Clinical Paper

Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest∗

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A B S T R A C T

Background: The rate and effect of coronary interventions and induced hypothermia after out-of-hospital cardiac arrest (OHCA) are unknown. We measured the association of early (<24 h after arrival) coronary angiography, reperfusion, and induced hypothermia with favorable outcome after OHCA.

Methods: We performed a secondary analysis of a multicenter clinical trial (NCT00394706) conducted between 2007 and 2009 in 10 North American regions. Subjects were adults (>18 years) hospitalized after OHCA with pulses sustained >60 min. We measured the association of early coronary catheterization, percutaneous coronary intervention, fibrinolysis, and induced hypothermia with survival to hospital discharge with favorable functional status (modified Rankin Score ≤3).

Results: From 16,875 OHCA subjects, 3981 (23.6%) arrived at 151 hospitals with sustained pulses. 1317 (33.1%) survived to hospital discharge, with 1006 (25.3%) favorable outcomes. Rates of early coronary catheterization (19.2%), coronary reperfusion (17.7%) or induced hypothermia (39.3%) varied among hospitals, and were higher in hospitals treating more subjects per year. Odds of survival and favorable outcome increased with hospital volume (per 5 subjects/year OR 1.06; 95%CI: 1.04–1.08 and OR 1.06; 95%CI: 1.04–1.08, respectively). Survival and favorable outcome were independently associated with early coronary angiography (OR 1.69; 95%CI 1.06–2.70 and OR 1.87; 95%CI 1.15–3.04), coronary reperfusion (OR 1.94; 95%CI 1.34–2.82 and OR 2.14; 95%CI 1.46–3.14), and induced hypothermia (OR 1.36; 95%CI 1.01–1.83 and OR 1.42; 95%CI 1.04–1.94).

Interpretation: Early coronary intervention and induced hypothermia are associated with favorable outcome and are more frequent in hospitals that treat higher numbers of OHCA subjects per year.

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1. Introduction

Out-of-hospital cardiac arrest (OHCA) is the third leading cause of death in North America, afflicting an estimated 382,000 persons in the US per year,1 with a case-mortality rate of 94.7%.2 Reversal of cardiac arrest requires rapid restoration of cardiac activity using defibrillation, reperfusion, mechanical or pharmacological support.
Differences between communities and emergency medical services (EMS) response systems contribute to differences in survival after OHCA between regions.2,3

In-hospital interventions after OHCA4–7 may prevent secondary injury and ameliorate ischemia-reperfusion injury to multiple organs, especially the heart and brain.8 Induced hypothermia,9,10 coronary artery reperfusion,11–13 hemodynamic optimization,14–16 ventilator management15 and neurological prognostication16 all can influence outcomes. However, the use of these interventions is variable. While there are a number of European studies about the prevalence of hypothermia implementation,17–19 in North America neither the prevalence of these intervention nor the relationship of these interventions with patient outcomes have been measured.

This study was a planned secondary analysis of a randomized controlled trial to examine the relationship between in-hospital interventions and outcomes after OHCA in a large North American network. The parent trial tested the influence of two EMS interventions, which were found to have no effect on outcome.20,21 The primary hypothesis of this study was that early coronary angiography or reperfusion and induced hypothermia are associated with survival and favorable functional status after OHCA.

2. Methods

2.1. Study design and setting

Between June 2007 and October 2009, 10 US and Canadian clinical sites in the Resuscitation Outcomes Consortium (ROC) enrolled consecutive OHCA patients treated by 150 EMS agencies in a multi-center, randomized controlled trial (ROC-PRIMED; clinicaltrials.gov NCT00394706). This trial tested the effect on functional recovery and on survival to hospital discharge of performing cardiopulmonary resuscitation (CPR) for a brief (~30 s) interval or for 3 min prior to rhythm analysis and defibrillation attempt for ventricular fibrillation (VF). The trial simultaneously compared the effect of using an impedance threshold device (ITD) with using a sham device. Neither the CPR strategies nor the ITD device affected survival or functional outcome.20,21

Institutional review boards or research ethics boards at all sites and hospitals granted an Exception from Informed Consent for enrollment. As soon as feasible, we notified surviving subjects or their legally authorized representatives about the study and provided opportunity to withdraw from continued data collection. We reviewed hospital medical records for all subjects until hospital discharge. Primary outcomes were available for all subjects in this secondary study.

