6-month vital status was unavailable from medical records, we searched the Social Security Death Index Master File (accessed May 14, 2013).

Statistical Analysis

Descriptive statistics are used to characterize the patient cohort. Continuous variables are described using medians and interquartile ranges (IQRs). Categorical variables are described as frequencies and percentages within each group. Baseline comparisons between SR and nSR groups were analyzed parametrically or nonparametrically as appropriate using Student *t* tests or Wilcoxon rank sum tests for continuous variables and Pearson chi-square or Fisher exact tests for categorical variables.

Logistic regression models were used to compare neurologic outcome for the two types of arrests at discharge and at follow-up. For these models, the five-category CPC score was dichotomized (CPC 1–2, favorable; CPC 3–5, unfavorable). Favorable neurologic category was modeled as the outcome in these models. Separate logistic regression models were fit to compare available CPCs for nSR versus SR patients at hospital discharge and then again at follow-up. Multivariable logistic regressions were conducted when analyzing categorical outcomes data first unadjusted and then adjusted for variables which differed between the two groups including past history of diabetes mellitus, whether the event was witnessed, and whether the patient received bystander cardiopulmonary resuscitation (CPR). Although history of dialysis dependence was significantly different between the SR and nSR groups, regressions were not adjusted for dialysis dependence because all dialysis patients ($n = 9$) had an unfavorable outcome. Adjusting for such a covariate results in a quasi-complete separation in the logistic regression model, which produces an infinite bound for the CI, so dialysis was not included as a covariate.

To test for trend in CPC over time, first we include a McNemar test comparing CPC at discharge to CPC at follow-up. We then conduct a logistic regression model with generalized estimating equations (GEE) in order to adjust for the same covariates used in the aforementioned adjusted logistic regressions. The GEE analysis takes into account the within-subject correlation by adding a repeated measures structure to the logistic regression. Individuals with missing data points were excluded from relevant analyses. All data were analyzed using SAS 9.3 (SAS Institute, Cary, NC).

A power calculation was performed based on previous studies that captured outcomes for both nSR versus SR treated with hypothermia (11, 16). These prior data suggest an unadjusted odds ratio (OR) of approximately 0.25 for a good CPC at either discharge or follow-up for an nSR compared with SR, and proportion of SR with good outcome was approximately 40–60%. Based on these estimates, we would need a total sample size of at least 92 to detect such differences with 80% power at a 0.05 level of significance.

RESULTS

Patient Characteristics

The population screened included 509 adult patients presenting to the ED or diagnosed with OHCA in the ED within the given dates (**Fig. 1**). We were able to ascertain whether the initial rhythm was shockable in 506. Of these 506, there were 339 nSR, 194 of whom had any ROSC, and 57 had cooling initiated. Of the 506, there were 167 SR, 126 of whom had any ROSC, and 67 had cooling initiated. One SR patient who would have been eligible did not have a CPC available at either discharge or follow-up, so 66 SR patients were included. Of adult OHCAs with ROSC who were admitted, cooling was initiated in 59 of 150 (39%) of nSR arrests versus 67 of 114 (59%) of SR arrests ($p = 0.002$). Among included nSR, 9 of 57 (16%) terminated the cooling protocol prematurely due to deteriorating clinical condition; among included SR, 8 of 66 (12%) did so ($p = 0.55$).

Patient baseline characteristics for included patients are displayed in **Table 1**. The two groups had similar distributions of demographic variables, but those with nSR were more likely to have a history of diabetes mellitus ($p = 0.006$), be dialysis dependent ($p = 0.01$), not have bystander CPR ($p = 0.047$), and tended to have more unwitnessed arrests ($p = 0.052$). Etiology of arrests was also significantly different ($p < 0.0001$) with cardiac causes most prevalent in the SR group and respiratory causes more prevalent in those with nSR.

Among those who expired, life support was withdrawn prior to expiration in 38 of 48 patients (79%) with nSR and 24 of 28 patients (86%) with SR ($p = 0.48$).

Comparison of nSR Versus SR Outcomes

No CPCs were missing at discharge. Two of 57 nSR patients (4%) versus 6 of 66 SR patients (9%) had a CPC missing at follow-up ($p = 0.28$).

