RESUSCITATION OUTCOMES CONSORTIUM (ROC) PROGRESS REPORT (2003-2013) AND PROMISE FOR THE FUTURE

FROM THE STEERING COMMITTEE OF ROC

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1. EXECUTIVE SUMMARY AND RATIONALE FOR EXTENSION OF ROC

Key Points

- Large-scale multicenter controlled clinical trials are necessary to obtain definitive answers
- Research in this field faces special time and effort intensive requirements including building an EMS and technical infrastructure, commitment from EMS agencies and personnel, and IRB and community commitment to conduct research with exemption from informed consent
- NHLBI and other funding partners have made the investment to create the ROC infrastructure and established collaboration with EMS agencies
- EMS agencies, IRB's and the public are committed to ROC studies
- ROC continues to be extremely successful in conducting clinical trials in resuscitation from cardiac arrest and severe traumatic injury with high impact publications and remarkable citation numbers.

Past and Current Studies

Name	Type	Design	N	Status
Cardiac Arrest Epistry	**Cardiac**	**Observational**	**179,310**	**Ongoing**
Trauma Epistry/PROPHET	**Trauma**	**Observational**	**21,656**	**Completed**
PRIMED impedance threshold device (9224 were also co-enrolled in AEvAL)	**Cardiac**	**RCT**	**11,892**	**Completed**
PRIMED analyze early vs later (AEvAL) (9224 were also co-enrolled in ITD)	**Cardiac**	**RCT**	**13,126**	**Completed**
CPR feedback	**Cardiac**	**Ancillary RCT**	**1,586**	**Completed**
Hypertonic saline/dextran - shock	**Trauma**	**RCT**	**895**	**Completed**
Hypertonic saline/dextran - TBI	**Trauma**	**RCT**	**1,331**	**Completed**
Dallas RESCUE (estrogen TBI)	**Trauma**	**RCT pilot**	**50**	**Completed**
Dallas RESCUE (estrogen shock)	**Trauma**	**RCT pilot**	**50**	**Completed**
BLAST ground cohort (lactate as predictor)	**Trauma**	**Case series**	**389**	**Completed**
Hypotensive Resuscitation - shock	**Trauma**	**RCT pilot**	**192**	**Completed**
ALPS (amiodarone/lidocaine/placebo for VF	**Cardiac**	**RCT**	**3,000**	**Ongoing**
Continuous chest compressions vs 30:2	**Cardiac**	**RCT**	**23,600**	**Ongoing**
BLAST air cohort (lactate as predictor)	**Trauma**	**Case series**	**235**	**Ongoing**
PROPPR (ratio plasma/platelets/RBCs)	**Trauma**	**RCT**	**680**	**Ongoing**

Research Impact

- 47 peer-reviewed publications (12 in journals with an impact factor of >5)
- 54 abstracts at national and international meetings
- Changes in medical practice by AHA/ILCOR Resuscitation Guidelines (GL) involvement using ROC data as key resource (15 GL worksheets, 31 chapters in CPR GL, 7 publications, 41 consensus statements)
- New hypotheses funding related to resuscitation including 490 additional resuscitation/trauma publications by ROC PIs and Leadership (2003-2102) and 51 additional grants.

Future Studies

- ROC intends to perform crucial studies in resuscitation from severe trauma such as
  1. Low volume replacement of fluids in severe hemorrhage from trauma, and
  2. Tranexamic acid infusion to reduce mortality from severe blunt traumatic brain injury.
- ROC intends to perform crucial studies in resuscitation from cardiac arrest including
  1. A critically important randomized dose ranging study of epinephrine.
  2. A test of the value of recently discovered physiology for brain cooling by insufflation of dehumidified air into the nasopharynx and
  3. A test of a non-invasive assisted circulation device in PEA arrest and post arrest hypotension.

CONCLUSION: ROC NEEDS CONTINUED FUNDING TO SAVE LIVES AND LIFE YEARS LOST FROM OUT-OF-HOSPITAL CARDIAC ARREST AND SEVERE TRAUMATIC INJURY.

The Resuscitation Outcome Consortium (ROC) is the first organized research program to use extensive quantitative data and prospective trials to address the high mortality and morbidity associated with out-of-hospital cardiac arrest (OHCA) and severe traumatic injury. The ROC network conducts most of its clinical trials at the scene of the cardiac arrest or injury, when the beneficial effect on survival and outcome would likely be the greatest.

Extensive data are gathered, and interventions are performed by emergency medical services (EMS) first responders, emergency medical technicians (EMTs) and paramedics. Never have such consistent data been gathered on the location, time, and initial features of the arrest or injury or on the performance of these personnel in their efforts to save lives. ROC has enabled EMS providers to demonstrate progressive improvement in cardiopulmonary resuscitation (CPR) performance, and the consortium has implemented quality performance standards that EMS agencies must achieve to qualify for participation in the randomized trials.

The results of ROC observational studies and randomized trials consistently have been published in prominent, high-impact journals. The number of ROC publications, citations, and papers appearing in high-impact journals has been compared with two NIH supported clinical trials (not identified by name) receiving similar funds over the same time period. ROC outperformed these comparison networks by all parameters measured. Most impressively, 12 ROC papers have been published in journals with an impact factor greater than five compared to only one and four in the other two networks.

Thus far, five ROC studies have demonstrated that although interventions achieved favorable outcomes in the laboratory, observational epidemiology settings, and in small clinical trials, none improved outcomes in effectiveness studies. These include:

1. Two randomized controlled double-blind trials of hypertonic saline or hypertonic saline with dextran vs normal saline for patients with traumatic brain injury or hemorragic shock due to traumatic injury.
2. A cluster randomized crossover trial of EMS agencies using a short period of chest compressions (30-60 seconds) vs longer periods of chest compressions (180 seconds) before initial ECG evaluation to determine the need for shock in cardiac arrest.
3. A sham controlled blinded study of an airway device to improve circulation during cardiopulmonary resuscitation from cardiac arrest.
4. A cluster randomized crossover trial of real time audio and visual feedback to improve CPR process during resuscitation from cardiac arrest.

The above results are important since health care resources are limited, and demonstration that these interventions did not improve clinical outcomes will allow allocation of resources towards more effective therapies.

Ongoing trials include two definitive clinical trials in resuscitation from cardiac arrest and one for life-threatening trauma:

1. A double-blind 3-arm clinical trial of the new captisol-enabled preparation of amiodarone vs lidocaine vs placebo in refractory ventricular fibrillation/ventricular tachycardia in cardiac arrest.
2. A cluster randomized crossover trial of continuous cardiac compression during CPR with interposed ventilations vs standard American Heart Association (AHA) CPR with periodic interruption of chest compression for ventilation (30 compressions: 2 ventilations).
3. A randomized controlled trial comparing two different ratios of blood products for administration to trauma patients with massive hemorrhage. (Note this study has incorporated 4 of the original ROC sites along with 8 additional satellite sites -- a network of high volume Level I trauma centers to enroll these patients.)

These clinical trials are projected to be completed by the end of the current funding cycle (December 31, 2015).

ROC has also completed two (Phase II) randomized studies in the use of IV estrogen vs placebo in resuscitation from severe traumatic injury, one in patients with shock and one in patients with TBI.

In hypotensive resuscitation of traumatic injury without TBI, the consortium also completed a pilot feasibility study. The study showed that a difference in the volume of fluid administered in the field and for the first two hours after hospital arrival can be achieved between patients randomized to minimal fluid administration vs routine high volume fluid administration for hypotension. This pilot study will provide critical data to inform the design of a definitive Phase III trial of this resuscitation strategy.

Finally, ROC completed a prospective observational study demonstrating the feasibility of obtaining point of care lactate in the prehospital environment and its greater ability (compared to a systolic blood pressure criteria) to predict the need for resuscitative care in severely injured patients.

ROC has also published numerous papers from its registries of cardiac arrest and traumatic injury patients. As reviewed in the report these publications have addressed critically important issues for the respective fields and form the basis of many changes in guidelines for resuscitation from cardiac arrest and traumatic injury as summarized in this report.

Proposed Studies

Although the future funding of ROC beyond 2015 is uncertain, ROC investigators have prepared initial proposals for definitive and pilot clinical trials examining critically important interventions holding great promise for improving survival from cardiac arrest and severe traumatic injury.

In resuscitation from severe traumatic injury:

1. We plan to perform a pre-hospital randomized trial of Tranexamic Acid (TXA) in TBI using two doses vs placebo begun at the scene of injury and continued into the hospital. A number of randomized trials have suggested survival benefit in a subgroup of TBI patients, presumably through its prothrombotic anti-fibrinolytic action.

2. Based on the favorable result of the pilot feasibility trial mentioned above, ROC would perform a definitive trial of high versus low volume fluid administration during early resuscitation from traumatic shock. This study will assess whether allowing a lower blood pressure vs current efforts to use fluid to maintain normal blood pressure will lead to less severe hemorrhage and greater survival from severe traumatic injury without TBI.

3. There is great interest in the hypothesis that hyperventilation or hyperoxmia may impair outcome following severe traumatic brain injury. Thus a trial of controlled ventilation/oxygenation is being considered for severely injured patients who require prehospital endotracheal intubation.

In resuscitation from cardiac arrest:

4. Overall survival from cardiac arrests with initial pulseless electrical activity (PEA) is less than 3%. We would study the value of noninvasive immediate-assisted circulation via synchronized elevation of intrathoracic pressure with cardiac systole (timed by using the ECG) in arrest victims with initial PEA rhythm. We would also use this approach in ventricular tachycardia/ventricular fibrilation (VT/VF) arrest with post-defibrillation hypotension. Animal studies strongly suggest this form of noninvasive assisted circulation may be useful in improving survival in both of these common events. ROC has established that initial PEA arrests are now as common as initial VT/VF arrests but far more lethal. Several device companies are working to develop a testable device that will serve this purpose.

5. We propose a dose-ranging study of epinephrine in cardiac arrest. Although laboratory studies suggest that epinephrine results in greater frequency of initial return of

circulation in cardiac arrest, human observational studies suggest that this benefit is transient and that, ultimately, fewer patients survive cardiac arrest with administration of the usual large and repeated doses of epinephrine. ROC investigators do not believe there is currently equipoise for a placebo controlled study but support a dose-ranging study with a low dose similar to the dose effective in acute allergic reactions but far lower than currently used in cardiac arrests. The initial study might test usual multiple dosing vs single controlled dose vs low dose, with the possibility of moving toward placebo if study monitoring suggests that lower doses have a neutral or superior effect.

6. ROC would like to test a device that in animal studies cools the brain rapidly and effectively through nasal insufflations of dehumidified air. This device appears safe in normal human volunteers. Initial testing in the ICU environment will establish the efficacy of this intervention to achieve appropriate temperature control before initial ROC studies. ROC would pursue a pilot feasibility and safety study before launching a definitive trial of both post-arrest patients after return of circulation and during cardiac arrest. The latter study would be of particular interest because laboratory studies suggest that intra-arrest cooling would be more effective than post arrest cooling by preventing reperfusion injury.

7. The optimal strategy for advanced airway management in OHCA is unknown. Supraglottic airway (SGA) insertion would seem more prudent than endotracheal intubation (ETI) in OHCA, and many EMS practitioners and agencies (including many in ROC) are opting for primary SGA insertion to expedite airway management efforts and avoid the pitfalls of ETI. However, a secondary analysis of more than 10,000 adult OHCAs in the ROC PRIMED study receiving advanced airway insertion efforts showed that ETI was associated with higher odds of ROSC, 24-hour survival, and survival to hospital discharge compared with SGA (9). No randomized clinical trials evaluating the effectiveness of advanced airway management strategies in adult OHCA have been performed. We propose to perform such a randomized prospective trial.

Continued funding beyond 2015 is imperative in order to achieve improved survival and less morbidity.

Is there any evidence that it takes longer term consistent research and investigation to improve outcome from severe cardiovascular medical catastrophes? In the case of acute transmural myocardial infarction, the NHLBI sponsored Myocardial Infarction Research Unit Program and then Specialized Centers of Research Programs in ischemic heart disease began in the mid-1960s but it was not until the mid-1980s that early thrombolytic therapy emerged as lifesaving treatment and even later for angioplasty and stent placement to prove of further benefit. From the mid-1980s to 2000 the one-year mortality for patients hospitalized with acute transmural

myocardial infarction declined from 40% to 4%! This monumental achievement required a consistent 30-plus-year effort and consistent NHLBI funding to achieve its primary goal. **We anticipate that a similarly consistent effort will achieve a significant impact in resuscitation from cardiac arrest and severe traumatic injury.**

2. AIMS AND OBJECTIVES OF ROC

The general aim of ROC is to conduct multiple, collaborative, out-of-hospital clinical trials to evaluate strategies for treatment of patients with cardiac arrest or severe injury. Long-term objectives include:

1. Designing and implementing a series of high-quality Phase II and Phase III randomized trials that have high internal and external validity using performance-based management of patient enrollment and study participation to increase study validity and efficiency

2. Providing a knowledge base that will improve therapeutic decision-making by testing treatment approaches for cardiopulmonary arrest and life-threatening trauma and continued observational study of EMS care processes and outcomes

3. Encouraging collaboration between community EMS providers and clinical research centers to permit efficient out-of-hospital resuscitation research and facilitate resuscitation training among clinical physician investigators

4. Disseminating and implementing the methods and results of these trials in the clinical setting.

ROC was formed as a result of the NIH-sponsored Post-Resuscitation and Initial Utility in Life Saving Efforts (PULSE) workshop and the evolving nature of EMS system research. The PULSE workshop in July 2000 and PULSE II in July 2003 recognized the time-dependency of cellular injury mechanisms noting that similar cellular pathophysiologic processes occur whether the cellular injury arises from physical trauma or cardiac arrest. The evolution of EMS system research has led to a recognition that these fundamental processes of cellular injury are most likely to be favorably treated with early EMS intervention (i.e., treatment brought directly to the site of the injured or ill patient). Pertinent examples include basic treatments, such as cardiopulmonary resuscitation, defibrillation, airway and breathing management, fluid resuscitation and early pharmacologic resuscitation.

Meaningful translational and outcomes research related to EMS is best done when interventions can be tested across large patient populations during a relatively brief time frame. The latter expectation has many advantages: a) regional factors that might unduly

affect results in a single center study are reduced; b) the interval from study initiation until study completion and results dissemination is reduced; c) implementation and operational factors that affect translation of the results to other EMS systems are identified more readily; and d) experienced multi-institutional investigative teams that are knowledgeable and skilled in multidisciplinary resuscitation research can implement sequential resuscitation investigations.

ROC was established to overcome the existing limitations of single-site EMS-related research and to expedite the translation of promising laboratory-based findings to clinical practice. Most out-of-hospital resuscitation practices are based on extrapolation of in-hospital clinical practices and have not undergone rigorous clinical trials in the appropriate setting or in the appropriate population. The establishment of a multi-community EMS resuscitation consortium has become the most efficient means of providing such translational research.

3. BURDEN OF OUT-OF-HOSPITAL CARDIAC ARREST AND TRAUMATIC INJURY

Out-of-hospital cardiac arrest (OHCA) and life-threatening traumatic injury are common, serious, debilitating, and costly public health problems. Before the advent of ROC, there was no estimate of the incidence or outcome of either condition that was derived from large geographic areas that used common definitions and methods of data collection. Consequently, the reported incidence of EMS-treated cardiac arrest varied from 17 to 129 per 100,000 population,(1, 2) and the reported incidence of hospital admissions due to all types and severity of injury was 6.19 to 9.02 per 1,000 population. (3) Of these admissions, 10-12% were reported to involve major trauma, (3, 4) but these data underestimated the incidence of fatal injury by overlooking patients who die in the field. ROC investigators recognized that such variations may reflect in part regional differences in patient risk factors and the severity of disease, in the structure and function of EMS care, or in the method of measuring the process and outcome of care.

To facilitate surveillance of both conditions, as well as the conduct of planned and ongoing randomized trials, ROC implemented prospective registries (see section on ROC epistries). Data from these registries confirmed large regional variation in the incidence of each condition,(5, 6) the proportion of patients treated or transported,(5, 7) and the proportion of patients who survive to discharge.(5, 6) There is significant temporal variation in the frequency and outcome of OHCA.(8) Extrapolation of the data to the total U.S. population suggests that annually 359,400 individuals experience EMS-assessed out-of-hospital cardiac arrest,(9) and 114,379 experience severe traumatic injury.(5)

Unadjusted comparisons suggest that the proportion of patients who survive out-of-hospital cardiac arrest has progressively improved throughout the ROC funding period (Table).

Table: Survival after Cardiac Arrest in ROC Communities participating in 2006 and 2010*

	EMS Assessed	EMS Treated	Initial Rhythm VT/VF
2006	4.5%	8.2%	21.5%
2010	5.5%	10.4%	29.4%

*Unpublished confidential data

Such comparisons are not feasible for severe traumatic injury because its definition has changed over time. Nonetheless, ROC has demonstrated that outcomes after acute life-threatening conditions in the out-of-hospital setting are improving.

