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Original Contribution

# Sex differences in cardiac arrest survivors who receive therapeutic hypothermia☆,☆☆,★

Marna Rayl Greenberg, DO, MPH [a,*], Amy M. Ahnert, MD [b], Nainesh C. Patel, MD [b], Courtney E. Bennett, DO [b], Nicole Elliott, DO [a], Mark Lundquist, MD [a], Andrew Miller, DO [a], Ellina C. Feiner, MD [b], Anita Kurt, PhD, RN [a], Bernadette Glenn-Porter, BS [a], Mercedes Scott, BS [b], David B. Burmeister, DO [a]

[a] Department of Emergency Medicine, Lehigh Valley Hospital and Health Network, Allentown, PA 18103
[b] Department of Medicine, Division of Cardiology, Lehigh Valley Hospital and Health Network, Allentown, PA 18103

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ABSTRACT

*Objective:* Sex differences have not been well defined for patients undergoing therapeutic hypothermia (TH). We aimed to determine sex differences in mortality and Cerebral Performance Category (CPC) scores at discharge among those receiving TH.

*Methods:* This retrospective cohort study used data abstracted from an "ICE alert" database, an institutional protocol expediting mild TH for postarrest patients. Quality assurance variables (such as age, time to TH, CPC scores, and mortality) were reviewed and compared by sex. $\chi^2$ Test and Wilcoxon rank sum test were used. Stepwise logistic regression was used to assess the association between mortality and sex, while controlling for patient characteristics and clinical presentation of cardiac arrest.

*Results:* Three hundred thirty subjects were analyzed, 198 males and 132 females. Subjects' mean age (SD) was 61.7 years (15.0); there was no significant sex difference in age. There were no statistically significant sex differences in history of coronary artery disease, congestive heart failure, arrhythmia, hypertension, chronic obstructive pulmonary disease, renal disease, type 1 and/or type 2 diabetes mellitus, or those previously healthy. Obesity (body mass index >35 kg/m$^2$) was more likely in females (37, 28.0%) than males (35, 17.7%); $P = .03$. Females (64, 49.6%) were more likely than males (71, 36.8%) to have shock; $P = .02$. There was no difference in arrest to initiating hypothermia, but there was a significant difference in time to target temperature (in median minutes, interquartile range): male (440, 270) vs female (310, 270), $P = .003$. There was no statistical difference in CPC at discharge. Crude mortality was not different between sexes: male, 67.7%; female, 70.5%; $P = .594$. However, after controlling for differences in age, obesity, shock, and other variables, females were less likely to die (odds ratio, 0.46; 95% confidence interval, 0.23-0.92; $P = .03$) than males.

*Conclusion:* There is no statistically significant difference in CPC or crude mortality outcomes between sexes. After adjusting for confounders, females were 54% less likely to die than males.



## 1. Introduction

In the United States, implementation of "therapeutic hypothermia" (TH) programs in intensive care units has become the standard of care for patients that experience return of spontaneous circulation (ROSC) with coma after cardiac arrest. Studies have demonstrated the mortality benefit, improved outcomes, and improved long-term functioning of patients who receive this therapy [1-8]. Based on these initial studies, the American Heart Association has recommended that TH be considered in any comatose patient after cardiac arrest [9]. Patients are cooled to between 32°C and 34°C for 12 to 24 hours with the goal of appropriate neurologic recovery by decreasing the inflammatory process responsible for neurologic damage and slowing the brain's metabolic requirements [10].

It has been observed in the literature that there are sex differences in survival of cardiac arrest [11-13]. However, TH outcomes by sex have not been well defined. Patients undergoing TH have been reported as less likely to be male [14], and yet, most studies that evaluate outcomes include a minority of female participants [1,2,4,5,15]. We set out to determine sex differences in mortality and Cerebral Performance Category (CPC) scores at discharge among survivors of cardiac arrest who received TH.

☆ All authors are affiliated with Lehigh Valley Hospital and Health Network, Cedar Crest and I-78, Allentown, PA 18103.

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★ MG, AA, NP, AM, EF, and DB conceived the study, designed the trial, and obtained research funding. MG, AK, BP, and MS supervised the conduct of the trial and data collection. MS, BP, and AK managed the data, including quality control. MG, CB, NE, and ML drafted the manuscript, and all authors contributed substantially to its revision. MG takes responsibility for the study as a whole.