At hospital discharge, 3 of 57 patients (5%) with nSR versus 28 of 66 (42%) with SR had a favorable outcome (unadjusted OR, 0.08; 95% CI, 0.02–0.3; $p < 0.0001$; adjusted OR, 0.1; 95% CI, 0.03–0.4; $p = 0.0005$) (**Fig. 2, *A*** and ***C***).

Follow-up occurred at a median 6.8 months (IQR, 6.0–8.6). Length of follow-up was similar between nSR and SR groups ($p = 0.85$). At follow-up, 4 of 55 (7%) versus 29 of 60 (48%) of patients with nSR and SR, respectively, had a favorable CPC (OR, 0.08; 95% CI, 0.03–0.3; $p < 0.0001$; adjusted OR, 0.09; 95% CI, 0.09–0.3; $p = 0.0001$) (**Fig. 2, *B*** and ***C***).

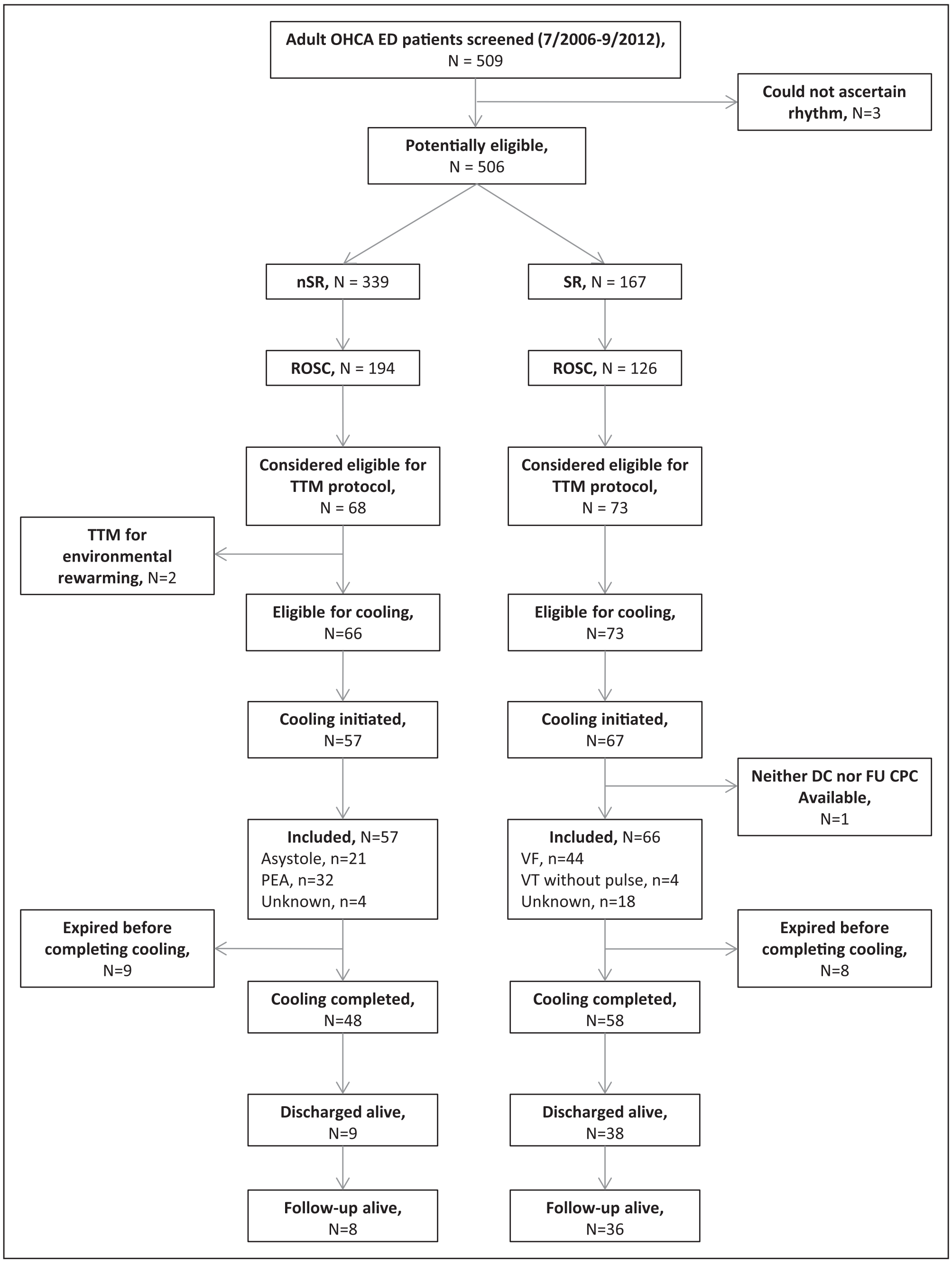


Figure 1. Case selection. CPC = Cerebral Performance Category, DC = discharge, ED = emergency department, FU = follow-up, nSR = nonshockable rhythm, OHCA = out-of-hospital cardiac arrest, PEA = pulseless electrical activity, ROSC = return of spontaneous circulation, SR = shockable rhythm, TTM = therapeutic temperature modulation, VF = ventricular fibrillation, VT = ventricular tachycardia.

Comparison of Follow-Up Versus Discharge Outcomes for All Patients

Individual outcomes over time for all patients by rhythm are traced in **Figure 3, *A* and *B***. As displayed in Figure 2, among patients with nSR arrests, 3 of 57 (5%) had a favorable outcome at discharge versus 4 of 55 (7%) at follow-up (McNemar test $p = 0.16$). Among SR arrests, 28 of 66 (42%) had a favorable outcome at discharge versus 29 of 60 (48%) at follow-up, respectively (McNemar test $p = 0.046$). Overall, 31 of 123 patients (25%) had a favorable outcome at hospital discharge versus 33 of 115 patients (29%) at follow-up (McNemar test $p = 0.01$).

Comparison of Follow-Up Versus Discharge Outcomes Among Hospital Survivors

