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A Randomized Trial of Continuous Versus Interrupted Chest Compressions in Out-of-Hospital Cardiac Arrest: Rationale for and Design of the Resuscitation Outcomes Consortium CCC Trial

Siobhan P. Brown, PhD^{*},

University of Washington, Seattle, Washington

Henry Wang, MD,

University of Alabama at Birmingham, Birmingham, Alabama

Tom P. Aufderheide, MD, MSc,

Medical College of Wisconsin, Milwaukee, Wisconsin

Christian Vaillancourt, MD, MSc, FRCP(C),

University of Ottawa, Ottawa, Ontario

Robert H. Schmicker, MSc,

University of Washington, Seattle, Washington

Sheldon Cheskes, MD, CCFP (EM), FCFP, Rescu,

Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Sunnybrook
Osler Centre for Prehospital Care, University of Toronto, Toronto, Ontario

Ron Straight, BGS, MEd,

British Columbia Emergency Health Services, Vancouver, BC, Canada

Peter Kudenchuk, MD,

University of Washington, Seattle, Washington

Laurie Morrison, MD, MSc, FRCPC(C), Rescu,

Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of
Toronto, Toronto, Ontario, Canada

Riccardo Colella, MD,

Medical College of Wisconsin, Milwaukee, Wisconsin

Joseph Condle,

University of Pittsburgh, Pittsburgh Pennsylvania

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^{*}Corresponding Author: Siobhan P. Brown, Resuscitations Outcome Consortium, 1107 NE 45th St, Suite 505, Seattle, WA 98105-4680, 509-679-2169, spes@uw.edu.

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George Gamez, EMT-P,
Dallas Fire-Rescue, Dallas, Texas

David Hostler, PhD,
University of Pittsburgh, Pittsburgh Pennsylvania

Tami Kayea, EMT-P,
Dallas Fire and Rescue, Dallas, Texas

Sally Ragsdale, ARNP,
University of Washington, Seattle, Washington

Shannon Stephens, EMT-P, and
University of Alabama at Birmingham, Birmingham, Alabama

Graham Nichol, MD, MPH, FRCP(C)
University of Washington, Seattle, Washington And The Resuscitation Outcomes Consortium
(ROC) Investigators

Abstract

The Resuscitation Outcomes Consortium is conducting a randomized trial comparing survival to hospital discharge after continuous chest compressions (CCC) without interruption for ventilation versus currently recommended American Heart Association cardiopulmonary resuscitation (CPR) with interrupted chest compressions (ICC) in adult patients with out-of-hospital cardiac arrest (OHCA) without obvious trauma or respiratory cause. Emergency medical services perform study CPR for three intervals of manual chest compressions (each about 2 minutes), or until restoration of spontaneous circulation (ROSC). Patients randomized to the CCC intervention receive 200 chest compressions with positive pressure ventilations at a rate of 10/minute without interruption in compressions. Those randomized to the ICC study arm receive chest compressions interrupted for positive pressure ventilations at a compression:ventilation ratio of 30:2. In either group, each interval of compressions is followed by rhythm analysis and defibrillation as required. Insertion of an advanced airway is deferred for at least the first 6 minutes to reduce interruptions in either study arm. The study uses a cluster randomized design with every-six-month crossovers. The primary outcome is survival to hospital discharge. Secondary outcomes are neurologically intact survival and adverse events. A maximum of 23,600 patients (11,800 per group) enrolled during the post-run-in phase of the study will provide at least 90% power to detect a relative change of 16% in the rate of survival to discharge; 8.1% to 9.4% with overall significance level of 0.05. If this trial demonstrates improved survival with either strategy, more than 3,000 premature deaths from cardiac arrest would be averted annually.

Keywords

out-of-hospital cardiac arrest; cardiopulmonary resuscitation; continuous chest compressions; interrupted chest compressions; emergency medical services; resuscitation

Introduction

About 10% of patients treated for out-of-hospital cardiac arrest (OHCA) survive to hospital discharge.(1) Interruption of chest compressions is associated with decreased survival in animal models of cardiac arrest.(2) In a swine model of non-asphyxial cardiac arrest, continuous chest compressions (CCC) are as effective as chest compressions with rescue breathing when ventilations only interrupt compressions for four seconds (i.e. compression: ventilation ratio 15:2).(3) In a similar swine model, CCC compared to compressions interrupted for ventilations had significantly better neurological survival.(2) Conversely, ventilation improves outcomes in animal models of asphyxial cardiac arrest.(4) Importantly, it is difficult to distinguish the etiology of arrest in the field. The net impact of interrupting compressions to ventilate those with non-asphyxial arrest versus not interrupting compressions in those with asphyxia arrest is unclear. Observational studies suggest that CCC is associated with better survival than interrupted compressions.(5, 6) Thus, the Resuscitation Outcomes Consortium (ROC) investigators designed a randomized trial to test whether interruption of manual compressions to provide ventilations is effective. The purpose of this paper is to describe the rationale and methodology for this randomized trial.