Collectively, ROC has demonstrated that the burden of out-of-hospital cardiac arrest and traumatic injury is similar to that of major myocardial infarction or heart failure and that outcomes are improving after cardiac arrest in participating communities.

References (ROC publications in **Bold**)

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4. NETWORK AND COMPOSITION OF ROC

ROC was established in 2004 by the NHLBI in partnership with the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research (CIHR) and other government and non-government funding partners, including the U.S. Army Medical Research & Materiel Command, Defence Research and Development Canada, and the Heart and Stroke Foundation of Canada. In 2005, the American Heart Association became a funding partner and agreed to contribute $500,000 per year to support the U.S. cardiac arrest registry (Epistry). CIHR, Heart and Stroke, and Defence R&D Canada have contributed approximately $7 million to the Epistry effort for Canadian sites. Manufacturers of monitor/defibrillators provided in-kind support, including supplying new or modified equipment to participating EMS agencies to facilitate monitoring of CPR processes.

ROC initially comprised 10 regional clinical centers representing 11 distinct geographic regions in the U.S. and Canada. In March of 2008, the Iowa site withdrew citing multiple impediments to success in launching ROC trials. ROC's Data Coordinating Center (DCC) is based in the Department of Biostatistics in the School of Public Health at the University of Washington in Seattle. A total of 218 EMS and fire agencies covering 35,000 square miles and serving almost

24 million people participate in ROC protocols. In addition, approximately 4,000 vehicles are used to carry out ROC interventions, and more than 36,000 EMS personnel are trained to enroll seriously ill patients and administer treatments in ROC trials. The EMS transports patients to 224 acute care hospitals.

The practical and strategic considerations of working with public, private, and volunteer EMS and fire agencies are enormous; yet the field is so hungry for evidence-based treatments that they are willing to overcome these obstacles and join forces to determine how survival can be improved in cardiac arrest and severe trauma. Administratively, 100 IRBs oversee ROC sites. Sites also must conduct community notification and consultation as determined by their local IRB to fulfill the requirements for emergency research using the FDAs rules regarding informed consent. The ROC sites accepted these challenges with enthusiasm to implement multiple observational and randomized studies.

EMS Agency Commitments to Quality CPR

The large number of EMS agencies and personnel cited previously have altered educational programs and implemented continuous quality improvement (CQI) programs to ensure the best quality CPR foundation on which to develop clinical interventional trials. Although one might argue that this effort should be a high priority in all EMS agencies, these entities face many competing priorities. However, involvement in ROC has elevated the performance of quality CPR in most of these agencies to ensure the success of the ROC without real cost to the ROC.

ROC has had a significant impact on EMS providers' impression of how scientific discovery may affect their practice. Additionally, their participation has helped their EMS agencies address concerns outlined in NHTSA's "EMS Research Agenda for the Future." EMS agencies participating in ROC protocols have been able use scientific evidence to advance their scope of practice. Prior to participating in ROC, some EMS agencies viewed research as an added burden without remuneration. After participating in numerous ROC protocols, EMS providers now view the results as very relevant in defining appropriate provision of care. New EMS staff is educated from the outset to expect and value these added research requirements as part of their "overall mission." ROC has fostered this cultural evolution. This paradigm shift is elevating out-of-hospital practice by EMS providers to the level of other health care disciplines. EMS provider support is critical toward defining EMS research success and, in turn, improving patients' lives.

Instead of depending on tradition and "eminent" leaders to direct the standard of care because of the paucity of EMS research, this new evidence is starting to finally help define care. Through participation in ROC, EMS agencies are taking ownership of their scope of practice. The progress EMS has made to advance the science of integrating scientific discovery into out-

of-hospital practice would be hard to replicate at individual sites. The collective whole of the ROC group is the catalyst for this transformation within ROC's EMS agencies.

NIH ROC Funds Are Extensively Leveraged

Funding partners have contributed greatly to ROC's success. The NHLBI funds invested are managed efficiently, but also are leveraged with partners to achieve far more than would otherwise be possible.

Primary funding partners will have contributed the following real dollars (total over the life of the consortium) by the end of the second funding cycle:

American Heart Association	$5 million
U.S. Department of Defense	$51 million for PROPPR $8.7 million for other protocols
Canadian Partners: Canadian Institutes of Health Research Heart and Stroke Foundation of Canada Defense Research and Development Canada	$7 million

Multiple Investigators at each of the 10 sites contribute far more time and effort than they are compensated from ROC or their universities.

The greatest in-kind support comes from the emergency medical and fire service agencies that employ the nurses, paramedics, EMTs and, other first responders who enroll ROC patients in prehospital trials. The formal amount of ROC funds in the two funding cycles targeted for training paramedics in specific protocol procedures, quality CPR techniques, and patient care information transfer for quality monitoring has averaged only $25,000 for each of the six protocols. In contrast, to train 80% of paramedics (approximately 2,500) in a one day face-to-face educational session at one site (BC Ambulance Service) alone costs $1 million. Each study trains 10,000 to 36,000 emergency services personnel. Thus, for all ROC studies, more than 100,000 paramedics, EMTs, and first responders were trained in how to enter patients in clinical trials. In addition, many U.S. paramedics have taken the training courses in Good Clinical Practice and Human Subjects on time that their supporting agencies have donated. The EMS training, logistics, and operations leadership in each of these agencies does not receive any direct ROC funding but spends considerable time ensuring training is planned and delivered, monitoring CPR quality, providing feedback to improve study compliance, and implementing systems to track investigational interventional materials. Although not officially recorded, it is conservatively estimated that the sum of in-kind support for the ROC from EMS agencies exceeds $25 million.

ROC leadership has nurtured this commitment to prehospital resuscitation research and helped to change the culture in most of these agencies. The foundation for research has now been established across ROC communities. The process of research is now, more than ever before, becoming part of the everyday workflow. The expectation of these agencies and the community is that ROC's research will answer many important clinical scientific questions. The NHLBI's investment and the in-kind contributions from these agencies established an extremely effective and efficient prehospital research partnership that is unprecedented, unparalleled, and unlikely to be replicated if dissolved.

Davis DP, Garberson LA, Andrusiek DL, Hostler D, Daya M, Pirrallo R, Craig A, Stephens S, Larsen J, Drum AF, Fowler R. A descriptive analysis of Emergency Medical Service systems participating in the Resuscitation Outcomes Consortium (ROC) network. Prehospital Emergency Care 2007; 11:369-382

5. COMPARISON TO OTHER NETWORKS

In an effort to compare ROC with NIH networks, the research staff in Dr. Weisfeldt's department examined NIH available data for networks in similar areas of biomedical research conducting clinical trials over a similar period of time with similar budgets. Two networks were identified, which are listed below as Network A and Network B. This table lists the years of funding and the amount of funds in each year. Total ROC funding between 2004 and 2012 was $69 million. Network B was funded beginning in 2002 and experienced some decrease in funding beginning in 2011 but had continued funding to 2012 for a total of $43 million. Network B was funded from 2006 through 2012 for a total of $62 million.

The number of publications for each of the networks was obtained from the Network bibliography. The bibliography of Network A and Network B were obtained from the data coordinating center for each of the two networks. The number of citations for all papers beginning with initial date of publication through the year 2012 was obtained from http://code.google.com/p/citations-gadget/. The impact factor for each of the published papers was determined from an impact factor index for journals provided by http://apps.webofknowledge.com/UA_GeneralSearch_input.do?product=UA&search_mode=GeneralSearch&SID=2EbfIoH1agahMbg1DIp&preferencesSaved=. Figure 1 below shows the total number of publications for each of the three networks. Figure 2 shows the impact factor for the papers published by each network grouped by impact factor >5, impact factor >30, and median impact factor. The median impact factor for ROC is slightly higher than the other networks. What is most impressive is the larger number of papers for ROC that have an impact factor greater than 5. The number is more than double of either comparison network. ROC published 12 papers with an impact factor greater than 5, Network A published 1 paper, and Network B

published 4 papers. Figure 3 shows the number of citations related to the year of publication. Finally the table also indicates the "cost per citation." The cost per citation to date for ROC is $50,000 compared with $850,000 for Network A and $392,000 for Network B.

Years	ROC	Network A	Network B
2002		7,391,899	
2003		6,604,672	
2004	7,850,000	7,860,723	
2005	11,150,000	962,452	
2006	10,560,000	4,998,288	6,657,495
2007	9,483,332	1,567,807	14,926,969
2008	8,983,332	2,782,013	5,911,591
2009	833,332	5,568,572	7,189,605
2010	5,992,600	4,311,286	7,758,890
2011	7,217,100	846,532	9,003,233
2012	7,160,569	466,582	10,460,627
2013			
2014			
2015			
TOTAL $	69,230,265	43,360,826	61,908,410
TOTAL CITATIONS	1,373	51	158
$/CITATIONS	50,422	850,212	391,825

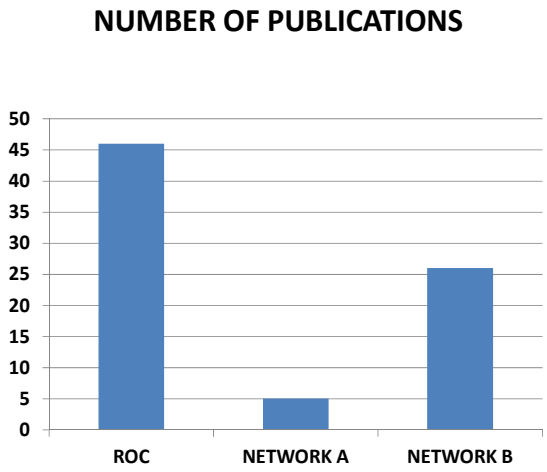

Figure 1

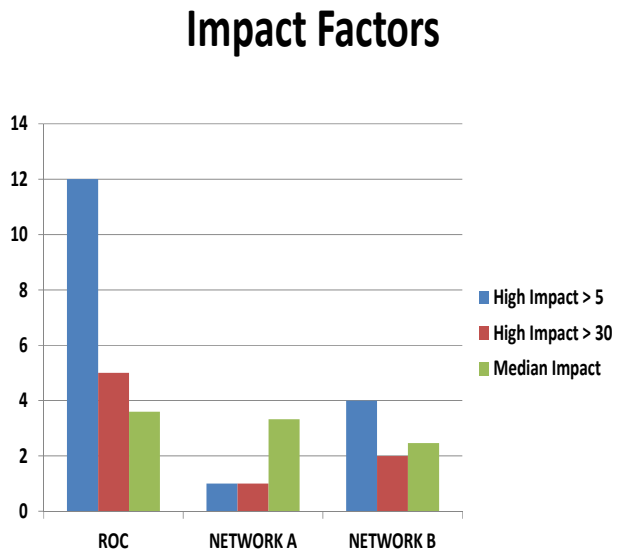

Figure 2

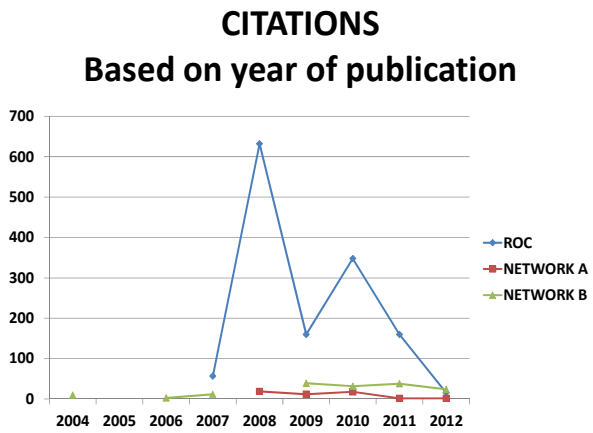

Figure 3

6. REGISTRY (EPISTRY) STUDIES AND SUMMARY RESULTS: CARDIAC ARREST

EMS/Temporal Variations in Model System/Outcome/Performance

Although outcomes from OHCA have improved recently, according to the AHA 2012 Statistical Update, they remain low, and variation continues to exist across communities, including those within the ROC network. (1, 2) Eisenberg et al first highlighted these disparities in 1990, (3) and partly attributed the variations to differences in definitions. To standardize definitions and

allow for meaningful data comparisons across communities, the Utstein template for the reporting of cardiac arrest outcomes was developed. The original Utstein reporting guidelines were published in 1993 and updated in 2004. In addition to definition differences, the observed variability in outcomes may also be related to patient, event, EMS system configuration, and response patterns and treatment factors (prehospital and in-hospital). Several Utstein predictors of survival have been identified and validated as important analytic variables in cardiac arrest research.

Through its prospective population based cohort registry of OHCA (ROC-Epistry Cardiac Arrest) as well as the secondary analysis of clinical trial data, ROC has begun to closely examine each of these factors in order to better understand their effects on outcome and to identify areas for improvement. The rich dataset combined with the large geographic catchment area of participating sites allows for meaningful studies with comparisons between nations (Canada and U.S.) as well as across and within sites. A key aspect of the Epistry dataset is the availability of a large amount of CPR process data for OHCA.

The first ROC paper published described the EMS systems participating in the consortium. At that time the ROC research network consisted of 260 EMS agencies, 287 receiving hospitals, and 154 dispatch centers across North America.(4) Although many service configurations were reported across sites, more than 80 percent of the EMS agencies are fire service-based. Most sites reported service delivery models included a combination of fire, governmental, and private EMS agencies. Deployment differences (BLS/ALS vs. all ALS) were noted as well as major differences in provider training levels (BLS vs. ALS) across sites. There were also marked differences in the capabilities of receiving hospitals especially with respect to cardiac catherization, which was more commonly available in the U.S. than in Canada. Dispatch centers were similar in that most used computer-aided dispatch, and nearly all provided pre-arrival instructions for OHCA.

Subsequent ROC epistry publications have looked at the effect of patient and event characteristics on outcomes from OHCA within the ROC sites. Rea et al.(2) used several methods to estimate the extent to which the traditional Utstein elements (age, sex, location, witnessed status, bystander CPR, and initial rhythm and EMS response intervals) predicted survival and explained outcome variability between 7 ROC sites. They found that although the Utstein elements predicted survival, they accounted for only a modest portion of the observed variability overall and between ROC sites. Zive et al. (5) found marked variation in the initiation of resuscitation efforts as well as transport of OHCA. Furthermore, the reporting of return of spontaneous circulation (ROSC) prior to transport also varied markedly across sites. This suggests that EMS system practice patterns (when to initiate resuscitation, when to terminate, when to transport) has a significant impact on observed survival and deserves further study. Another as yet unpublished ROC study looked at whether the number of providers on the scene had an effect on outcomes from OHCA. Findings (7) suggest having more providers on scene is associated with improved survival. This has major implications with regard to fire and EMS unit staffing levels and patterns. More research is needed to determine whether the type of personnel on scene (BLS vs. ALS) affects outcomes. Brooks et al. (6) examined the impact of

temporal variability on OHCA frequency and survival, noting frequency variation by time of day, day of week, and month. Survival also varied by time of day and day of week. These findings confirm that temporal differences deserved consideration with regards to EMS deployment strategies within communities.

Several ROC papers have examined the impact of EMS and hospital interventions on OHCA. Using voice and CPR process data collected from a single ROC site, Wang et al. (8) noted that paramedic efforts at endotracheal intubation (ETI) during OHCA were associated with frequent and multiple CPR interruptions. In light of this finding, as well as the challenges associated with maintaining ETI competency, many EMS agencies have added supraglottic airway (SGA) devices as first-line options in OHCA. The SGA devices are easier to insert and can be placed without interrupting CPR. Wang et al. (9) have examined the impact of the ETI vs. SGI in a secondary analysis of data from the ROC-PRIMED trial. Successful ETI was associated with better outcome when compared with successful SGA placement, although the overall survival difference was merely 0.8%. Because many unmeasured confounding factors could explain this difference, ROC investigators are actively planning a large RCT that would directly compare these two airway management strategies.

The importance of hospital care for patients that have been successfully resuscitated from OHCA has been recognized in Europe and prompted a call for a system of care approach for cardiac arrest similar to what is currently in place for trauma, stroke and ST segment myocardial infarction. Callaway et al. (10) used the ROC-Epistry Cardiac to study hospital characteristics associated with survival from OHCA. Unadjusted survival to discharge was greater in hospitals performing cardiac catheterization and in hospitals that received ≥40 patients/year when compared with those that received <40 patients per year. Bed number, teaching status, or trauma center designation did not appear to affect survival. Cudnik et al. (11) used the ROC dataset to study survival by transport distance and hospital proximity. Survival to discharge was higher in OHCA patients taken to hospitals located further than the closest hospital, whereas transport distance was not associated with survival. Together, these 2 studies add to the evidence base supporting the need for dedicated cardiac arrest treatment centers.