Given that CPCs of patients who expired in the hospital will not change over time, we then conducted detailed analyses of the 47 of 123 patients (38%) who were discharged from the hospital alive in order to characterize neurologic recovery overall and according to rhythm among survivors.

Among nSR arrests who survived, 3 of 9 (33%) had a favorable outcome at discharge versus 4 of 7 (57%) at follow-up (McNemar test $p = 0.16$) (**Fig. 3C**). Note that these numbers do not exactly match those in Figure 3*C* because Figure 3*C* includes patients only if they have an outcome available at both discharge and follow-up. Among those patients with a CPC at both time points, 2 of 7 (29%) improved, 2 of 7 (29%) worsened, and 3 of 7 (43%) did not change CPC (**Fig. 3*D***).

Among SR arrests who survived, 28 of 38 (74%) had a favorable outcome at discharge versus 29 of 32 (91%) at follow-up, respectively (McNemar test $p = 0.046$) (Fig. 3*C*). Among those patients with a CPC at both time points, 12 of 32 (38%) improved, 4 of 32 (13%) worsened, and 16 of 32 (50%) did not change CPC (Fig. 3*D*).

Overall, 31 of 47 survivors (66%) had a favorable outcome at hospital discharge versus 33 of 39 (85%) at follow-up (McNemar test $p = 0.01$) (Fig. 3*C*). No patient of either rhythm who had a favorable CPC at discharge declined to an unfavorable CPC at follow-up, though patients did improve from an unfavorable to a favorable CPC. There was no difference in distribution of CPC improvement according to rhythm ($p = 0.63$) (Fig. 3***D***).

We then conducted regressions using GEEs to determine if neurologic recovery of hospital survivors was modified by rhythm and to adjust for confounders (**Table 2**). In a

TABLE 1. Baseline Clinical Characteristics of Patients with Nonshockable Versus Shockable Presenting Rhythms