2.2. Patient population

This secondary analysis studied all screened or randomized adult (age > 18 years) subjects with OHCA, defined as receiving chest compressions from a professional provider or a rescue shock from a defibrillator. We included only subjects who were delivered to any of 151 participating hospitals with a pulse or who regained a pulse in the emergency department, and who survived for > 60 min after hospital arrival, because these subjects were potential recipients of in-hospital interventions. We excluded subjects for whom resuscitation efforts were discontinued prior to hospital arrival or for whom no pulse was established even after hospital arrival (Fig. 1). Patients with EMS-witnessed cardiac arrest and patients with tracheostomies were included although these subgroups were excluded from some out-of-hospital interventions in ROC-PRIMED. We excluded prisoners, pregnant women, patients with “do not resuscitate” directives made prior to EMS treatment, and patients with blunt, penetrating or burn-related trauma or with cardiac arrest due to exsanguination.

2.3. Data collection

Research coordinators abstracted data into web-based case report forms from EMS and hospital records and from the electronic data captured by EMS monitor–defibrillators. The Data Coordinating Center trained data abstractors, provided on-line assistance with ambiguous cases, and performed site visits and audits to ensure data integrity. Automated within-form and between-form data checks followed by written resolution of conflicting data were performed to reduce errors.

2.4. Interventions and covariates

We recorded whether any coronary angiography was performed, whether the angiography was early (< 24 h from admission) or > 24 h after admission, and whether a percutaneous coronary intervention (PCI) was performed. More precise timing of PCI was not available in this dataset. We noted the acute administration of any fibrinolytic drugs. Because acute coronary artery reperfusion can be accomplished using fibrinolysis or PCI, we examined a composite intervention of early coronary reperfusion therapy (any fibrinolysis or PCI).

We defined induced hypothermia as any active attempt to lower core body temperature at the hospital. We recorded the time of the first attempt to initiate hypothermia, the time when rearming began, and the lowest temperature achieved. In this cohort, documented efforts to lower body temperature by EMS were rare (n = 188 cases), and the time of initiation of hypothermia for those cases was defined as the time of hospital arrival.

We recorded the presence or absence of ST-elevation myocardial infarction (STEMI) on the ECG obtained at the hospital, in-hospital events (stroke, seizures, bleeding requiring transfusion, pulmonary edema, recurrent cardiac arrest, organ failure, pneumonia or sepsis, myocardial infarction at any time), and hospital length of stay.

Prior studies using different data sets reported associations between the number of cardiac arrest subjects treated at each

![Diagram](image-url) Fig. 1. Subjects included and excluded from analysis.
Therefore, we examined the number of ROC study subjects admitted to each hospital per year, both as a continuous variable and categorically (5–9, 10–19, 20–29, 30–39, >40 subjects per hospital). When a subject was transferred from one hospital to another on the first hospital day, the second hospital was considered the treating hospital.

2.5. Study outcomes

The primary outcome was survival to hospital discharge with favorable functional status defined as modified Rankin Score (mRS < 3). Survival to hospital discharge was defined as transfer from an acute care hospital to rehabilitation, skilled nursing or home residence. The mRS at hospital discharge was determined by review of clinical records using a standard instrument. Research coordinators assigned the circumstances of in-hospital death to one of four categories: (1) medically unable to support (multiple organ failure, intractable shock or recurrent arrest), (2) brain death, (3) withdrawal of life sustaining treatment for non-neurological reasons (for example, advanced directives or antecedent terminal illness), and (4) withdrawal of life sustaining treatment based on neurological prognosis.

2.6. Sample size and statistical analysis

The original trial proposed to enroll 14,154 subjects to have 90% power for a difference in favorable functional recovery between treatments of 5.3% versus 6.7%, but was stopped for futility according to a priori stopping rules after 16,875 subjects were screened of whom 12,579 subjects were randomized to study treatments.