1. **Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. Journal of the American Medical Association 2008; 300:1423-1431**

2. **Rea T, Cook A, Stiell I, et al. Predicting survival following out-of-hospital cardiac arrest: role of the Utstein data elements. Annals of Emergency Medicine 2010; 55:249-257**

3. Eisenberg MS. Horwood BT, Cummins RO et al. Cardiac Arrest and Resuscitation: A tale of 29 cities. Annals of Emergency Medicine 1990; 19:179-186

4. **Davis D, Garberson L, Andrusiek D, et al. A descriptive analysis of emergency medical service systems participating in the Resuscitation Outcomes Consortium (ROC) network. Prehospital Emergency Care 2007; 11:369-382**

5. **Zive D, Koprowicz K, Schmidt T, et al. Variation in out-of-hospital cardiac arrest resuscitation and transport practices in the Resuscitation Outcomes Consortium: ROC Epistry-Cardiac Arrest. Resuscitation 2011; 82:277-284**

6. **Brooks S, Schmicker R, Rea T, et al. Out-of-hospital cardiac arrest frequency and survival; evidence for temporal variability. Resuscitation 2010; 81:175-181**

7. Nichol 2012 (personal communication)

8. Wang HE, Simeone SJ, Weaver MD, et al. Interruptions in cardiopulmonary resuscitation from paramedic endotracheal intubation. Annals of Emergency Medicine 2009; 54:645-652

9. Wang HE, Szydlo D, Stouffer JA, et al. Endotracheal intubation versus supraglottic airway insertion in out-of-hospital cardiac arrest. Resuscitation 2012; 83:1061-1066

10. **Callaway C, Schmicker R, Kampmeyer M, et al. Receiving hospital characteristics associated with survival after out-of-hospital cardiac arrest. Resuscitation 2010; 81: 524-529**

11. **Cudnik MT, Schmicker RH, Vaillancourt C, et al. A geospatial assessment of transport distance and survival to discharge in out of hospital cardiac arrest patients: Implications for resuscitation centers. Resuscitation 2010; 81:518-523**

Confirmation of the Value of Bystander Use of Automatic External Defibrillators (AEDS) and Support for the Three-Element Model of Cardiac Resuscitation

The randomized prospective Public Access Defibrillation Study demonstrated a twofold increase in survival at special sites where a bystander was equipped and trained to use an AED versus similar randomized sites where no AED was present and volunteers were instructed to call 911 and start CPR. ROC investigators sought to examine whether contemporary bystander use of AEDs without any specialized training of volunteers through the Public Access Defibrillation Trial achieved favorable results. In the ROC Epistry database, an AED application by a bystander, regardless of whether a shock was administered, resulted in a statistically significantly greater likelihood of survival (odds ratio 1.75 95% CI 1.23-2.50 p<.002). (1) This odds ratio was adjusted for the following: age, gender, bystander CPR performed, type of location, EMS response interval, witness status, initial rhythm, ROC site. Similar results were obtained with a stratified propensity score analysis. In 170 patients who were shocked by a bystander employing the AED, 38% survived to leave the hospital alive, whereas 22% of 1,280 patients survived when the bystander performed CPR, there was no AED present, and the EMS shocked the patient.

A second study from the ROC Epistry database examined the importance of the decline in VT/VF frequency as the initial post-arrest rhythm on the value of AEDs. This study, published in

the *New England Journal of Medicine*, demonstrated clearly that witnessed arrests occurring in a public location continue to be characterized by an overwhelmingly high frequency of initial rhythm VT/VF. (2) Thus, bystander use of an AED can be of significant value in providing access to care for patients arresting in public places. An adjusted odds ratio for initial rhythm VT/VF in a public place arrest versus home was 2.28 (95% CI 1.962 2.66) p<.001. If a bystander applied an AED in a public place versus home, the odds ratio for VT/VF was 4.48 (95% CI 2.232 8.97) p<.001. When a bystander in a public setting applied an AED, 34% of patients survived to leave the hospital alive. This study strongly supports deployment of AEDS in public locations and explains why AEDs failed to improve survival when used in the home in the randomized study that Bardy et al conducted previously. (3)

The studies cited above continue to support the three-element model of cardiac resuscitation in which defibrillation within the first four minutes after cardiac arrest is the primary intervention of value in VT/VF arrest (4). In the three-element model, after four minutes, based largely on animal data, a period of CPR and restoration of circulation is valuable and would improve survival. Again using the epistry data, survival was compared for very short-term or no CPR before defibrillation (less than 45 seconds) with longer periods of CPR before the first shock. The association between increased survival and 45 to 195 seconds of EMS CPR was more pronounced among patients with longer time to first EMS unit arrival and witnessed out of hospital cardiac arrest. (5)

Finally, using Epistry, the group examined whether survival after EMS-witnessed cardiac arrest compared favorably with arrests that were not EMS witnessed. (6) Even though the most common initial rhythm for EMS-witnessed arrest was PEA, which is associated with a poorer outcome, the adjusted odds ratio of survival in bystander-witnessed arrest with bystander performing CPR versus EMS witnessed arrest was 0.41 (95% CI 0.36-0.46) p<.001.

Taken together these studies support the value of early defibrillation by bystanders using an AED, and for arrest lasting longer than several minutes, the value of bystander performing CPR and immediately summoning EMS with rapid EMS arrival and implementation of EMS-based protocols for resuscitation.

1. **Weisfeldt ML, Sitlani CM, Ornato JP, Rea T, Aufderheide TP, Davis D, Dreyer J, Hess EP, Jui J, Maloney J, Sopko G, Powell J, Nichol G, Morrison LJ, ROC Investigators. Survival after application of automatic external defibrillators before arrival of the emergency medical system: evaluation in the resuscitation outcomes consortium population of 21 million. *Journal of the American College of Cardiology* 2010; 55: 1713-1720**

2. **Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL, Bigham B, Brooks SC, Foerster C, Gray R, Ornato JP, Powell J, Morrison LJ, ROC Investigators. Ventricular tachyarrythmias after cardiac arrest in public versus at home. New England Journal of Medicine 2011; 364:313-21**

3. Bardy GH, Lee KL, Mark DB, Poole JE, Toff WD, Tonkin AM, Smith W, Dorian P, Packer DL, White RD, Longstreth WT, Anderson J, Johnson G, Bischoff E, Yallop JJ, McNulty S, Ray LD, Clapp-Channing NE, Rosenberg Y, Schron EB, for the HAT Investigators. Home use of automated external defibrillators for sudden cardiac arrest. New England Journal of Medicine 2008; 358:1793-1804

4. **Weisfeldt ML, Becker L. Resuscitation after cardiac arrest - A 3-phase time-sensitive model. Commentary: Journal of the American Medical Association 2002; 288:23, 3035-3038**

5. **Bradley S, Gabriel E, Aufderheide T, Barnes R, Christenson J, Davis D, Stiell I, Nichol G, ROC Investigators. Survival increases with CPR by emergency medical services before defibrillation of out-of-hospital ventricular fibrillation or ventricular tachycardia: Observations from the Resuscitation Outcomes Consortium. Resuscitation 2010; 81:155-162**

6. **Hostler D, Thomas EG, Emerson SS, Christenson J, Stiell IG, Rittenberger JC, Gorman KR, Bigham BL, Callaway CW, Vilke GM, Beaudoin T, Cheskes S, Craig A, Davis DP, Reed A, Idris A, Nichol G, ROC Investigators. Increased survival after EMS witnessed cardiac arrest. Observations from the Resuscitation Outcomes Consortium (ROC) epistry-cardiac arrest. Resuscitation 2010; 81:826-830**

Studies Relating to CPR Performance

Understanding and implementing the best possible CPR is fundamental to the success of ROC cardiac arrest research. Each ROC site has energetically advocated and educated prehospital personnel on best CPR practices and has monitored the delivery of CPR to understand opportunities for improvement and to measure the effect of education and feedback programs. Scientific observations better defining quality CPR and improved survival are clear evidence of ROC's impact.

Monitoring CPR quality

EMS agencies have collaborated with the ROC research staff at each site to implement CPR monitoring aimed at broad system improvements in the quality of CPR. Collection of ECG recordings for the majority of cardiac arrest cases has facilitated a local system of quality assurance including feedback to individual rescue personnel on CPR performance feedback.

Agency-specific aggregate quarterly and annual reports from the Data Coordinating Center document important predictors of survival and the proportion of patients who survive to hospital discharge. These reports have been well received and have facilitated further improvement.

Real-time feedback on quality CPR

The ability to provide feedback on important aspects of quality CPR in real time has varied across ROC sites. The engagement of defibrillator manufacturers in supporting ROC sites allowed some locations to improve the technology and have supplied immediate feedback to rescuers on compression depth, complete compression release, and compression rate.

A formal randomized substudy nested in the randomized PRIMED study compared real-time feedback on CPR performance with no feedback demonstrated that in high-performing centers, variability decreased in the feedback patients. Although no effect on survival was demonstrated, the ability to change behavior is an important observation and may represent an effective mechanism to distinctly improve CPR in settings where these events are less common and skill maintenance is therefore difficult.

Hostler D, Everson-Stewart S, Rea TD, Stiell IG, Callaway CW, Kudenchuk PJ, Sears GK, Emerson SS, Nichol G, ROC Investigators. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: prospective, cluster-randomised trial. BMJ 2011; 342:d512

Observational studies on quality of CPR parameters

The Resuscitation Outcome Consortium is internationally recognized as the best source of CPR quality data and outcomes analysis. The following observational studies focused on individual parameters and the strength of association with survival to discharge and neurologic outcomes. These studies have generated international interest in guidelines modifications (see section 16).

1. **Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide, TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. Journal of the American Medical Association 2008; 300:1423-1431**

2. **Vaillancourt C, Emerson-Steward S, Christenson J, Andrusiek D, Powell J, Nichol G, Cheskes S, Aufderheide TP, Berg R, Stiell IG, ROC Investigators. The impact of increased chest compression fraction on return of spontaneous circulation for out-of-hospital cardiac arrest patients not in ventricular fibrillation. Resuscitation 2011; 82:1501-1507**

3. **Christenson J, Andrusiek D, Everson-Stewart S, Kudenchuk P, Hostler D, Powell J, Callaway C, Bishop D, Vaillancourt C, Davis D, Aufderheide T, Idris A, Stouffer J, Stiell I, Berg R, ROC Investigators. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation 2009; 120:1241-1247**

4. **Stiell IG, Brown SP, Christenson J, Cheskes S, Nichol G, Powell J, Bigham B, Morrison LJ, Larsen J, Hess E, Vaillancourt C, Davis DP, Callaway CW, ROC Investigators. What is**

the role of chest compression depth during out-of-hospital cardiac arrest resuscitation? Critical Care Medicine 2012; 40:1192-1198

5. **Cheskes S, Schmicker RH, Christenson J, Salcido DD, Rea T, Powell J, Edelson DP, Sell R, May S, Menegazzi JJ, Van Ottingham L, Olsufka M, Pennington S, Simonini J, Berg RA, Stiell I, Idris A, Bigham B, Morrison L, and on behalf of the ROC Investigators. Perishock Pause: an independent predictor of survival from out-of-hospital shockable cardiac arrest. Circulation 2011; 124:58-66**

6. **Idris AH, Guffey D, Aufderheide TP, Brown S, Morrison LJ, Nichols P, Powell J, Daya M, Bigham BL, Atkins DL, Berg R, Davis D, Stiell I, Sopko G, Nichol G, ROC Investigators. Relationship between chest compression rates and outcomes from cardiac arrest. Circulation 2012; 125:3004-3012**

7. REGISTRY (EPISTRY) STUDIES OF TRAUMATIC INJURY: TRAUMA TRIAGE, GOLDEN HOUR, AND AIRWAY MANAGEMENT

Life-threatening injury remains a major public health problem in the U.S. and Canada. Studies have shown that trauma centers have been able to improve outcomes from severe injury, fostering the development of regionalized trauma systems across North America. (1)

An important and integral component of any trauma program is its regional EMS system. Despite advances in care, many scientific questions remained regarding optimal out-of-hospital assessment and management of injured patients. Through its prospective population-based cohort registry of severely injured trauma patients (ROC Epistry-Trauma) as well as secondary analyses of controlled clinical trial data, ROC has been able to rigorously investigate important EMS issues, such as existing trauma triage criteria; importance of prehospital time intervals, particularly the concept of the "golden hour"; epidemiology of airway interventions; risks vs. benefits of advanced airway management; and optimal modes (air vs. ground) of transportation. The results have contributed to the effectiveness of prehospital assessment and interventions in trauma while highlighting potential areas of policy change.

The sensitivity of the 3 variables currently included in the physiological assessment of the trauma patient—systolic blood pressure, respiratory rate and Glasgow coma score—have been validated, and the importance of attempted airway management as an independent predictor of mortality has been recognized for consideration in future trauma triage guidelines. (2) In civilian trauma, where blunt injuries are more common, the concept of the "golden hour" appears to be less crucial than previously believed, and routine lights-and-sirens transport of injured trauma patients may be unwarranted. (3)

Early management of the airway is considered an imperative in treatment of injured patients. However, an epidemiological analysis of airway interventions within ROC sites however showed

dramatic variation across sites with regard to type, rate, and selection of patients for airway interventions. (4) A negative association between field advanced airway management and outcomes was found in patients with a GCS ≤ 8, although EMS systems with more advanced airway management attempts had lower mortality than those with less. (5) This finding confirms that EMS experience is an important consideration when evaluating the risk vs. benefit of any intervention. The negative impact of prehospital advanced airway management has also been highlighted in the secondary analyses of the ROC hypertonic saline Dextran shock and TBI cohorts. (6) Much more investigation is needed to better understand the optimal timing and technique of prehospital airway interventions in trauma.

Recently, a ROC study has added to the debate on the preferred mode of transport for trauma patients, demonstrating no difference in outcomes between ground and air EMS agencies. (7) In addition, although outcome differences between trauma and non-trauma centers have fostered the trauma systems model of care for severely injured individuals, comparative studies of survival across trauma centers have been limited. Outcome comparisons within 9 geographic ROC sites showed dramatic variation in survival ranging from 39.8 to 80.8%. (8) These differences were sustained for both blunt and penetrating trauma. A better understanding of the factors associated with these survival differences is needed in order to reduce the public health burden from trauma across communities.

1. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. New England Journal of Medicine 2006; 354:366-378

2. **Newgard CD, Rudser K, Hedges JR, et al. A critical assessment of the out-of-hospital trauma triage guidelines for physiologic abnormality. Journal of Trauma 2010; 68:452-462**

3. **Newgard C, Schmicker R, Hedges J, et al. Out-of-hospital time and survival: assessment of the "Golden Hour" in a North American prospective trauma cohort. Annals of Emergency Medicine 2010; 55:235-264**

4. **Newgard C, Koprowicz K, Wang H, et al. Variation in the type, rate, and selection of patients for out-of-hospital airway procedures among injured children and adults. Academic Emergency Medicine 2009; 16:1269-1276**

5. **Davis DP, Koprowicz KM, Newgard CD, et al. The relationship between out-of-hospital airway management and outcome among trauma patients with Glasgow Coma Scale scores of 8 or less. Prehospital Emergency Care 2011; 15:184-192**

6. **Wang HE, Brown SP, McDonald R, et al. Association of out-of-hospital advanced airway management with outcomes after traumatic brain injury and hemorrhagic shock in the ROC Hypertonic Saline Trial. Accepted for publication, Emergency Medicine Journal 2013**

7. **Bulger EM, Guffey D, Guyette FX, et al. Impact of prehospital mode of transport after severe injury: A multicenter evaluation from the Resuscitation Outcomes Consortium. Journal of Trauma and Acute Care Surgery 2012; 72:567-575**

8. **Minei JP, Schmicker RH, Kerby JD, et al. Severe traumatic injury: regional variation in incidence and outcome. Annals of Surgery 2010; 252:149-157**

8. REGISTRY (EPISTRY) STUDIES OF CARDIAC ARREST AND TRAUMATIC INJURY IN CHILDREN

Life-threatening injury and cardiac arrest are of great concern in pediatric patients. Traumatic injury is the leading cause of death among children, and although pediatric cardiac arrest is uncommon, it has devastating consequences, with fewer than 10% of victims surviving in most communities (1, 2). Hence, efforts that effectively improve prevention or treatment of these conditions can improve overall public health. Rigorous investigation among children is especially challenging given the low individual rate of serious injury or arrest coupled with the regulatory and clinical protections often required for study. As a result, there is essentially no high-level evidence to guide pediatric resuscitation (3). Instead, emergency rescuers generally rely on protocols derived from resuscitation evidence among adults, a group for whom the underlying physical anatomy and arrest etiology may be quite different and require distinct treatment.