Clinical Characteristics	Nonshockable (n = 57) n (%)	Shockable (n = 66) n (%)	p
Median (IQR) age (yr)	59 (52–71)	62 (52–72)	0.5
Median (IQR) body mass index (kg/m^2)	28 (23–33)	27 (24–30)	0.23
Sex (male)	32 (56%)	47 (71%)	0.08
Past medical history			
Myocardial infarction	8 (14%)	15 (23%)	0.22
Congestive heart failure	8 (14%)	11 (17%)	0.69
Cerebrovascular disease[a]	7 (12%)	8 (12%)	0.98
Dementia	0 (0%)	2 (4%)	0.21
Diabetes mellitus	21 (37%)	10 (15%)	**0.006**
Dialysis	8 (14%)	1 (2%)	**0.01**
Witnessed	41 (72%)	56 (86%)	0.052
Bystander cardiopulmonary resuscitation	34 (61%)	51 (77%)	**0.047**
Etiology			**< 0.0001**
Cardiovascular	3 (5%)	28 (42%)	
Respiratory	13 (23%)	1 (2%)	
Unknown	30 (53%)	31 (47%)	
Other[b]	11 (19%)	6 (9%)	
Time to target (hr)[c]	5.9 (3.8–8.5)	5 (3.5–8.2)	0.3

IQR = interquartile range.

[a]Includes ischemic or hemorrhagic stroke, or transient ischemic attack.

[b]Includes electrolyte abnormality (1 shockable rhythm [SR], 1 nonshockable rhythm [nSR]), drowning (1 nSR), allergic reaction (1 nSR), hanging (2 nSRs), drug overdose (4 nSRs), sepsis (1 nSR), trauma (1 nSR), electrocution (4 SRs), and coitus (1 SR).

[c]Duration between emergency department arrival and consecutive recorded core body temperatures < 33.5°C.

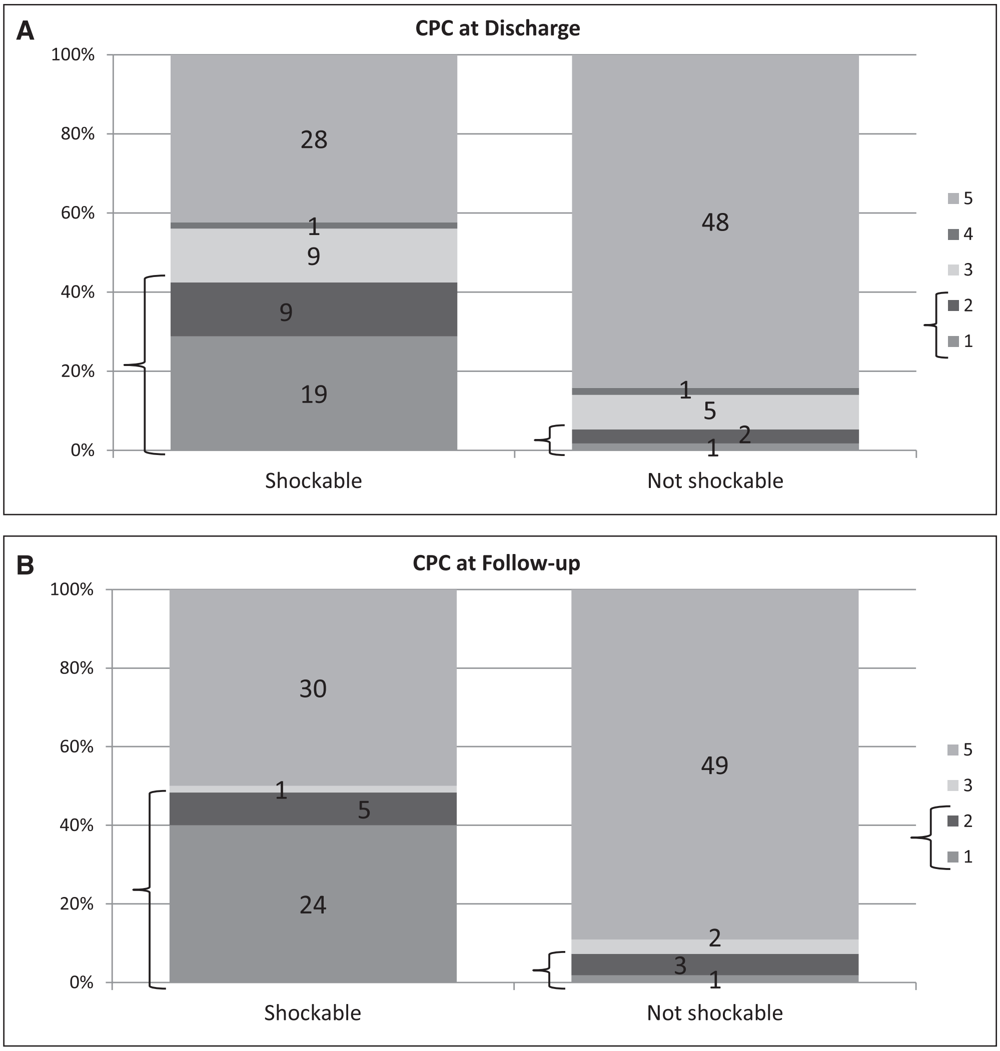
p values < 0.05 are indicated in boldface font.