Conceptual Framework

Achieving adequate coronary perfusion pressure (CPP) is a marker for the successful return of spontaneous circulation (ROSC).(7, 8) Once chest compressions are initiated, it takes time to develop an adequate CPP and in the absence of effective and continuous external chest compressions, CPP decreases rapidly.(3) Interruptions in chest compression decrease CPP with a consequent reduced chance for a successful outcome.(2) The CPP achieved during resuscitation is correlated with the quality of external compressions.(9) Current cardiopulmonary resuscitation (CPR) guidelines recommend 100 compressions per minute with complete recoil following each compression.(10) The optimal compression rate may actually be higher.(9) Some observational studies suggest that CPR quality is poor and that improved quality may be associated with improved outcomes.(12, 13) The ability to maintain chest compressions during resuscitation is affected by the need to provide ventilations, defibrillator considerations (time for analysis and time required to charge) and human factors (rhythm assessment, pulse checks, advanced airway placement, rescuer fatigue). Recognition that previous recommendations of a compression:ventilation ratio of 15:2 with stacked shocks was associated with a low CPP and fewer compressions per minute led experts to recommend a ratio of 30:2 combined with single shocks in non-intubated patients in cardiac arrest.(14)

Blood in the heart and large arteries remains well saturated with O₂ for several minutes after the onset of arrest.(15) Compression-induced ventilation is common with passive inhalation of gas following elastic recoil of the chest wall during the relaxation phase.(16–20) This ventilation may be substantial,(17, 19–22) but can decrease after 4 to 10 minutes of CPR due to progressive atelectasis and chest wall deformity.(17, 23) Spontaneous gasping (i.e. agonal breathing) also contributes to total ventilation.(19, 20, 23, 24) Supplemental oxygenation can be given during chest compression ventilation or spontaneous gasping without mechanical ventilation.(23, 24)

Clinical Studies

The use of CCC has been studied in observational studies of OHCA. EMS providers were taught and expected to perform 200 uninterrupted compressions before rhythm analysis, in two rural Wisconsin communities.(25) They also were instructed to use single rather than stacked shocks and to eliminate post-shock rhythm and pulse checks. Initial airway management used an oral airway with passive delivery of oxygen through a non-rebreather mask. During the historical control period, EMS providers were expected to use a compression:ventilation ratio of 15:2. Among patients with bystander-witnessed arrest with an initial shockable rhythm, neurologically intact survival rate was 48% during the intervention period versus 15% during the control period (p value = 0.001). CCC in combination with early administration of epinephrine and delayed endotracheal intubation was assessed in two metropolitan cities in Arizona.(6) Among those with bystander-witnessed arrest with an initial shockable rhythm, survival was 4.7% during the control period versus 17.6% during the intervention period (odds ratio (OR) = 3.0; 95% confidence interval (CI) = 1.1, 8.9). Among all cardiac arrests, survival was 1.8% during the control period versus 5.4% during the intervention period (OR = 8.6; 95% CI = 1.8, 42.0).

The effect of passive versus positive pressure ventilation in combination with CCC in patients with OHCA was assessed in an observational study in regions served by 60 fire departments in Arizona.(26) EMS providers were instructed to give 200 pre-shock chest compressions, 200 post-shock compressions before rhythm or pulse check, delayed intubation for three cycles of compression and rhythm analysis, and attempted intravenous (IV) or intraosseous (IO) epinephrine before or during the second cycle of chest compressions. Among patients with witnessed arrest with an initial shockable rhythm, survival was 38% with passive oxygen insufflation versus 26% with bag-mask assisted ventilation (adjusted OR 2.5, 95% CI 1.3–4.6). Among patients with an initial non-shockable rhythm, survival did not differ. An observational study of a similar modified CPR strategy including passive oxygenation in Kansas City, Missouri also showed improved survival.(27)

