CRC IRB Protocol
Alexandra Reynolds, PGY-1
February 2013

Outcomes in pulseless electrical activity and asystolic cardiac arrest with and without therapeutic hypothermia in those who remain comatose after return of spontaneous circulation

A. Study Purpose and Rationale

According to the CDC, approximately 300,000 Americans per year have cardiac arrest outside of a hospital setting [1]. Historically, outcomes have been poor, with reports of survival to discharge ranging from 6-14% [1]. Among all out-of-hospital cardiac arrest (OHCA) patients between 2000-2006, patients who found in asystolic arrest had the worst outcomes (1% survival to discharge and 0.5% 30 day survival)[2] while those with shockable initial rhythm (ventricular fibrillation (VF) or pulseless ventricular tachycardia) had the best outcomes (15-20% survival to discharge) [3-5]. Those with pulseless electrical activity (PEA), fell somewhere in the middle (5-8% survival to discharge) [6]. Frequently, survivors of arrest would be discharged with devastating neurological deficits because of hypoxic brain injury as well as multiple other medical co-morbidities from a complicated hospitalization.

Beginning in the 1950s, cardiothoracic surgeons used moderate hypothermia (28 to 32 degrees C) during cardiac surgery to prevent brain ischemia [7]. The idea of cooling after unexpected cardiac arrest and subsequent resuscitation, however, was not seriously pursued until the early 1990s, when animal studies became popular. In 2002, two randomized controlled trials were published suggesting that patients in cardiac arrest with an initial rhythm of VF who remained comatose after ROSC had better outcomes after mild therapeutic hypothermia to 32-33 degrees C for 12-24 hours [8,9].

No similarly controlled prospective trial has been done to compare outcomes after pulseless electrical activity (PEA) or asystolic arrest and total-body hypothermia. There has been conflicting data published among nonrandomized studies, and outcomes are rarely measured in the same way [10-13]. Of the three most recent publications, one retrospective chart review study investigated outcomes after OHCA and cooling and found a 30% in-hospital mortality rate for those with VF arrest, versus a 63% mortality rate for those with non-VF arrest. In addition, 66% of VF patients were discharged with "favorable" neurological status, versus 8% of non-VF patients. Of note, in that institution it is not protocol to cool every comatose survivor of cardiac arrest [14]. Another study on hypothermia showed significantly fewer patients with favorable neurological outcome at 30 days in patients with non-VF when compared to VF arrest, although their data suggested an association with time to ROSC [15]. In a retrospective study of nearly 550 patients in asystolic cardiac arrest without intentional hypothermia, investigators found that the only survivors of unwitnessed asystolic arrest were those who had survived near-drowning or were hypothermic from environmental factors [2].

CUMC has been a pioneer in therapeutic hypothermia to preserve neurological function; initially, cooling was used only for patients with massive stroke, but since 2007 the institution

has been more consistently cooling patients who remain comatose after ROSC. As of January 2013, twelve hospitals in Manhattan offer therapeutic cooling,[*] and it is now recommended that all comatose survivors of cardiac arrest be cooled [16-18], despite there being a dearth of data supporting cooling after PEA or asystole.

There has been no evidence of harm to patients with cooling [11]; however, in our current political environment there will be calls for evidence-based implementation of protocols. In particular, recent data show that 75-80% of cardiac arrests are PEA or asystolic and that the proportion of non-VF cardiac arrests that survive to hospital admission has been increasing [1]. Intensive care resources will soon become limited. At this point in time, however, cooling has become the standard of care in New York City, particularly since January 2008 when CUMC led the effort to make policy that post-arrest patients be brought by ambulance only to hospitals that had the capability to cool [19], making it difficult to justify doing a randomized, controlled trial at any New York City hospital.

This study aims to compare short- and long-term medical and neurological outcomes after cardiac arrest both before and after widespread institution of the cooling protocol by doing a single center retrospective chart review. Given that other medical therapies have also changed, it is possible that this study will show a benefit that is not solely attributable to the institution of hypothermia itself; however, we expect to find no difference in those with asystolic arrest even with our extensive technology.