model including rhythm, follow-up, and their interaction, patients with nSR arrests nonsignificantly tended to be more likely to have a favorable CPC at discharge versus follow-up (unadjusted OR, 3.0; 95% CI, 0.7–13; p = 0.13; adjusted OR, 1.6; 95% CI, 0.4–6.7; p = 0.52), and patients with SR arrests were significantly more likely to have a favorable CPC at discharge versus follow-up (unadjusted OR, 2.8; 95% CI, 1.2–6.3; p = 0.0.01; adjusted OR, 3.1; 95% CI, 1.4–7.1; p = 0.007). The interaction between rhythm and follow-up was not significant (unadjusted p = 0.93; adjusted p = 0.93), which indicates that CPC improvement did not significantly change according to rhythm. We therefore refit the model dropping the interaction term. In such a model, patients had a significantly higher odds of a favorable CPC at follow-up versus discharge (unadjusted OR, 2.5; 95% CI, 1.3–4.7; p = 0.004; adjusted OR, 2.9; 95% CI, 1.4–6.2; p = 0.005).

We performed a sensitivity analysis excluding all dialysis-dependent patients, given that dialysis patients did overwhelmingly poorly. All analyses were repeated, and no results significantly changed.

DISCUSSION

MTH has been demonstrated to reduce neurologic morbidity and mortality in randomized trials for survivals of OCHA with shockable presenting rhythms (3–5). Since then, clinicians have been left to struggle with whether MTH should be applied to other comatose survivors of cardiac arrest (29). With regard to patients presenting with nSR, there are essentially no informative randomized controlled data. One meta-analysis (9) has examined the effect of hypothermia on patients presenting with nSR. They identified only two pilot randomized studies including a total 22 patients with nSR treated with MTH (30, 31) from which they estimated a relative risk 0.85 (0.65–1.11) for 6-month mortality compared with a nSR arrest not treated with hypothermia. In addition to being too small to inform clinical decision making, these two studies employed experimental cooling methods that are not generally used in practice, limiting their external validity. Observational studies have been heterogeneous (11, 13, 14, 32). Ten observational studies included in the meta-analysis suggested an relative risk of 0.84 (95% CI, 0.71–0.92) and 0.93 (95% CI, 0.88–1.00) for hospital



C

OR (95% CI) for a Favorable Neurological Outcome Comparing nSR vs SR

		Unadjusted	Adjusted*
Time Point	Discharge	0.08 (0.02-0.3)	0.1 (0.03-0.4)
	Follow-up	0.08 (0.03-0.3)	0.09 (0.03-0.3)

*Adjusted for past history of diabetes, whether the event was witnessed, and whether the event received bystander CPR