Summary of Rationale

Each of these studies used observational designs with historical controls that may overestimate the benefit of treatment.(28) None used contemporary methods of CPR process monitoring to assess protocol compliance during either study period. These studies implemented multiple changes simultaneously including CPR before analysis, continuous chest compressions, reduced ventilations for at least three compression cycles, single rather than stacked shocks, early administration of vasopressor therapy, and elimination of post-shock pulse and rhythm checks. The oxygen flow rates associated with use of a non-rebreather mask were not measured. This lack of measurement is important since low or high oxygen flow rates are achievable with non-rebreather masks.(29, 30) High dose oxygen is associated with adverse outcomes in animal models of cardiac arrest.(31) and in observational studies of cardiac arrest.(32) Therefore it is difficult to assess the relative contribution of CCC versus other changes intended to improved survival in these

observational studies. Therefore, we designed a large trial to test CCC versus ICC in patients with OHCA.

Materials and Methods

Design

This trial is an unblinded randomized cluster design with crossover, comparing survival to hospital discharge between subjects who receive CCC or ICC in patients with non-traumatic OHCA (Figure 1).

Setting

ROC is a network of clinical sites and a central data coordinating center with experience conducting large randomized trials in patients with OHCA in North America.(33–35) Eight sites are participating in this study: Birmingham, Alabama; British Columbia; Dallas-Fort Worth, Texas; King County, Washington; Milwaukee, Wisconsin; Ottawa, Ontario; Toronto, Ontario, and Pittsburgh, Pennsylvania. Contributors and investigators are available at www.onlineplaceholder.com.

This study is being conducted under exception from consent for emergency research, including community consultation and public notification before enrollment, notification of patients or their legally-authorized representative as soon as feasible after enrollment, and providing an opportunity to withdraw from ongoing participation. The study was approved by all applicable institutional review and research ethics boards. Its ClinicalTrials.gov registration number is NCT01372748.

Population

Included are adults with non-traumatic OHCA who receive chest compressions provided by ROC EMS providers dispatched to the scene. Excluded are patients with an EMS witnessed arrest; a written advance directive to not resuscitate; blunt, penetrating, or burn related injury; obvious cause of arrest is asphyxia, respiratory (asthma), drowning, strangulation, hanging, foreign body obstruction, or mechanical suffocation; uncontrolled bleeding or exsanguinations; known prisoners; known pregnancy; non-ROC EMS agency/provider first to initiate chest compressions or place pads; mechanical compression device used before any manual CPR by ROC personnel; advanced airway prior to ROC agency arrival; pre-existing tracheostomy; or a priori opted out from resuscitation research.

Study Interventions

Continuous Chest Compressions—EMS providers are instructed to initiate chest compressions as soon as cardiac arrest is identified. This is intended to occur as soon as feasible i.e. before electrocardiographic (ECG) leads are attached to the patient's chest. Note that it is difficult for a single provider to simultaneously initiate compressions and ventilations. We previously showed no significant difference in outcome between early rhythm analysis (about 30 secs. of compressions) versus later rhythm analysis (about 3 minutes of compressions) (35). Based on these results, medical directors instructed their providers to give either 30 secs. of compressions or 2 minutes of compressions while

attaching defibrillator electrodes to the chest. Providers using the latter approach may have time to apply a bag-valve mask and initiate the study intervention before the first rhythm analysis is performed.

Patients allocated to the CCC (intervention) group shall receive continuous chest compressions without pauses for ventilations (Figure 2). The airway will be opened and maintained with an oral airway and positive pressure ventilation given before insertion of an advanced airway (e.g. endotracheal tube or supraglottic airway). Since insertion of an advanced airway may be associated with interruption of CPR, participating EMS agencies will defer insertion of an advanced airway until after ROSC or three intervals of compressions followed by rhythm analysis (i.e. about 6 minutes). Positive pressure ventilation will consist of insertion of an oral airway followed by ventilations interposed at a rate of 10/minute using a volume ~400–500 mL over 1–1.5 seconds as compressions continue.

Note that the number and skill level of EMS provider on scene may vary from case to case. (36) Since early administration of epinephrine may be associated with better outcomes as compared with late (or non) administration of epinephrine, (37, 38) EMS providers capable of giving advanced life support will be encouraged to obtain intravenous or intraosseous access and give epinephrine 1 mg or vasopressin 40 IU within 5 minutes of arrival.