* Corresponding author. 1909 Earls Court, Allentown, PA 18103. Tel.: +1 610 967 3140 (h); 610 360 4849 (c).
*E-mail address:* mrgdo@ptd.net (M.R. Greenberg).

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## 2. Methods

This study was reviewed and approved by the hospital's institutional review board. This retrospective cohort study used abstracted data from an existing database of patients who had an ICE alert (an institutional protocol designed to expedite mild TH [goal 33°C] for post–cardiac arrest patients) from January 1, 2005, to September 19, 2013, at a level I trauma center with an annual adult emergency department (ED) census of 75 000, located in Pennsylvania. Patients were included in the database if they meet criteria for an ICE alert. Criteria for an ICE alert are defined as pulseless cardiac arrest with ROSC (pulses for 20 minutes continuously), persistent coma after ROSC (Glasgow Coma Scale score, ≤6), 18 years or older, time from arrest to ROSC less than 60 minutes, systolic blood pressure greater than 90 with mean arterial pressure greater than 60 mmHg for 30 minutes spontaneously or with vasopressors, and initiated within 6 hours of collapse. Patients are excluded from the registry if they have a do-not-resuscitate/do-not-intubate order or advanced medical illness precluding the possibility of meaningful recovery, persistent hypoxia with $O_2$ saturation of less than 85% for more than 15 minutes after ROSC and before TH, initial body temperature of less than 30°C, known active bleeding, or coagulopathy (warfarin therapy is not an absolute contraindication).

Therapeutic hypothermia induction is accomplished with the infusion of 2 L of 4°C normal saline solution, and maintenance is performed with the Artic Sun Temperature Management System (Medicance, Inc, Louisville, CO). The goal of the treatment protocol is to cool the patient to 33°C for 24 hours and then rewarm them 1°C every 4 to 6 hours. A database is maintained of the patients that undergo this protocol, and their outcomes are reviewed by a dedicated committee that includes physicians, nurses, and pharmacists. These outcome measurements include mortality, health performance measures, and brain injury. Brain injury is measured by the Glasgow-Pittsburgh CPC, a recognized outcome categorization tool for brain injury (see Table 1) [16].

We assessed standard quality assurance data points from the existing database, and these were reviewed and compared by sex. They included age, admission electrocardiogram, initial rhythm, time from arrest to ICE alert, time to TH set point, intensive care unit length of stay, mortality, and CPC scores. The distribution of the data for some of the points was markedly skewed by outliers with longer cooling times. Therefore, results were reported as percent or median minutes when applicable. Data analysis was completed using Pearson $\chi^2$ test for categorical variables and Wilcoxon rank sum test for univariate comparisons of nonnormally distributed variables by patient sex. *P* values were used to report differences in therapies between the female and male groups, with significance set at .05. Stepwise logistic regression was used to assess the association between mortality and sex, while controlling for patient characteristics and clinical presentation of cardiac arrest. All data management and analyses were performed using Stata software (version 12.1; Stata Corporation, College Station, TX).

**Table 1**
Cerebral performance categories

1. Good cerebral performance: Conscious, alert, and able to work and lead a normal life. Might have minor psychological or neurologic deficits (mild dysphasia, noncapacitating hemiparesis, or minor cranial nerve abnormalities).
2. Moderate cerebral disability: Conscious. Sufficient cerebral function for part-time work in a sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). Such patients may have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.
3. Severe cerebral disability: Conscious; patient dependent on others for daily support (in an institution or at home with exceptional family effort) because of impaired brain function. Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbance or dementia precluding independent existence to those who are paralyzed and can communicate only with their eyes, as in the locked-in syndrome.
4. Coma/vegetative state: Not conscious, unaware of surroundings, no cognition. No verbal and/or psychological interaction with environment.
5. Brain death: Certified brain dead or dead by traditional criteria.