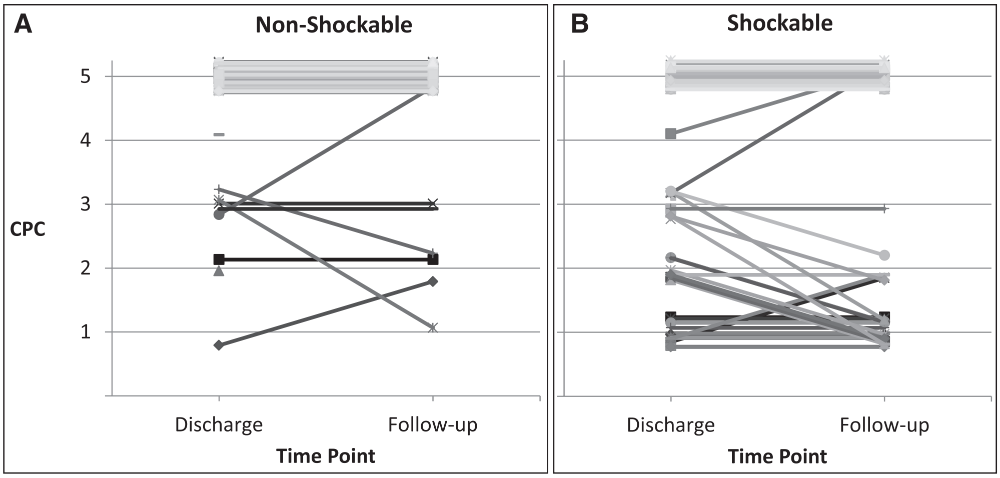
Figure 2. Comparison of neurologic outcomes for nonshockable rhythm (nSR) and shockable rhythm (SR) arrests and discharge and follow-up. **A** and **B**, Bracket markers delineate favorable Cerebral Performance Category (CPC) (1 or 2). Numbers inside each category on the graph indicate *n* values. **C**, Results of multivariable logistic regression for a favorable neurologic outcome (dichotomized outcome) comparing nSR versus SR arrests at hospital discharge and again at follow-up. CPR = cardiopulmonary resuscitation, OR = odds ratio.

mortality and unfavorable neurologic outcomes, respectively, both in favor of hypothermia. Controlled trial data are still needed to determine efficacy of MTH in these expanded patient populations.

The association between presenting rhythm and outcome has been evaluated in the prehypothermia era (33–36). One study in the prehypothermia era suggested that survivors of both nSR and SR arrests had similar cognitive, physical, and psychosocial function at follow-up regardless of presenting rhythm (37). Another prehypothermia study found that 73% of those surviving 1 year beyond the arrest returned to prearrest function, though they did not differentiate between nSR and SR (38). On the other hand, delayed deaths and disability may also occur in survivors of cardiac arrest (39, 40), so an appreciation of patient outcomes over time is essential to make informed treatment decision and prognoses. Furthermore, it is appreciated that conventional prognostic signs may be altered in the presence of hypothermia and continue to be evaluated (19), so studying such questions specifically in the hypothermia population is essential.

In the hypothermia era, studies have been conducted with short-term endpoints (10, 11, 14). For example, Oddo et al (10) sought to define factors associated with favorable neurologic outcomes at hospital discharge by reviewing medical records and found that 3 of 36 (8%) and 21 of 38 (55%) patients with nSR and SR arrests, respectively, had a favorable neurologic outcome ($p < 0.001$). However, after multivariable analysis adjusting for time from collapse to ROSC, blood lactate, and other covariates, initial rhythm was no longer a significant predictor. This differs from our results possibly because we did not adjust for time to ROSC. Doing so would have excluded all unwitnessed arrests, an important subgroup, from our analysis. The results of Oddo et al (10) support the presumption that the effect of rhythm may be a surrogate for ischemic duration, severity of injury, or ability to promptly correct the underlying etiology, that is, poor prognosis may not be inherent to the nSR itself.

It is also important to understand long-term outcomes of different cooled patient populations to determine if potential treatment effects are sustained. Several prospective studies seeking to determine factors associated with prognosis have evaluated patients at time points several months after discharge and have found nSR to be a significantly, albeit not



C

All Arrests		Favorable CPC at Follow-up: No	Favorable CPC at Follow-up: Yes	McNemar's Test p-value
Favorable CPC at DC	No	6	6	p=0.01
	Yes	0	27	

Shockable Arrests		Favorable CPC at Follow-up: No	Favorable CPC at Follow-up: Yes	McNemar's Test p-value
Favorable CPC at DC	No	3	4	p=0.046
	Yes	0	25	

Non-shockable Arrests		Favorable CPC at Follow-up: No	Favorable CPC at Follow-up: Yes	McNemar's Test p-value
Favorable CPC at DC	No	3	2	p=0.16
	Yes	0	2	