The duration of CPR before the first rhythm analysis will be 30 or 120 seconds based on local medical directive. This will be followed by two intervals of compressions (each of approximately 2 minutes duration) then rhythm analysis, which will be performed as quickly as possible after cessation of compressions (i.e. goal < 10 seconds). Patients in VF will be defibrillated once, followed by immediate restart of chest compressions. After three intervals of compressions and rhythm analysis, an advanced airway will be inserted as soon as feasible while the study intervention continues. Then CPR will continue with compressions 100/min. and ventilations 10/min. without pause until ROSC is achieved, resuscitation efforts are terminated or care is transferred to emergency department staff. This approach to compression and ventilations in a patient with an advanced airway is consistent with what is recommended by current AHA guidelines for emergency cardiovascular care.(11) All other resuscitation and post-resuscitation care will be per local practice.

IV or IO access along with delivery of a vasopressor (epinephrine 1 mg or vasopressin 40 IU) is expected to occur within 5 minutes of arrival of an EMS provider capable of providing advanced life support if vasopressor therapy is required.

Interrupted Chest Compressions—EMS providers are instructed to initiate chest compressions as in the intervention group. Medical directors have instructed their providers to give either 30 secs. or 2 minutes of compressions while attaching defibrillator electrodes to the chest. Patients allocated to the ICC (control) group shall receive compressions using a compression: ventilation ratio of 30:2 (Figure 3). Ventilations will be given using positive pressure during a pause in compressions of less than 5 seconds duration. Tidal volume will be approximately 400–500 mL per breath. The EMS providers will be taught to not pause for any reason other than for ventilation during the first three CPR intervals and to perform

CPR up to the moment of rhythm analysis and immediately after the shock is delivered. EMS providers will be encouraged to minimize CPR interruptions during all advanced airway placement. Defibrillations, other resuscitation and post-resuscitation care will be per local practice.

After three intervals of compressions and rhythm analysis, an advanced airway will be inserted as soon as feasible while the study intervention continues. Then CPR will continue without pause as in the intervention group.

CPR Process Monitoring—The ability to monitor CPR process is essential to interpretation of cardiac arrest trials as the quality of CPR performance is associated with improved outcomes after resuscitation.(39)

Sites were required to demonstrate an ability to adequately acquire and analyze these CPR process data, including compression fraction, rate, and depth; identify and attempt to correct any observed deficiencies; and meet minimum performance standards before beginning enrollment in this trial (www.onlineplaceholder.com). In the ROC PRIMED Trial, CPR process data were available on 65% of eligible, enrolled patients.(35) CPR process data will be used to assess compliance/adherence to study intervention during the trial.

Internal Study Monitoring—As with previous studies by our collaborative group, a multidisciplinary study monitoring committee (SMC) will periodically review data masked to treatment outcome.(40) This committee assesses whether prespecified targets for performance are met for measures such as enrollment and eligibility rates, event rate, adherence/compliance rate, retention rate and data quality (www.onlineplaceholder.com).

Post-Resuscitation Care—Post-resuscitation care, including hospital procedures such as hypothermia and cardiac catheterization, will be monitored but not standardized in this trial. (Online Appendix available at www.onlineplaceholder.com)

Random Allocation—The intervention (i.e., ICC or CCC) was randomly allocated using a cluster-crossover design. Each site was subdivided into multiple clusters by EMS agency, station, or other unit as appropriate to the site's EMS structure. Randomization of clusters was stratified by site and by blocks of concealed size within sites. After six months on the original randomized arm, clusters crossed over to the other arm of the study. For the duration of the study, clusters are re-randomized to the same study arm or cross over every six months. This approach is intended to lead to balance of the study arms both within clusters and overall.

Comparison Populations—The effectiveness population will consist of all randomized subjects from the post-run-in phase of the study. Safety summaries will be based on all randomized subjects from both the run-in and post-run-in phases.

Outcomes—The primary outcome is survival to hospital discharge. Secondary outcomes are neurologic status at discharge, measured with the modified Rankin score based on review of the clinical record (27–28), and adverse events. Other surrogate outcomes will be

collected for descriptive purposes, and include the total number of defibrillatory shocks, sustained ROSC, survival to 24 hours from time of arrest, survival to awakening, survival to withdrawal of care, and in-hospital morbidity.