In response to these challenges, ROC has developed rigorous observational data resources to help inform the topics of cardiac arrest and serious trauma among children (4,5). For example, ROC investigations underscore and inform strategies aimed at preventing or accurately triaging pediatric injury (6,7). ROC also has investigated variability in the use of critical field procedures (e.g., airway intervention) (8) and has validated more efficient methods for out-of-hospital data collection among children and adults (9). In a study evaluating the golden hour in trauma, children were independently assessed in a key subgroup analysis (10).

ROC is now positioned to inform health care decisions and approaches related to pediatric management of cardiac arrest. One of the primary challenges for pediatric cardiac arrest is to accurately characterize the event–including the incidence, circumstances, care, and outcome. ROC's large, population-based design has produced an unprecedented accrual of pediatric out-of-hospital cardiac arrest events. The prospective, registry-style informational resource has enabled rigorous and formative descriptive evaluation of major metrics involving pediatric arrest and resuscitation. Specifically, a high-profile ROC study provided a robust estimate of

pediatric incidence and outcome based on nearly 700 treated out-of-hospital cardiac arrest events (2).

Importantly, the registry has now accrued nearly 2,800 pediatric arrest events. Given the sample size and detailed nature of the database, ROC investigation is now underway to evaluate how incidence, treatment, and outcome vary across regions and systems of emergency care. Understanding this variation is a key step toward defining best practice and identifying promising approaches for additional investigation. For example, one current investigation is evaluating core CPR metrics (rate and extent of chest compressions) to assess if and how variation in this essential intervention influences outcome. The pediatric-specific findings will address a critical gap in our understanding of resuscitation for children (3).

ROC will continue to consider opportunities to enroll children in interventional trials after incorporating physiologic, regulatory, and ethical considerations. We believe the consortium's ongoing, rigorous observational investigations provide a unique and compelling strategy to advance knowledge and provide the foundation for potential meaningful interventional trials among children suffering from emergent and critical conditions such as serious trauma and cardiac arrest.

1. Center for Disease Control, National Vital Statistics. 61:7; http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_07.pdf

2. **Atkins DL, Everson-Stewart S, Sears GK, Daya M, Osmond MH, Warden CR, Berg RA, ROC Investigators. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. Circulation 2009; 119:1484-1491**

3. Kleinman ME, de Caen AR, Chameides L, Atkins DL, Berg RA, Berg MD, Bhanji F, Biarent D, Bingham R, Coovadia AH, Hazinski MF, Hickey RW, Nadkarni VM, Reis AG, Rodriguez-Nunez A, Tibballs J, Zaritsky AL, Zideman D. Pediatric basic and advanced life support chapter collaborators. Part 10: Pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010; 122:S466-515

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9. IMPORTANCE OF EFFECTIVENESS STUDIES

ROC's primary purpose is to conduct clinical trials to measure the effectiveness of resuscitation strategies for cardiac arrest and severe trauma in the out-of-hospital emergency setting. The studies that ROC investigators conduct will continue to have great impact on public health. Studies currently under investigation are examining new methods, devices, or drugs for cardiopulmonary resuscitation; new approaches to fluid resuscitation; and improved approaches to identifying patients with severe traumatic injury.

The goal of ensuring that resuscitation strategies are effective on a population level is driven by the lack of patient choice in emergency treatment. Treatment protocols are established on a community basis by the local EMS agencies that respond to emergency calls. In this setting, it is of significant importance that researchers make the distinction between the efficacy and the

effectiveness of a new treatment. ROC studies are performed in a network of EMS agencies within a representative cross-section of North American communities and thus provide a level of generalizability that will continue to guide future EMS practices and thereby impact public health.

Efficacy trials focus on whether a treatment affects disease or outcome in a beneficial way. To maximize the probability of demonstrating any effect, such trials usually restrict the patient population studied, as well as the treatment environment and the use of ancillary treatments. Treatment providers tend to receive extraordinary training in use of the treatment and the monitoring of patients to determine clinical outcomes. Furthermore, efficacy studies might use as measures of primary outcome some biological or surrogate clinical outcome. For instance, efficacy trials of resuscitation strategies might be conducted in an emergency department on a small subset of the patients who might eventually receive the proposed treatment, and the primary outcome might be based on return of spontaneous circulation or short-term survival. The study may demonstrate that a therapy is useful for an important clinical outcome but not necessarily useful when applied in a broader patient population.

Conversely, effectiveness trials focus on demonstrating the effect a therapy would have on the population when fully adopted. Such trials are crucial before the results of efficacy trials will or should be adopted widely by EMS agencies. A strategy that has proven to have some efficacy may, in fact, be ineffective when introduced into the general out-of-hospital emergency setting due to the differences in patients treated, the mode of treatment administration, subsequent systems of care, or the definition of a favorable outcome. By conducting effectiveness trials of resuscitation strategies, ROC will continue to ensure that proposed treatments provide general benefit in settings where:

- Subjects are representative of the true patient population (instead of being restricted, for example, to patients surviving to the ED)
- Treatments are initiated or administered wherever appropriate by paramedics and EMTs and are potentially continued in the ED
- The availability of diagnostic procedures and ancillary treatments accurately reflects availablility and routine use in the field, and the primary measure of treatment outcome is the most clinically relevant outcome of neurologically intact survival to hospital discharge or beyond (instead of intermediate or surrogate measures of efficacy)

EMS medical directors may then use the results of these effectiveness trials to judge which therapies to implement in order to improve outcomes. The end result should be a steady improvement in the rates of successful resuscitation of out-of-hospital cardiac arrest and severe trauma.

10. SPECIAL CHALLENGES: EXCEPTION FROM INFORMED CONSENT, COMMUNITY CONSULTATION AND PUBLIC NOTIFICATION, MULTIPLE IRBS, AND GOVERNMENT AGENCIES

ROC has faced some special challenges by virtue of being one of the first multinational research networks to conduct large-scale out-of-hospital research involving patients who are unable to give consent. Most ROC studies use an "exception from the requirement to obtain informed consent (EFIC) for emergency research" as outlined in FDA regulation 21 CFR 50.24 and the provisions stipulated in the Canadian Tri-Council Agreement for research in emergency health situations (Article 2.8). Since its inception, ROC has garnered substantial experience with this process. As a result, ROC is positioned to help define best practices in meeting these regulations and conducting this type of research and has contributed substantially to the literature in this regard. (1)

An important requirement for conducting EFIC research in the U.S. centers is the need for community consultation. When ROC started there was little consensus about what forms of community consultation should be used in EFIC research. The methods that could be used included, but were not limited to, public meetings, focus groups, interviews with key stakeholders, and electronic communication via websites. One tool that ROC investigators adapted and extended is the random telephone survey, in which a sample of the population is asked to answer specific questions regarding a research protocol, and the data obtained is then collated by phone number and zip code to determine the degree of public acceptance. (2) ROC's experience with this technique has uniformly shown good public acceptance for EFIC research. ROC sites have also started using social media (e.g., Facebook, Twitter) in their community consultation efforts.

Another requirement for EFIC research is public notification through traditional means, including press releases to newspapers, television, and radio; newspaper advertisements targeted at community groups; and signage in public places, such as buses or community recreational facilities. ROC's experience has shown that the specific method of community consultation and public notification activity should be left to the local investigator based on the expected target population and local IRB requirements.

An interesting practical challenge that has emerged is the need to work with multiple IRBs within single communities given the realities of emergency care and treatment. In particular, patients could be identified by multiple EMS agencies and transferred to many different receiving hospitals. Thus, oversight by several IRBs may be required. ROC investigators have learned that this issue can be managed effectively by having a lead IRB, usually one that is university-based, review an initial IRB application and develop plans for community consultation. This initial review can then be used to work with other local IRBs, which generally look to the lead IRB for guidance. Most IRBs will work together and agree on a common community consultation process, which ultimately saves costs. This process may also involve direct input from local authorities, including city councils, county boards of supervisors, mayors, and other local leaders.

Another issue that ROC has needed to address stems from the differences in consent requirements across FDA divisions. Depending on the nature of what a specific trial is seeking to evaluate, a ROC trial may be overseen by the Division of Blood and Biologicals; the Division of Pulmonary, Allergy and Rheumatology Products; the Division of Cardiovascular and Renal Products, the Division of Cardiovascular Devices; or the Office of Human Research Protection. Such variation has led to delays in study approval and initiation of subject enrollment. Subjectively, ROC investigators perceive that ongoing dialogue with these federal entities has led to some harmonization of requirements over time and consequent improvements in the efficiency of study conduct. (3)

Even when all regulatory requirements are satisfied, EFIC research can raise a variety of ethical questions. One concern is that EFIC research in general, and ROC research in particular, might disproportionately enroll ethnic and racial minorities. However, analyses using ROC's Epistry database and showed that this concern was unfounded. (4)

Finally, ROC has encountered the concerns as to whether subjects ought to be coenrolled in multiple studies conducted under EFIC for emergency research. ROC investigators have determined that no regulation is in place that would prohibit coenrollment and therefore have proposed criteria for allowing or facilitating coenrollment in order to accelerate evidence-based changes in resuscitation practices. (5) In addition, ROC has used research designs that encourage coenrollment without undue respondent burden. (6)

ROC has risen to the regulatory challenges associated with EFIC research and has helped to set standards for the ethical conduct of this research on a national basis. ROC investigators have been actively engaged in identifying optimal methods to engage the community in this important research.

IRB Centralization Experience

Conceptually, a centralized process for each community would be efficient and cost-effective.

ROC carries out a a wide range activities that could be enhanced or negatively affected through centralized IRB reviews. Examples are as follows:

Milwaukee, WI, has recently established "One City, One IRB," a single, community-wide IRB process for clinical trials using exception from informed consent under emergency circumstances. Each of the four other IRBs in Milwaukee, covering all 15 paramedic-receiving hospitals in the community, have agreed to provide reciprocity with the Medical College of Wisconsin IRB for such trials and have developed and approved a single informed consent, valid at all paramedic-receiving hospitals. This system has reduced both the number of applications required and in-person meetings with other IRBs, which, in turn, reduced research coordinator and investigator effort, time, and cost.

Overall experience: is very promising with the new centralized system.

British Columbia, CA, is moving ahead on a process of REB Unification Policies, which are under development with with stakeholders now providing input.

Overall experience: moving forward but implementation is a year away.

Seattle, WA, continues to use the University of Washington IRB providing primary oversight over ROC trials, including oversight of community notification/consultation and all exception from informed consent issues. ROC must request separate IRB approval from each hospital that provides records that are reviewed in the studies.

Dallas-Forth Worth, TX,in 2005, ROC PI tried to organize the, IRBs into a regional system. All IRB directors and chairs attended a meeting to discuss this proposal, and most thought it was a good idea. However, after they discussed the idea with their institutions and attorneys, they decided to retain their autonomy.

Overall experience: status quo.

Toronto, ON, CA, have convened many task forces many times but no action has occurred toward a central IRB.

Overall experience: status quo

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11. COMPLETED AND ONGOING CLINICAL TRIALS IN TRAUMA RESUSCITATION (COMPLETED)

Hypertonic Saline vs Hypertonic Saline-Dextran (HSD) in Severe Trauma with Hypertension and a Second Parallel Study in Traumatic Brain Injury

A great deal of preclinical data suggests that hypertonic solutions have beneficial effects on patients with severe injury and hypovolemic shock. A trial in 2005 comparing the use of HSD with lactated ringers following blunt traumatic injury with hypovolemic shock. The study provided evidence of improved outcomes for patients who were in severe shock as manifested by the need for ≥10 units of packed red blood cells (PRBCs) in the first 24 hours after injury. These data were used in the design of two trials that the ROC conducted in 2006 to 2009: randomized controlled trials of 250cc 7.5% saline (HS), 7.5%saline/6%dextran-70 (HSD), or 0.9% saline (NS) as the initial resuscitation fluid administered in the prehospital setting following severe traumatic injury with evidence of either hypovolemic shock or in the second trial traumatic brain injury (TBI).

The Data Safety Monitoring Board suspended enrollment in the shock cohort secondary to futility and a potential safety concern in the hypertonic groups (N=894). There was no difference in 28-day survival: HSD 74.5%, HS 73.0%, and NS 74.4%, p=0.91. Enrollment in the TBI study was suspended in 2009 secondary to futility (N=1327). There was no difference in six-month neurologic outcome: extended Glasgow outcome score ≤ 4 (death or severe disability) HSD 53.7%, HS 54.3%, NS 51.5%, p=0.67.

Clinical trials of hypertonic resuscitation early after injury failed to demonstrate significant benefit for resuscitation of hemorrhagic shock. Likewise clinical trials of early administration to TBI patients also failed to show benefit.

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Prehospital Lactate for the Identification of Shock in Trauma (Completed and Ongoing)

This study was initiated to compare a model of prehospital lactate (P-LAC) levels plus systolic blood pressure to systolic blood pressure alone to predict the need for resuscitative care (the administration of packed red blood cells (PRBCs), emergent intervention for hemorrhage control using thoracotomy, laparotomy, pelvic fixation, or interventional radiologic control) or death within 6 hours of ED arrival in patients with $70 < SBP \leq 100$ mmHg in the prehospital setting.

A secondary aim was to evaluate the usefulness of P-LAC, when combined with other prehospital variables (heart rate, systolic blood pressure, GCS), in predicting the need for resuscitative care.

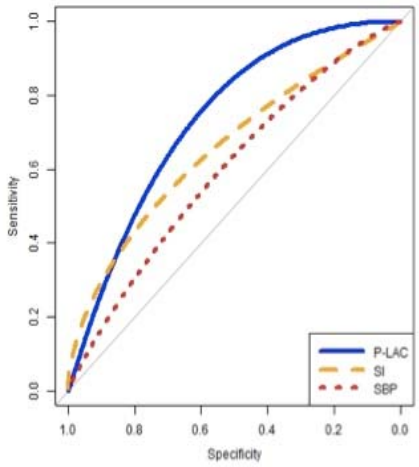
Patients who met local trauma triage criteria for traumatic injury, required placement of an IV, and were transported to a level I or II trauma center or died in the field or en route (with $SBP \leq 110$ mmHg and after placement of an IV) were entered.

The ground transported patient study was analyzed and presented at the AHA's Resuscitation Science Symposium 2012. The study showed that a prehospital lactate ≥ 2.4 mmol/L can identify trauma patients at increased risk of death or need for resuscitative resources better than SBP alone.

ROC Investigators are currently designing a study to confirm the value of lactate measurement on clinical outcomes when compared to SP < 90 mmHG alone. If prospectively validated, prehospital lactate might be useful as a tool for notifing trauma centers as to which patients will require additional resources. Measurement of lactate could be easily deployed on all EMS

vehicles providing additional information to clinicians at relatively low cost using a reliable device whose operation is already familiar to paramedics.

A separate study of the same design is ongoing in air medical services. This study has 90% power to detect a difference of 12.9% if 235 patients with SBP between 70 and 110 mmHg are enrolled (two-sided test with alpha=0.025).



Usual Aggressive Fluid Administration vs. Low Volume Fluid Administration in Traumatic Injury with Early Hypotension (Pilot) (Completed)

This multicenter pilot trial was designed to compare the feasibility and safety of standard aggressive fluid resuscitation to hypotensive resuscitation for the prehospital treatment of patients with traumatic shock. Blunt and penetrating trauma patients with a prehospital systolic blood pressure < 90 mmHg were eligible. The study is a randomized interventional trial comparing the 2 resuscitation strategies. In the hypotensive resuscitation group, an intravenous line (IV) will be placed and if SBP >70 a 250cc bag of fluid was hung and maintained to keep the vein open. If the SBP was ≤70 the fluid was administered and the process repeated until the SBP >70. Patients in the standard aggressive fluid resuscitation group had an IV placed, and a 1000cc bag of fluid was hung. Two liters of fluid were administered before checking the SBP afterwhich an SBP of >110 would allow reduction in fluid administration. Patients with severe traumatic brain injury were excluded due to the known relationship between hypotension and poor neurologic outcomes. Due to obvious differences in the treatment of enrolled patients, the study will not be blinded after randomization.

To determine the feasibility of performing the proposed hypotensive resuscitation study, investigators elected to first do a pilot study of 200 patients. The hypothesis of this pilot study

was that patients undergoing hypotensive resuscitation would receive less than one half the amount of fluid of patients undergoing standard resuscitation. Six centers enrolled patients in this trial. Initial review of the data after 111 patients had been enrolled revealed that the hypothesis was correct; however, only 20 of the 111 patients were severely injured as defined by an ISS > 15. Many of the patients being enrolled had sustained ground-level falls. After identifying this issue, a protocol clarification was sent out to all of the sites stating that ground-level falls were ineligible for randomization in this study. Analysis of the next 60 enrolled patients revealed that 20 were severely injured suggesting that this intervention was successful. The enrollment was completed on April 19, 2013 with 192 patients. Two higher enrolling sites started another ROC study (PROPPR) in January 2013 and enrollment became increasingly difficult.