**Table 2**
Cross-classification of patient characteristics by patient sex

| Variable | Overall, n = 330 | Male, n = 198 | Female, n = 132 | *P* |
|---|---|---|---|---|
| Age, mean (SD), y | 61.7 (15.0) | 60.7 (15.4) | 63.2 (14.3) | .14 |
| | n (%) | n (%) | n (%) | |
| Previously healthy | 35 (10.6) | 26 (13.1) | 9 (6.8) | .07 |
| Hx coronary disease | 99 (30.0) | 58 (29.3) | 41 (31.1) | .73 |
| Hx heart failure | 66 (20.0) | 39 (19.7) | 27 (20.4) | .87 |
| Hx arrhythmia | 42 (12.7) | 26 (13.1) | 16 (12.1) | .79 |
| Hypertension | 186 (56.4) | 111 (56.1) | 75 (56.8) | .89 |
| COPD | 67 (20.3) | 37 (18.7) | 30 (22.7) | .37 |
| Renal disease | 54 (16.4) | 30 (15.1) | 24 (18.2) | .47 |
| Obesity (BMI >35 kg/m$^2$) | 72 (21.8) | 35 (17.7) | 37 (28.0) | .03 |
| Type 1 DM | 39 (11.8) | 22 (11.1) | 17 (12.9) | .63 |
| Type 2 DM | 71 (21.5) | 42 (21.2) | 29 (22.0) | .87 |

Abbreviations: Hx, history; COPD, chronic obstructive pulmonary disease; BMI, body mass index; DM, diabetes mellitus.

**Table 3**
Cross-classification of treatment characteristics by patient sex

| Variable | Coding | Male | Female | *P* |
|---|---|---|---|---|
| | | n (%) | n (%) | |
| CPC prior | CPC-1 | 175 (88.4) | 108 (81.8) | .25 |
| | CPC-2 | 14 (7.1) | 17 (12.9) | |
| | CPC-3 | 7 (3.5) | 4 (3.0) | |
| | Unknown | 2 (1.0) | 3 (2.3) | |
| Admit ECG | Abnormal, LBBB | 13 (7.1) | 14 (10.6) | .19 |
| | Abnormal, STEMI | 42 (22.8) | 18 (13.6) | .08 |
| | Abnormal, other | 117 (63.6) | 80 (60.6) | .78 |
| | ECG not done/unknown | 15 (7.6) | 11 (8.3) | .80 |
| | Normal | 11 (5.6) | 9 (6.8) | .64 |
| Witnessed | Yes | 166 (84.7) | 105 (80.2) | |
| Bystander CPR | No | 64 (33.2) | 42 (33.3) | .20 |
| | Yes | 99 (51.3) | 55 (43.7) | |
| | N/A (arrested with med person present) | 30 (15.5) | 29 (23) | |
| Shock | Yes | 71 (36.8) | 64 (49.6) | .02 |
| Initial rhythm | PEA | 66 (33.3) | 44 (33.3) | 1.0 |
| | VT/VF | 62 (31.3) | 22 (16.7) | .003 |
| | VT/VF/AED-advised shock | 30 (15.2) | 23 (17.4) | .58 |
| | Asystole | 37 (18.7) | 40 (30.3) | .02 |
| | Unknown | 3 (1.5) | 3 (2.3) | .61 |
| Angiography | Yes | 99 (52.9) | 35 (29.2) | <.001 |
| Obey commands | Yes | 60 (32.1) | 35 (28) | .44 |
| CPC at discharge | CPC-1 | 28 (14.1) | 12 (9.1) | .82 |
| | CPC-2 | 20 (10.1) | 15 (11.4) | |
| | CPC-3 | 12 (6.1) | 7 (5.3) | |
| | CPC-4 | 6 (3) | 5 (3.8) | |
| | CPC-5 | 77 (38.9) | 55 (41.7) | |
| | N/A | 55 (27.8) | 38 (28.8) | |
| | | Median (IQR) | Median (IQR) | |
| Arrest to hypothermia | Time (min) | 175 (157.5) | 135 (160.0) | .07 |
| Time to target temperature | Time (min) | 440 (270) | 310 (270) | .003 |
| ICU LOS | Time (d) | 6 (6) | 5 (6) | .14 |

Abbreviations: ECG, electrocardiogram; LBBB, left bundle-branch block; STEMI, ST-elevation myocardial infarction; CPR, cardiopulmonary resuscitation; N/A, not available; PEA, pulseless electrical activity; VT, ventricular tachycardia; VF, ventricular fibrillation; AED, automated external defibrillator; IQR, interquartile range; ICU, intensive care unit; LOS, length of stay.