Sample Size and Study Duration—Enrollment began in June 2011. We plan to enroll a maximum of 23,600 patients (11,800 per group) during the post-run-in phase of the study. This will provide 90% power in the primary analysis to detect a change in survival to discharge from 8.1% to 9.4% with overall two-sided α (adjusted for interim analyses) equal to 0.05. The baseline survival rate was based on the ROC PRIMED Trial (34, 35) and the power calculations account for a 5% loss of precision due to randomizing by cluster (with crossover). Based on historic enrollment rates in the consortium as well as initial enrolment into the trial, we estimate that the maximum enrollment will require an study duration of four years.

Data Collection and Data Entry—Data is abstracted from source material, such as ECG files, patient care reports, and hospital records, at the clinical sites and entered into a central web database maintained by the DCC. Data quality control measures include internal checks for consistency of the data, comparisons to reference ranges, data audits and site visits to verify the accuracy of the data.

Safety Monitoring—Many adverse events are commonly observed in patients who experience cardiac arrest and resuscitative efforts, and may or may not be attributable to specific resuscitation therapies. These include pulmonary edema, hemodynamic instability, airway bleeding, complications of endotracheal intubation, pneumonia, sepsis, cerebral bleeding, stroke, seizures, bleeding requiring transfusion or surgical intervention, re-arrest, rib fractures, sternal fractures, internal thoracic or abdominal injuries, neurological impairment, and death.(41) An independent data safety board will monitor the rates of these pre-specified events as well as any unexpected or spontaneously reported adverse events.

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Results

Primary Analyses

The primary test of the null hypothesis will be performed using a test statistic calculated as difference in event rates divided by the estimated “robust” standard error based on the Huber-White sandwich estimator (42, 43) in order to account for within-cluster correlation and variability which might depart from the classical assumptions. A 95% CI for the difference in event rates will be calculated with an adjustment for the interim analysis plan to provide a clinically meaningful quantification of the treatment effect.

Interim Analyses

The formal stopping boundaries are symmetric, two-sided designs (44) which are included in the unified family of group sequential stopping rules.(45) The tests for superiority of either intervention will be based on boundaries intermediate to the well-known O'Brien-Fleming and Pocock designs.(46, 47) Formal interim analyses are to be performed at semiannual intervals throughout the duration of the trial.

Secondary Analyses

Analyses of secondary outcome measures will use the Mann-Whitney test and proportional odds regression for ordinal outcomes, and the chi-squared test and logistic regression for binary outcomes.

Other Outcomes

Other outcomes will be assessed to give insight into possible mechanisms underlying any observed treatment effect. These will be summarized descriptively: results will be reported using point estimates and 95% confidence intervals rather than p-values. These analyses will be considered exploratory and will not be used as a basis for treatment recommendations.

Pre-specified Subgroups

The effect of treatment upon primary and secondary outcomes by the presence or absence of prognostic factors will be examined separately in the subgroups defined below. Tests for key interactions will also be performed. Subgroup analyses will be considered exploratory and will not be used as a basis for treatment recommendations. We will examine the treatment effect on survival to discharge for subgroups defined by first recorded rhythm: a) VT/VF or shockable, b) pulseless electrical activity (PEA), c) asystole, and d) other or unknown rhythm. Tests for interaction in the listed subgroups will be done in those patients with an initial rhythm of VF/VT unless an overall treatment effect is found in non-shockable initial rhythms. The key subgroups of interest are: response time interval from call to arrival at scene < 10 minutes versus ≥ 10 minutes; arrests witnessed by bystanders versus unwitnessed arrests; arrests in a public place versus a private location; advanced airway placement within 5 minutes of arrival of EMS provider capable of advanced life support versus > 5 minutes; field cooling versus hospital cooling versus both versus neither; percutaneous coronary intervention within 4 hours after hospital arrival versus more than 4 hours after hospital arrival versus not performed during index hospital admission; incidence rate of neurologic status at discharge in control group by study site; bystander CPR administered versus not administered; and cardiac etiology of arrest versus non-cardiac etiology.

Conclusions

A large randomized trial is underway to compare survival to hospital discharge after continuous chest compressions versus currently recommended CPR with interrupted chest compressions at a rate of 30 compressions to 2 ventilations in patients with OHCA. If this trial demonstrates a significant improvement in survival with either strategy, it is estimated that more than 3,000 premature deaths from cardiac arrest would be averted in the United States alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Design

Figure 2.
Treatment in Intervention Group

Figure 3.
Treatment in Control Group