Dallas RESCUE: Estrogen vs. Placebo Pilot in Traumatic Shock and Traumatic Brain Injury (Completed)

For more than 30 years, diverse injury models from numerous laboratories have found estrogen offers significant protection from secondary injury following trauma. The ROC recently completed the first clinical pilot studies examining the use of early estrogen in trauma patients. RE*SCUE* (Resuscitative Endocrinology: *Single-dose Clinical Uses for Estrogen*) Shock and RE*SCUE* TBI are each randomized, double-blinded, placebo-controlled, multisite studies testing early, therapeutic doses of estrogen (intravenous Premarin®) vs placebo as an acute resuscitation drug in a population of male and female patients with traumatic hemorrhagic shock and severe TBI, respectively . Each of these studies entered 50 patients.

Relevant clinical outcomes were assessed along with serial samples of blood, urine, and cerebrospinal fluid in those patients with a therapeutic ventriculostomy. In addition to evaluating markers of inflammation and oxidant injury, by measuring levels of estrogen in these fluids, researchers hoped that these data would help to inform a larger, definitive, prehospital study regarding dose, timing of administration, and appropriate patient population for estrogen usage. However, initial data analysis did not show any suggestion of benefit of estrogen on outcome.

Ongoing ROC Study of Ratio of Plasma to Platelets and Red Cells in Massive Transfusion Patients

An ongoing question in deciding the optimal resuscitative therapy for trauma patient centers is the optimal blood product ratio. Currently, there is no universally accepted Massive Transfusion (MT) guideline. Many trauma centers now apply a ratio-driven MT protocol rather than a laboratory-directed approach. After reviewing previous retrospective and prospective observational studies, the ROC investigative team has developed a large randomized clinical trial to determine the optimal blood product ratio for traumatic injury resuscitative treatments.

The primary aims of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial are as follows:

- To separately compare as co-primary outcomes 24-hour and 30-day mortality between the two treatment groups (1:1:1 and 1:1:2 platelets: plasma: RBCs), adjusting for clinical site
- To compare subjects predicted to have a MT and randomized to the 1:1:1 and 1:1:2 ratio groups on a variety of ancillary clinical outcomes measured from randomization to initial hospital discharge after adjusting for site
- To develop models characterizing trauma-induced coagulopathy (TIC) and inflammation in enrolled subjects
- To develop models characterizing the dynamics of TIC to identify mechanistic drivers and sequelae of coagulation and inflammation and to characterize the natural history of the coagulation/inflammatory milieu in enrolled subjects
- To assess the effect of coagulation and inflammatory models on primary and ancillary outcome

Subjects enrolled in PROPPR are randomized to receive blood products based on either 1:1:1 or 1:1:2 ratio of platelets:plasma:RBCs. The trauma physician team is blinded to the ratio group until it is deemed necessary to open the first study blood cooler. The order of products based on the treatment group is then followed until hemostasis has been achieved. In addition, research blood samples are collected at 0, 2, 4, 6, 12, 24, 48, and 72 hours following ED admission to assist in answering the TIC and inflammation complications identified in the primary aims above. PROPPR is being conducted at 12 Level 1 trauma centers across North America with a target enrollment of 580 subjects who are predicted to require a MT based on the ABC scoring system (heart rate >120 bpm, systolic B/P < 90 mmHg, penetrating injury, + FAST exam) or physician judgement. ROC sites and satellite sites are part of this study. The University of Washington data coordinating center is playing a collaborative role but the primary coordination is through the satellite Data and Clinical Coordinating Centers in Houston. PROPPR started enrollment in August 2012, is enrolling ahead of schedule with an estimated enrollment period of 18 to 24 months. The PROPPR trial includes a Vanguard phase for the initial 25% of subject enrollment (146 subjects) to assess trial procedures and feasibility of the trial. This phase of the study is completed, and the DSMB recommended increasing the sample size to 680 patients to increase the power of the study.

12. COMPLETED AND ONGOING CARDIAC ARREST TRIALS

ROC-PRIMED (Completed)

The first ROC cardiac arrest trial employed a partial factorial design that tested: 1) an intervention (the Impedance Threshold Device, or "ITD") shown to improve cardiac output during CPR by increasing the degree of negative intrathoracic pressure and venous return vs. a sham ITD device; and 2) whether survival is better when rhythm analysis is performed after only 30 to 60 sec (analyze early) vs. 180 sec (analyze later) of EMS-administered CPR. The primary outcome was survival to hospital discharge with satisfactory neurologic function (i.e., a score of ≤3 on the modified Rankin score, which ranges from 0 to 6, with higher scores indicating greater disability).

In the ITD trial, 4,345 patients were randomly assigned to treatment with a sham ITD and 4,373 to treatment with an active device. There was no statistically significant difference between groups in the primary outcome measure (6.0% in the sham-ITD vs. 5.8% in the active-ITD groups). There were also no significant differences in the secondary outcomes, including rates of return of spontaneous circulation on arrival at the emergency department, survival to hospital admission, and survival to hospital discharge.

In the Analyze-Early vs. Later trial, 5,290 patients were assigned based on cluster-randomization to early vs. 4,643 to later analysis of cardiac rhythm. There was no difference between groups in the primary outcome measure (5.9% for either group). Analyses of the data with adjustment for confounding factors as well as subgroup analyses also showed no survival benefit for either study group. Both studies were reported in the *NEJM.* (1,2)

Although both trials showed no significant difference between study groups, the results have had a significant impact on the field of resuscitation. For example, many EMS systems no longer spend their precious funds on a mechanical device that does not appear to improve outcome when applied in a setting similar to that studied in the trial. In addition, finding no material advantage to a more prolonged period of chest compression prior to rhythm analysis has allowed many EMS medical directors to abandon this strategy and focus on improving the quality of CPR and beginning ACLS interventions (e.g. defibrillation and medications) more quickly.

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Ongoing Continuous Chest Compression vs. Chest Compression with Interruption for Ventilation (AHA Standard CPR)

Animal models of cardiac arrest (1-3) and observational studies in humans (4-8) show that continuous chest compression (CCC) during the early resuscitation period is a more promising intervention than standard compression with interposed pauses for ventilations (ICC). But each of these studies implemented multiple changes simultaneously, so it is difficult to assess the relative contribution of CCC versus other changes in CPR strategies. A state of equipoise exists regarding the effectiveness of CCC for patients with OHCA, which is reflected in the variation in practice within ROC. Therefore, the ROC investigators initiated a large trial to compare survival to hospital discharge after CCC versus standard AHA recommended CPR with ICCs in patients with OHCA. For this study, CCC is defined as a series of three cycles of continuous chest compressions without pauses for ventilation (instead ventilations are interposed with compressions) followed by rhythm analysis or until restoration of spontaneous circulation (ROSC), whichever occurs first. ICC consists of series of three cycles of standard CPR, with each cycle comprising chest compressions with a pause for ventilations at a compression:ventilation ratio of 30:2 (per AHA guidelines) followed by rhythm analysis or until ROSC, whichever occurs first. In either patient group, the duration of manual CPR before the first rhythm analysis will be 30 seconds or 120 seconds. This treatment period will be followed by two cycles of compressions then rhythm analysis (i.e. each of approximately 2 minutes duration) in either group.

Clusters consisting of EMS agencies or stations will be randomized to control versus intervention and will be scheduled to cross over to the opposite treatment at least once during the trial. The study will involve adults with non-traumatic arrest outside of the hospital. Patients with obvious primary asphyxia, respiratory cause of arrest, advanced airway placed prior to ROC EMS arrival, and EMS-witnessed arrest will be excluded from the study.

The primary measure of outcome will be survival to hospital discharge. Secondary outcomes include modified Rankin score (MRS) at discharge, mechanistic outcomes, and adverse events. Analyses of primary and secondary outcomes will be conducted on an intent-to-treat basis.

Secondary analyses will assess treatment effect in patients by initial rhythm. The primary analysis will use generalized estimating equations to compare the rate of survival to discharge in the two treatment groups with robust standard errors used to accommodate clustering. We require 23,600 patients (11,800 per group) to have at least 90% power to detect a difference of 1.3% between treatment groups in the rate of survival to hospital discharge using an overall significance level (adjusted for interim analyses) equal to 0.05. As of May 2013 14,022 patients have been screened with 9,705 enrolled.

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Ongoing ALPS Randomized Trial of Amiodarone, Lidocaine, or Placebo in Refractory Ventricular Fibrillation/Tachycardia

The antiarrhythmic medications amiodarone and lidocaine are frequently used as part of advanced care to treat ventricular arrhythmias that persist or recur during cardiac arrest. Although the pharmacological effects of these drugs are well-known, a considerable gap persists in understanding of their mechanisms of action and whether their use actually improves survival after cardiac arrest. No studies have shown that any pharmacologic agent improves survival to hospital discharge after cardiac arrest. These drugs may cause harm.

The primary goal of ROC's amiodarone, lidocaine, or placebo study (ALPS) is to determine if survival to hospital discharge improves with early and, if necessary, repeated therapeutic administration of a new captisol-enabled formulation of IV amiodarone (PM101) compared to no antiarrhythmic drug (placebo) or lidocaine. The study will compare the benefit of what is believed to be the most effective antiarrhythmic drug (amiodarone) against the traditional standard drug (lidocaine) and against placebo in shock-resistant VF cardiac arrest. As such, this study may provide the answer to 2 critical questions: Are antiarrhythmic drugs effective for the treatment of VF cardiac arrest, and is amiodarone preferable to lidocaine for such treatment? Answering these questions will determine the role of antiarrhythmic drugs for future generations of patients with out-of-hospital cardiac arrest.

The study is being conducted at 10 locations across the U.S. and Canada. Approximately 70 EMS organizations comprising more than 10,000 EMS providers who serve a combined population of nearly 15 million people from diverse urban, suburban, and rural regions will participate. Approximately 3,000 patients will be enrolled. The study is expected to last approximately 3 years. As of May, 2013, a total of 5,937 patients had been screened for ALPS eligibility. Of 774 patients with original eligibility (initial rhythm VT/VF, recurrent VT/VF, and meeting inclusion/exclusion criteria), 462 had sustained eligibility and have been enrolled in the trial.

13. FUTURE ROC STUDIES IN TRAUMA

A. Prehospital Tranexamic Acid (TXA) for Blunt TBI

TXA is a synthetic derivative of the amino acid lysine that competitively inhibits plasminogen activation and, at higher concentrations, noncompetitively inhibits plasmin. TXA binding blocks the interaction of plasminogen with fibrin thereby preventing the breakdown of the fibrin clot. The use of TXA to control bleeding has been described in a number of clinical studies.

The MATTERs trial was an observational study of 896 patients admitted to a Role 3 U.K. combat support hospital in Afghanistan in 2009-2010 who received at least 1 unit of packed red blood

cells within 24 hours of admission. (1) A total of 293 patients received TXA. The TXA group had significantly lower mortality (17.4% versus 23.9%) despite being more severely injured.

The safety and efficacy of using TXA in trauma patients was recently studied in a large placebo-controlled trial of 20,211 trauma patients in 40 countries. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) study (2) involved patients who were being treated within 8 hours of injury and had a SBP < 90mmHG and/or heart rate > 110 beats per minute or were considered to be at risk for significant hemorrhage.

The results from CRASH-2 raised the possibility that TXA may also be effective in TBI. CRASH-2 did not exclude patients with TBI; however, the first report did not provide detailed outcomes for this cohort. To further examine the use of TXA in TBI, the investigators presented separately the results in a cohort of 270 patients with TBI (defined as brain CT compatible with TBI and GCS ≤ 14) who were enrolled in CRASH-2. The study was prospective with detailed CT data and prespecified outcomes. (2, 3, 4) The primary outcome of the study was growth of the intracranial hemorrhage (ICH), measured using CT at hospital admission and 24-48 hours later. Secondary outcomes were death from any cause, dependency (measured using the 5-point Modified Oxford Handicap Scale, dichotomized into dead or dependent versus independent) the need for neurosurgical intervention, and the appearance of new focal cerebral ischemic lesions on follow-up CT. In this analysis, the mean total hemorrhage volume growth was reduced from 8.1 ml in the placebo group to 5.9 ml in the TXA group. Equally important, was the finding that patients in the TXA group developed fewer new focal cerebral ischemic lesions than in the placebo group (4.9 versus 9.5%), and fewer patients died in the TXA group than in the placebo group (10.5 versus 17.5%). Whereas none of these results was statistically significant, however, the authors concluded that neither moderate benefit nor moderate harm of TXA in TBI could be excluded.

ROC proposes a phase II study--a randomized double-blind placebo controlled trial evaluating the efficacy and safety of TXA in subjects with TBI. The primary outcome will be the proportion of subjects with a favorable neurologic outcome 6 months after injury (defined as a GOS-E score of >4). The secondary outcomes will be 28-day mortality, intracranial hemorrhage (ICH) growth, frequency of neurosurgical interventions, and hospital-free, ventilator-free, and ICU-free days measured from randomization to initial hospital discharge. Safety will be assessed by evaluating the proportion of subjects experiencing cerebral ischemic events, myocardial infarction, deep venous thrombosis, pulmonary thromboembolism, and seizures measured from randomization through 1 month or discharge, whichever occurs first. In addition, functional laboratory studies will comprehensively characterize coagulation and will provide insight into dynamic changes in coagulation and their relationship to treatment and outcome. Subjects will be randomized to one of the following 3 arms in the prehospital environment:

1. 1gm IV TXA bolus followed by a 1 gm maintenance IV TXA infusion over 8 hours
2. 2 gm IV TXA bolus followed by a maintenance placebo infusion over 8 hours
3. Placebo bolus followed by a maintenance placebo infusion over 8 hours

Inclusion Criteria- *subjects must meet ALL of the following:*

1. Prehospital Glasgow Coma Scale (GCS) score ≤ 13 at any time prior to hospital arrival
2. Enrolled directly at the injury scene
3. Anticipated time from injury to hospital arrival less than 1 hour
4. Estimated age ≥ 15

Exclusion Criteria- *subjects are ineligible if they meet any of the following*:

1. Penetrating injury in any location
2. SBP < 70 or SBP ≥ 70 and less than 90 with HR > 108 prior to randomization
3. Received CPR in the field
4. Known prisoner
5. Known or suspected pregnancy

Thrombelastography will be performed at the same time points at individual sites.

Additional blood will be collected and stored for later analysis of inflammatory markers.

CT scans will be obtained on hospital admission. All CT scans will be de-identified and uploaded to a website maintained by ROC where a technician and radiologist will view file galleries and obtain quantitative hemorrhage measurements. The type and size of ICH, ischemic lesions, and mass effect will be evaluated for ICH progression.

Sample size: The total sample size is 1,002 (334 per group), which will allow for 80% power to detect an 8.2% absolute difference in long-term neurological outcome as determined by the GOS-E 6 months after injury for each of the true TXA-placebo comparisons.

Statistical analysis of primary hypothesis: Intention-to-treat analysis using logistic regression to test for association and estimate the strength of the association of treatment group with a favorable 6-month outcome (defined as a GOS-E > 4) after adjustment for study site.

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B. Intubation Value and Hyperoxia Prevention

Traumatic shock and TBI account for substantial morbidity and mortality. Early, aggressive airway management is advocated to prevent secondary brain injury from hypoxia and provide airway protection from aspiration. Although such protocols are ubiquitous in EMS and emergency medicine, the benefits of this approach remain unproven. In fact, most evidence–including ROC data–points to an association between early intubation and increased mortality. Although this link likely reflects some degree of selection bias, with more severely injured patients undergoing early intubation, it also is possible that the increased mortality is related to adverse effects associated with the procedure.

The high incidence of inadvertent hyperventilation and hypocapnia and the association with a profound increase in mortality may explain researchers' inability to document improved outcomes with early aggressive airway management. Physiologically, this process is mediated by both an increase in intrathoracic pressure as well as hypocapneic cerebral vasoconstriction, both of which appear to be common with manual ventilation following intubation during the resuscitation phase of trauma care. Capnography, ventilation bags, and other technologies that regulate ventilation rate and inspiratory time offer the potential to improve early resuscitative care, but their effects on mortality remain unproven.

More recently, an association between hypoxia and increased mortality has been documented in patients with severe traumatic injury. This association appears to be related to metabolic events involving oxygen metabolism, which may be impaired following ischemic or traumatic events. Whereas standard resuscitative care emphasizes maximizing oxygen delivery to prevent tissue hypoxia, recent data also suggest an association with extreme hyperoxemia and increased mortality in TBI, neonatal asphyxia, stroke, and cardiac arrest. Oxygen regulation strategies during early resuscitation offer potential benefits but remain unproven.