B. Study Design and Statistical Analysis

In this retrospective chart review, we will collect all consecutive cardiac arrest cases with initial nonshockable rhythm admitted to any this hospital between January 1, 2000 and December 31, 2004 (i.e. normothermia after cardiac arrest). If the clinical chart states that the patient was treated with hypothermia (as may have been the case rarely towards the latter one to two years), those patients will be excluded. Additionally, we will collect all consecutive cardiac arrest cases with initial nonshockable rhythm admitted to the hospital between January 1, 2008 to December 31, 2012 (i.e. hypothermia after cardiac arrest). If the clinical chart states that the patient was *not* treated with hypothermia, the contraindication to cooling [17] will be recorded and that case will not be included in the hypothermia cohort. For each case, the following variables will be noted: demographic data including age, gender, past medical history, when possible, pre-arrest CPC and mRS; initial rhythm of PEA, asystole, or unknown non-VF/VT; time down before initiation of CPR; time to ROSC; time from ROSC to initiation of cooling, time from ROSC to reaching temperature goal, and duration at temperature goal (for those who received hypothermia); etiology, if known, of the cardiac arrest; additional medical interventions used including pressors/inotropes, continuous venous venous hemofiltration/hemodialysis (CVVH/CVVHD), intra-aortic balloon pump (IABP), Impella device, and extracorporeal membrane oxygenation (ECMO); surgical interventions; medical complications; length of ICU stay; length of hospitalization.

---

[*] Bellevue Hospital Center; Beth Israel Medical Center – Petrie Campus; Harlem Hospital; Lenox Hill Hospital; Metropolitan Hospital; Mount Sinai Medical Center Hospital; New York Downtown Hospital; New York Presbyterian Hospital – Columbia Campus; New York Presbyterian Hospital – Weill Cornell Campus; New York University Medical Center – Tisch Hospital; St. Luke's Hospital; Roosevelt Hospital. Per Center for Resuscitation Science at University of Pennsylvania – Perelman School of Medicine.

The primary outcome will be survival to hospital discharge. Secondary outcomes will be Cerebral Performance Category (CPC) at discharge; modified Rankin Score (mRS) at discharge; and CPC and mRS at 1 year post-discharge.

Existing data suggests that prior to cooling there was a 1% survival to discharge for asystolic arrest [2] and 8% survival to discharge for PEA arrest [6], which is approximately a 5% survival to discharge for non-VF arrest without cooling. The most recent published chart review on outcomes after non-VF arrest with cooling found a 63% in-hospital mortality rate, meaning 37% survived to discharge [14]. To ensure 80% power with alpha of 5% we will assume that normothermic survival to discharge will be 5% and hypothermic survival to discharge will be 15%, in which case 160 subjects in each group will be required (total 320).

Chi-square tests will be used to compare rates of the indicated outcomes between the two groups. Univariate logistic regression will be used to screen all variables for predictors of outcome, and any variable with $p<0.1$ will be included in a multivariate stepwise logistic regression (both forwards and backwards) to look for final predictors.

To evaluate for an effect simply by virtue of time passing and improvement in medical devices, the Cochran-Mantel-Haenszel test will be used to trend any changes in baseline characteristics in each group and then again by calendar year.

C. Study Procedure
Retrospective chart review as discussed above. Study duration likely six months for data collection and analysis.

D. Study Drugs
None.

E. Medical Device
None.

F. Study Questionnaires
None.

G. Study Subjects
Inclusion criteria: (1) Out-of-hospital cardiac arrest with documented non-shockable initial rhythm on EMS arrival; (2) Comatose immediately following ROSC; (3) Survival to at least 24 hours after admission.

Exclusion criteria: (1) Unknown or VF/pulseless VT as initial rhythm on EMS arrival; (2) Following commands immediately following ROSC; (3) Near-drowning or other hypothermic exposure; (4) Second cardiac arrest during the hospitalization; (5) Expiration within first 24 hours of hospital admission; (6) Institution of comfort care measures, ICU treatment restrictions, or withdrawal of care during hospitalization; (7) Known coagulopathy; (8) Evidence of severe systemic infection within 12 hours of presentation to the hospital; (9) known terminal stage illness with less than one year predicted survival.

Subjects classified in the normothermic group will be those admitted to the hospital between January 2000-December 2004, and those classified in the hypothermic group will be those admitted between January 2008-December 2012.

H. Recruitment of Subjects
Not applicable.

I. Confidentiality of Study Data
All information obtained from patient charts will remain confidential. A unique number will identify each subject and the subject's data. Only primary research staff will have access to subject names. Data will be recorded in an encrypted file that will be securely maintained on a private server.