D

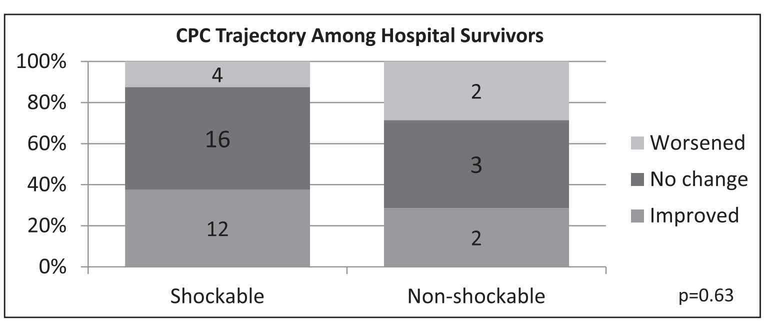


Figure 3. Comparison of neurologic outcomes for nonshockable rhythm and shockable rhythm arrests and discharge and follow-up. **A** and **B**, Each line represents an individual patient. Data appear staggered around Cerebral Performance Category (CPC) integers to assist visualization, though all CPCs are integer values. Plots include all patients, according to rhythm. Individuals with only a single data point available are represented by a point. **C**, Comparison of dichotomized outcomes at discharge versus follow-up. **D**, Depiction of whether individuals who were discharged alive worsened, remained stable, or improved in CPC between hospital discharge and follow-up. Numbers inside each category on the graph indicate *n* values. *p* value is for chi-square test. DC = discharge.

did not consider those that did not survive to 6 months. Bro-Jeppesen et al (15) evaluated patients treated with hypothermia after cardiac arrest and determined CPC at ICU discharge and then again at hospital discharge, but only reported data for the 52 presenting with SR. They also evaluated survival, cognitive function, and health-related quality of life at 6 months in 21 of these SR patients. Changes occurred in CPC between ICU and hospital discharge, but they did not evaluate CPC at 6 months so it is difficult to make conclusions about long-term trajectories from their data. Rossetti et al (17) found a favorable CPC in 9% versus 32% of those with nSR and SR ($p = 0.005$) at 3–6 months. However, as was the case in aforementioned studies, they did not record CPCs at more than one time point for comparison to fully evaluate recovery.

Such studies suggest that rhythm is associated with outcomes, whether or not a patient suffering OHCA is treated with hypothermia. However, an important question unanswered by these studies is the degree to which survivors recover brain function after discharge and whether recovery back to adequate cerebral function depends upon the presenting rhythm. The postcardiac arrest syndrome involves a complex physiological cascade of brain and myocardial dysfunction followed by a systemic ischemic reperfusion response which is in rapid flux post-ROSC (41). The ability to trace individual-level data over time as we have done is extremely useful to explore the interaction between rhythm and time in determining outcomes as patients transition from the dynamic acute to a more stable chronic state postarrest care.

invariably, poor prognostic factor in the context of multimodal clinical evaluation (17–19). Testori et al (12) recorded the best 6-month outcome in 135 patients with nSR treated with MTH and found a treatment effect as compared to a normothermic cohort. However, they did not evaluate the trajectory of recovery or compare long-term recovery to patients with SR. They also excluded arrests that were unwitnessed or fatal within 24 hours, which may overestimate favorable outcomes and exclude and important patient population. Cronberg et al (16) evaluated victims of cardiac arrest that had been treated with hypothermia and were still alive at 6 months. They found a favorable CPC (1, 2) in 31% of those with nSR as compared to 63% of those with SR, but did not examine recovery trajectory and

We evaluated outcomes for each patient at both discharge and at 6–12 months postdischarge. We then evaluated within-subject change in CPC between hospital discharge and 6- to 12-month follow-up. As expected, nSR patients exhibited poorer outcomes compared with SR patients at both time

TABLE 2. Comparison of Neurologic Outcomes for Nonshockable Rhythm and Shockable Rhythm Arrests and Discharge and Follow-Up: Results Are Obtained From Generalized Estimating Equations Analysis

	OR (95% CI) for a Favorable Neurologic Outcome Comparing Follow-Up Versus Discharge Among Hospital Survivors	
Presenting Rhythm Type	Unadjusted	Adjusted[a]
All (no interaction term)	2.5 (1.3–4.7)	2.9 (1.4–6.2)
Nonshockable rhythm only	3.0 (0.7–13)	1.6 (0.4–6.7)
Shockable rhythm only	2.8 (1.2–6.3)	3.1 (1.4–7.1)

OR = odds ratio.