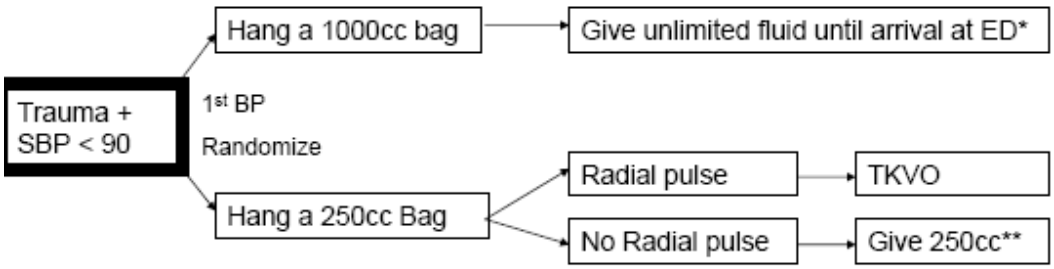
An analysis of ROC data has been initiated to define the incidence of hyperventilation and extreme hyperoxemia among intubated trauma patients and to explore their potential

association with increased mortality. This analysis will employ a complex statistical model to adjust for various covariates and to independently evaluate the effects of both hyperventilation and hyperoxemia. The results of this evaluation will inform ROC's efforts to design a prospective interventional trial that will implement strategies to regulate oxygenation and ventilation in the early resuscitative phase for severely injured trauma patients. To avoid hyperventilation, investigators anticipate the use of a self-regulating ventilation bag that limits ventilation rate and inspiratory time or the implementation of mechanical ventilators in the prehospital environment. Oxygen regulation will occur via strategies that limit flow from the oxygen source, producing low FiO2 values and avoiding excessive PaO2 values. The feasibility of these approaches will be explored through a pilot study conducted in a small number of ROC sites.

C. Usual Aggressive Fluid Administration vs. Low Volume Fluid Administration in Traumatic Injury with Early Hypotension

This multicenter trial will compare the efficacy and safety of standard aggressive fluid resuscitation with hypotensive resuscitation for the prehospital treatment of patients with traumatic shock. Blunt and penetrating trauma patients with a prehospital systolic blood pressure < 90 mmHg will be eligible. In the hypotensive resuscitation group, an IV will be placed and a radial pulse will be palpated. The study design is the same as recently completed and previously described pilot study. The primary outcome measure of the study will be 28-day survival. Secondary outcome measures will include prehospital fluid volume, 24 hour fluid volume, 24 hour blood product requirements, and incidence of acute respiratory distress syndrome, incidence of multiple organ failure, ventilator days, hospital length of stay, and ICU length of stay.

Randomization Scheme:



*If transport will exceed 20mins discontinue fluid administration when SBP ≥ 110

** Reassess and repeat PRN

It is estimated that 2,000 patients will need to be treated in this manner to see a 3.7% relative reduction in mortality in the hypotensive resuscitation group.

14. FUTURE ROC STUDIES IN CPR

A. Rapid Induction of Therapeutic Hypothermia in Witnessed Out-of-Hospital Cardiac Arrest: (Pilot Study)

Early induction of therapeutic hypothermia in the ED after survival from cardiac arrest with poor CNS function is associated with improved neurologically intact survival. Animal studies and one pilot human study suggest that earlier hypothermia may increase the value of hypothermia. This proposal investigates the feasibility, safety, and efficacy of transnasal high-flow dry air for hypothermia induction in witnessed out-of-hospital cardiac arrest on EMS arrival.

Background

High-flow transnasal dry air results in a flow-dependent decrease in brain temperature in porcine subjects. This drop in temperature is due to evaporative heat loss as a consequence of the nasal turbinates' humidification of the inflowing air. Cooling is transmitted from the nasal cavity to the brain both by direct cooling through the nasal bone and by the circulating blood. The rate of reduction in brain temperature is ~0.3°C/minute, and a target brain temperature of 34°C is achieved in less than 10 minutes. A similar mechanism of upper respiratory heat loss occurs in humans and can be harnessed to extract heat and thereby directly cool the brain. In conscious human subjects, transnasal airflow rates up to 40 liters/min are well tolerated without any serious consequence. Rate of heat extraction in humans appears to be similar to procine subjects, although the temperature change is slower due to larger brain and body mass. This method of heat loss is easy to implement in an out-of-hospital setting and relatively safe and devoid of any chemicals or toxins as it uses ambient air. The goal of the study is to assess the feasibility of this approach in the field and the safety and efficacy of high-flow air in inducing therapeutic hypothermia.

Study type

Interventional

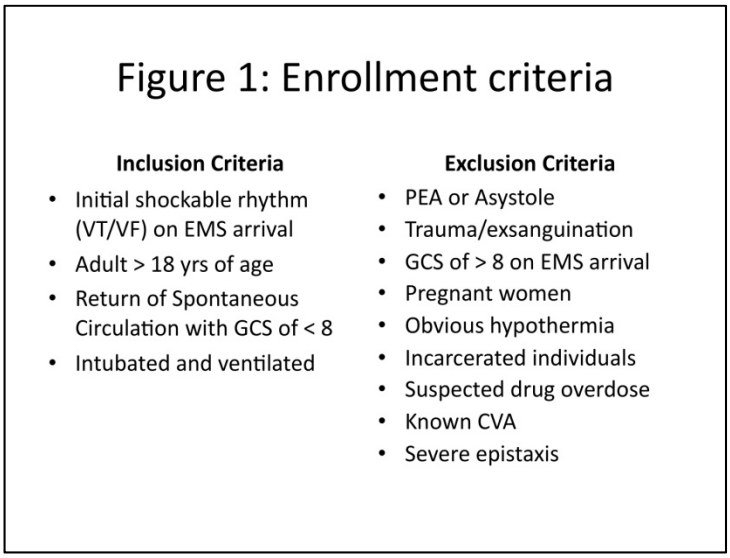
Study design

OpenlLabel randomized controlled Trial (1:1 randomization)

Endpoint classification

Feasibility/safety/efficacy study

Figure 1: Enrollment criteria



Number of patients enrolled
200

Study Procedures
Inclusion and exclusion criteria are shown in Figure 1. Patients with an initial shockable rhythm who achieve ROSC are eligible for enrollment. After initial resuscitation attempt, if the subject has ROSC and has a GCS of <8 then the subject is randomized for intervention after endotracheal intubation. Patients are randomized in an open-label fashion to either transnasal hypothermia or standard of care in a 1:1 fashion. Tympanic temperature is recorded at the time of randomization using a tympanic temperature sensor (Smith Medical, TX, USA). No other out-of-hospital hypothermia intervention is permitted either before or after randomization during the study. Transnasal hypothermia is continued until the subject is transitioned to an intravascular or external hypothermia method in the hospital. Other reasons for discontinuation of transnasal hypothermia are death or ROSC with GCS of >8. All patients will be subject to standard post-resuscitation treatment on arrival at the hospital per the institution's standards. Intravenous sedation, analgesia, and neuromuscular blockade will be initiated according to institutional cooling protocols. Transnasal airflow is discontinued if any serious device-related adverse event occurs.

Hypothermia device
The hypothermia device includes a base unit that weighs ~ 4 Kg that is a source of compressed air, a nasal mask, and an oral airway. Dry, ambient air generated from the device is propelled through the nasal mask at a flow rate of 80 liters/min. In patients who are intubated, the oral airway is placed adjacent to the endotracheal tube to keep the mouth open. The device has a safety feature that will shut off airflow if the pressure in the nasal mask exceeds 60 cm of H20.

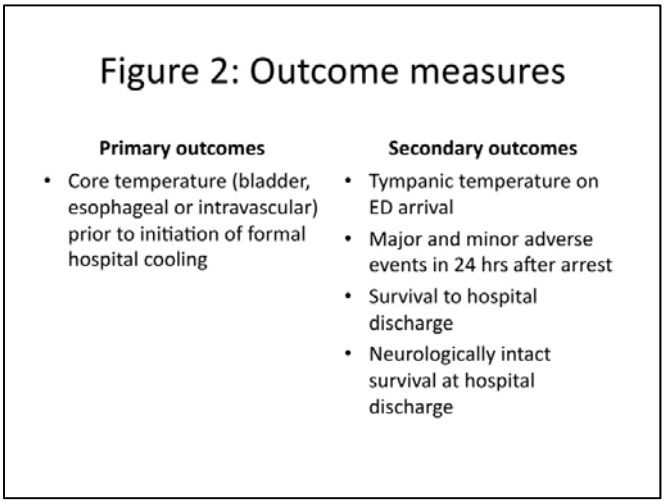
The humidity and temperature of the air in the mask is constantly displayed on the device. The device is designed to dehumidify ambient air by passing it though a desiccant. During prolonged use (> 60 minutes), if the relative humidity of the air in the nasal mask is >20% then a desiccant cartridge replacement indicator will indicate the need for replacement. No other intervention is needed. The device can be deployed in less than a minute, and all EMS personnel will be trained in the device deployment prior to study commencement.

Treatment protocol

In all patients, the resuscitation attempt will be made according to the AHA CPR guidelines or modified local guidelines as defined by medical direction. Patients will be assessed for study inclusion only if they have ROSC with GCS of <8; these patients then will be randomized. ROSC is defined as an organized rhythm and palpable pulse sustained for at least 2.0 minutes. All patients will have an oral or tympanic temperature according to local practice prior to randomization.

In the transnasal cooling group, the nasal mask will be placed, and transnasal cooling will be initiated. Transnasal cooling will be continued in the ambulance unless consciousness is regained.

All subjects will receive standard postresuscitation treatment on hospital arrival per the institution's standards. Tympanic temperature will be measured with a tympanic thermometer (Smith Medical, TX) upon arrival at the ED. Intravenous sedation, analgesia, and neuromuscular blockade will be initiated according to institutional cooling protocols. Transnasal cooling will be continued until formal hospital cooling begins. Transnasal cooling will be discontinued if any serious device-related adverse event occurred or if resuscitation efforts are abandoned. Before in-hospital cooling is initiated, core temperature will be recorded either in the bladder, central vein, or esophagus according to institutional protocols.



Outcome measures

The primary and secondary outcome measures are shown in figure 2. The primary outcome measure of the study is core body temperature prior to initiation of formal hospital cooling, which is monitored either in the bladder or esophagus or intravascularly using a sterile fiberoptic temperature probe in a central vein**.**

Secondary outcome measures are tympanic temperature on ED arrival and safety issues, such as the incidence of major and minor adverse events in the first 24 hrs. Total and neurologically intact survival will be assessed at hospital discharge. Neurologically intact end hospital survival will be measured by modified Rankin score.

Statistical Analyses and Sample Size

Continuous variables will be compared with the use of the Student t test. Variables that were not normally distributed, such as time to events, will be described as medians and interquartile ranges, and differences will be analyzed with the Kruskal-Wallis method. Categorical variables will be compared by the $\chi 2$ test or Fisher exact test.

Sample size for primary outcome

A prior study in cardiac arrest using transnasal cooling detected 0.8 degrees C difference in core body temperature between the treatment and control groups using a sample size of 100 patients in each of the treatment and control arms.

B. "ROC AIRWAY" Primary Endotracheal Intuation vs. Supraglottic Airway (SGA) insertion

Airway management, the establishment of a passage to the patient's lungs to facilitate oxygen delivery, is one of the most common and prominent interventions in the treatment of OHCA (1). In North America, the most common method of advanced airway management is **endotracheal intubation (ETI)**. Although common North American prehospital practice for more than 25 years, numerous studies highlight the pitfalls of paramedic ETI, including unrecognized tube misplacement or dislodgement, repeated intubation attempts, iatrogenic hyperventilation, hypoxia and bradycardia, hypotension, and unintended interruptions in chest compression continuity (1-6). National standards for paramedic ETI training are inadequate and opportunities for paramedic clinical ETI experience are sparse; in Pennsylvania, paramedics perform a median of 1 ETI annually (7, 8).

EMS practitioners also may accomplish airway management using **supraglottic airway (SGA)** devices, such as the King Laryngeal Tube (King LT - King Systems, Noblesville, IN), Combitube Esophageal/Tracheal Double-Lumen Airway (Combitube – Covidien, Inc., Boulder, CO), and the Laryngeal Mask Airway (LMA – LMA North America, San Diego, CA). Unlike ETI where rescuers directly visualize the vocal cords to facilitate direct placement of an endotracheal tube, SGAs involve blind insertion techniques. SGA insertion is simpler than ETI, may require less rigorous training, and may be inserted without interrupting chest compressions.

The optimal strategy for advanced airway management in OHCA is unknown. SGA insertion would seem more prudent than ETI in OHCA, and many EMS practitioners and agencies (including many in ROC) are opting for primary SGA insertion to expedite airway management efforts and avoid the pitfalls of ETI. However, a secondary analysis of more than 10,000 adult OHCAs in the ROC PRIMED study receiving advanced airway insertion efforts showed that ETI was associated with higher odds of ROSC, 24-hour survival, and survival to hospital discharge

compared with SGA.(9) No randomized clinical trials evaluating the effectiveness of advanced airway management strategies in adult OHCA have been performed.

The objective of this study is to compare the outcomes of adult OHCAs treated with primary ETI versus those treated with primary SGA insertion.

Specific Aim I: Determine how EMS advanced airway management strategy affects outcomes (survival to hospital discharge with MRS≤3, 24-hour survival, return of spontaneous circulation) after adult OHCA.

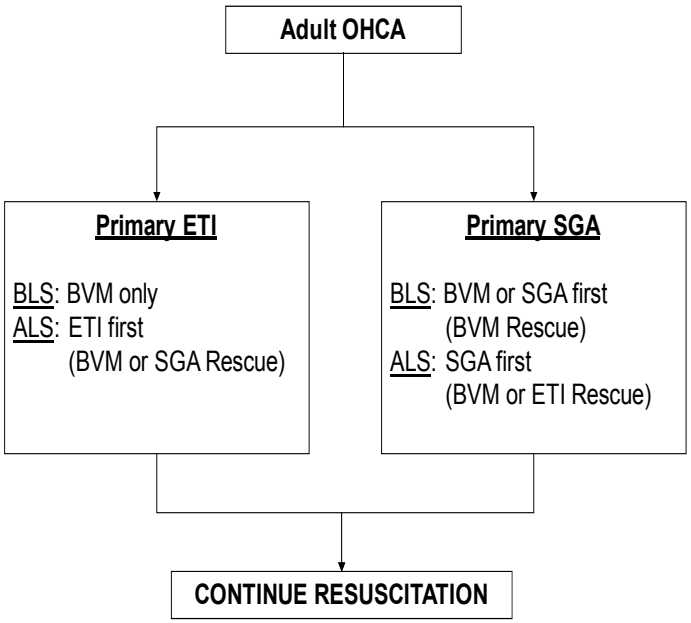


Figure: Protocol Summary

Specific Aim II: Determine how EMS advanced airway management strategy affects processes of resuscitation care (chest compression interruptions, airway insertion attempts, speed, and success) and hospital adverse events (admission hyperoxia, airway injury, pneumonia, aspiration pneumonitis, or acute lung injury) after adult OHCA.

Treatment Groups
The study will involve two treatment categories:

- **Primary (ETI) Airway Management**. In this "traditional" arm, basic life support personnel (BLS) will use bag-valve-mask (BVM) ventilation only, while advanced life support (ALS) personnel will use ETI as the primary advanced airway technique. ALS rescuers may revert to BVM or SGA in the event of failed ETI efforts.
- **Primary SGA Airway Management.** This "experimental" part of the study will be executed in two different ways. In systems where BLS agencies do not use SGA, BLS personnel will use BVM ventilation only, and ALS personnel will attempt SGA insertion

as the primary airway strategy. In systems where BLS agencies use SGA (select agencies in British Columbia and Ottawa), both BLS and ALS personnel will attempt SGA insertion as the primary airway strategy, reverting to BVM or ETI in the event of failed SGA insertion.

Execution of the airway interventions (including selection of SGA type) will be guided by local protocol. This study will not dictate the timing or sequence of airway interventions. Preliminary queries suggest that the vast majority of EMS agencies currently use the King LT as their designated SGA device.

Treatment randomization

The trial will use cluster randomization at the EMS agency level; ROC EMS agencies and personnel are already accustomed to this approach. Patient-level randomization requires the preparation of blinded airway equipment pouches, which is neither feasible nor practical given the range of airway equipment used by EMS. If more than one ROC EMS agency is at the scene, the first arriving unit will determine the study arm assignment. If a non-ROC BLS first responder agency arrives on scene first, the first-to-arrive ROC ALS agency will perform airway management as randomized, if required.

Study Inclusion Criteria

Inclusion criteria

This trial will include adult (age ≥18 years or per local interpretation), non-traumatic OHCA with ALS personnel on scene and receiving advanced airway insertion (ETI, King LT, Combitube, or Laryngeal Mask Airway) attempts by EMS practitioners.