J. Potential Conflict of Interest
None.

K. Location of the Study
Data collection will occur at New York Presbyterian Hospital, Columbia University.

L. Potential Risks
No risks, as this is chart review only.

M. Potential Benefits
No direct benefits to individual patients.

N. Alternative Therapies
Not applicable.

O. Compensation to Subjects
None.

P. Costs to Subjects
None.

Q. Minors as Research Subjects
Not applicable.

R. Radiation or Radioactive Substances
None.

References:
[1] McNally, B., Robb, R., Mehta, M., Vellano, K., Valderrama, A. L., Yoon, P. W., et al. (2011). Out-of-hospital cardiac arrest surveillance --- Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005--December 31, 2010. MMWR.

Surveillance Summaries : Morbidity and Mortality Weekly Report. Surveillance Summaries / CDC, 60(8), 1–19.

[2] Vayrynen, T., Kuisma, M., Maatta, T., & Boyd, J. (2008). Medical futility in asystolic out- of- hospital cardiac arrest. Acta Anaesthesiologica Scandinavica, 52(1), 81–87.

[3] Rea, T. D., Eisenberg, M. S., Sinibaldi, G., & White, R. D. (2004). Incidence of EMS-treated out-of-hospital cardiac arrest in the United States. Resuscitation, 63(1), 17-24.

[4] Atwood, C., Eisenberg, M. S., Herlitz, J., & Rea, T. D. (2005). Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation, 67(1), 75-80.

[5] Bigham, B. L., Koprowicz, K., Rea, T., Dorian, P., Aufderheide, T. P., Davis, D. P., et al. (2011). Cardiac arrest survival did not increase in the Resuscitation Outcomes Consortium after implementation of the 2005 AHA CPR and ECC guidelines. Resuscitation, 82(8), 979–983.

[6] Saarinen, S., Kämäräinen, A., Silfvast, T., Yli-Hankala, A., & Virkkunen, I. (2012). Pulseless electrical activity and successful out-of-hospital resuscitation - long-term survival and quality of life: an observational cohort study. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 20, 74.

[7] Benson DW, Williams GR, Spencer FC, et al. (1959). The use of hypothermia after cardiac arrest. Anesth Analg, 38, 423–428.

[8] Bernard, G. R., Vincent, J. L., Laterre, P. F., LaRosa, S. P., Dhainaut, J. F., Lopez-Rodriguez, A., et al. (2001). Efficacy and safety of recombinant human activated protein C for severe sepsis. The New England Journal of Medicine, 344(10), 699–709.

[9] Hypothermia after Cardiac Arrest Study Group. (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. The New England Journal of Medicine, 346(8), 549–556.

[10] Oddo, M., Schaller, M.D., Feihl, F., et al. (2006). From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Critical Care Medicine, 34, 1865–1873.

[11] Arrich, J., and the European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. (2007). Clinical application of mild therapeutic hypothermia after cardiac arrest. Critical Care Medicine, 35, 1041–1047.

[12] Don, C.W., Longstreth, W.T., Jr., Maynard, C., et al. (2009). Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. Critical Care Medicine, 37, 3062–3069.

[13] Dumas, F., Grimaldi, D., Zuber, B., et al. (2011). Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. Circulation, 123, 877–886.

[14] Laish-Farkash, A., Matetzky, S., Oieru, D., et al. (2011). Usefulness of Mild Therapeutic Hypothermia for Hospitalized Comatose Patients Having Out-of-Hospital Cardiac Arrest. The American Journal of Cardiology, 108(2), 173-178.

[15] Soga, T., Nagao, K., Sawano, H., Yokoyama, H., Tahara, Y., Hase, M., et al. (2012). Neurological Benefit of Therapeutic Hypothermia Following Return of Spontaneous Circulation for Out-of-Hospital Non-Shockable Cardiac Arrest. Circulation Journal, 76(11), 2579–2585.

[16] Nolan, J. P., Hazinski, M. F., Billi, J. E., Boettiger, B. W., Bossaert, L., de Caen, A. R., et al. (2010). Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation, 81 Suppl 1, e1–25.

[17] Deakin, C. D., Nolan, J. P., Soar, J., Sunde, K., Koster, R. W., Smith, G. B., & Perkins, G. D. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. Resuscitation, 81(10), 1305–1352.

[18] Taccone, F., Donadello, K., Beumier, M., & Scolletta, S. (2011). When, where and how to initiate hypothermia after adult cardiac arrest. Minerva Anestesiologica, 77(9), 927–933.

[19] Hartocollis, A. (2008, December 3). City pushes cooling therapy for cardiac arrest. The New York Times, page A1, available at [http://www.nytimes.com/2008/12/04/nyregion/04cool.html].