[a]Adjusted for past history of diabetes, whether the event was witnessed, and whether the event received bystander cardiopulmonary resuscitation. The “All” model is also adjusted for nonshockable rhythm vs shockable rhythm.

The “nonshockable rhythm only” and “shockable rhythm only” rows are obtained from the full models including an interaction term between time and rhythm. The “All” row includes patients of both rhythms, and does not include an interaction term, given that the interaction term was not significant.

points. Patients who survived the hospitalization tended to improve over time, that is, had a significantly higher odds of favorable CPC at follow-up compared with discharge. This improvement was not significantly modified by presenting rhythm, though it is possible that with a larger sample of surviving nSR an interaction would have been seen. SR patients alone had a significantly higher odds of favorable outcome at follow-up versus discharge. The small number of nSR who survived hospitalization had a nonsignificant trend toward improvement over time, though our available sample size was too small to draw definitive conclusions regarding the trajectory of recovery for nSR survivors, except to say that no survivor who was discharged with a favorable outcome deteriorated to an unfavorable outcome over time and only a small number of initial survivors died within the year postdischarge.

Limitations and Strengths

First, there are several potential sources of selection bias. Chart review studies may suffer from missing data. However, no outcomes data were missing at discharge, and only 4% versus 9% of nSR versus SR CPCs were missing at follow-up ($p = 0.28$). Therefore, missingness was not a significant issue in the present study. Selection bias may have also stemmed from who was selected for cooling. A higher proportion of SR than nSR arrests received cooling. This is partly attributable to a higher proportion of SR achieving ROSC, but also attributable to a higher proportion of admitted patients received cooling in the SR group. We have clearly described patient flow in our Table 1 to allow the reader to assess such biases. It should also be noted that the “self-fulfilling prophecy” and differential selection of patients receiving hypothermia is an important limitation of all available prognostic studies in cardiac arrest, surely not limited to the current study (18).

Second, we conducted a single-center study. This was a disadvantage in terms of sample size. Few nSR patients survived over a 5- to 6-year period at our institution. This limited our ability to draw conclusions about neurologic recovery for nSR survivors. However, our sample size still enabled us to detect plausible statistical differences regarding outcomes by rhythm at both time points and significant improvement over time in the SR and total population. Perhaps if we had had more nSR survivors we would have detected a difference in the effect of time on outcomes by rhythm, or an interaction would have been detected. However, we did have a substantial SR and total patient population sizeable enough to draw a number of statistical conclusions, and a sizeable enough nSR overall population to compare with the overall SR population. Even with a small number of nSR survivors, we can still observe that no patient deteriorated from a favorable to an unfavorable outcome. This might suggest that benefits of cooling may be sustained in both rhythms and that cooling these patients may not be a futile effort, though we do not make claims in this study regarding the efficacy of cooling for nSR patients. Also, being a single-center study may preclude generalizing our results to smaller community institutions without endovascular capability. However, being a single-centered study did increase internal validity by allowing a more consistent application of a single cooling protocol to all patients.

Third, initial detected rhythm may misclassify patients given that rhythm is dynamic and may not reflect the patient’s true initial rhythm. This nondifferential misclassification of the exposure variable would likely bias our results toward the null, so if anything, the true association between initial rhythm and neurologic outcome would have even been stronger if no misclassification occurred.

Fourth, retrospective evaluation of CPC may be too crude to fully capture neurologic outcomes, and large-scale prospective multicentered data could better characterize outcomes.

Our study also has strengths in terms of our data collection and statistical analysis. To our knowledge, no study has thus far carefully charted individual patient trajectories over time as we have done. Furthermore, we have charted such outcomes according to rhythm in detail. Our statistical approach is especially novel and informative within this literature. Our data structure allowed us to perform GEE regression analysis to evaluate recovery over time both overall and according to rhythm.

CONCLUSIONS

These data are consistent with an association between resuscitation from nSR and significantly worse short- and long-term outcomes than resuscitation from SR in patients treated with MTH. Among survivors, neurologic status tended to improve between hospital discharge and long-term follow-up. This effect was not modified by rhythm, given that an interaction between time and rhythm was not seen. Future research on patient and process variables will be needed to elucidate the independent factors underlying this relationship and to better identify the subpopulations of patients surviving cardiac arrest that benefit from therapeutic hypothermia.

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