Exclusion criteria

This study will exclude children (age <18 or per local interpretation), pregnant women, prisoners, patients with a suspected traumatic trigger of OHCA, patients with cardiac arrest onset witnessed by EMS, patients not requiring advanced airway management (for example, those who regain consciousness after initial CPR or AED use), patients with "do not resuscitation" (DNR) orders, and patients with a preexisting tracheostomy.

The study will monitor instances where EMS personnel did not attempt advanced airway insertion—for example due to a short transport time to the receiving hospital. The patient's level of consciousness and airway interventions in the ED will be used to affirm exclusion. For example, if a patient remains awake and is not intubated within 30 minutes of ED arrival, then the patient will be excluded from the analysis. However, if the patient undergoes ETI within 30 minutes of ED arrival, then the patient will be included in the analysis per intention-to-treat principles.

Rationale and Justifcation for Intended Population Size and Statistical Analysis

Differences between treatment arms will be analyzed by intention to treat as well as treatment received. The **primary outcome measures** will be: 1) survival to hospital discharge with MRS≤3, 2) 24-hour hospital survival, and 3) sustained return of spontaneous circulation. **Secondary**

outcome measures will include: 1) chest compression fraction for first 10 minutes of resuscitation, 2) airway insertion success, 3) airway insertion first-pass success, 4) number of airway insertion attempts, 5) time to successful airway insertion, 6) ED hyperoxia, 7) airway anatomic injury, 8) inpatient pneumonia or aspiration pneumonitis, and 9) inpatient acute lung injury.

The projected maximum sample size is 18,705 subjects. The estimated sample size is based on the primary outcome **survival to hospital discharge with modified Rankin score ≤3.** Using data from the PRIMED study, we identified all subjects receiving prehospital advanced airway attempts. Survival with MRS ≤3 were: ETI 674/11,657 (5.8%), SGA 83/2,292 (3.6%). We then identified all subjects who would have met inclusion criteria for our study but did not receive an airway attempt. Survival with MRS ≤3 were: 30/640 (4.7%). We calculated an overall survival estimate of 4.7% using a weighted combination of these rates. We defined an alternative hypothesis based upon a 25% relative change in survival (5.9% survival with MRS ≤3). We allowed for a statistical power (1-β)=90%. We allowed for up to six (6) interim analyses and as well as stopping for both superiority and futility. We also inflated the estimates by 5% to account for a cluster randomized design.

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C. ROC Epinephrine Trial: Dose Response in OHCA

Null hypothesis

The use of any dose of vasopressor improves neither short- nor long-term survival and functional survival outcomes in OHCA.

Primary aim

To determine the dose-effect on short- and long-term outcomes with vasopressor (Epinephrine) concentration during out-of-hospital cardiac arrest

Secondary aims

1. To compare short- and long-term outcomes with timing of drug administration. (Rittenberger 2007, 134)
2. To compare short- and long-term outcomes with differences in total drug administered
3. To compare short- and long-term outcomes with different presenting rhythms and bystander interventions (witnessed, CPR, AED)

Design

Randomized controlled trial in out-of-hospital cardiac arrest to determine whether different epinephrine concentrations versus standard-dose epinephrine improve functionally favorable (mRS<3) survival to 30 days.

Background and rational

This topic was reviewed in ILCOR as a worksheet (ALS-D-023B). The ILCOR consensus on science published in 2010 summarizes the literature to date as follows: “There is no placebo-controlled study that shows that the routine use of any vasopressor at any stage during human cardiac arrest increases survival to hospital discharge. Current evidence is insufficient to support or refute the routine use of any particular drug or sequence of drugs.” (page III-29) Animal studies suggest early drug delivery and high dose epinephrine increase likelihood of ROSC, suggesting

that the current standard protocol for epinephrine drug administration needs to be tested further in humans.

The literature on the efficacy and safety of epinephrine when compared with placebo is limited. In a study of 602 patients in Australia, 1mg boluses of epinephrine compared to placebo increased ROSC (30.4% vs. 11.1%) but did not change survival to hospital discharge (4.1% vs. 1.9%) (1). Introduction of advanced life support paramedics in Ontario, allowed drug administration as an adjunct in cardiac arrest resuscitation (2). Although that study design allows researchers to determine the individual effect of epinephrine, that study also found increased rates of hospital admission (14.6% vs. 10.9%) with no change in survival to hospital discharge (5.1% vs. 5.0%) In Japan, introduction of epinephrine into clinical practice increased rates of ROSC (18.5% vs 5.7%) but had no effect on survival (5.4% vs. 4.7%) and decreased functionally favorable survival to one month (1.4% vs.2.2%) (3).

Vasopressin is a vasoconstricting drug that may be superior to epinephrine for increasing coronary perfusion pressures during chest compressions (4-6). Two randomized clinical trials found no difference in survival between vasopressin and epinephrine as the first-line drug during resuscitation (7, 8), The subgroup of subjects who received both vasopressin and epinephrine appeared to have better survival than the group who received epinephrine alone (7), perhaps because of a synergistic effect of epinephrine and vasopressin (9-11). However, combined administration of vasopressin and epinephrine were not superior to epinephrine alone in two randomized clinical trials (12, 13).

Proposed intervention

Subjects with cardiac arrest persisting after one rescue shock *or* after a rhythm check identifies a non-shockable rhythm, will receive a randomized study preloaded syringe as a bolus administration. The study drug will be standard epinephrine 1 mg administered over 5 minutes versus infusion of a range of concentrations (low dose similar to epinephrine infusion in the ICU) up to and including 0.125 mg up to maximum of 5 doses. Study drug may be administered intravenously or intraosseously.

Key elements of the intervention strategy

Random allocation will be performed by dispensing kits with placebo or epinephrine to each paramedic crew. Drug kits will be identical in order to ensure blinding of paramedics and hospital providers. Other acute resuscitation care, including chest compressions, rescue shocks, and antiarrhythmic drugs, will proceed as usual. ROC will recommend best practices for post-ROSC care in synchrony with the literature and guidelines at the time of launch. Outcomes will be determined based on the records of EMS providers and the admitting hospitals as well as interviews with survivors at 3 months and 1 year after cardiac arrest.

Key considerations

The best way to address the emergency care professionals' reluctance to perform a placebo trial with vasopressor and use high dose epinephrine is to use an adaptive design with sequential looks at the data and a proviso in the analytical plan to drop or raise the dose based on the interim results. Sequential looks at the data combined with a blinded bolus syringe design would allow the evaluation of different doses of epinephrine. For example, if 0.1 mg proved better than 1 mg, the bolus kits could be adjusted for even smaller dosages; if 1 mg proved better than 0.1 mg in the initial comparison, the bolus kits could be adjusted for even larger dosages of epinephrine without stopping and restarting the trial.

Inclusion and exclusion criteria

The study will will include adult patients ≥18 years old with non-traumatic, out-of-hospital cardiac arrest treated by advanced care paramedics and who are eligible for randomization

- Exclusion criteria include:
    - advance DNR
    - blunt, penetrating trauma
    - burn-related injury
    - exsanguination
    - protected population (pregnant women, prisoners)
    - prior receipt of open label IV epinephrine or another vasopressor

Primary outcome measure

- Alive to discharge or transfer to non-acute bed in bystander witnessed VF (initial rhythm) arrest.

Secondary outcome measures

Short-term outcomes include:

- ROSC
- Arrive at the ED with pulses
- Sustained ROSC
- Alive at 24 hours after sentinel event

Long-term outcomes include:

- Modified Rankin score at discharge or transfer to a non-acute bed
- Alive at 30 days
- Modified Rankin score at 30 days
- Alive at 3 months
- Modified Rankin score at 3 months
- Alive at one year
- Modified Rankin score at 1 year

Safety measures

- Acute myocardial infarction rates
- Multisystem organ failure

Important covariates to control through randomization and protocol compliance or to be identified a priori as a subgroup analysis

- Initial rhythm
- Timing of first shock, first IV, and first drug administration
- Timing of advance airway intervention
- Total dosage of vasopressor
- Intraosseous administration versus intravenous administration
- CPR indices of high quality CPR
- Post-arrest care parameters of optimized post-arrest care, including targeted temperature management, angiography and PCI when appropriate.

Consider 20 min Cardiac Arrest – starting comparison doses underlined

	Total dose	Bolus dose
1.	3 mg	1 mg (standard)
2.	1.5 mg	0.5 mg
3.	0.75 mg	0.25 mg
4.	0.375 mg	0.125 mg
5.	0.1875 mg	0.063 mg
6.	0.0937 mg	0.031 mg
7.	0.04685 mg	0.0125 mg
8.	0 mg	0

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D. What Is the Optimal Combination of Chest Compression Depth and Chest Compression Rate for Use with the LUCAS Device?

Background

Guidelines for cardiopulmonary resuscitation (CPR) recommend a chest compression rate of at least 100 compressions/min without an upper limit (AHA). Animal and human CPR studies have reported that blood flow is greatest with chest compression rates near 120/min. Two recent studies reported that the likelihood of return of spontaneous circulation and survival-to-hospital discharge was greatest with rates between 100 to 120/min during out-of-hospital (OOH) CPR. (Idris, 2012)

Studies showed that the greatest likelihood of shock success and ROSC occurred with chest compression depths > 5 cm. (Edelson, 2006; Babbs, 2008) The ROC Epistry depth study showed increased likelihood of survival with depth of 38 – 51 mm compared (reference <38 mm). (Stiell, 2012) The depth study based on ROC PRIMED data did not show improved survival when depth was >51 mm. However, AHA and ILCOR guidelines currently recommend using a depth of at least 5 cm during adult CPR.

The optimal combination of chest compression rate and depth is unknown, either during manual or mechanical CPR.

Objective

The purpose of this study is to determine the optimal combination of chest compression rates and chest compression depths that is associated with the greatest likelihood of survival-to-hospital discharge.

Hypothesis

There is no difference in likelihood of survival-to-hospital discharge when groups are compared that receive chest compression rates of 100 or 120 compressions/minute and depths of 4 cm or 5 cm (100/min @ 4 cm vs 100/min @ 5 cm vs 120/min @ 4 cm vs 120/min @ 5 cm).

Trial design
This is a prospective, randomized (by device), pilot study conducted by the Resuscitation Outcomes Consortium. Devices are block randomized within each ROC site. The study will also include a parallel control group.

Study population
Adults, age ≥ 18 years, who have out-of-hospital cardiac arrest and receive CPR from a ROC EMS agency

Exclusions
Subjects who are obviously pregnant, have a traumatic arrest, have an arrest due to exsanguination, have an opt-out bracelet, are a prisoner, have a DNR order, or received initial CPR from a non-ROC agency.

Primary outcome
Return of spontaneous circulation

Secondary outcomes
Arrival at ED with a pulse, 24-hour survival, survival to discharge, shock success

Important co-variates or a priori subgroup analysis
Initial cardiac rhythm, time to apply the LUCAS device, quality of CPR before the device is placed, preshock pause, Utstein variables

Intervention
The LUCAS device is a mechanical chest compression device that can be programmed to give chest compressions at a fixed rate and depth. LUCAS devices will be programmed to give one of four possible combinations of chest compression rates and depths (Table). The devices will be distributed to 100 ambulances with the highest numbers of cardiac arrest cases annually among ROC agencies that choose to participate. The number of devices is limited, thus to maximize enrollment, ten stations with the highest number of cardiac arrest cases annually were identified from each ROC site. We estimate that this strategy of deployment will yield about 3,000 cases per year.

Table

	CC Depth 4 cm	CC Depth 5 cm
Chest compression rate 100/min	100/min and 4 cm	100/min and 5 cm
Chest compression rate 120/min	120/min and 4 cm	120/min and 5 cm

Paramedics onboard each ambulance will apply the device as soon as possible after the start of CPR, preferably within three minutes of arrival. The device will give chest compressions until ROSC, arrival at an Emergency Department, or the patient is declared dead.

Devices will be block randomized within each site. The study includes a parallel control group of patients with PEA who receive manual chest compressions. The next five highest enrolling rigs from each site will enroll these patients.

Analysis

ROSC and Survival from Epistry and ROC PRIMED data (unadjusted)

	ROSC	Survival
Rate 100/min	29%	8%
Rate 120/min	37%	10%

Shock success and ROSC (Edelson and Babbs)

	Shock success	ROSC
Depth 39-50 mm	88%	8.3%
Depth >50 mm	100%	17.7%

Absolute difference for rate at 120/min: 8% for ROSC and 2% for survival.

Absolute difference for depth at > 5 cm: 12% for shock success, 9.4% for ROSC.

[The depth analysis from ROC PRIMED data did not show increased survival when depth was >51 mm.]

A sample size analysis is being done for two main outcomes: (1) a pilot study with ROSC as the primary outcome and (2) a definitive study with survival as the primary outcome.

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E. Chest Compressions Synchronized with the ECG for Pulseless Electrical Activity Cardiac Arrest

Background

Pseudo-electromechanical dissociation (P-EMD) is a type of cardiac arrest with organized cardiac electrical activity and residual cardiac contractions producing systemic blood flow, but insufficient to generate a palpable pulse.(1) A recent study showed improved coronary perfusion pressure, lower right atrial pressure, and higher aortic pressure when chest compressions were synchronized with the systolic phase in P-EMD cardiac arrest.(2)

This is a potentially important finding because the incidence of pulseless electrical activity cardiac arrest is increasing and a majority of those with PEA will actually have P-EMD with detectable cardiac motion, if measured.(3) Unfortunately, survival from PEA is very low compared with survival from ventricular fibrillation (3% vs 22%, ROC data). This low survival rate occurs in spite of the fact that these patients may be salvageable, since most still have some intrinsic perfusion during cardiac arrest. Thus, better therapies are urgently needed to improve survival.

Objective

The purpose of this pilot study is to determine if synchronizing chest compressions with the ECG is associated with improved return of spontaneous circulation (ROSC) and survival-to-hospital discharge (survival).

Hypothesis

There is no difference in likelihood of ROSC or survival when groups are compared that receive synchronized chest compressions vs unsynchronized chest compressions during PEA cardiac arrest.

Trial design

This is a prospective, block randomized (by device) pilot study conducted by the Resuscitation Outcomes Consortium. The study will also include a parallel control group.

Study population
Subjects, age ≥ 15 years, who have out-of-hospital cardiac arrest and receive CPR from a ROC EMS agency. Subjects have an initial cardiac rhythm of PEA.

Exclusions
Subjects who are obviously pregnant, are less than 15 years old or appear to be less than 15 (if actual age is unavailable), have a traumatic arrest, arrest due to exsanguination, have an opt-out bracelet, are a prisoner, have a DNR order, or if they received initial CPR from a non-ROC agency. Additionally, subjects who have and initial cardiac rhythm that is other than PEA will be excluded.

Primary outcome
ROSC

Secondary outcomes
Survival-to-hospital discharge, arrival at ED with a pulse, 24-hour survival

Important co-variates or a priori subgroup analysis
Time to apply the LUCAS device, quality of CPR, Utstein variables, conversion of PEA to some other rhythm

Intervention
The LUCAS device is a mechanical chest compression device that can be programmed to give chest compressions at a fixed rate and depth and that can be synchronized with the ECG. LUCAS devices will be programmed to give chest compressions either synchronized with the systolic cardiac phase (synchronized group or unsynchronized chest compressions (unsynchronized group). If the intrinsic cardiac rate is <50/min or >120/min, the default rate of 100 compressions/min will be used. If the rhythm changes to VF or asystole, the default rate will be used.

The devices will be distributed to 100 ambulances with the highest numbers of cardiac arrest cases annually among ROC agencies that choose to participate. The number of devices is limited, thus to maximize enrollment, ten stations with the highest number of cardiac arrest cases annually were identified from each ROC site. We estimate that this strategy of deployment will yield about **750 cases per year with an initial cardiac rhythm of PEA**.

Paramedics onboard each ambulance will apply the device as soon as possible after the start of CPR, preferably within three minutes of arrival. The device will give chest compressions until ROSC, arrival at an Emergency Department, or a decision to terminate CPR has been made in the field. The device will be connected to a cardiac monitor carried by EMS paramedics.

Devices are block randomized within each ROC site.

The study includes a parallel control group of patients with PEA who receive manual chest compressions. The next five highest enrolling rigs from each site will enroll these patients.

Analysis

In PRIMED, PEA subjects had ROSC at a rate of about 40%, and about 7% survived to discharge. With 750 cases, that would give 90% power to detect an increase in ROSC by 11%; 1500 gives 90% power to detect an increase of 9%.