We examined the relationship of outcome with the individual interventions and with clinical features of the patients using unadjusted and adjusted odds ratios. Separate models were created for the outcome of survival to hospital discharge and survival with mRS < 3 at hospital discharge. Adjusted odds ratios were estimated using multivariable logistic regression including covariates a priori thought to potentially confound the relationship between outcome and each intervention: sex, age (modeled as a cubic spline with nodes at 40, 60); interval from EMS dispatch to first agency arrival (cubic spline with nodes at 4, 12); first EMS rhythm (VT/VF, asystole, PEA, perfusing rhythm, AED no-Shock/Unknown); witnessed collapse (EMS, bystander, not witnessed, unknown); bystander CPR; study site; mean CPR fraction (cubic spline with a node at 0.4); public location of collapse. We also included covariates associated with each intervention a posteriori: advanced airway placement; home residence prior to arrest; subjects treated at that hospital per year (cubic spline with node at 20); time from left scene to ED arrival (cubic spline with nodes at 5, 20, 40); time from EMS arrival to return of spontaneous circulation (cubic spline with node at 20); and total prehospital epinephrine dose (cubic spline with nodes at 4, 8). Because coronary artery bypass grafting (CABG), and the placement of a permanent pacemaker or implantable cardioverter-defibrillator (ICD) are generally offered only to patients who will clearly survive hospitalization, these variables were not considered to be potential predictors of survival or outcome. Likewise, coronary angiography performed more than 24h after OHCA is prone to be selectively provided to survivors, and was not included as a predictor of survival or outcome.

Collinearity between covariates was checked with variation inflation factor (VIF). Data management was performed in S-PLUS (version 6.2.1, 2003, Insightful Corporation, Seattle, WA), while regression analysis was performed in Stata (Release 11, 2009, StataCorp, College Station, TX).

Fig. 2. Rates of (A) early coronary angiography, and (B) induced hypothermia versus number of subjects treated at each hospital per year for All Subjects and for Subjects with VF as initial rhythm. Rates of (C) survival to hospital discharge and favorable functional outcome (mRS < 3) versus number of subjects treated at each hospital per year. Hospitals treating <5 subjects total were excluded. The number of hospitals (n) in each stratum is indicated.

3. Results

Of 16,875 subjects treated by EMS, 3981 (23.6% of all subjects) arrived at a hospital and had pulses lasting for >60 min (Fig. 1). A total of 1317 subjects (33.1% of hospitalized; 7.8% of total) survived to hospital discharge, and 1006 (25.3% of hospitalized; 6.0% of total) had favorable functional status at hospital discharge (Table 1).

Subjects were treated in 151 hospitals with a median of 262 (IQR 172, 419) beds of which 72 (47.7%) had residency programs, and 21 (14.0%) were level 1 trauma centers. The majority (n = 92, 60.9%) of hospitals had a cardiac catheterization lab. Hospitals treated a median of 12.3 (IQR 5.5–25.3) study subjects per year.

The clinical features of 765 (19.2%) hospitalized subjects who received early coronary angiography, and 705 (17.7%) who had early coronary reperfusion (either PCI or fibrinolysis) are in Table 1.
The proportion of patients receiving early angiography varied across hospitals (range 0–75% among hospitals treating 5 or more subjects per year), and was associated with the number of subjects treated annually at each hospital (OR 1.01; 95%CI 1.01, 1.02) (Fig. 2). Early coronary angiography (n = 356, 62.1%) or fibrinolysis (n = 81, 14.1%) was provided to 76.3% of 573 subjects for whom STEMI was identified on initial ECG. Early angiography (n = 409, 12.0%) or fibrinolysis (n = 109, 3.2%) was provided to 15.2% of the remaining 3408 subjects.

Induced hypothermia was provided to 1566 subjects (39.3%) with clinical features described in Table 1 including 54.3% of patients with an initial rhythm of VF (n = 879) and 29.6% of subjects with non-VF (n = 684). The proportion of patients treated with hypothermia varied between hospitals (range 0–83% among hospitals that treated 5 or more subjects per year) and was associated with the number of subjects treated annually by each hospital (OR 1.02; 95%CI 1.02, 1.03) (Fig. 2). Clinical features of induced hypothermia included initiation at a median of 106 (IQR 53.6–226.5) min after return of pulses, median duration of 24 (IQR 18–26.7) h and median lowest documented temperature of 32 °C (IQR 31.5–33.0).

Each increase in five treated subjects per year at a hospital was associated with an increase in the odds of survival (OR 1.06; 95%CI: 1.04, 1.08) and survival with favorable functional status (OR 1.06; 95%CI: 1.04, 1.08) (Fig. 2). In-hospital events were recorded for 2922 (73.4%) subjects including circumstance of death for 2130 (81.5%) of 2613 subjects with in-hospital death (Table 2). Withdrawal of life-sustaining treatment for neurological reasons was the most common circumstance preceding in-hospital death (61.2% of cases) and was highest among hypothermia subjects (69.3%). Among survivors of cardiac arrest with VF as an initial rhythm, an ICD was implanted in 35.0%, including 44.5% of survivors without STEMI, and in 54.1% of survivors with neither PCI nor CABG.