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May 3, 2013

Myron Weisfeldt, MD
William Osler Professor of Medicine
Director of the Department of Medicine
Johns Hopkins University School of Medicine
Suite 9026 1830 East Monument Street
Baltimore, MD 21287

Dear Dr. Weisfeldt,

At your request, Physio-Control, Inc. (Physio) is providing a letter of intent to support a potential study on noninvasive assisted chest compressions for cardiac arrest patients in PEA using the LUCAS™ Chest Compression System. Ifthe funding by the National Heart Lung and Blood Institute for the Resuscitation Outcomes Consortium (ROC) goes beyond the current 2014/2015 timeline, we understand this study may be pursued by the ROC in the 2016 timeframe. Physio is providing this letter of intent to support the potential noninvasive assisted chest compression study for cardiac arrest patients in PEA, by developing LUCAS™ Chest Compression System devices that have the added capability of delivering compressions timed to the R-wave of the ECG. Physio's ability to support the study is dependent on being able to develop a LUCAS device which can meet the design requirements to provide R-wave timed compressions. Physio applauds the work and accomplishments of the ROC and is pleased to

meet your request to provide this letter of intent to support a potential future cardiac arrest study.

If there are any questions regarding this information, please contact me at
(425) 867-4644.

Sincerely,

PHYSIO-CONTROL, INC.
Paula Lank
VP, Regulatory and Clinical Affairs

15. ROC IMPACT ON CARDIAC ARREST GUIDELINES

ROC Investigators at the 2008 Consensus Conference on Resuscitation Outcomes (May 5-6, 2008, Washington, DC)

In 2008, the AHA convened a consensus conference to develop and promulgate recommendations on the optimal outcome measurements and timing of outcome measurements for resuscitation research. Seven ROC investigators were among the 69 conference attendees: Tom P Aufderheide; Clifton W. Callaway; Al P. Hallstrom; Graham Nichol; Joseph P. Ornato; Myron L Weisfeldt; Jane G. Wigginton.

This conference in part led to the following consensus statement: Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT, Halperin HR; American Heart Association Emergency Cardiovascular Care Committee; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation 2011; 124:2158-77

The consensus statement references these ROC investigations:

1. **Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Resuscitation Outcomes Consortium Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome. Journal of the American Medical Association 2008; 300:1423-1431**

2. **Raina KD, Callaway C, Rittenberger JC, Holm MB. Neurological and functional status following cardiac arrest: method and tool utility. Resuscitation 2008; 79:249-256**

ROC Investigators at 2010 ECC Consensus on Science

A total of 15 ROC investigators presented 24 of the 476 (5.0%) worksheets in the the guidelines source material. These are posted online and are the primary documents for the EVIDENCE REVIEW FOR AHA GUIDELINES FOR RESUSCITATION.

Ahamed Idris	http://circ.ahajournals.org/site/C2010/BLS-006A.pdf http://circ.ahajournals.org/site/C2010/BLS-034A.pdf
James Dunford	http://circ.ahajournals.org/site/C2010/BLS-010A.pdf
Tom P. Aufderheide	http://circ.ahajournals.org/site/C2010/BLS-017A.pdf http://circ.ahajournals.org/site/C2010/EIT-032.pdf http://circ.ahajournals.org/site/C2010/BLS-045A.pdf
Robert A. Berg	http://circ.ahajournals.org/site/C2010/BLS-022A.pdf http://circ.ahajournals.org/site/C2010/Peds-012A.pdf
Thomas D. Rea	http://circ.ahajournals.org/site/C2010/BLS-046B.pdf
Peter J. Kudenchuk	http://circ.ahajournals.org/site/C2010/BLS-049A.pdf http://circ.ahajournals.org/site/C2010/ALS-D-020B.pdf
Daniel P. Davis	http://circ.ahajournals.org/site/C2010/BLS-051B.pdf
Jon Rittenberger	http://circ.ahajournals.org/site/C2010/ALS-PA-045A.pdf
Clifton Callaway	http://circ.ahajournals.org/site/C2010/ALS-PA-053B.pdf http://circ.ahajournals.org/site/C2010/ALS-SC-077.pdf
James J. Menegazzi	http://circ.ahajournals.org/site/C2010/ALS-SAM-063A.pdf
Alan M. Craig	http://circ.ahajournals.org/site/C2010/ACS-007B.pdf
Valeria Rac	http://circ.ahajournals.org/site/C2010/ACS-018B.pdf
Joseph P. Ornato	http://circ.ahajournals.org/site/C2010/ACS-021A.pdf http://circ.ahajournals.org/site/C2010/ALS-SC-077.pdf
Steven C. Brooks	http://circ.ahajournals.org/site/C2010/ACS-026B.pdf http://circ.ahajournals.org/site/C2010/ACS-027A.pdf

Graham Nichol http://circ.ahajournals.org/site/C2010/EIT-027.pdf

ROC Investigators Also Occupied Leadership Positions in the 2010 Evidence Evaluation and Guideline Process

Laurie Morrison was the Co-Chair of the ILCOR ALS Task Force. Clifton Callaway served one term as chair of the AHA ACLS Subcommittee and was one of three evidence evaluation experts for the 2010 Guidelines.

2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Circulation 2010; 122

The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science are the primary source for teaching resuscitation practices to laypeople, emergency care professionals, and member of health care organizations. These guidelines are reexamined approximately every 5 years, and guidelines issued in 2010 were considerably influenced by ROC scientists and ROC publications.

CPR AHA 2010 guidelines: Section 1: Executive Summary references

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None

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None

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CPR AHA 2010 guidelines: Section 10: Acute Coronary Syndromes

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ROC Investigators at Summit Meeting and on Manuscript In Press: CPR Quality: Improving Cardiac Resuscitation Outcomes Both Inside and Outside the Hospital. A Scientific Statement From the American Heart Association

In 2012 the American Heart Association commissioned a CPR Quality Summit to discuss the following topics and to subsequently produce a practical manuscript to help providers of CPR improve the quality of care delivered titled “CPR Quality, Monitoring, CQI Programs and Logistics”. The purpose of the summit and subsequent activities is to accelerate the implementation of the 2010 guidelines updated as needed to keep pace with emerging scientific evidence. The summit included 28 CPR experts, 4 of whom are members of the ROC leadership group (Nichol, Berg, Aufderheide, Christenson). The manuscript authors included

12 members of the summit team, 3 of whom are ROC leaders (Berg, Aufderheide, Christenson).

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Impact of ROC presentations at RESS 2012: CPR Quality: Improving Cardiac Resuscitation Outcomes Both Inside and Outside the Hospital. A Scientific Statement from the American Heart Association

Summit leaders agreed that finalization of the manuscript should be postponed until key ROC research was presented at the Resuscitation Science Symposium and the American Heart Association Annual Scientific Sessions, November 2012, in Los Angeles, CA. Subsequent discussion of the presentations on optimum compression depth (Stiell), optimum compression rate (Idris) and the effect of pre-shock pauses (Cheskes) resulted in changes in the initial draft of the manuscript, which is currently under review for publication in *Circulation*.

16. ROC IMPACT ON TRAUMA GUIDELINES AND CARE

Recommendations for optimal trauma care are more diffuse than for cardiac arrest, having been developed by a number of professional organizations. The American College of Surgeons Committee on Trauma (ACS COT) periodically updates to *Resources for Optimal Care of the Injured Patient*, which focuses on trauma triage as well as clinical care in both the prehospital and inhospital settings. Their algorithms for trauma triage are developed and published in conjunction with the Centers for Disease Control and Prevention, with the most recent iteration released in 2009, prior to a series of ROC investigations that will almost certainly have a major impact on future guidelines. In fact, ROC investigators have been intimately involved in ongoing efforts to refine these guidelines, with ROC producing some of the best evidence to date on the topic.

Furthermore, the recent ROC BLAST trial represents some of the most innovative and potentially influential work in combining traditional clinical assessment with point-of-care testing to improve both sensitivity and specificity for early identification of severe injuries. Finally, the ongoing ROC study evaluating aggressive versus conservative fluid resuscitation strategies in cases with suspected traumatic shock will address a question that the ACS COT and the Institute of Medicine posed in its seminal publication on fluid therapy in trauma. Future iterations of the Advanced Trauma Life Support® (ATLS®) and Prehospital Trauma Life Support (PHTLS) courses, which are presented by the ACS, the American College of Emergency Physicians (ACEP), and the National Association of EMS Physicians (NAEMSP), will heavily reflect the influence of ROC investigation and ROC publications.

Historically, the military has contributed substantially to our knowledge regarding optimal care of severely injured patients, particularly in times of war. The strong partnership between ROC and the armed forces of both the U.S. and Canada represent a unique opportunity to formally investigate how hypotheses generated in the military theater may be used to provide civilian trauma care. This practice clearly has been applied in the ROC hypertonic saline studies for

both traumatic shock and TBI, the evaluation of aggressive blood product replacement strategies, the refinement of trauma triaging strategies, including the use of field point-of-care testing, the ROC airway investigations, and ongoing efforts to define optimal oxygenation and ventilation strategies following insertion of an advanced airway. All of these studies have been designed and implemented with significant input and insight from our military medical colleagues. Similarly, the inclusion of ROC investigators as active participants, presenters, and co-authors for the Joint Forces Combat and Casualty Care summits reflects the influence and insights that ROC has had on the care of our nations' injured troops.

The care of TBI, the leading cause of civilian trauma deaths, is consolidated in the Brain Trauma Foundation (BTF) guidelines. The foundation has taken a unique approach in underscoring the limited data currently available to guide therapeutic recommendations in the prehospital care of TBI and outlining critical questions to guide future investigations. Virtually all of these questions are being addressed in various ROC investigations, with ROC uniquely able to answer these questions due to the integration of sophisticated prehospital data with hospital outcomes. No other trauma database contains the breadth of data from both sources, which is necessary to fully define the tremendous impact of early resuscitative care and simultaneously adjust for injury severity using radiologic, operative, and autopsy data. The most recent BTF guidelines were published prior to the availability of ROC studies in this area. However, the symmetry between ROC's past and future investigations and the BTF-identified critical questions, as well as the current participation of multiple ROC investigators in ongoing BTF guideline development, reflects the tremendous influence ROC is having on TBI care recommendations.

In summary, ROC investigative efforts are closely aligned with the research trajectory outlined by the various organizations that establish guidelines for trauma care, including ACS COT and ATLS/PHTLS, the military, NAEMSP, ACEP, and BTF. Completed and ongoing ROC programs will certainly influence and, in many cases, define future guidelines that these groups issues.

17. CHANGES IN THE ACADEMIC EMERGENCY MEDICINE COMMUNITY

Emergency medicine is a relatively new academic discipline with board certification becoming available in both the U.S. and Canada in the early 1980s. Residency training programs in the field have expanded greatly with more than 120 accredited programs in both nations combined and many more in the U.K. and Australia. Research in emergency medicine has increased in recent years and now supports seven peer-reviewed English language journals. The recognition of pathophysiologic states warranting resuscitation and the resuscitation techniques are the focus of practice and active research and have helped to define emergency medicine as a specialty. These efforts have also encouraged emergency physicians and other medical

disciplines to forge important links. Cardiologists, anesthesiologists, intensivists, and trauma surgeons have a shared interest in the resuscitation and optimal management of patients with cardiac arrest and life-threatening injuries. Emergency physicians and EMS personnel represent important connections between the out-of-hospital and ED sites where patients requiring resuscitation first present. ROC has united leading emergency medicine centers and their associated researchers to design and perform innovative resuscitation research. Through its training cores, ROC also provides an opportunity for residents, fellows, and junior faculty members to participate in the ROC scientific process. This collective effort will continue to define the discipline of resuscitation further within emergency medicine and associated specialties.

18. EMS AND HOSPITAL STRUCTURE AND FUNCTION PRIOR TO AND DURING ROC INVESTIGATIONS

EMS systems evaluate, treat, and stabilize critically ill patients in the community and transport them to medical facilities for additional care. EMS organizational structures vary widely—from those where dispatch centers, BLS andALS responders are tightly integrated under a single, military-like administrative structure to those with a looser network of public, professional, and entrepreneurial components, each with its own administrative oversight and funding source(s). Record handling also varies from paper forms stored in less-organized filing systems to computer-based systems that closely track events from dispatch time through ED admission and hospital outcome. Although attempts had been made to standardize data collection and definition prior to the formation of ROC (1-3), there was a lack of operational definitions for each data element. The advent of the ROC epidemiologic observational registry and standardized data collection for cardiac arrest and trauma in 2005 allowed researchers to compare EMS performance across agencies and geographic regions. The results were published in a series of manuscripts describing the methodology, the incidence, and outcome as well as a variety of subgroup observations (see publication listing). Hospitals, too, vary in their ability to treat trauma and cardiac arrest and in their record collection. Trauma hospitals are given a trauma level designation (1 to 5), and ROC trauma trials are typically conducted in Level 1 or 2 hospitals. No such designation yet exists for cardiac arrest, and yet post-resuscitation care, such as hypothermia and cardiac catheterization, is recommended for specific cases.

Before ROC, each EMS or fire agency typically followed the AHA Advanced Cardiac Life Support recommendations for cardiac arrest or the ATLS recommendations for trauma. Occasionally agency medical directors and ED directors would apply a different guideline based on the outcomes of small research studies or even personal preference.

Research published prior to ROC demonstrate that better cardiac and trauma resuscitation is associated with better survival (5-7, 12, 13) and health-related quality of life, (8-10, 14)

although comparison of results across different sites is challenging because many sites have not reported standardized outcomes.(1-4) Outcomes after cardiac arrest and trauma vary widely. (5,11, 15, 16) This variation is attributable in part to regional differences in the availability of emergency cardiac care. (5, 17) Factors potentially affecting the outcome after cardiac arrest include: bystander CPR, lay-responder defibrillation programs, EMT experience level, and interventions pefromed by EMS providers or at receiving hospitals. Some of these factors have been associated with differences in outcome after resuscitation, although no analysis has had adequate ability to detect the independent effects of all factors. Standard treatments used at the scene of the injury include airway management, fluid resuscitation, topical control of hemorrhage, needle decompression of the chest, stabilization of fractures, extrication, and rapid transport to a trauma center. Standard treatments used in trauma centers focus on limiting blood loss, restoring systemic and cerebral perfusion, limiting secondary brain injury, and modulating the inflammatory response to prevent multiorgan failure.

To facilitate the design and implementation of our interventional trials, each ROC site described the structure and function of their participating EMS agencies by using a standardized data collection tool entered into a centralized database. The data from this survey resulted in the first ROC publication in 2007 describing the ROC agencies. ROC continues to maintain the EMS structures database, which includes information on all current and previous agency participation and, with regulatory approval, uses this information to conduct studies and data entry access.

Davis D, Garberson L, Andrusiek D, Hostler D, Daya M, Pirrallo R, Craig C, Stephens S, Larsen J, Drum A, Fowler R, ROC Investigators. A descriptive analysis of emergency medical service systems participating in the Resusciation Outcomes Consortium (ROC) network. Prehospital Emergency Care 2007; 11:369-382

Regulatory

Before ROC, most EMS agencies were not covered by Federal Wide Assurance (FWA), which is required to conduct research with federal funds. ROC established FWAs for all agencies and hospitals where research is conducted. In addition, data-use agreements were established for receiving hospitals that only allow access to the patient for data. For any large study, ROC sites must confer with at least 100 IRBs representing 287 hospitals to gain approval to implement the study protocols. A few sites have explored a central IRB model under which a lead IRB would represent all other hospital IRBs specifically for prehospital exception from consent for research in which the intervention ends before hospital arrival. One site was successful in creating this model for the ALPS trial. Although the process took a year to complete it is anticipated that review and approval of future studies will be expedited and that ongoing annual review requirements will be exponentially reduced.

Exception from Informed Consent (EFIC)

Before ROC, few sites and IRBs had experience with EFIC studies, especially those involving central regulatory agencies such as the Food and Drug Administration (FDA), the Office of Human Subjects Protection, and Health Canada. Through the experience of conducting ROC research, sites have been able to streamline their community consultation and notification efforts. One site has a continuous model of consultation and notification in which results from prior studies and potential new studies are provided to the community at regular intervals, rather than each time a new study is conducted. Furthermore, ROC has shaped FDA policies on monitoring of EFIC. FDA monitors all EFIC studies involving a manufactured product, regardless of whether it has been approved for use.

Continum of Care and Multidisiplinary Collaboration

ROC research has brought together a variety of medical disiplines for the first time, including prehosptial medical directors, emergency medical department physicians and staff, blood bank personnel, anesthesiologists, trauma surgeons, neurologists, neurosurgeons, cardiologists, and intensivists. ROC studies such as the Hypo Resus Trial require cooperation and collaboration between prehospital and in-hospital staff. Some studies are conducted solely in the prehospital setting (ALPS, CCC), whereas others are conducted solely in the early hospital (PROPPR) setting. ROC has carefully nurtured these collaborative efforts over the last 9 years, resulting in important changes to the process and structure of patient care.

This diverse collaboration is also mirrored within the consortium, with site investigators representing such specialties ranging from cardiology to emergency medicine to trauma surgery. Developing a governance and decision-making structure has not always been easy, but the process has evolved and matured.

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