Survival (64.7%) and favorable recovery (54.0%) were higher among subjects receiving early coronary angiography than among subjects not receiving early angiography (27.1% and 18.4%). Among all subjects treated with hypothermia, survival (40.7%) and favorable recovery (30.4%) were higher than among subjects not treated with hypothermia (30.3% and 21.9%). After adjusting for all covariates, early coronary angiography, any coronary reperfusion and induced hypothermia were independently associated with survival to hospital discharge and favorable functional status (Table 3). There was no significant interaction between the hospital interventions, but the subset of patients with both coronary reperfusion and hypothermia (n = 355) had high rates of survival (n = 225; 63.4%) and favorable functional recovery (n = 188; 53.0%). No covariates were collinear (all had VIF < 10).

4. Discussion

This study confirms that use of induced hypothermia and a strategy of early coronary angiography and reperfusion are associated with survival and favorable functional outcomes after OHCA. These are the largest prospective data from a North American cohort to date to provide estimates of the rate early coronary angiography (19.2%) and induced hypothermia (39.3%) for OHCA patients. These procedures are used more often in hospitals that treat higher numbers of OHCA subjects, and the number of subjects treated at each hospital is associated with rates of patient survival and favorable functional recovery.

These data confirm that acute coronary interventions are associated with improved outcome after OHCA. Acute coronary occlusion
occurs in up to 70% of patients resuscitated from cardiac arrest.11–13 Observational studies indicate that coronary angiography and successful PCI are associated with improved survival.12,13,22 In this study, reperfusion therapy was instituted for the majority of subjects diagnosed with STEMI (76%), indicating that antecedent cardiac arrest is not a barrier to aggressive care, although this rate is below the 100% that would be recommended by Guidelines. However, observational data cannot confirm a causal relationship between intervention and outcome, because there is a real risk that clinicians selected those patients most likely to benefit using variables not measured in this study. Nevertheless, these data support recommendations to consider early coronary reperfusion for patients with return of pulses after OHCA.21 Future studies should collect detailed information about provider decision making to intervene early in specific cases.

This study cannot determine whether presence of coma on hospital arrival reduced enthusiasm for early coronary interventions, because level of consciousness was not recorded. Clinical features (Tables 1 and 2) of patients with early angiography and less frequent withdrawal of life sustaining treatment for neurological reasons suggest that some of these patients may have been awake at hospital arrival. Nevertheless, excellent survival (63%) and favorable functional recovery (53%) in the hypothermia with reperfusion group support recommendations to consider both therapies concurrently in comatose patients.22,24 The overall rate of cardiac catheterization (12%) or fibrinolysis (3.2%) for non-STEMI cases appears low. These rates are similar to the rate (11%) in a German study,22 but much lower than the rate (73%) reported in a French study.25 Higher rates of angiography are probably justified, because angiography for consecutive post-cardiac arrest patients identifies significant coronary lesions in 58%13 or 45%26 of non-STEMI patients. A recent scientific statement discussed how interventional cardiologists in the United States are incentivized to avoid performing angiography on patients with high risk of death from neurological injury.27 Unfortunately, this environment may deprive many patients of potentially beneficial therapy.

This study provides the first direct estimate of the rate of induced hypothermia use after OHCA in North America (39.3%). Prior estimates relied on provider surveys.28–30 The present data are a good estimate of North American practice because we sampled 151 hospitals, including both the academic medical centers associated with investigators and neighboring community hospitals with no academic affiliation. The rate of hypothermia use is low given that international guidelines have recommended use of induced hypothermia since 2003.23,31 Hospitals that treated higher numbers of post-cardiac arrest subjects were more likely to induce hypothermia (Fig. 2) and to utilize early coronary angiography, suggesting that higher volume centers more often implement guideline-based practice. In a recent study,
temperature management protocols using 36 °C or 33 °C resulted in equivalent survival.

Those data suggest that induced hypothermia may be associated with better outcome in our study and in others because it is a marker of protocolized, aggressive, hospital care, rather than because of specific effects of temperature.

Caution is required when interpreting the association between induced hypothermia and favorable outcomes in multivariable models (Table 3). The lower rate of advanced airway use in non-hypothermia subjects may indicate that some in this group were awake at hospital arrival, which would inflate the rate of good outcomes in the non-hypothermia group, although the association between hypothermia and outcomes persisted in the multivariable model corrected for use of EMS advanced airways. Conversely, the higher rates of hypothermia subjects who were living at home prior to arrest and who were younger suggest that hypothermia may be selectively applied to patients suspected to have better chances for recovery. While multivariable models attempt to adjust for these factors, future studies of hypothermia should prospectively determine eligibility for hypothermia and baseline levels of coma in order to make clear comparisons. Finally, any effect of induced hypothermia is intertwined with the effects of the associated ancillary care such as fever suppression, sedation, blood pressure management, and neurological evaluations.

The rate of secondary prevention with ICD implantation for survivors of VF was low (35.0%). Survival after VF cardiac arrest is an indication for ICD unless an acute reversible cause of the VF is identified. ICD implantation was more frequent among VF survivors who did not receive reperfusion therapy (46.8%). Nevertheless, future studies should examine the reasons why secondary prevention is not used more often after VF OHCA.

Higher numbers of subjects treated by each hospital were associated with improved outcomes. This result is consistent with associations noted in prior data but contrasts with findings in other data sets. The present per-patient analysis of specific in-hospital interventions, for which hospital volume was a surrogate marker in prior studies, confirmed that guideline-based care such as early coronary reperfusion and hypothermia are used more often in hospitals that treat higher numbers of OHCA patients (Fig. 2). Other series have noted that the choice of destination hospital is related to the probability of receiving specific therapies associated with survival. These data support the need for systems of care that ensure that all OHCA patients have reliable access to coronary interventions and protocolized care that includes temperature management.

Finally, many subjects died within one day after hospitalization. Longer (median 3 days, Table 2) survival for subjects who died after reperfusion or hypothermia therapy may indicate that patients who are very unstable immediately after hospital arrival do not survive long enough to receive advanced therapies. In order to further improve in-hospital survival, future studies should examine in detail the reasons for early mortality. Overall, withdrawal of life sustaining treatment because of poor neurological status was the most frequently noted reason for in-hospital death (Table 2). This fact emphasizes the need for accurate and systematic determination of prognosis after cardiac arrest.

Strengths of this study include prospective data collection during a trial, assuring that the information is accurate and of high quality. Trial interventions were completed prior to hospital admission and were unlikely to affect in-hospital care. The implementation of the parent trial also involved rigorous training and monitoring of EMS care, ensuring that out-of-hospital care was of high quality in all regions. Selection bias was unlikely because all subjects were identified at the time of EMS treatment, and study sites included all OHCA in their regions. Additionally, we adjusted for most known confounders with multivariable regression.

5. Limitations

This observational study cannot establish causal connections between hospital interventions, survival and functional outcome. Survival bias may contribute to apparent beneficial effects of coronary reperfusion or hypothermia, because patients who are very unstable and die soon after cardiac arrest are less likely to receive further interventions. Clinician assessment of prognosis through unmeasured variables may have influenced the selection of patients for treatment.

6. Conclusions

Early coronary angiography and induced hypothermia are associated with improved outcomes after OHCA. Hospitals that treat a higher numbers of OHCA subjects are more likely to attempt early coronary reperfusion and to induce hypothermia, and these hospitals have higher rates of favorable outcome.

Conflict of interest statement

There are no reported conflicts of interest directly related to this work. The ROC is supported by a series of cooperative agreements to nine regional clinical centers and one Data Coordinating Center (5U01 HL077863 – University of Washington Data Coordinating Center, HL077866 – Medical College of Wisconsin, HL077867 – University of Washington, HL077871 – University of Pittsburgh, HL077872 – St. Michael’s Hospital, HL077873 – Oregon Health and Science University, HL077881 – University of Alabama at Birmingham, HL077885 – Ottawa Hospital Research Institute, HL077887 – University of Texas SW Medical Ctr/Dallas, HL077908 – University of California San Diego) from the National Heart, Lung and Blood Institute in partnership with the National Institute of Neurological Disorders and Stroke, US Army Medical Research and Material Command, The Canadian Institutes of Health Research (CIHR) – Institute of Circulatory and Respiratory Health, Defence Research and Development Canada and the Heart, Stroke Foundation of Canada and the American Heart Association. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung and Blood Institute or the National Institutes of Health.

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